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Type 2 diabetes, hearing loss, and contributors to hearing loss in older Mexican Americans

by

Elizabeth Anne Thomas

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Nursing

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[redacted]

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by

Elizabeth Anne Thomas

Dedication

This work is dedicated to the memory of my father, L. D. Thomas, born September 28, 1924, died January 5, 2009. He supported and loved me my whole life. His life was an example of perseverance and resilience and he was an inspiration to me in both my personal life and in my nursing career. I have been a better person and a better nurse because of his influence. He persevered with grace through severe health problems my entire adult life. His resilience in the face of adversity always kept hope alive, even in the darkest moments. Unfortunately, he is not here to witness the culmination of this accomplishment, although I believe he is with me in spirit. Thank you, Dad, for being proud of me. This is for you.

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Abstract

Type 2 diabetes, hearing loss, and contributors to hearing loss in older Mexican Americans

Elizabeth Anne Thomas

Mexican Americans have a high prevalence of type 2 diabetes. Among the elderly, hearing loss is also a significant chronic condition. Understanding of the co-occurrence of these conditions is important for planning screening, intervention and support for a vulnerable population. **Aims:** The objective of this study was to test a model of predictors of hearing loss in type 2 diabetes. The model tested was developed through a process of answering several research questions in a two part analysis. Part 1 of the analysis explored the relationship between hearing loss and type 2 diabetes in an existing sample of Mexican Americans (N=990) from the greater Sacramento area of California. Additional analysis in Part 2 was focused on predictors of high frequency hearing loss in diabetes in the sub-cohort of participants with type 2 diabetes (n=405). **Methods:** A cross-sectional subset of data from the Sacramento Area Latino Study on Aging (SALSA) was analyzed to meet the study aims. Analysis included correlations, non-parametric testing, and logistic regression models. **Results:** High frequency hearing loss in the worse ear was significantly more prevalent in those with diabetes. In logistic regression modeling, age and gender were significant predictors of hearing loss but diabetes was only significantly related to hearing loss in the worse ear. This effect was found to be explained by females in the sample as it was not significant for males on gender-specific analysis.

Analysis of participants with diabetes revealed that age, gender, and pesticides use predicted high frequency hearing loss in the worse ear while age, gender and two diabetes symptom factors relating to energy/fatigue and cardiac/pulmonary symptoms were predictors in the better ear. There was an interaction effect between diabetes and pesticides use that suggests a need for further study to determine if diabetes makes an individual more vulnerable to the negative effects of pesticides. The results provided partial support for the conceptual model developed for the study and suggested directions for future research on hearing loss in individuals with diabetes.

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Chapter 1: Statement of the Problem

The Study Problem

Type 2 diabetes has reached epidemic proportions in this country and disproportionately affects older adults (Centers for Disease Control and Prevention, 2008). Mexican Americans have a high prevalence of type 2 diabetes. Among older adults, hearing loss is also a significant chronic condition (Wallhagen, Pettengill, & Whiteside, 2006). Diabetes, its symptoms and hearing loss all have potential to impact functional status including the ability to work and quality of life with aging. Understanding of the co-occurrence of these conditions is important for planning screening, intervention and support for this vulnerable population. Several workplace exposures have been linked to hearing loss (Morata, 2003) yet none of the research published to date has evaluated diabetes and hearing loss within the context of work-related exposures. Understanding of long-term work-place exposures within the context of diabetes may allow for effective preventive activities within work environments to prevent hearing loss and its impact with aging on this population with multiple comorbidites.

This paper describes results of a secondary analysis of data collected on older Mexican Americans who were participants in the Sacramento Area Latino Study on Aging (SALSA). SALSA is a large cohort study including more than 1,789 Mexican Americans who were aged 60 or greater in 1998-1999 at the study's inception and living in a targeted six county area of the greater Sacramento area in California. Following baseline data collection, follow-up

home visits were conducted every 12-15 months for seven years through late 2007 and is presently continuing for mortality surveillance. Two subsets of participants from the SALSA were included in the current analyses: those with a baseline hearing test performed in years four through seven of the study (N=990); and a subset of this cohort with hearing tests who had a diagnosis of diabetes at the time of their hearing test (n=405). Part I analysis identified the relationships between diabetes and hearing loss. For Part 2 analysis, a conceptual framework developed for this study directed selection of variables that were potential predictors of high frequency hearing loss within the context of diabetes. These potential predictors include: clinical factors, both subjective and objective indicators of microangiopathy and macroangiopathy, work-related exposures and diabetes signs and symptoms factors determined from a factor analysis of a 35-item symptom questionnaire. Variables grouped by concepts were evaluated initially to determine predictors of high frequency hearing loss in those with diabetes. Those variables reaching or approaching significance were included in a final composite logistic regression model of high frequency hearing loss among Mexican Americans with diabetes age $\geq$ 65.

The focus of this research is on type 2 diabetes and hearing loss in older Mexican Americans. Unless otherwise specified to be type 1 diabetes, all references to diabetes pertain to the type 2 variant throughout this paper.

Study Objective and Specific Aims

The overall objective of this study was to test a model of predictors of hearing loss in type 2 diabetes. The model tested was developed through a

process of answering specific research questions in a two part analysis. Part one of the analysis explored the relationship between hearing loss and type 2 diabetes in an existing sample of Mexican Americans (N=990) from the SALSA study. This section of the analysis addressed several research questions. 1) What is the prevalence of hearing loss among Mexican Americans with diabetes compared to those without diabetes? and 2) What is the relationship between hearing loss (low-mid and high frequency) and type 2 diabetes when controlling for age and gender? Age and gender are the two strongest predictors of hearing loss cited in the published literature (Bainbridge, Hoffman, & Cowie, 2008; Cruickshanks et al., 1998; Davanipour, Lu, Lichtenstein, & Markides, 2000; Torre, Moyer, & Haro, 2006). Both ears, modeled as worse and better hearing ears, were evaluated for hearing loss.

Part 2 of the analysis explored the relationship between diabetes and hearing loss when modeled as worse and better hearing ears. Based on the published literature, high frequency loss is known to be associated with diabetes; therefore, the analysis on the diabetes subset was focused only on high frequency hearing loss to determine predictors of high frequency hearing loss in diabetes. In this subset of SALSA participants with type 2 diabetes (n=405), the following research questions were included:

1) Are selected signs and symptoms of diabetes, such as neuropathic, vascular and diabetes-specific symptoms associated with and predictive of high frequency hearing loss?

2) Are selected clinical indicators (duration of diabetes, hypertension, metabolic syndrome, BMI, waist circumference, ototoxic drugs, smoking (pack years), and ETOH use (in years) associated with and predictive of high frequency hearing loss?

3) Are clinical indicators of microangiopathy (fasting glucose, HbA1c, Semmes-Weinstein Monofilament Test and/or Vibration Threshold testing, glomerular filtration rate, and diabetic retinopathy) associated with and predictive of high frequency hearing loss?

4) Are clinical indicators of macroangiopathy (coronary artery disease, peripheral vascular disease, cerebrovascular disease, blood lipids) associated with and predictive of high frequency hearing loss?

5) Are work-related exposures associated with and predictive of high frequency hearing loss?

6) Of the variables found to be predictive of high frequency hearing loss in individual model analyses conducted in questions 1-5, what is the relative contribution of each variable in predicting high frequency hearing loss in those with type 2 diabetes? Variables that reached a significance level of .10 in their group models were included in the final composite model.

The co-occurrence of diabetes and hearing loss is an important phenomenon to study. Understanding how these two chronic diseases occur in older Mexican Americans has potential to improve the quality of life and functional status of these older adults and provide guidance for prevention in younger working cohorts to reduce impairment as they age.

Chapter 2: Literature Review and Theoretical Framework

Literature Review

America is aging. The proportion of the U.S. population that is over age 65 is growing and will continue to grow as the largest age cohort is reaching retirement age (Dychtwald, 2002). The number of people that are working beyond the traditional retirement age is also increasing. The potential for chronic disease to impact the lives of this growing older population, including their ability to work, is becoming clear. Nursing professionals have the ability to make a positive difference in the detection, treatment, and self-management of chronic disease.

Type 2 diabetes mellitus is one chronic disease that has reached epidemic proportions. Diabetes disproportionately impacts older individuals at increasing rates. In 2005, diabetes affected 20.9% of those over age 60 compared to 9.6% of the total population (Centers for Disease Control and Prevention, 2005). By 2007, that statistic increased to 23.1% of those over age 60, compared to 7.8% of the total population (Centers for Disease Control and Prevention, 2008). It is ranked number six as a cause of death with significant underreporting known as studies have found that approximately 35% to 40% of individuals with diabetes who die have it listed anywhere on the death certificate and only 10% to 15% had diabetes listed as the underlying cause of death (Broom & Whittaker, 2004; Centers for Disease Control and Prevention, 2005). The care required and the human impact of diabetes creates a significant and costly disease burden (Hogan, Dall, & Nikolov, 2003).

Diabetes diagnosis by self-report was found to be twice as prevalent in Mexican Americans as in non-Hispanic whites in the National Health and Nutrition Examination Study (NHANES) 1999-2002 nationally-representative survey (Cowie et al., 2006). For those over age 60, 24.5% of Mexican American women and 25.6% Mexican American men have known diabetes. An estimated 3% have undiagnosed diabetes. Another 30.4% of women and 34.3% of men in this population were found to have impaired glucose tolerance consistent with 'pre-diabetes'. Current thinking regarding pre-diabetes is that it progresses to diabetes in 10 years, on average, everything else being equal. Given the aging of the American population and the American workforce, the increasing prevalence of type 2 diabetes, its disease burden and cost, what are the implications for older individuals, including older workers, with diabetes?

Hearing loss represents another common chronic condition that increases with age and has significant potential for impairing quality of life and functional levels, including the ability to work (Bogardus, Yueh, & Shekelle, 2003; Wallhagen, Strawbridge, Shema, Kurata, & Kaplan, 2001). As one of the most common chronic health conditions, Bogardus and his colleagues note that it is under detected and undertreated.

The 1994 National Health Interview Survey (NHIS) Core and the 1994 NHIS Second Supplement on Aging (SOA II) included data that allowed estimates of hearing loss among elders in the United States (Campbell, Crews, Moriarty, Zack, & Blackman, 1999). The NHIS is conducted annually as a cross-sectional household survey of a nationally representative sample of the U.S.

population. Hearing impairment, for the purposes of the study, was defined as deafness in one or both ears or any other report of difficulty hearing. For those aged 70 and over, 33.2% of survey respondents (n=8,767) reported hearing impairment. For the Hispanic respondents, 29.3% reported hearing impairment. For the entire age cohort, geographical locale impacted the reported number with the Western United States reporting the highest level of hearing impairment at 35.3%. Hearing aid use in the last year before data collection was reported by 11.6% of these elders and cochlear implants by only 0.1%, representing a rare treatment for impaired hearing (Campbell et al., 1999).

Human hearing mechanism

The human ear and its neurological connection to the brain represent a complex and sensitive system that is vulnerable to damage by different illnesses, injuries and toxic exposures (Sataloff & Sataloff, 2005b). The outer ear, middle ear, inner ear, and acoustic nerve (8^{th} cranial nerve) are the major components of this system. The outer ear serves to gather sound energy and transmit it to the middle ear. Separating the outer ear from the middle ear is the tympanic membrane (or ear drum). Movement of the tympanic membrane by sound energy is transmitted through the tiny bones in the middle ear known as the ossicles to the inner ear. The middle ear is filled with air and connects to the throat via the Eustachian tubes that are instrumental in equalizing pressure on either side of the eardrum. The inner ear is filled with fluid and has two parts: the vestibular labyrinth and the cochlea. The vestibular labyrinth is an organ of balance rather than of hearing. The cochlea is the portion of the inner ear that contains the

hearing sensitive structure, the organ of Corti. Within the organ of Corti are found thousands of tiny hair-like cells that have a sensory function. When the sound wave transmitted by the ossicles through the middle ear reaches the inner ear, vibration of membranes covering openings within the structure cause the fluid within the inner ear to begin moving. This fluid in motion stimulates the hair-like nerve cells in the organ of Corti, generating electromechanical impulses. Sataloff and Sataloff aptly describe the organ of Corti “as the switchboard of the auditory system” (2005b, p. 22). The acoustic nerve transmits these electromechanical impulses created by the sound energy in the organ of Corti to the brain where these signals are interpreted and experienced as sound.

Hearing loss can be conductive, in which the transmission of the sound energy is impaired in some way, or it can be sensorineural in nature. Conductive losses are often temporary or correctable through increasingly sophisticated surgical techniques. Sensorineural hearing loss due to aging or noise exposure is rarely correctable. Sensorineural hearing loss can be treated with hearing technologies such as hearing aids and cochlear implants and individuals can receive aural rehabilitation which may reduce the psychological, social and functional implications of hearing loss (Sataloff & Sataloff, 2005a).

Sensorineural hearing loss affects either the inner ear (sensory) or the auditory nerve (neural) from the base of the hair cells all the way to the origin of the nerve in the brain. These two types of hearing loss, sensory and neural, are commonly grouped together despite their occurring in different segments of the hearing system. This is mainly due to inadequate diagnostic techniques

historically to differentiate between these two causes of hearing loss. As techniques for assessing hearing loss are improving, differentiating the source of the loss is becoming more refined making determination of either sensory or neural loss possible (Sataloff & Sataloff, 2005b). Sensory and neural loss can occur in isolation or be concurrent. Either or both can also co-occur with conductive hearing loss which is referred to as mixed hearing loss.

Sound and human responses

Sound is a stimulus that results in psychophysical effects in humans. Different sound intensities and frequency levels (Hz level), experienced as pitch, produce a range of effects. Immediately upon sound hitting the structures of hearing, adaptation occurs. A reversible threshold shift results that is dependent upon the sound intensity and its frequency (Sataloff, Sataloff, & Virag, 2005).

Under conditions of acute exposure to loud noise, fatigue in the structures occurs which is most likely caused by metabolic processes that occur as a result of the sound level pressure. This shift is pathological but reverses over time, usually in hours. Sataloff and his colleagues state about this temporary threshold shift (TTS) that “its development and recovery are proportional to the logarithm of exposure time” (Sataloff et al., 2005, p. 421). An increase in metabolic processes is thought to be responsible for TTS. Sataloff and Sataloff report that “an increase in number and size of lysosomes, primarily in the outer hair cells” occurs with TTS (p. 421). The TTS phenomenon is known experientially to many urban workers who raise the level of their radios while driving home after a long day of work and exposure to noise only to cringe at the loudness of the music

when they start their cars the next morning after a good night's rest. The night away from noise exposure was sufficient to allow recovery of the hearing structures from the TTS.

Hearing loss that is permanent is a result of permanent threshold shifts (PTS) in hearing. Occupational exposure to excessive noise over prolonged periods of time results in such permanent shifts in hearing thresholds. For noise to damage hearing takes sufficiently high sound levels and sufficiently extended periods of time, usually years. Very high noise levels, known as impact noise (over 125-140 dB) has been shown to cause PTS as well, but is not commonly seen. The noise exposure over time leads to damage and loss of the hair cells in the organ of Corti. This process is believed by experts to be the result of two mechanisms of action: direct mechanical destruction of the hair cells due to high intensity sound and metabolic decompensation with exposure to moderately intense sound. This metabolic process leads to degeneration in the sensory structures of hearing. The second quadrant of the basal turn of the cochlea is most sensitive to the effects of noise. This portion of the cochlea is responsible for hearing in the 3000 to 6000 Hz range (Sataloff & Sataloff, 2005b). Hearing levels for speech is considered to be an average of the 500, 1000, 2000 and 3000 Hz frequencies. The voices of women and children fall in the upper frequencies of this range and are therefore, less likely to be heard or understood in the presence of higher frequency hearing loss (Sataloff, Sataloff & VIrag, 2005).

Hearing loss is usually significant by the time help is sought. The early stages of loss go unnoticed or are discounted (Sataloff & Sataloff, 2005a). Hearing loss commonly leads to embarrassment, feelings of inadequacy, friction in relationships, isolation, and stigma. All of these outcomes are important for older adults in terms of functionality, ability to work and key factors related to quality of life such as self-esteem, normal socialization, and reduced risk for depression (Wallhagen, Pettingill & Whiteside, 2006).

Significance of Hearing Loss

The importance of being able to hear normally is not fully appreciated by the general public or even medical professionals. Sataloff and Sataloff (2005a) state that there is little difference from the days when society cursed the deaf, believing those afflicted were being punished by God. In modern times, we don't view hearing impairment as a curse but still view it as embarrassing, associated with old age and senility and even as a cause for loss of sexual desirability.

It is very common for those with significant hearing impairment to avoid seeking medical attention without pressure from others. Many deny their hearing loss and tolerate the difficulties it causes for a long time before giving in to a family member's pleas to seek evaluation and care. Most individuals accept the need for eyeglasses without difficulty, but it is unusual to tell someone that they need hearing aids without resulting distress (Sataloff & Sataloff, 2005).

Hearing loss in an older population can be due to many causes, aging and noise-induced hearing loss being among the most common causes. Whether the hearing loss is a result of age or of noise (or both), high frequency loss usually

occurs first. As a result, consonant speech sounds are harder to discriminate than are vowel sounds. This difficulty in sound discrimination has serious implications for understanding speech. Difficulty in understanding the speech of others results in misunderstanding of meaning and frustration for all parties involved. Sataloff and Sataloff (2005a) indicate that hearing loss is an under recognized source of friction in marital relationships. The frustration and embarrassment of not being able to hear well ultimately may lead to isolation as an individual tires of always asking others to repeat themselves or speak louder, and they eventually give up trying.

Extending this discussion into a consideration of hearing loss in a work setting, inability to distinguish words appropriately has potential to create a significant safety issue in the work environment. If work instructions are not heard correctly, employees may do the wrong thing (Sataloff & Sataloff, 2005a). In emergency situations, they may not hear emergency instructions adequately to follow them. They are hindered in their ability to receive training that is delivered verbally. Just as it is common for elders to deny and tolerate the effects of hearing loss at home, doing so in the workplace can lead to poor performance on the job. Carried to its extreme, this results in loss of income and future employment potential.

Diabetes and hearing loss

An association between diabetes and hearing loss has been controversial for more than a century (Fowler & Jones, 1999). Early studies found conflicting associations. Many of these studies suffered from methodological issues or

inadequate power to detect an effect. Interestingly, in the community of professionals who deal most often with hearing loss, including otologists and otolaryngologists, diabetes as a causative factor for hearing loss is widely accepted (Fowler & Jones, 1999). Sataloff and Sataloff (2005d) cite that up to 40% of individuals with diabetes develop hearing loss. These hearing loss experts indicate that hearing loss in diabetes is sensorineural, bilateral, is more severe in higher frequencies, and is most often worse in older individuals with diabetes.

Part of the reason that determining the contribution of diabetes to hearing loss is difficult is because of the many contributors to hearing loss that are possible. As stated by one group of diabetes and hearing loss researchers: “attributing hearing loss to diabetes alone is often difficult because of other vascular diseases in these patients and because of compounding variables such as presbycusis” (Kakarlapudi, Sawyer, & Staecker, 2003, p. 384).

Fowler and Jones (1999) conducted a review of studies for diabetes and hearing loss. The studies they reviewed were published between 1857 and 1998. Fowler and Jones indicated that studies of diabetes and hearing loss have found conflicting results but have been deeply flawed (Kuvien, Thomas & Bhanu, 1989; Roach, 1973; Taylor & Irwin, 1978; Wackym & Linthicum, 1986). Problems cited in these studies include: inadequate sample size, poor choice of controls or inadequate description of controls to support group equivalency; lack of description of inclusion criteria; potential for asymptomatic diabetes to be present in subjects without methods used to detect diabetes if present; and setting

issues, such as use of a workforce that under-represents those with advanced diabetes and significant hearing loss due to the healthy worker effect (Hodgson, Talbott, Helmkamp & Kuller, 1987). The largest study reviewed by Fowler and Jones (Kindler, 1955; n=8,000) did not show an association between diabetes and hearing loss. Age was controlled for but noise exposure was not. Given that this study was done over 50 years ago, prior to monitoring of noise levels required by hearing conservation programs, this limitation of failing to statistically control for noise exposure is understandable. More recent studies are more likely to control for noise exposure.

Fowler and Jones conclude that as of their writing (1999), there was insufficient evidence to make conclusions about whether or not diabetes has an association with hearing loss. They further concluded that longitudinal studies of more rigorous design are needed to answer this question.

Important to the research in this dissertation study, Fowler and Jones state that many of the studies they reviewed excluded older adults so as not to confuse hearing loss due to diabetes with presbycusis, hearing loss due to age. They further point out that the elderly are the very ones who are most likely to have diabetes with significant complications so this group would most likely show the association between diabetes and hearing loss if it is present (Fowler & Jones, 1999).

The remaining studies reviewed in this paper on diabetes and hearing loss were published from 2000 to 2008. A total of 137 articles result from a PubMed search with the search terms diabetes and hearing loss when limited to English

language and adults aged 45 and over. Nine of these studies were directly applicable to the current study and were reviewed in the remainder of this section of this paper. Additionally, one older study of interest was reviewed as was a study relating specifically to hearing loss in the SALSA participants.

A cross-sectional study to investigate hearing problems in older (over age 65) Mexican Americans was conducted as part of a longitudinal cohort study (Davanipour, Lu, Lichtenstein, & Markides, 2000). This study used probability sampling in five southwestern states to identify the sample from census data. To ensure representativeness of the sample, a process of weighting was assigned to each participant based on the census count of Mexican Americans in that person's region of residence. Up to four elders over age 65 in any given home were interviewed. Hearing problems were identified from self-reported data collected via the Hearing Handicap Inventory for the Elderly-Screening Version (HHIE-S).

The authors (Davanipour et al., 2000) report that the HHIE-S inventory has been validated against pure-tone audiometry and a reference is provided for the validation study. Hearing problems were identified if an individual had ever used a hearing aid, if the interviewer perceived difficulty in hearing was present, or the individual scored greater than 8 on the HHIE-S. The HHIE-S specifically assesses the social and emotional impact of difficulty hearing in situations where effective communication is needed. As such, it is a functional assessment of hearing impairment. Self-report of chronic conditions (arthritis, diabetes, hypertension, MI, stroke, cancer), depressive symptoms (using CES-D), smoking

history (duration, age when began, years since quitting, and average number of cigarettes daily), and having ever consumed alcohol was gathered. It was estimated that 24.5% of Mexican Americans over age 65 living in the Southwestern United States have hearing problems. In univariate analysis, the factors that were associated with hearing problems included older age, male gender, diagnosis of several chronic diseases (hypertension, arthritis, cancer, stroke), depressive symptoms, history of using alcohol, cigarette smoking including higher smoking levels. Diabetes, participant educational level and age-adjusted history of MI were not significantly related to hearing loss. Multiple logistic regression with forward step-wise variable selection was conducted. The optimal combination of greater age by decade groups (OR: 2.7; 95% CI: 2.3-3.1), male gender (OR: 1.9; 95% CI: 1.6-2.4), depressive symptoms (OR: 1.4; 95% CI: 1.2-1.8), history of arthritis (OR: 1.5; 95% CI: 1.2-1.8) or hypertension (OR: 1.4; 95% CI: 1.1-1.7), and ever having ingested alcohol (OR: 1.4; 95% CI: 1.1-1.7) was significant for increased likelihood of hearing problems. An increased odds was found for greater number of cigarettes smoked in the multivariate model when categorized by 10 cigarette incremental increasing groups, but this failed to reach statistical significance (OR: 1.1; 95%CI: not given; p = .07*)*.

Although Davanipour and his colleagues cited validity from the literature of the hearing problem questionnaire compared to objective measures such as pure-tone audiometry, the lack of actual audiometric testing makes the levels of hearing loss that may be associated with perceived hearing problems and the various findings uncertain. As the authors note, “the hearing problem inventory

used is a measure of social problems related to hearing loss" (Davanipour et al., 2000, p. 171). It is important to note that the HHIE-S is intended for functional evaluation of hearing loss. This study found a higher prevalence of hearing problems among men than among women consistent with other studies. No history of noise exposure (military, occupational, or recreational) was gathered.

Davanipour's study may have suffered from a lack of independence of measurement issue as multiple interviews were conducted in the same household. Sampling multiple participants from one household has potential to alter questionnaire responses. When participants are from the same location, control for lack of independence is indicated. No statistical controls for this lack of independence were discussed in this study. Future studies would improve upon this one if both a valid subjective measure such as the HHIE-S was used in conjunction with pure-tone audiometry or other objective measures of hearing loss.

The authors (Davanipour et al, 2000) suggest that hypertension's association with hearing problems in this study may be related to a common vascular pathology and that rheumatoid arthritis's association may be due to middle ear or inner ear pathology related to arthritis. This latter conjecture appears to be an overstatement of their findings as no data was collected to determine if the arthritis reported was of the rheumatoid type or osteoarthritis. However, additional research would be warranted to determine if a relationship exists with one or both types of arthritis. This study adds to the understanding of prevalence of hearing problems in Mexican American elders; however,

longitudinal designs are needed in future research to determine cause and effect. The association of current depressive symptoms with hearing problems in this study is a case in point as depression may be a result of hearing loss.

A major methodological flaw of Davanipour et al.'s study was the use of step-wise regression analysis as the analytic strategy. Step-wise regression is flawed in that results can vary from iteration to iteration of the analysis done by the computer as the method enhances results found by chance. Therefore, results must be viewed with skepticism as alternate results are equally likely with the same data, particularly if there is any correlation within the predictors in the model (Babyak, 2004).

A retrospective case-control study using electronics health records (EHR) to review 12,575 patients with diabetes and 53,461 age-matched controls without diabetes was conducted by Kakarlapudi and colleagues (Kakarlapudi, Sawyer, & Staecker, 2003) to determine effects of diabetes on sensorineural hearing loss, specifically related to prevalence and diabetes control. The tertiary-level medical center utilized EHR exclusively beginning in 1989. For this study, sensorineural hearing loss was identified by International Classification of Diseases (ICD) code data extracted from the EHR. Patients who were receiving care only for psychiatric illness, HIV, or substance abuse were excluded from analysis to focus on comorbidities more related to diabetes and hearing loss. Average pure tone hearing level thresholds were calculated for those with sensorineural hearing loss for 500, 1000, 2000, and 4000 Hz. Laboratory data of total cholesterol, LDL cholesterol, serum triglycerides, HbA1c (diabetes only), and creatinine were

gathered for a five-year period and averaged for analysis. Serum creatinine was chosen as a marker of microangiopathy as increasing creatinine levels over time leading to renal failure are well established to be due to this process.

In Kakarlapudi's study (Kakarlapudi et al., 2003), diabetes was present in 23% of patients with hearing loss and only 19% in those without hearing loss, which was a significant difference at $p < .05$. Groupings were created to evaluate the laboratory data in relation to hearing loss. Serum creatinine levels were correlated with hearing loss when patients with diabetes were divided into five groups based on their creatinine levels. Hearing loss increased progressively at these progressively larger creatinine levels and was significantly different; however, the average hearing threshold differences between the lowest creatinine group and the highest was only 7.3 dB which is not clinically significant. Speech discrimination scores decreased as creatinine rose with a 7.5% difference between the low group and the highest group which was statistically significant, but also of limited clinical significance.

The very large sample size with use of chi-square and ANOVA for analysis in the study may be responsible for the findings as statistical significance can nearly always be found for small effect sizes in large enough samples. This study does demonstrate the potential value of case-control designs using data from EHR to accomplish research aims. One limitation of the study common to all such studies is the use of ICD codes. Comorbidities frequently are not documented in the medical record unless the person sought

care specifically for that comorbidity and thus, may have been missing from the record.

A major limitation of the study by Kakarlapudi and colleagues relates to its case-control design. Generalizability is limited in case-control studies due to the lack of random selection and no cause and effect conclusions are possible due to the cross-sectional retrospective nature of the study. Another problem with Kakarlapudi's study was how it was documented in the published article. It was difficult to understand what the actual findings in the study were because the literature review and discussion sections were blended so thoroughly, it was hard to separate out when the authors were discussing their own findings versus what was in the literature. The authors appropriately identified that without hearing data on those with diabetes and no hearing loss, their ability to evaluate the effect of diabetes on hearing loss was limited. Prospective screening of individuals with diabetes is suggested for future studies to provide for better understanding of the relationship between diabetes and hearing loss.

A cross-sectional study of racial and gender differences in age-related hearing loss examined a random sample of adults aged 73 to 84 enrolled in the Health, Aging and Body composition study (Health ABC) (Helzner et al., 2005). All participants were Medicare beneficiaries (n=2,052), residing in the greater metropolitan areas of Memphis, Tennessee and Pittsburgh, Pennsylvania, with ethnicity of 63% white and 37% black. Data for this analysis was collected during the 5th study year of the prospective Health ABC study. Potential participants with bilateral obstructed ear canals were dropped from analysis (n=156). Hearing loss

for the purposes of this study was defined as either/both ears >25 db average pure tone thresholds for 500, 1000, and 2000 Hz and/or >40 db average thresholds for 2000, 4000, and 8000 Hz. Factors considered for association with hearing loss were collected by questionnaire. Factors that were determined to be associated with hearing loss after multivariate adjustment included: older age, white race, diabetes, cerebrovascular disease, poor cognitive status, history of work-related noise exposure, ear surgery, and smoking. Specific race and gender risk factors were found to be associated with hearing loss. These included higher blood pressure and work related noise exposure for white males; smoking and poor cognitive status for black females; and low hip bone density in black males. Interestingly, salicylate use was found to be protective in black males and moderate alcohol intake was protective for black females in this study.

Hearing loss was highly prevalent in Health ABC sample at 59.9% for the pure tone average of 500, 1000 and 2000 Hz at > 25 dB and 76.9% for the higher frequency average of 2000, 4000 and 8000 Hz at >40 dB (Helzner et al., 2005). White males had the highest prevalence in both hearing loss categories. For lower frequency averages (500, 1000 and 2000 Hz), white women had the next highest prevalence, followed by black males and then black females. Males had higher prevalence of hearing loss in the higher frequencies with white males highest, black males next, then white females, and lastly, black females. Diabetes was univariately significantly associated with hearing loss (age adjusted OR: 1.45; 95% CI: 1.14-1.84) but the relationship was only significant in whites in the multivariate logistic regression model that also included location (Memphis or

Pittsburgh), cardiovascular disease, blood pressure, ototoxic drugs (salicylates, quinine derivatives, and loop diuretics each as a separate variable), Mini-Mental Status Examination score (as a measure of cognitive status), history of ear surgery, work-related noise exposure, income, education, and smoking (white males diabetes OR: 2.12; 95% CI: 1.29-3.48; white females diabetes OR: 1.89, 95% CI: 1.07-3.35). Contrary to other studies, use of ototoxic quinine derivatives and loop diuretics did not reach significance in this study. To further check this possible association, the researchers analyzed ototoxic drugs using three years of study data (years 1, 3, 5) and did not find any association. Aspirin use, which was found to be protective in black men, was believed to be a result of its cardioprotective effect.

Helzner and associates (2005) concluded that findings from their study allow estimates of modifiable factors for hearing loss to represent 31% of the variance in hearing loss. This estimate has important implications for consideration of interventions to modify risk factors related to diabetes, congestive heart failure, cerebrovascular disease, smoking, and work-related noise exposure..

The authors appropriately identified threats to their study in that there were statistically significant differences between those who participated and those who were unable to. Nonparticipants were more likely to be older, homebound, black and from one of the two study geographic regions, Memphis, Tennessee. It is unknown what effect inclusion of these missing participants would have had on the study results (Helzner et al., 2005).

Ologe and colleagues (Ologe & Okoro, 2005) conducted a cross-sectional study of type 2 diabetes and hearing loss in Nigeria. Participants were native Africans of Yoruba and Ibo ethnic extraction. The study was a group comparison between participants with diabetes (n=56) and non-diabetes participants as controls (n=52). The groups did not significantly differ in age or gender distribution. A predominate percentage of the participants (84.3%) were employed in only 3 occupations: petty trade, low-level civil service, or small businesses. Exclusion criteria were: history of ear disease, head or ear trauma, hearing handicap in a first degree relative, ototoxic drug use, smoking, noise exposure, hypertension, and conductive hearing loss. Mean Hearing Level Threshold for each group was compared at all PTA frequency levels (125-8000 Hz) in both ears. Participants with diabetes had significantly higher hearing level thresholds on average in every frequency than did controls. The mean difference between the groups did slightly increase as the frequency level increased. Tests for significance of this difference were not reported by the researchers. Duration of diabetes and level of glucose control were significant influences on the extent of hearing loss. The researchers propose that hearing loss and type 2 diabetes may both be due to the same genetic cause. As this study was conducted exclusively among black Africans and found similar associations that other studies of European and Asian populations found, the authors conclude that race is not an important factor in the development of hearing loss in diabetes.

Vaughan and her colleagues (Vaughan, James, McDermott, Griest, & Fausti, 2006) conducted a longitudinal prospective study to evaluate the

relationship between diabetes and hearing loss in a sample of veterans. A questionnaire was used in which participants (diabetes n=342; non-diabetes controls n=352) rated their difficulty in hearing in 13 specific situations involving communication. Pure-tone audiometry was tested at the usual octave frequencies between 250 Hz and 8000 Hz, interval frequencies of 3000 Hz and 6000 Hz, and additional ultra-high frequencies of 10000, 12500, 14000, and 16000 Hz. Word recognition was tested at 20 db above the individual hearing thresholds identified by audiometry. Glucose levels, HbA1c, and peripheral neuropathy (vibration and temperature sensitivity via standardized computer-aided sensory testing) were tested at the same time as the audiometric evaluation. The age of the two groups was similar (range 25-83 years) and both groups had few women (diabetes n=20; non-diabetes controls n=7) as would be expected from a veteran population. A significant proportion of the diabetes group was on insulin (43%). Average duration of diabetes was 12.5 $\pm$ 8.2 years.

Analysis by Vaughan and colleagues (2006) was done by dichotomous age groupings with 60 years old as the cut point. In those 60 years old and younger, only 20% of those with diabetes had normal hearing thresholds (<25 db) while 34% of those without diabetes had normal hearing thresholds. In those over age 60, 3.8% of those with diabetes had normal hearing while 6.4% of normal controls did. Repeated measures ANCOVA with diabetes as the between-subjects factor and sound frequency levels as the within-subjects factor was performed, controlling for age as a covariate. Right and left ears were analyzed rather than worse and better ear. The relationship for diabetes was

statistically significant in both ears for hearing loss in high frequencies (10000 Hz through 16000 Hz) after adjustment for age. An interaction term of diabetes by age was significant only for the right ear. These findings were unchanged when military-related noise exposure was controlled for. Neither work-related nor recreational noise exposure was found to be significant. Participants with diabetes in the younger cohort (≤60) had greater differences in their mean hearing thresholds compared to non-diabetes controls than were present in the older cohort (>60), especially at 10000 and 12500 Hz. Subjectively, those with diabetes in the younger cohort reported more difficulty hearing in certain communication situations than did those without diabetes. These differences diminished as age increased. Duration of diabetes, HbA1c level, and insulin use had only minimal effect on hearing loss when added to the model that controlled for age and military noise exposure. The potential contribution of peripheral neuropathy on hearing level thresholds at ultra-high frequencies was also tested with age, diabetes, and military noise exposure in the model. Diabetes, age, and military noise exposure remained significant predictors of hearing loss in this model with peripheral neuropathy significant only in the right ear. Left ear results were just above the significance cut-off (p = .052). The authors concluded that the ultra-high frequency differences in the younger cohort reflect early changes due to diabetes. Routine audiometric testing does not include frequencies over 8000 Hz. Changes in hearing that occur with aging obscure the effect of diabetes and aging has a more profound effect on hearing.

Torre, Moyer and Haro (2006) studied the accuracy of self-reported hearing loss in a sample (n=59; ages 42-88; mean age ~62) of older Latino-Americans. Answers to questionnaire items involving self-perceptions of hearing loss, use of hearing aids, and opinions of others regarding their hearing loss were compared to averages of pure-tone audiometry for frequencies 500, 1000, 2000, and 4000 Hz in the worse hearing ear (testing was done at standard octave frequencies from 250 Hz to 8000 Hz). Otoscopic and screening tympanometry were performed to rule out common conductive sources of hearing loss. Prevalence of hearing loss by self-report in this sample was 57.6% compared to 62.7% prevalence found by pure tone audiometry with 25 dB average loss as the criteria. The single screening question that the researchers were interested in, “do you feel you have a hearing loss?” was 75.7% sensitive and 72.7% specific for hearing loss. Sensitivity was higher in women and in the older age cohort (over 60). Specificity was higher in women and in the younger cohort (42-59). Total accuracy of the question was 74.6%. The authors reported that these findings of age and gender differences are consistent with other studies that have looked at similar questions.

In Torre et al.’s (2006) study, 25% of those who reported hearing loss did not fit the average >25 dB criteria for 500 to 4000 Hz frequencies. The authors note that these individuals may have hearing loss that did not fit the study criteria, i.e. if an individual had a sloping loss from 500 to 4000 Hz and only the two higher frequencies had hearing threshold levels above 25 dB, they would not fit the definition in this study but most certainly may have perceived difficulty in

hearing in certain situations. The authors conclude that a single screening question for hearing loss is valuable for use in primary care and health-care underserved areas. This study has insufficient power to detect differences between the groups the authors were intending to study (male/female; age cohorts) as no statistically significant findings were found in the analysis. It also suffers from probable selection bias as all participants were referred for the study. It can be reasonably assumed that individuals referred were having hearing difficulty. This is reflected in the high percentage of participants that had hearing loss, particularly in the 42-59 age group.

A study was conducted with a sample of middle-aged men who are members of the Japanese Self-Defense Forces (n=699; mean age 52.9 $\pm$ 1.0) to evaluate the association of type 2 diabetes and hearing loss (Sakuta, Suzuki, Yasuda, & Ito, 2007). PTA average thresholds for 500, 1000, 2000, and 4000 Hz of >25 dB in the worse ear was the criteria for hearing loss. Type 2 diabetes was present in 103 of the participants. Hearing loss was found to be more prevalent among those with diabetes than among those without (OR: 1.87, 95% CI: 1.20-2.91) when adjusting for age, military rank, smoking, and alcohol use. The authors concluded that type 2 diabetes is associated with hearing loss in middle-aged men and that this association does not depend on lifestyle factors. Some additional interesting findings from this study are that light drinking (defined as less than 30 ml ethanol intake daily) was found to be protective for hearing loss in a model of lifestyle factors and hearing loss. In the same model where type 2 diabetes was found to be significant, hypertriglyceridemia was also found to be

significantly associated with hearing loss (OR: 1.58, 95% CI: 1.04-2.40). Greater differences between hearing level thresholds were found in the higher frequencies (2000-8000 Hz) than in lower frequencies (250-1000 Hz).

The Japanese SDF study (Sakuta et al., 2007) did not specifically control for noise exposure (a weakness that was acknowledged) but the researchers note that nearly all SDF personnel have work-related noise exposure. They therefore conclude that their findings support diabetes contributing to the development of noise-induced hearing loss.

An additional finding of interest from the Sakuta et al. study (2007) has potential theoretical importance. In a linear regression model of metabolic parameters that included fasting glucose levels, 2 hr oral glucose tolerance test (OGTT) results, BMI, total cholesterol, triglyceride level, systolic blood pressure, and γ-glutamyl transferase, both OGTT and γ-glutamyl transferase were associated with hearing loss. This model adjusted for age, military rank and selected lifestyle factors (smoking and alcohol use). Serum γ-glutamyl transferase is an indicator of oxidative stress. Elevated glucose and elevated triglycerides are also associated with increased oxidative stress in studies cited by these researchers. Noise-induced hearing loss is generally considered to be a result of oxidative stress and research about the potential to protect workers from noise via antioxidants is being conducted (Henderson et al., 2002).

An older study of interest is one in which hearing was evaluated via audiometry in 20 patients with diabetes and peripheral neuropathy (Friedman, Schulman, & Weiss, 1975). Compared to age-matched subjects, 55% of those

with diabetes and neuropathy had symmetric sensorineural hearing loss in a minimum of one frequency. Nine of 11 sound frequencies tested demonstrated significantly higher hearing level thresholds in regression analysis. The authors concluded that their findings represented “subclinical but widespread hearing abnormalities” (p. 575) in a majority of their participants who had both diabetes and peripheral neuropathy. These authors propose neuropathy of the auditory nerve as the cause of hearing loss in diabetes.

Hearing Loss in the SALSA Cohort

Hong, Haan and Moore (in press) have reported the prevalence of hearing loss in the Sacramento Area Latino Study of Aging (SALSA) study, a large dataset from which the current study has drawn data. The mean age of this population at the time of their baseline hearing test was 76.3 years. A predominance of the participants, more than 87%, had hearing loss of at least 25 dB at speech frequencies (500 – 3000 Hz) with the level of loss increasing as the sound frequency levels increased from 2000 to 8000 Hz until nearly all participants, 98.6%, had loss at sound frequencies of 4000 to 8000 Hz. These findings were consistent with a high level of presbycusis, or age-related hearing loss that quite dramatically exceeds the 29.3% level reported for a Hispanic population in the nationally-representative 1999-2002 NHANES study (Cowie et al., 2006). Participants in the SALSA study are known to have greater prevalence of diabetes and impaired glucose tolerance than is reported in national data as well. The SALSA researchers report prevalence for type 2 diabetes of 32.7% of the study participants at study baseline (Haan et al., 2003).

A recent population study by Bainbridge and her colleagues (Bainbridge, Hoffman, & Cowie, 2008), which drew cross-sectional data that included random assignment to hearing testing and completion of a diabetes-specific questionnaire for half of the nationally representative sample (hearing n=5,140) in the National Health and Nutrition Examination Study (NHANES) from 1999 to 2004, provides support for diabetes as an independent risk factor for hearing loss when other known risk factors have been accounted for. Bainbridge et al. controlled for military service, occupational noise exposure, and ototoxic drug use in the last 30 days, in addition to age.

The Bainbridge (2008) study utilized pure tone average hearing level thresholds for low to mid frequencies (500, 1000, and 2000 Hz) and for high frequencies (3000, 4000, 6000, and 8000 Hz) to assess mild or greater severity of hearing loss (>25 dB) and moderate or greater severity (>40 dB). The goal of their research was to determine if the prevalence of hearing loss was greater in adults with diabetes than adults without diabetes in the United States. Their random sample included adults aged 20 to 69 years of age. Of the 5,140 participants, 399 had diabetes. Results of the research when all age groups were analyzed showed that hearing loss in the worse ear was more prevalent among those with diabetes in the low to mid frequencies (21.3%; 95% CI: 15%-27.5%) compared to those without diabetes (9.4%; 95% CI: 8.2%-10.5%) after adjustment for age. In the high frequencies, hearing loss was more prevalent among those with diabetes (54.1%; 95% CI: 45.9%-62.3%) compared to those without diabetes (32.0%; 95% CI: 30.5%-33.5%) after adjustment for age. The

oldest cohort in the study, those aged 60-69, had the highest prevalence of high frequency hearing loss >25 dB in the worse ear: 89.9% for those with diabetes compared to 77.7% for those without diabetes (p = .003); they also had the highest prevalence of high frequency hearing loss >40 dB in the worse ear: 63.2% for those with diabetes compared to 50% for those without (p = .016). In the low to mid frequencies, the difference in prevalence in this oldest age group studied did not differ significantly between those with diabetes and those without.

Using logistic regression modeling, diabetes remained a predictor of hearing loss when age, gender, race or ethnicity, education, income-poverty ratio, excessive noise exposure (occupational, leisure, military), ototoxic medication use, and smoking were controlled for. For low to mid frequency loss, the odds were 1.82 higher (95% CI: 1.27-2.60) to sustain any hearing loss if diabetes was present. In the high frequencies, the odds were 2.16 higher (95% CI: 1.47-3.18) (Bainbridge et al., 2008).

Bainbridge and her colleagues (2008) also reported on the better ear findings which were significantly different between the two groups. These details will not be presented here. The authors acknowledged limitations of their study in that diabetes status was by self-report as was noise exposure. Individuals with undiagnosed diabetes may have been in the group considered not to have diabetes. This would have dampened the effect of the association found and, therefore, would only be a concern if the findings were negative. They did not differentiate between those with type 1 or type 2 diabetes but report that nearly all of their participants with diabetes had type 2 diabetes. The authors conclude

that diabetes appears to be an independent risk factor for hearing loss and as such, hearing loss is an inadequately recognized complication of diabetes. They urge routine audiometric screening for all individuals with diabetes.

The association of diabetes and hearing loss complicated by occupational noise exposure has also been studied (Ishii, Talbott, Findlay, D'Antonio, & Kuller, 1992). This retrospective study sampled 229 men aged 55 to 68 (mean = 63) who worked in a metal assembly plant and had been chronically exposed to excessive noise at work (≥89 dBA) for more than 30 years. Severe noise induced hearing loss was the outcome of interest and was defined as ≥ 65 dB hearing loss at 3000, 4000, or 6000 Hz in at least one ear. Type 2 diabetes was present in 16.4% of the men who had severe noise induced hearing loss and only 8.3% of the those without severe noise induced hearing loss (OR 3.9; 95% CI: 1.2-11.9). In logistic regression modeling, diabetes and age were significant predictors of severe noise induced hearing loss while alcohol consumption and cigarette smoking were not. The prevalence of hypertension and noisy leisure activities did not differ between the group with severe noise induced hearing loss and the group without. The authors conclude that those with type 2 diabetes are more likely to develop severe noise induced hearing loss. They caution that longitudinal analysis is needed to confirm the temporal relationship between diabetes and noise induced hearing loss.

Hearing Loss in Farm Workers

A study of interest relating to farm workers that did not consider diabetes (Rabinowitz, Sircar, Tarabar, Galusha, & Slade, 2005) evaluated the hearing of

150 migrant and seasonal agricultural workers. Both PTA (500 – 6000 Hz) and tympanometry were assessed. Over half the participants in the study had some degree of hearing loss, most notably in higher frequencies. Hispanic males that were in this sample had significantly greater prevalence of hearing loss than what was found in the Hispanic Health and Nutrition Examination Survey. Additionally, 35% of the study participants reported subjective difficulties understanding speech. When language was controlled for, Hispanic farm workers remained more likely to report difficulty hearing or understanding speech. Both noise and pesticides exposure was frequently occurring in this sample and rarely was hearing protection used. The researchers concluded that hearing loss is inadequately recognized in migrant workers and that the impact of hearing loss appears to be complicated by language barriers.

Ototoxic Medications and Hearing Loss

For individuals with type 2 diabetes, the long-term use of loop diuretics such as furosemide, known to be ototoxic, is common. Study of such a population as the current study contains provides an opportunity to evaluate long-term ototoxic drug use. Aspirin and other NSAID use are also common among the elderly, most commonly taken over-the-counter for arthritis.

Ototoxic drug use has been studied in relation to hearing loss. The short-term ototoxic effect of various classes of medications is well documented and is generally known to clinicians. Among the medications known to be ototoxic from studies conducted are: aminoglycoside antibiotics, other antibiotics (erythromycin, vancomycin, polymixin B, Chloramphenicol, ampicillin,

minocycline, capreomycin, colistin), loop diuretics (furosemide and ethacrynic acid), certain chemotherapeutic agents (cisplastin, nitrogenated mustard, 6-amino nicotinamide, vincristine sulphate, misonidizole) (Jacob, Aguiar, Tomiasi, Tschoeke, & Bitencourt, 2006). Non-steroidal anti-inflammatory drugs (NSAIDS), anti-malarials and certain topical medications have also been found to be ototoxic (Seligmann, Podoshin, Ben-David, Fradis, & Goldsher, 1996). However, long-term consequences of ototoxic drug use have not been adequately studied. The potential for ototoxic medications to interact with noise has been studied but with few published results (Brown et al., 1981).

Complications of Diabetes: Potential Predictors of Hearing Loss

Many complications of diabetes are well documented and have significant potential to impact the ability of an individual to maintain functionality (including working) and quality of life with aging. Potential negative impacts of diabetes include both macro-vascular and micro-vascular diseases: heart disease and stroke, high blood pressure, diabetic retinopathy, kidney disease, neuropathies both peripheral and central, and amputations (Centers for Disease Control and Prevention, 2005). These complications generate symptoms that may be experienced by an individual with diabetes. These symptoms themselves have functional, emotional, and quality of life impact as well as increasing health care costs, limiting work productivity, and leading to premature loss of employment (Hogan et al., 2003;Valdmanis, Smith, & Page, 2001).

This section of the literature review addresses several complications of diabetes that have theoretically been considered to share a common pathway of

damage with hearing loss. These complications include microangiopathic processes resulting in nephropathy, neuropathy, and retinopathy; macroangiopathic processes resulting in large blood vessel diseases (coronary, cerebrovascular, and peripheral vascular).

Diabetes Nephropathy. Glomerular Filtration Rate (GFR) is considered the best measure of kidney function as well as an indicator of stages of kidney disease. GFR cannot be easily measured directly, so the value is calculated from the results of serum creatinine level, age, gender, and in some formulas, body size. There are several different formulas that have been developed for calculating GFR. Rigalleau and his colleagues compared the commonly used formula with the Modification of Diet in Renal Disease (MDRD) study formula and found that the MDRD formula better estimated GFR than did the common formula when impaired renal function was present (Rigalleau et al., 2005).

Kidney disease that occurs with diabetes is due to microangiopathic changes in the kidneys that result in impaired renal functioning in terms of creatinine clearance. This microangiopathic process first presents as albumin in the urine with normal GFR. As kidney damage progresses, lower GFR, rising creatinine levels and eventually, rising blood urea nitrogen (BUN) levels develop. The National Kidney Foundation has developed staging criteria for chronic kidney disease (CKD) based on GFR (National Kidney Foundation, 2009b). Stage 1 CKD is the earliest stage with normal GFR and protein (albumin) present in the urine; Stage 2 CKD is present when GFR is reduced slightly (60-89); Stage 3 CKD is characterized by moderate decreases in GFR (30-59); Stage 4 CKD is

present when there are severe decreases in GFR (15-29) and Stage 5 CKD, or kidney failure, is when GFR falls below 15.

The National Kidney Foundation considers anyone with diabetes, high blood pressure, older age, family history of kidney disease, and certain ethnicities as at risk for chronic kidney disease (National Kidney Foundation, 2009b). Poorly controlled hypertension represents a major route to kidney disease and eventual kidney failure. As hypertension and diabetes are frequently comorbid in the same individuals, chronic renal failure is most commonly seen in this population. The average length of time between the beginning of kidney damage due to diabetes and subsequent kidney failure is five to seven years (National Kidney Foundation, 2009a). Decreasing kidney function also occurs with aging and is more common in certain ethnic groups.

Neuropathy and Diabetes. Neuropathy from diabetes is the result of oxidative stress in neurons that is induced by hyperglycemia. This stress activates a number of biochemical pathways that result in the damage that manifests as neuropathic signs and symptoms. Neuropathy with diabetes is heterogeneous and presents in diverse ways, both focally and diffusely. It is reported by experts to be both the most common and most debilitating of the many complications of diabetes (Edwards, Vincent, Cheng, & Feldman, 2008). Chronic sensorimotor distal symmetric polyneuropathy and autonomic neuropathy are the most common forms seen (American Diabetes Association, 2008).

Classically, peripheral neuropathy in diabetes presents in a bilaterally symmetrical ‘stocking and glove’ pattern, affecting the longest peripheral nerves first and moving proximally over time. This is known as distal symmetric polyneuropathy (DPN) and can affect sensory, motor and autonomic nerve function. The sensory deficit poses the greatest risk for ulceration and future amputation because the lack of sensory perception increases the risk for injury to the foot. Thorough diagnosis of the extent of DPN involves assessing all components of nerve function, but clinically, choosing two of the available measures is considered sufficient for diagnosis and research (American Diabetes Association, 2008; Mayfield & Sugarman, 2000).

Edwards and his colleagues (Edwards et al., 2008) conducted a recent extensive review on neuropathy in diabetes, covering and synthesizing information on the biochemical mechanisms of action leading to neuropathy, its epidemiology, prevention and current treatments. They report that neuropathy is present in as much as 8% of newly diagnosed individuals and 50% of those with longstanding diabetes. Both the peripheral and autonomic forms are diffuse and progressive. Some evidence exists for neuropathic changes to occur even before diabetes reaches clinical detection. Neuropathy is not a single entity but has a wide range of clinical and subclinical forms. Whether all of these result from the same pathogenetic mechanisms is not yet known, although there are several known and hypothesized biochemical pathways that lead to damage.

The sensory aspects of DPN are known to eclipse any motor dysfunction that may be present (Edwards et al., 2008). Its prevalence increases both with

age and with duration of diabetes and it occurs more frequently in those with type 2 diabetes than in those with type 1. Edwards et al. discussed several major large studies (Rochester Diabetic Neuropathy Study, EURODIAB, DCCT, UKPDS) that confirm this prevalence pattern as well as the reduction of neuropathic symptoms, clinical confirmed diagnosis and associated complications that can be realized from intensive treatment aimed at glycemic control in both type 1 and type 2 diabetes.

Height is considered a risk factor for peripheral neuropathy which is thought to be due to the longer nerve fibers that are present in taller individuals. This possible explanation is consistent with the pattern of DPN that is known to occur – in the longest nerve fibers first (Edwards et al., 2008). Up to 70% of all foot ulcers that occur with diabetes are considered to be neuropathic in origin. Suggested risk factors for DPN that need additional research to determine their salience include smoking, excessive alcohol use, hypertension and low plasma insulin levels.

Diabetic autonomic neuropathy (DAN) is the other common diffuse neuropathy that is common with diabetes (Edwards et al., 2008). DAN can affect both sympathetic and parasympathetic function within the autonomic nervous system (ANS). Although it is very common in diabetes, it is still poorly understood. Part of the reason for this, according to Edwards and his colleagues, is because the symptoms associated with DAN can be due to many other causes, making definitive diagnosis difficult. DAN can clinically manifest in almost any body system that is enervated by the ANS. As the vagus nerve is the longest

nerve in the autonomic nervous system, mediating nearly 75% of the body's parasympathetic activity, DAN manifests here first. This is due to the nerve's length. DAN therefore presents as parasympathetic-mediated symptoms initially and tends to be widespread. Subclinical autonomic neuropathy can be detected in the first year or two of diabetes diagnosis, long before symptoms appear (Edwards et al., 2008).

Despite its usually diffuse presence potentially in many body systems, DAN is, however, most commonly assessed in the cardiac system. Unlike DPN, DAN is more common in type 1 diabetes (20.9%) than in type 2 (15.8%) as measured by heart rate variability, one of the key signs of DAN (Edwards et al., 2008). Cardiovascular autonomic neuropathy (CAN) has been associated with risk for silent myocardial ischemia and resulting mortality (Boulton et al., 2005). As with DPN, reduction in the prevalence and ultimate negative outcomes of DAN can be accomplished with intensive treatment that realizes improved glycemic control (Edwards et al., 2008).

Focal or mononeuropathies also commonly occur in diabetes and are discussed in detail in Edwards et al.'s review (2008). These forms of neuropathy are beyond the scope of the present discussion and will not be presented.

Screening for neuropathy is important as, according to the ADA (2008), up to 50% of individuals with it are asymptomatic and at risk for injury as a result. The ADA recommends annual screening for distal neuropathy in individuals with diabetes. Sensory assessment testing via pinprick, vibration threshold, 10-g monofilament pressure sensation and assessment of ankle reflexes are the

recommended choices. The ADA states that combinations of these methods (2 or more) are reported to have 87% sensitivity in detecting peripheral neuropathy. Loss of ability to detect the 10-g monofilament pressure and reduced vibration perception are further maintained to be predictive of foot ulcer risk (Boulton et al., 2005).

Mayfield and Sugarman (2000) conducted a systematic review of literature regarding the use of several different methods for peripheral neuropathy screening, including Semmes-Weinstein Monofiliment (SWM) and vibration perception threshold (VPT) testing among others. Their research question was focused on determining if SWM or an alternate method of screening for neuropathy reduced ulceration and amputation in individuals with diabetes. Citing the expense and time required for some testing techniques, the authors note that several of the psychosomatosensory techniques available (SWM and VPT being the most common) are inexpensive and fast to perform, making them useful in ambulatory practice as neuropathy screening tools.

SWMs that are used in neuropathy screening are calibrated to provide a specific force in grams that is exerted against the skin. The 5.07 monofiliment is known to exert 10 grams of force when used correctly (Mayfield & Sugarman, 2000). The use of nylon monofilaments evolved from horsehairs used for the same purpose with leprosy patients in India who suffered from insensate limbs in the late 1800s. The concept was first applied to patients with diabetes in the 1960s and their size and use has since become standardized.

Mayfield and Sugarman (2000) developed an appropriate search strategy and found 13 studies that met their search criteria. Studies were evaluated for their design, the sample used including potential for selection bias, the degree of examiner blinding, presence of standardized methods of testing, and reproducibility (intrarater and interrater reliability). Several different SWM sizes were used in the studies, 4.17, 5.07, and 6.10. The 5.07 (10 g force) size was used most frequently and was found in three of the observational studies to correlate most closely with history or presence of ulceration. Selection of sites for SWM testing varied among the reviewed studies. For individuals with diabetes, the plantar surface of the forefoot provided the best discrimination for determining risk for ulceration. Heel sensitivity to the SWM provided no meaningful discrimination. One study specifically identified the great toe and metatarsal heads of the first, third, and fifth digits as being able to identify 95% of those with insensate areas of the feet. Agreement has not been reached on how many insensate sites are needed to qualify as insensate consistent with peripheral neuropathy; the range used being between one and four. However, one or more was most commonly used in the prospective studies. This cut-off criterion makes clinical sense as even one insensate area increases risk.

Four prospective studies that were reviewed by Mayfield and Sugarman that drew participants from very different populations found the SWM testing to be predictive of ulceration. Relative risk for ulceration was as high as 9.9 (95% CI: 4.8-21) with an increased odds of 17 (95% CI: 4.5-95) for amputation. Mayfield and Sugarman conclude from their review that SWM is currently the

best method for clinically detecting loss of sensation associated with distal diabetic neuropathy. The authors support annual retesting when no insensate areas are found to identify the development of clinically significant neuropathy.

Other than the previously cited studies that evaluated diabetic neuropathy and hearing loss (Friedman et al., 1975; Vaughan et al., 2006), the potential contribution of common signs and symptoms of diabetes complications to hearing loss has not been extensively studied. Theories of hearing loss in diabetes propose that mechanisms that cause the signs and symptoms may be the same that lead to hearing loss. More details on these proposed connections are covered in this paper in the section on conceptual framework.

Diabetic Retinopathy and Hearing Loss.

Only two studies were found that dealt with diabetic retinopathy and hearing loss that were not either specific to a rare genetic variant of diabetes or to type 1 diabetes. Sasso and his colleagues (Sasso et al., 1999) evaluated evoked otoacoustic emissions (e-OAEs) in 110 participants with type 2 diabetes and 106 controls matched on age and gender. Participants with diabetes were in good glycemic control on diet or oral medication only and all participants were normotensive (by WHO criteria of <140/90). e-OAEs were impaired in significantly more participants with diabetes (51.8%) than in controls (4.7%) ($\chi 2 = 56.24$, $p < .0001$). The researchers found a difference between those with diabetes with impaired e-OAEs and those with diabetes without impaired e-OAEs in terms of the prevalence of peripheral neuropathy (47% vs 23%; $p < .02$) but no difference in the prevalence of retinopathy or nephropathy. The association

between impaired e-OAEs and peripheral neuropathy did not remain significant in multiple regression analysis. Duration of diabetes (OR: 1.187; 95% CI: 1.102-1.272) and level of glycemic control (OR: 1.632; 95% CI: 1.326-2.938) remained significant for impaired e-OAEs in logistic regression analysis.

Tay and his colleagues (Tay, Ray, Ohri, & Frootko, 1995) conducted a prospective study on hearing loss and retinopathy in 102 participants and compared pure tone hearing thresholds (at each frequency level) to three different population groups as controls. Participants with diabetes had worse hearing threshold levels than all three of the control populations ($p < .0001$). In this sample, duration of diabetes correlated with hearing loss but the presence of retinopathy did not. Retinopathy was categorized in three groupings: no retinopathy or only background diabetic retinopathy; diabetic maculopathy or pre-proliferative diabetic retinopathy; proliferative retinopathy or end-stage diabetic eye disease. The researchers reported that those with diabetes had differences from controls particularly in the lower frequencies, but review of their results indicates that the differences were significant at all thresholds compared although there did appear to be larger dB differences at 250, 500, 1000 and 2000 Hz levels. This sample was different than many of the samples of studies reviewed as both type 1 and type 2 diabetes participants were represented. Age of participants ranged from 19-70.

Macroangiopathic Processes. The risk for heart disease for individuals with diabetes is so high that its presence is equated with existing heart disease in individuals without diabetes when determining risk for myocardial infarction

(Grundy et al., 2004). The inclusion of diabetes as high risk is based on review of clinical trials that was performed by the Coordinating Committee of the National Cholesterol Education Program. The reviewers based their conclusion on five clinical trials conducted on statin use for lowering cardiovascular risk. Results of one of these studies reviewed, the Heart Protection Study, are of interest for the current discussion. The Heart Protection Study was conducted in the United Kingdom and participants aged 40 to 80 were selected based on the presence of coronary disease, other occlusive artery disease or diabetes. Statin use resulted in lower all-cause mortality and reductions in all major vascular endpoints. The reduction of risk for those with diabetes was similar for participants with either cardiovascular disease or other occlusive artery disease. For those who had pre-existing cardiovascular disease and diabetes, the greatest risk reduction of any group was seen.

Gates and colleagues (Gates, Cobb, D'Agostino, & Wolf, 1993) studied cardiovascular events and hearing loss in 1662 elderly men and women (676 men, 996 women) to explore the relationship of presbycusis to both cardiovascular pathology (coronary heart disease, stroke, and intermittent claudication) and cardiovascular risk factors (hypertension, diabetes, glucose intolerance, smoking status, weight, and serum lipid levels). Pure tone averages for low frequencies (250, 5000, and 1000 Hz) and for high frequencies (4000, 6000, and 8000 Hz) were used as audiometric variables. Worse or better hearing ear was based on the average threshold values at 500, 1000, 2000, and 3000 Hz. Low frequency hearing loss at 40 dB was associated with overall

cardiovascular pathology in both genders, although the effect was greater for women (OR: 3.06; 95% CI: 1.84-5.10) than for men (OR: 1.75; 95% CI: 1.01-3.03). For high frequency loss at 40 dB in women, the OR for any cardiovascular disease event was 1.75 (95% CI: 1.28-2.40). In men with 40 dB low frequency loss, the OR was highest for stroke at 3.46 (95% CI: 1.60-7.45) while for coronary heart disease the OR was 1.68 (95% CI: 1.10- 2.57). The odds for women were lower for coronary heart disease: 40 dB low frequency hearing loss was associated with an OR for of 2.14 (95% CI: 1.21-3.79). However, for intermittent claudication, the OR was 4.39 (95% CI: 2.02-9.55). The addition of cardiovascular disease risk factors to the logistic regression models did not alter the relationships found.

Gates and his colleagues found that hypertension and systolic blood pressure were related to hearing thresholds in both men and women while blood glucose levels were related to low frequency hearing loss in the women. Higher high density lipoprotein (HDL cholesterol) levels were inversely related to low frequency hearing loss only in women, suggesting a protective effect of HDL cholesterol. The researchers concluded that there was a small but statistically significant association between cardiovascular disease and hearing loss in the elderly with a greater effect for women than men and more in low frequencies than high frequencies. Additionally, the researchers commented that the fact that hearing loss was associated with actual cardiovascular events rather than with risk factors for cardiovascular disease suggests that the actual disease process itself shares a common pathway with the process leading to presbycusis. They

advise that additional studies of the relation of vascular disease and hearing loss in the elderly is needed to clarify the pathophysiologic mechanisms that lead to hearing loss (Gates et al., 1993).

Occupational Exposures and Hearing Loss

Noise exposure in the occupational milieu has a strong association with high frequency hearing loss. As a result of years of study, standards to limit noise exposure in occupational settings have been mandated. The Occupational Safety and Health Act (OSHA) Noise Regulation and the subsequently mandated Hearing Conservation Amendment were created to ensure that workers' hearing would be conserved (Sataloff et al., 2005). Many states include hearing loss as a compensable injury or illness under their Workers' Compensation statutes. Despite this long-standing standard, many individuals over a certain age sustained significant occupational noise exposure prior to the enactment of the standard. Ensuring compliance with any standard is always an issue with the limited resources available to OSHA. Voluntary employer compliance has not resulted in universal compliance with the standard.

Sataloff and colleagues (2005) report that conservative estimates of occupational hearing loss costs are potentially over 20 billion dollars. They claim that occupational hearing loss is the "number one environmental and medico-legal problem in the United States" (2005, *p*. 405).

Noise is not the only exposure of concern in the workplace. Non-acoustic work-related factors may have a direct effect on hearing or interact with noise exposure (Henderson, Morata, & Hamernik, 2001). Studies have looked at

vibration, extreme temperatures, certain chemicals (metals, solvents, asphyxiants) and have found these exposures to be associated with hearing loss. High levels of exposure to some of these have been known to cause hearing loss in the absence of noise exposure.

None of this was known at the time the occupational noise standard was developed. The standard only addresses noise exposure and hearing conservation programs are targeted solely to the control of noise and the prevention of noise-induced hearing loss (Morata, 2003; Prasher et al., 2002).

Chemically-induced hearing loss is difficult to differentiate from that due to ototoxic drugs or noise, especially with standard audiometric evaluation (Morata 2007). Pure tone audiometry (PTA), the most common screening test (and typically the only test) for hearing loss, shows similar results for all three of these types of acquired hearing loss. Differences in the quality of sound perception and speech discrimination are not detected by PTA. All of these forms of hearing loss are bilateral, usually symmetrical, irreversible, and affect higher frequencies (3000 to 6000 Hz). Like noise exposure, damage from chemicals or ototoxic drugs is to the cochlear hair cells primarily, leading to sensorineural hearing loss (Henderson et al., 2001). Animal studies on the audiologic effects of certain chemical exposures have also found that the damage is similar to that induced by noise (Henderson et al., 2002). Animal studies have also raised the possibility of a protective effect from anti-oxidants, but more study is needed to verify this.

An international research commission, NoiseChem was formed to study the effects of industrial chemicals, with and without concurrent noise exposure,

on hearing and balance (Prasher et al., 2002). These researchers report that little is known about the combined effects of toxic chemicals on health, including hearing health. Despite the use of certain chemicals in industry for more than 150 years, evaluations for their potential to affect the auditory system have been done only in the last 20 to 25 years. Standards for chemical and noise exposures have been created in isolation with the single exposure's toxic properties in mind, not considering the potential for additive, synergistic, or interactive effects between exposures.

The NoiseChem team has set research priorities, specifically focusing on combinations of exposures that occur in the real working world. The proposed NoiseChem studies are designed to specifically evaluate toluene, styrene, xylene, trichloroethylene, carbon disulfide, and solvent mixtures. These substances will be studied both with and without simultaneous noise exposure and interaction effects will be evaluated. Of these common industrial chemicals, both trichloroethylene and carbon disulfide are found in pesticides.

Since 1998, the U.S. Army has required considering ototoxic chemical exposure for worker inclusion in hearing conservation programs (Morata 2007; Ohlin, 2002). As of 2003, the Army has increased this surveillance with a new cutoff level of 50% of the most stringent criteria for chemical exposure limits (OSHA PEL or ACGIH TLV) for workers to be included in hearing conservation programs. They recommend annual audiograms for all Army personnel working with these chemicals at the cutoff level, whether exposure is through inhalation, with or without respiratory protection, or through dermal exposure. Their intention

is to assure data collection at these lower exposure levels for evaluation. Reviewers of annual audiograms for Army personnel are instructed to evaluate potential for additive, potentiating, or synergistic effects with noise exposure. Among the substances included in the Army's recommendation are arsenic, organic tin, various carbon-based fuels, chemical warfare agents, carbon monoxide, cyanide, lead and derivatives, manganese, mercury and derivatives, n-hexane, Stoddard solvent, styrene, trichloroethylene, toluene, xylene and organophosphate pesticides (Hearing Conservation and Industrial Hygiene and Medical Safety Management, n.d.; Morata, 2003; Ohlin, 2002).

The Physical Agents TLV Committee of the ACGIH developed recommendations regarding concurrent noise and chemical exposure that were slated to appear in the next edition of their commonly used book of Threshold Limit Values (TLVs) (Johnson, 2002). TLVs provide guidance to professionals in industry on acceptable levels of exposure as well as conditions of exposure that will provide adequate protection from adverse health effects for nearly all healthy workers. These recommendations planned for inclusion were that exposure to noise and certain chemicals trigger annual audiograms if exposure is at 20% of the TLV value. The chemicals they cite for inclusion in this recommendation due to their known ototoxic effects are: toluene, lead, manganese, and n-butyl alcohol. Additional substances that are under investigation for ototoxicity are listed as: trichloroethylene, carbon disulfide, styrene, mercury, and arsenic. Both styrene and carbon monoxide were targeted for inclusion in the next TLV book (published in 2003). A review of the 2003 TLV publication (American Conference

of Governmental Industrial Hygienists, 2003) reveals that the version includes a notice of intended change to the notes section on acoustic TLVs to include the listing of ototoxic chemicals in conjunction with noise exposure for which periodic audiograms are recommended. No actual level of the chemical exposures is listed as a guide. This intended change in the recommendations was not actually adopted until 2006 (American Conference of Governmental Industrial Hygienists, 2006) with carbon monoxide, lead, manganese, styrene, toluene, and xylene included and notation as to the investigation of ototoxicity for arsenic, carbon disulfide, mercury, and tricholoroethylene as currently underway.

Morata's (2007) list of chemicals with known ototoxicity from human studies is even more extensive. The list of chemicals with evidence in the absence of noise exposure or with low level noise exposure includes: styrene, toluene, trichloroethylene, xylenes, ethylbenzene, ethanol, n-hexane, carbon disulfide, solvent mixtures, white spirit solvent, fuels, lead, mercury, manganese, and pesticides/insecticides. Many of these chemicals also have human evidence for synergism or interaction effects with noise exposures $\geq$85 dB A time-weighted average, the level for action in terms of hearing conservation in the OSHA noise standard. Other chemicals that have animal study evidence, as summarized by Morata, include: chlorobenzene, n-heptane, n-propylbenzene, trans-beta-methylstyrene, allylbenzene, polychlorinated biphenyls (PCBs). Carbon monoxide, hydrogen cyanide, and acrylonitrile have been found to potentiate hearing loss from noise exposure in animal studies.

A small cross-sectional study done in Brazil on ototoxicity of organophosphates found that seven of 18 rural farm workers exposed had sensorineural hearing loss while 16 workers had dizziness and balance disorders (Hoshino, Pacheco-Ferreira, Taguchi, Tomita & Miranda, 2008). Farm workers in this study ranged in age from 16 to 59 years (mean 39.6) and were predominantly female (72%). As dizziness and balance issues rather than hearing loss were the outcomes of interest in this study, no other analysis was done specific to hearing loss.

A study on hearing loss in workers exposed to both noise and carbon disulfide, although not in a pesticides formulation, found dramatically increased odds of hearing loss among workers exposed to both (n=131; OR: 18.7-35.5; 95% CI: 7.8-161.3) compared to those exposed just to noise (n=105; OR: 1.5; 95% CI: 0.8-2.8) or to neither exposure (n=110; OR: 1.0) (Chang, Shih, Chou, Chen, Chang, & Sung, 2003). This study involved male workers only in two plants in Taiwan, one where carbon disulfide was used in the manufacture of viscose rayon and the second where adhesive tape and electronics were manufactured (noise only group). The non-exposed group was comprised of men in the administration of the rayon manufacturing plant with no documented exposures. Precise industrial hygiene measures of both noise and carbon disulfide were conducted.

Pesticide exposure is an issue primarily for farm workers and those involved in pesticide manufacturing, but others are also exposed. In California, a majority of farm workers are Hispanic and commonly of Mexican origin. The

relationship of pesticide use to hearing loss is not yet well understood as it is listed as a priority for further study by researchers and organizations that have previously been cited. To this writer's knowledge, there have been no studies that have looked specifically at pesticide exposure within the context of type 2 diabetes and hearing loss.

Summary of Literature Review

Studies reviewed have found a relationship between diabetes and hearing loss that tends to be in the small effect size range. Not all studies have found a relationship, although the most recent large study that randomly assigned a nationally representative sample to hearing testing and diabetes questionnaire did find diabetes to be a risk factor for hearing loss, independent of other factors (Bainbridge et al., 2008). Studies have varied in findings that relate to comorbidities of diabetes such as hypertension, peripheral neuropathy, nephropathy and diabetic retinopathy, cardiovascular disease, and risk factors for cardiovascular disease. Studies have also varied on their findings of the relationship between duration of diabetes and level of glycemic control with hearing loss.

Diabetes, related symptoms and hearing loss are important chronic conditions that affect older adults. Diabetes occurs more frequently in Latino Americans and hearing loss occurs at about the same prevalence as in other Americans. The co-occurrence of these two conditions represents a substantial risk to the health, perceived health status, functionality and psychological well-being of older Mexican Americans and deserves additional research to further

explicate their co-occurrence and to add to the body of knowledge regarding diabetes as a risk factor for hearing loss.

A better understanding of the intersection of these chronic conditions will enable health care practitioners to better support an important national goal as it is stated in the Morbidity and Mortality Weekly Reader (MMWR), a publication of the CDC: “One important public health goal for an aging society is to minimize the impact of chronic disease and impairments on the health status of older adults, maintain their ability to live independently, and improve their quality of life” (Campbell et al., 1999).

Theoretical Framework

Theories of Hearing Loss

There are multiple physiologic problems associated with diabetes, each of which may contribute to hearing loss. Diabetes is ultimately a disturbance of energy metabolism that involves mitochondrial dysfunction, oxidative stress, and the deposition of glycated products in body tissues, leading to disturbances in metabolic functioning. Every body system is impacted by these processes in diabetes. The disturbed metabolism of diabetes may provide a pathway to damaging audiologic physiology and ultimately, function. Theories of hearing loss in diabetes and in other causes of hearing loss that are explored in this study are discussed in this section of this paper.

Theories of hearing loss in diabetes. There are a number of physiologically plausible theories about the underlying mechanism responsible for hearing loss occurring with diabetes. These include central nervous system

effects of diabetes, micro- and macroangiopathy, mitochondrial abnormalities and genetic causes. There have been studies that provide support for each of these theories but none have reached ascendancy (Sataloff & Sataloff, 1993; Wackym & Linthicum, 1986).

Fowler and Jones (1999) indicate that the mechanisms underlying peripheral neuropathy in diabetes are not fully understood but that metabolic factors such as the sorbitol and fructose buildup in nerve tissue has been proposed as the underlying pathology responsible. They hypothesize that the same process might affect the inner ear and/or the eighth nerve leading to hearing loss. Their rationale is that since this metabolic process affects all nerves in the presence of diabetes, it is logical that the nerve tissues involved in hearing are also affected.

A recent study by Al-azzawi and Mirza (2004) provides evidence for both central and peripheral auditory nervous system damage leading to hearing loss in diabetes. Their study used brainstem evoked auditory potentials (BAEP) to assess the central auditory pathways in a group of 67 participants with diabetes (both type 1 and type 2) and 32 age- and gender-matched healthy controls. Multiple evoked potential waveforms and interpeak latencies were evaluated. These various waves and latencies represent auditory nerve peripheral conduction time, conduction times from the nerve to the pons, central conduction time from the pons to the midbrain, full central conduction time, and latencies between the waveform peaks. All of the waveforms and interpeak latencies were significantly different for participants with diabetes than for those without diabetes

in both ears. The differences between participants with type 1 and type 2 diabetes were not significant. Duration of diabetes was not related to slowing of BAEP as even diabetes of short duration led to delayed BAEP response. These results indicate both peripheral auditory involvement and central conduction delay from the brainstem to the midbrain. The authors note that the lack of difference found between those with type 1 or type 2 diabetes may rule out hypoglycemia as a cause of delay in auditory signal transmission time. The researchers note that their findings are consistent with accumulation of glucose substrate in nerve tissue that leads to increases in aldose reductase activity, leading to slowing of BAEP response. They concluded that BAEP can be very useful as an objective non-invasive test capable of detecting early pathology in the auditory nerve and the brainstem in diabetes.

Abnormalities in mitochondria have been associated with development of diabetes (Mulder & Ling, 2009), including specific variants that also involve hearing loss such as DIDMOAD or Wolfram syndrome (Jackson et al., 1994) and MELAS (Remes, Majamaa, Herva, & Hassinen, 1993). Mitochondrial metabolism in the pancreatic beta cells is responsible for the secretion of insulin and failure of the beta cells to release insulin leads to type 2 diabetes. Therefore, there is speculation that mitochondrial abnormalities are responsible for the insulin failure in diabetes (Mulder & Ling, 2009). ATP production in the mitochondria is a result of oxidative processes. This mitochondrial-oxidative process takes on significance when viewed in light of oxidative stress that occurs in diabetes and with several exposures that are discussed later in this paper.

Evidence for genetic causes of diabetes is mounting (Mulder & Ling, 2009) but substantially more research is needed. Current thinking is that the genetic components are subject to ‘epigenetic’ change – from environmental processes affecting the underlying genetic predisposition. Genetic evidence for susceptibility to hearing loss has also been proposed. However, this phase of scientific research underlying diabetes and hearing loss causation is in its infancy and full discussion is beyond the scope of this paper.

Theories of noise-induced hearing loss. Hearing loss due to noise exposure is fairly well understood. Histological examination of the inner ear of individuals with noise-induced hearing loss shows both hair cell and nerve degeneration in the area of the cochlea responsible for hearing in the 3000 to 6000 Hz range of sound. Similar findings have been demonstrated in animal studies of noise exposure (Sataloff et al., 2005). It is generally accepted that noise-induced hearing loss begins at the 4000 Hz hearing frequency that is demonstrable on audiogram as a notch at that level. If damaging noise levels continue unabated, this notch deepens and widens to include other frequencies. Sataloff and colleagues (2005) warn that other mechanisms of injury also impact this hearing frequency and can be confused with noise-induced loss. Indeed, this greater susceptibility of the higher frequencies to insults of all types is one of the reasons it is difficult to sort out the causes underlying hearing loss in affected individuals.

Oxidative stress has been associated with noise-induced hearing loss (Henderson, Bielefeld, Harris & Hu, 2006; Kovacic & Somanathan, 2008).

Reactive oxygen species (ROS) have been found to be generated after noise exposure in several studies reviewed by these authors. Increased lipid peroxidation as a result of free radicals has been found to occur after noise exposure and is hypothesized to continue causing cell damage even after cessation of exposure. The oxidative stress of this process is due to impairment in mitochondrial function. Specifically, due to increased energy demands placed on the mitochondiria by excess noise exposure, excess superoxide is generated. This excess superoxide reacts with other molecules in the cochlea. Decreases in cochlear blood flow are also implicated in noise exposure, leading to oxidative stress and inefficient mitochondrial function. Blood flow returns to the cochlea after noise exposure abates. Unfortunately, this reperfusion can also lead to superoxide formation. Ultimately, this oxidative stress process, combined with the mechanical effects of noise exposure lead to hair cell death in the cochlea.

Theories of hearing loss due to ototoxic medications. Kovacic and Somanathan (2008) reviewed studies relating to ototoxic substances and conclude that there is evidence to support reactive oxidative species (ROS) and oxidative stress as the common pathway that leads to ototoxicity in medications. These authors note that common ototoxic medications contain substances or create metabolites that incorporate electron transfer functionality in their make-up. This process also causes oxidative stress. Certain illicit drugs also are implicated in ototoxicity from the same mechanisms. The drugs implicated include: cocaine, ecstasy, morphine and heroin.

Theories of hearing loss due to chemical exposures. Morata (2007), a prominent member of the NIOSH Hearing Loss Prevention Team, summarizes what is known about the mechanism responsible for hearing loss due to chemical exposures. Chemical toxins reach the inner ear via the bloodstream and damage inner ear structures and therefore, their normal functioning. Additionally, more central effects have been seen, notably with solvent exposures.

Kovacic and Somanathan (2008) reviewed evidence for electron transfer, ROS and oxidative stress to be the mechanism of ototoxicity for heavy metals. They state that the nature of the electrochemistry of metals in human biosystems can be expected to lead to electron transfer. Therefore, they conclude, the same processes that lead to hearing loss in noise exposure and ototoxic drugs are active with heavy metal exposure. Ethanol exposure, most often experienced as ingestion of alcoholic beverages, and nicotine exposure from smoking also have support for leading to the electron transfer, ROS, and oxidative stress mechanisms that cause ototoxicity.

The electron transfer-ROS-oxidative stress pathway has also been proposed for other ototoxic chemicals leading to hearing loss. Implicated chemicals include solvents and substances that are components of pesticides (Kovacic & Somanathan, 2008).

Common signs and symptoms associated with diabetes as shared pathologic pathways to hearing loss. There are a number of signs and symptoms that are commonly associated with diabetes. Many of these relate specifically to complications of the disease process or to the cardinal sign of diabetes,

hyperglycemia – a known precursor to oxidative stress and deposition of glycated products in body tissues. A number of these signs and symptoms are not unique to diabetes, occurring in other disease processes as well, although less commonly. Among these common signs and symptoms are: excessive thirst, frequent urination, blurry vision, numbness, burning and/or tingling in extremities, decreased sensation in extremities including impaired temperature or vibration sensitivity, excessive sensitivity to touch, daytime or nocturnal shortness of breath, daytime sleepiness, irritability, morning fatigue, unhealed sores particularly on the feet, leg pain with ambulation, lower extremity muscle cramping, and excessive skin dryness on the feet. Amputation is classically associated with diabetes although the incidence of this complication is significantly reduced over recent decades as a result of better treatment and improved glycemic control.

Signs and symptoms common to diabetes are often considered to stem from several pathologic processes: neurological impairment at peripheral or central levels or micro- or macro-vascular impairment. When hearing loss due to diabetes has been considered, some presume an association between other neurological or vascular problems in diabetes and the occurrence of hearing loss.

Hearing loss in the context of type 2 diabetes may be a result of microangiopathic processes that follow deposition of glucoprotein (due to hyperglycemia) in small blood vessels, impacting neurological function (Maia & Campos, 2005). Peripheral neuropathy, nephropathy, and diabetic retinopathy in diabetes are known to result from this same microangiopathic process. Hearing

loss in type 2 diabetes may also result from macroangiopathic processes. Coronary artery disease (CVD), cerebrovascular disease, and peripheral vascular disease (PVD) all result from this process and are widely accepted as complications of diabetes. Work-related exposure to noise is known to lead to hearing loss but its relative contribution in the context of type 2 diabetes is not fully understood. The potential relative impact of other work-related exposures, either in isolation or in combination with each other or noise exposure, is not well known. These work-related exposures include pesticides, lead, cadmium, solvents, and other heavy metals. Very little research has been done regarding the synergistic effects of multiple work-related exposures over time on hearing loss (Brown, 1981; Morata, 2003; 2007).

Complications due to diabetes, including nephropathy and retinopathy, have been shown to be at least partially a result of reactive oxygen species (ROS) (Ha, Hwang, Park, & Lee, 2008). ROS overproduction is a direct result of hyperglycemia. Mitochondrial function is believed to be involved in the process of ROS generation.

Summary of Theories Relating to Hearing Loss, Diabetes, Complications of Diabetes, and Various Exposures

There are consistent threads running throughout the theories relating to hearing loss – mitochondrial dysfunction, deposition of glycation products and oxidative stress. Aging and diabetes are both known to arise from and/or lead to mitochondrial dysfunction, to glycation deposition and to increased oxidative stress. Diabetes is considered to accelerate these processes more than aging

does (Yoshimaru, Suzuki, Inoue, Nishida, & Ra, 2008). Availability of direct measures of these pathologic processes were not available for study in this data analysis; however, measures of various endpoints of these processes are available to serve as markers for underlying pathologic processes.

Conceptual Framework for this Study

A conceptual model is proposed for this study (see Figure 1) that is designed to provide a framework for evaluating the relative contribution of various factors on high frequency hearing loss within the context of type 2 diabetes. The theoretical common biochemical pathways that lead to damage resulting in complications and signs and symptoms of diabetes was the rationale for choosing possible predictors of hearing loss for this study.

Included in the model are the demographic variables of age and gender which are consistently found to be predictors of hearing loss. Clinical factors that relate to or may impact diabetes, (duration of diabetes), relevant comorbidites (hypertension, metabolic syndrome), ototoxic drugs, anthropometric measures (BMI, waist circumference) and life-style factors (smoking status, alcohol use) are included. Indicators have been selected that reflect microangiopathic (FBG, HbA1c, Semmes-Weinstein Monofiliment test and Vibration Perception Threshold testing, GFR, and diabetic retinopathy) and macroangiopathic (cardiovascular disease, cerebrovascular disease, peripheral vascular disease, and blood lipids) damage. Reported signs and symptoms of diabetes from the Diabetes Symptom Questionnaire, divided into factors determined by factor analysis, are also included in the framework. Work-related exposures (pesticides,

lead, cadmium, solvents, other heavy metals, dusts, fumes, loud noise, and excessive heat) are included in the conceptual model as possible individual contributors. This framework provides the basis for exploration of variables used in this study to predict high frequency hearing loss in individuals with diabetes.

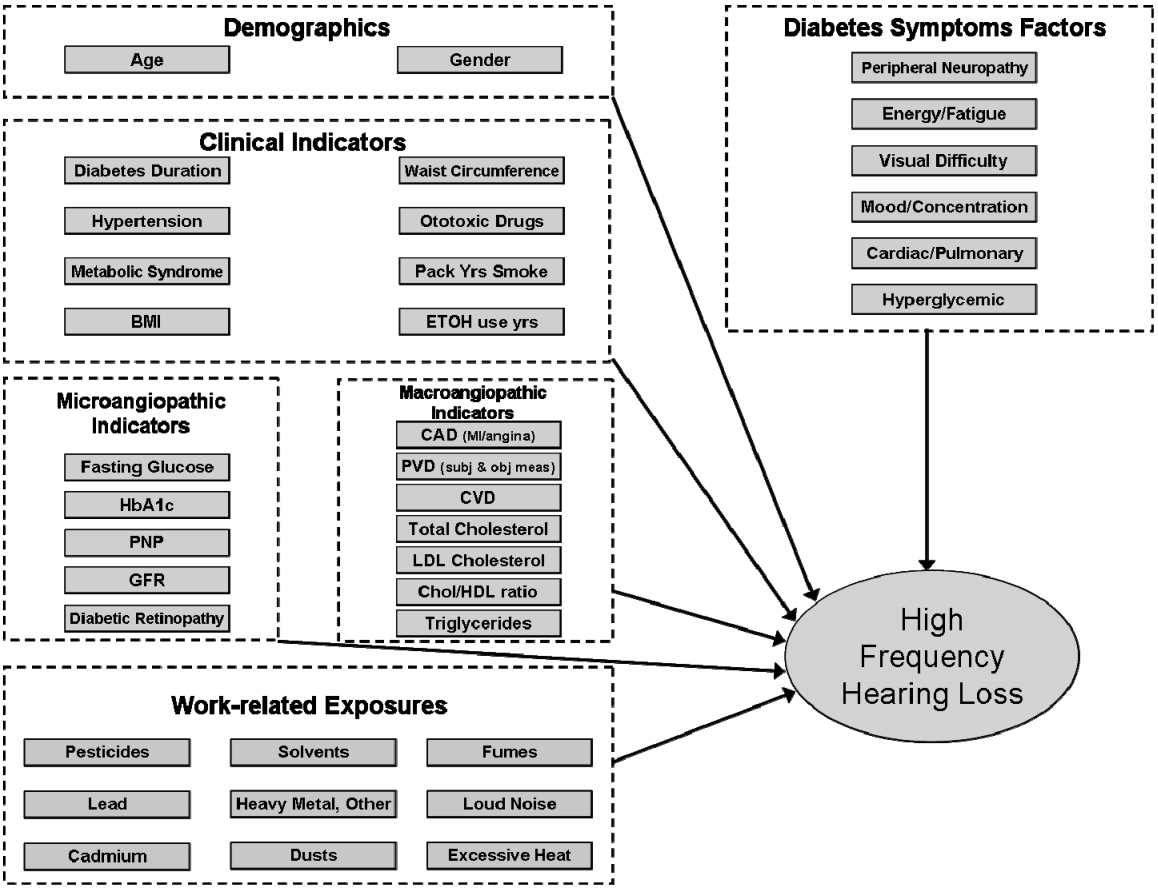

Figure 1: Conceptual Model of Contributors to High Frequency Hearing Loss in type 2 Diabetes

Chapter 3: Methods

Study Design

To accomplish the study aims, a cross-sectional secondary data analysis was conducted using selected variables extracted from the Sacramento Area Latino Study on Aging (SALSA) dataset. SALSA is a large longitudinal cohort study including 1,789 Mexican Americans who were aged 60 or greater in 1998-1999 at the study's inception and living in a six-county area of the greater Sacramento area in California (Haan et al., 2003). Following baseline data collection, follow-up home visits were conducted every 12-18 months for seven years through late 2007 for field work; mortality surveillance is continuing. Hearing tests were done beginning with the 4th follow-up visit and continued through the 7th follow-up visit. Information regarding diabetes, associated symptoms, hearing variables and clinically relevant indicators and biomarkers (glucose, HbA1c, blood lipids) were collected at baseline and every 12-15 months thereafter. The study design is a secondary data analysis of a portion of an existing data set. All the variables that were used in this analysis were collected during the same follow-up visit as the baseline audiogram except where data were collected only at study baseline, in which case, those variables were used. The unit of analysis is the individual ear, modeled as worse and better hearing ears. Analysis for each ear was run separately. This allows comparison to the landmark Bainbridge et al. (2008) study that identified diabetes as an independent risk factor for hearing loss.

Sample

The sample for the first part of this secondary analysis on hearing loss included 990 participants of the original 1789 SALSA study participants who had at least one hearing test during the 4th, 5th, 6th or 7th visit of the study and also had the other variables of interest collected at study baseline, during follow-up visits, or at the same visit as the hearing test. Subsequent analysis of features within type 2 diabetes include only the sub-cohort of participants (n=405) with a baseline hearing test from follow-up visit 4, 5, 6, or 7 and who were identified as having type 2 diabetes prior to or at the time of their baseline hearing test.

Variables and Measures

All the variables that were used in these analyses were collected during the same follow-up visit as the audiogram except where data were collected only at study baseline. In the latter case, baseline data were used. Alcohol use was operationalized as cumulative exposure over the follow up time up to the first hearing test. A brief description of the dependent and independent variables follows: See Appendix 1 for a detailed table of variables and measures.

Dependent variables: Hearing ability, assessed by conventional pure-tone audiometry thresholds for each ear at sound frequencies of 500 through 8000 Hz. Audiometric testing was performed using the Pocket HEARO LE Testing Device with Pocket PC (Otovation LLC, King of Prussia, PA). Participants with hearing aids were asked to remove the device during testing. The HEARO was in use beginning with the 4th follow-up visit and the hearing test was obtained at either the 4th or a subsequent follow-up visit through the 6th or 7th visit. The

HEARO device detects hearing thresholds beginning at 25 decibels and ending at 90 decibels. If a participant's hearing threshold at a particular frequency exceeded the upper detectable limit of the HEARO device, it was recorded as 90 decibels. Age-adjustment was not done on hearing thresholds from 1000 Hz through 6000 Hz as recommended by OSHA age-correction guidelines outlined in the Labor Code §1910.95 (2005) prior to averaging for determination of hearing impairment and analysis due to the age of the sample studied. OSHA age-correction guidelines only cover up to age 60. As all SALSA participants were age 60 or over at study initiation, hearing thresholds not adjusted for age were analyzed.

Hearing impairment is defined as pure tone average thresholds over low to mid-frequencies (500, 1000, and 2000 Hz) and high frequencies (3000, 4000, 6000, and 8000 Hz) with categories of mild or greater severity (pure tone average >25 decibels hearing level [dB HL] and moderate or greater severity (pure tone average >40 dB HL). Hearing impairment was assessed in left and right ears separately and recoded to reflect better and worse ears. This definition is consistent with that used by Bainbridge, Hoffman and Cowie (2008). This approach allows comparison with published data from the nationally representative sample in that study.

Data for other hearing-related variables including use of hearing aids, reports of difficulty hearing conversation in crowded rooms were also gathered and have been used to describe the study population.

Independent variables:

Demographic characteristics: Age (at time of hearing test), gender, education, marital status, income, primary language, country of birth, and age at migration to the U.S.

Occupationally-related variables: major occupation for most of life, and self-reported occupational exposure history (pesticide, lead, cadmium, other heavy metals, solvents, dusts, fumes, loud noise, excessive heat, and other exposures). Consultation with an Industrial Hygienist was done to identify ways to evaluate exposures by occupation and/or by multiple exposure history.

Type 2 Diabetes: Diabetes diagnosis at time of hearing test (by fasting glucose >125 mg/dL, HbA1c > 6.5%, self-report of physician diagnosis or the use of any medication for diabetes). Part one analysis dichotomizes diabetes diagnosis as yes/no at the time of the hearing test. Part two analysis was conducted on the subset of participants (n=405) with diabetes diagnosis at the time of their hearing test.

Clinical Indicators

Diabetes Duration: Diabetes duration in years was calculated based on self-reported duration at study baseline and number of years up to the hearing test. For those developing diabetes during the study and prior to the hearing test, the number of visit years from first report to the hearing test was calculated.

Hypertension: Hypertension at time of hearing test by self-report of physician diagnosis and/or the use of antihypertensive medication.

Ototoxic drug use: A composite variable of all reported drugs with known ototoxicity being taken at the time of the hearing test.

Metabolic Syndrome: At study baseline. Metabolic Syndrome was defined as 3 or more of the following abnormalities being present: waist circumference > 102 cm in men and > 88 cm in women; serum triglycerides $\geq$ 150 mg/dL; HDL cholesterol < 40 mg/dL in men and < 50 mg/dL in women; blood pressure of $\geq$ 130/85 or fasting serum glucose of $\geq$ 110 mg/dL (Ford, Giles, & Dietz, 2002; National Cholesterol Education Program Expert Panel on Detection & Treatment of High Blood Cholesterol in, 2002).

Body Mass Index (BMI): Calculated at time of test using the formula:

$$\text{BMI (kg/m}^2\text{)} = \frac{\text{Weight in lbs.}}{\text{Height in inches}}$$

Waist Circumference: Measured at time of test in centimeters. Waist circumference was dichotomized into low risk/at risk based on >102 cm (40.2 in) for males and > 88 cm (34.6 in) for females

Use of Ototoxic Drugs: Medication taken was assessed at each visit and recoded to reflect known ototoxicity reported in the literature. One ototoxic class, loop diuretics, was also evaluated.

Cigarette Smoking: Smoking status (current, quit, never).

Alcohol use: Alcohol use was assessed at baseline and follow-up visits. Alcohol exposure history was based on data available from study years up to the time of the hearing test and is reported as number of years from study baseline that alcohol was ingested.

Microangiopathic Indicators: Surrogate measures for physiologic microangiopathy.

Fasting Blood Glucose: Measured at time of test.

HbA1c: Measured at time of test.

Semmes-Weinstein Monofiliment Test: As a measure of peripheral neuropathy, results were used from assessment nearest to baseline hearing test. Data was available for most of the participants (n=868) on this variable.

Vibration Threshold Examination (VTE): As a measure of peripheral neuropathy, results were used from assessment nearest to the baseline hearing test. Data was available for most of the participants (n=868) on this variable.

Glomerular Filtration Rate (GFR): Calculated value from GFR was used from data collected closest to the time of the baseline hearing test. GFR was calculated by the SALSA team using MDRD gender-specific formulas appropriate for individuals with or without diabetes (Rigalleau et al., 2005). The MDRD formula used was:

$$186 \times (\text{serum creatinine [mg/dl]})^{-1.154} \times ([\text{years}])^{-0.203}$$

$$\times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$$

Diabetic Retinopathy: Presence or absence of physician diagnosis of diabetic retinopathy self-reported at time of test.

Macroangiopathic Indicators: Surrogate measures from physiologic macroangiopathy.

Coronary Artery Disease (CAD): History of myocardial infarction and angina pectoris at any time up to the hearing test, collapsed to single variable.

Peripheral Vascular Disease (PVD): History of intermittent claudication at any time up to the baseline hearing test and/or Ankle-Arm Index (AAI) <.9 (Newman et al., 1999).

Cerebrovascular Disease: History of stroke at any time up to the time of the hearing test.

Blood Lipids: Total cholesterol, LDL cholesterol, Cholesterol/HDL ratio, Triglycerides: Collected at time of hearing test.

Diabetes Symptoms Factors: Diabetes signs and symptoms reported at the time of the hearing test were rated on a six point scale based on participants' subjective rating of the symptom's presence and how much they were bothered by it: symptom not present, present but not bothered at all, bothered a little, moderately bothered, very bothered, and extremely bothered. These signs and symptoms were divided into factors determined from factor analysis performed as part of this secondary data analysis, were entered as possible predictors in a model for high frequency hearing loss. Principal Components Factor Analysis with Varimax Orthogonal Rotation was conducted of the diabetes signs and symptoms questionnaire data for the full SALSA cohort (N=1786) by the SALSA Principal Investigator, Mary Haan. A four factor structure was revealed in the orthogonally rotated factor pattern. Factors one through three had Cronbach's α of .85, indicating good internal consistency (M. N. Haan, personal communication, March 26, 2009). For validation, a Factor analysis of the diabetes signs and symptoms questionnaire was repeated with the diabetes sub-

cohort (n=405) data only by this author for the present study. This analysis is reported in the Results section of this paper.

Other Diabetes variables: Medication taken for diabetes (no medication, oral, non-oral, combination of oral/non-oral), other medications taken (antihypertensives; medication related to diabetes complications), special diet for diabetes, and self-monitoring of blood glucose were used to characterize the subsample with diabetes.

General health status: Self-report of general health status at time of hearing test.

Data Collection Protocols

Vibration Testing Examination (VTE). Vibration testing was done per SALSA protocol (M. Haan et al., 2003) using a 128 Hz tuning fork. Vibration sense is a sensitive indicator to early peripheral neuropathic changes; it is a simple test that is an appropriate screening test for peripheral neuropathy. Testing for reduced or absent vibration sense was done at the great toe. Normal vibration sense is the vibration of the tuning fork is felt in < 10 seconds. If > 10 seconds was needed to sense the vibration, the test indicated reduced vibration sense. Absent vibration sense was when the participant could not feel the vibration at all.

Semmes-Weinstein Monofiliment examination (SWM). Testing for insensate areas of both feet as a measure of neuropathic changes was performed per SALSA protocol (M. Haan et al., 2003). A standard Semmes-Weinstein 5.07 (10 g) monofilament was used following the study protocol that is consistent with that reported in the literature (Mayfield & Sugarman, 2000;

Santhanam, 2003). Multiple areas of both feet (great and fifth toes; over first, third and fifth metatarsals; and heels) were tested repeatedly in a random manner. Any report of not feeling the filament resulted in repeat testing to that area at a later point in the process. Areas of ulceration, necrosis, scarring, or callus formation were avoided during the testing procedure.

Statistical Analytic Approach

Analysis was conducted on SPSS for Windows, version 15.0 (SPSS, 2006) with the exception of Chi-Square goodness of fit analysis on changes in -2 Log Likelihood between nested logistic regression models. That analysis was conducted using NCSS Probability Calculator (NCSS, 1995).

Descriptive statistics were calculated for all demographic and other study variables. Bivariate nonparametric Spearman's Rho (r_s) were done in preliminary analysis to assist in determining which factors to include in the logistic regression statistical models to address the specific aims. Choices for inclusion in models were also made based on theoretical criteria where variables significantly correlated in bivariate analysis. Nonparametric tests (χ^2, Mann-Whitney) were performed on ordinal and nominal categorical variables to characterize sample characteristics and differences between those with and without diabetes.

Logistic regression modeling was used to determine predictors of hearing loss in each group of variables and for the final composite model. Prediction in logistic regression means that group membership is predicted by various characteristics or variables that are entered into the model. When employed in cross-sectional studies such as this one, it does not imply causation but rather

that, based on the values of the variables (or predictors) under study, participants having hearing loss can be predicted. Also, the strength of prediction for single predictors or sets of predictors can be determined (Hosmer & Lemeshow, 2000). Hosmer and Lemeshow Goodness of Fit statistics are not reported in the results unless they were significant indicating poor model fit to the data. In Part 1 analysis, where nested models were evaluated, a change in -2 Log Likelihood from one model to the next was evaluated via Chi-Square Goodness of Fit testing of the difference between two models. When done, the degrees of freedom for the test are the number of variables that were added to the subsequent model.

Multicollinearity Criteria

Multicollinearity that may result in unreliable estimates of regression coefficients was assessed when correlations were high between predictors. Because predictors that share variance have less unique contribution to exert on the outcome variable, this assessment increases confidence in the results (Cohen, Cohen, West, & Aiken, 2003). Hosmer and Lemeshow (2000). The tolerance test result from entering the predictors into multiple regression modeling was used for determining multicollinearity of variables prior to the use of potentially collinear predictors in logistic regression models when multicollinearity was suspected based on bivariate correlations. The tolerance statistic squared is interpreted as a percentage of shared variance. When multicollinearity was found, one of two methods to handle this were employed. When the standard errors of the estimates in logistic regression modeling was

small, all variables were entered into the equation per Hosmer and Lemshow's recommendations. When standard errors were higher for some of the variables, simple bivariate logistic regression models were fit for each predictor with the outcome variables and only those with significance < .10 were entered into the applicable group logistic regression model.

Part 1 Analytic Approach

For part one analysis (n=990):

1) What is the prevalence of hearing loss among Mexican Americans with diabetes compared to those without diabetes?

Crosstabulations with chi-square was conducted.

2) What is the relationship between hearing loss (low-mid and high frequency) and type 2 diabetes when controlling for age and gender?

A series of logistic regression analyses were conducted to evaluate the potential contribution of diabetes to hearing loss. Hearing loss was modeled as low-mid frequency hearing loss (mean of 500, 1000, 2000 Hz Hearing Level Threshold) and high frequency hearing loss (mean of 3000, 4000, 6000, 8000 Hz Hearing Level Threshold) in the better and worse hearing ears. Those with no hearing loss (< 25 dB) served as the reference group in some of the logistic regression models while those with no hearing loss to mild hearing loss (<40 dB) served as the reference group in other models. This was due to the high prevalence of hearing loss > 25 dB in this sample, making the no hearing loss group too small for meaningful comparisons in some of the analyses.

Standard logistic regression using the four different hearing outcome variables in different models was deemed the most appropriate approach. There is limited potential for Type 1 error despite testing multiple models because the four hearing loss outcomes are not independent of one another (worse and better ear, two different frequency levels in each ear on the same individuals), and therefore, no adjustment of significance level is required. The significance level of $\alpha < .05$ was used for each regression model. Due to non-independence of the outcome variables, downward adjustment would be too conservative and may have resulted in a Type II error. This is particularly true due to the limited power of the study (Rosnow & Rosenthal, 1989). Power in this study is limited by the uneven sample size of those with hearing loss compared to those without. The guidelines for logistic regression are that there should be approximately 10 participants having the event under study (or the non-event in this case; whichever is the smaller group) for each predictor for adequate power (Hosmer & Lemeshow, 2000). According to Hosmer and Lemeshow (2000), when exploratory model building is the goal of research, a less stringent α level is appropriate. The standard $\alpha = .05$ is appropriate for hypothesis testing research with downward adjustment for multiple testing when the outcomes are independent of one another.

Part 2 Analytic Approach

For part two analysis, only the subset of participants with diabetes (n=405) were included in the analysis. To answer question:

1) Are selected signs and symptoms of diabetes by self-report, such as neuropathic, vascular and diabetes-specific symptoms associated with and predictive of high frequency hearing loss?

Diabetes-specific signs and symptoms were factor analyzed with Varimax orthogonal rotation with Kaiser normalization to determine factor structure. This factor analysis was performed on the diabetes sub-cohort (n=405) data only. The factors determined were then correlated with high frequency hearing loss using non-parametric correlation testing (r_s). Logistic regression analysis that included all factors as variables followed.

2) Are selected clinical indicators [duration of diabetes, hypertension, metabolic syndrome, BMI, waist circumference, ototoxic drugs, smoking (pack years), and alcohol use (in years)] associated with and predictors of high frequency hearing loss?

Variables were correlated (r_s) and then logistic regression was performed.

3) Are clinical indicators of microangiopathy (fasting glucose, HbA1c, Semmes-Weinstein Monofilament Test (SWM) and/or Vibration Threshold testing (VTE), glomerular filtration rate, and diabetic retinopathy) associated with and predictive of high frequency hearing loss??

Variables were correlated (r_s) and then logistic regression was used. Prior to logistic regression, an analysis of the discriminative ability of SWM and VTE was performed with resulting collapsing of these variables into one to represent peripheral neuropathy.

4) Are clinical indicators of macroangiopathy (coronary artery disease, peripheral vascular disease, cerebrovascular disease, blood lipids) associated with and predictive of high frequency hearing loss?

Variables were correlated (r_s), assessment for multicollinearity was conducted, followed by simple logistic regression for each variable with the dependent variables. Logistic regression with all variables in this grouping followed.

5) Are work-related exposures associated with and predictive of high frequency hearing loss?

Variables were correlated (r_s), assessment for multicollinearity was conducted, followed by simple logistic regression for each variable with the dependent variables. Different logistic regression models with selected exposure variables in this grouping followed to determine the best fit to the data. This process was done according to guidelines for variable selection for logistic regression recommended by Hosmer and Lemeshow (2000). Assessment for confounding was also conducted with retention of variables found to confound the relationships in the model.

6) Of the variables found to be predictive of high frequency hearing loss in individual model analysis conducted in part 2 analysis questions 1-5, what is the relative contribution of these variables in predicting high frequency hearing loss in those with type 2 diabetes?

A composite logistic regression model was fit for each dependent variable. Variables that reached a significance level of <.10 in their group models were included in the final composite models.

Considerations for Protection of Human Subjects

The SALSA study data collection has concluded and no new data was collected for this secondary analysis. No contact with SALSA participants was conducted. SALSA did not include an intervention or treatment. The main study was approved by the University of Michigan (UM) IRB Med and both the UM IRBMED and University of California at Davis IRB reviewed the study annually including the human subject protection plan. The IRB number for this project is 200210457-9 and the latest project expiration date is 12/17/09.

During the data collection phase of the project, participants engaged in an informed consent process with staff of the SALSA Study Office at the University of California at Davis. Participants signed consent for study participation in addition to an 'EXPERIMENTAL SUBJECTS' BILL OF RIGHTS' outlining their rights while participating in a research study. HIPAA forms giving the SALSA staff permission to use personally identifiable data were also signed by participants including details for release of HIPAA protected information (i.e. to themselves, their doctor, etc.).

Self-certification of exemption from the University of California San Francisco Committee on Human Research (CHR) approval was done for this analysis based on the use of secondary analysis of de-identified data. This

certification is on file with the parent study Principal Investigator. A copy is included in Appendix 2.

Chapter 4: Results

Sample Characteristics

The sample for Part 1 analysis consisted of 990 of the original 1,789 SALSA participants who had a baseline hearing test performed during years 4, 5, 6, or 7 of the parent SALSA study. All participants were 65 years of age or over at the time of their first hearing test. The sample for Part 2 analysis consisted of the 405 participants who had diabetes at the time of their hearing test. Additional demographic characteristics for both the full cohort (N=990) and the diabetes sub-cohort (n=405) are listed in Table 1.

Job history for participants revealed the majority being employed in general labor jobs during most of their lives (56% of full cohort and diabetes sub-cohort) with 117 (12%) of the full cohort in farming/fishing/forestry jobs and 66 (16%) of the diabetes sub-cohort in this laborer subgroup. Following general labor, housewifery was the next most common job for most of the participants' lives.

Clinical baseline data for the diabetes sub-cohort is presented in Table 2. Nearly 60% of the participants with diabetes had disease duration of less than 10 years while 40% had diabetes for more than 10 years. An overwhelming majority of those with diabetes had comorbid hypertension at the time of their hearing test and metabolic syndrome assessed at the parent study baseline. Significant numbers had history of coronary artery disease (37.5%) as assessed by self-report of myocardial infarction or angina; peripheral vascular disease (40.2%) as assessed by report of intermittent claudication and/or abnormal Ankle-arm index;

while a minority had history of cerebrovascular disease (19.3%) as assessed by report of physician diagnosis of stroke. The majority of those with diabetes (52.6%) had some impairment in Glomerular Filtration Rate (GFR) but only 8% had moderate or severe decreases in GFR consistent with significant kidney disease.

A majority of participants with diabetes (58.7%) had either reduced or absent vibration sense as tested by tuning fork. The average number of insensate sites by the Semmes-Weinstein Monofiliment testing on the feet was < 1 site per participant.

A majority of the diabetes sub-cohort (55%) were either current or former smokers. However, all but 28 had quit smoking. Alcohol intake in this group was modest by self-report.

The average fasting blood glucose for the diabetes sub-cohort was 137 $\pm$ 54.1, consistent with the diagnosis. Glycemic control, however, was relatively good with a mean HbA1c of < 7 $\pm$ 1.5. The cohort had average BMI consistent with obesity (31 $\pm$ 5.8) and waist circumference indicative of central adiposity. The blood lipid values were, on average, good with total cholesterol < 180 mg/dL, LDL cholesterol < 100 mg/dL and cholesterol/HDL ratio of 3.5 on average. Triglycerides were less well controlled as the mean was > 150 mg/dL with a large standard deviation.

Of the 131 participants with diabetes for which data is available on selected self-care activities, nearly 2/3 perform blood glucose testing by

fingerstick (SMBG) and 60% follow an eating plan or diet that is specific to their diabetes.

The majority of participants with diabetes take oral agents for diabetes control (54.8%). Over 30% take no diabetes-specific medication, while over 13% take either non-oral medication such as injectables or a combination of oral and non-oral medication.

More than three-fourths of participants within the diabetes sub-cohort were taking antihypertensive medication and over half were taking statins for hypercholesterolemia. Nearly 40% of the participants were taking some type of medication known to be ototoxic with 14.1% taking loop diuretics specifically. Furosemide is most likely the loop diuretic being used by these participants although this level of medication detail was not available.

Very few (7.9%) of the participants with diabetes wore hearing aids at study baseline while a much larger percentage admitted to difficulty with hearing conversation in a crowded room, a common complaint in the presence of hearing impairment.

There were more women in the study (n=593) than men (n=397) as would be expected in an older cohort given the gender difference in longevity. More women participants had diabetes (n=226) than men (n=179); however, the percentage of men that had diabetes was greater than the percentage of women (45.1% vs. 38.1). This gender difference was significant ($\chi^2(df) = 4.788(1)$, $p = .034$).

Due to the importance of this analysis regarding the participants who worked as farm workers and were more likely to be exposed to pesticides, the analysis of gender breakdown was repeated for just the farm, fishery and forestry job category of participants (n=144). Males in this job category exceeded females (83 vs. 61) and males with diabetes exceeded females (36 vs. 30), however, this difference did not reach statistical significance ($\chi^2(df) = .478(1)$, $p = .490$).

Participants rating of their general health significantly differed by whether or not they had diabetes ($\chi^2(df) = 29.596(4)$, $p < .0005$). Higher percentages of participants without diabetes rated their health as excellent (11.6%), very good (24.7%) or good (33%) compared to those with diabetes (7.3%, 17.3%, and 29.8% respectively); while higher percentages of participants with diabetes rated their general health as fair (32%) or poor (13.6%) compared to those without diabetes (24.9% and 5.8% respectively).

Table 1

Demographic Characteristics of Sample

	Full cohort N=990		Diabetes sub-cohort n=405	
Age at time of test	Mean 75.67 ± 6.166		Mean 75.35 ± 5.95	
Years of Education	Mean 7.97 ± 5.387		Mean 7.98 ± 5.554	
Gender				
Males	397	40%	179	44%
Females	593	60%	226	56%
Job for most of life				
Professional	121	12%	48	12%
Sales/Admin Support	115	12%	40	10%
General Labor	555	56%	227	56%
Farming/Fishing/Forestry	*117*	*12%*	*66*	*16%*
Housewife	176	18%	81	20%
Missing	23	2%	9	2%
Marital Status				
Married	520	53%	224	55%
Cohabitating	10	1%	4	1%
Widowed	307	31%	115	28%
Divorced	96	10%	37	9%
Separated	35	4%	17	4%
Never Married	17	2%	7	2%
Missing	5	<1%	1	<1%
Language				
English	450	45%	184	45%
Spanish	540	55%	221	55%
Country of Birth				
U.S.	499	50%	215	53%
Mexico	423	43%	168	42%
Other Latin American	63	6%	18	4%
Missing data	5	<1%	4	<1%
Age at Migration to U.S.	n=476 Mean 32.55 ±17.3		n=184 Mean 33.4 ±16.83	

Table 2

Clinical Baseline Data for Diabetes Sub-Cohort

n=405	Diabetes sub-cohort		
Duration of Diabetes	Duration	n	%
Mean 10.6 ± 9.9	< 5 years	124	30.6%
	5 < 10 years	117	28.9%
	10 < 15 years	61	15.1%
	15 < 20 years	41	10.1%
	≥ 20 years	62	15.3%
Hypertension	Yes	329	81.2%
	No	76	18.8%
Metabolic Syndrome at Study	Yes	298	73.6%
Baseline	No	96	23.7%
	Missing	11	2.7%
Coronary Artery Disease	Yes	152	37.5%
	No	253	62.5%
Peripheral Vascular Disease	Yes	163	40.2%
	No	242	59.8 %
Cerebrovascular Disease	Yes	78	19.3%
(stroke)	No	327	80.7%
Glomerular Filtration Rate		n	%
Mean 89.6 ± 23.4			
Normal GFR ≥ 90		144	35.6%
Mild decrease in GFR 60-89		213	52.6%
Moderate decrease GFR 30-59		32	7.9%
Severe decrease in GFR < 30		2	0.4%
Missing		14	3.5%
Vibration Threshold reduced or absent (n=368)		216	58.7%
Semmes-Weinstein Monofiliment Test (# insensate sites)		Mean .59 ± 1.874	
Pack Years Smoking current smokers (n=28)		Mean 18.86 ± 19.113	
Pack Years Smoking former smokers (n=193)		Mean 20.04 ± 31.863	
Alcohol Use Years of study (at time of test)			

Table 2 (continued)

Clinical Baseline Data Diabetes Sub-Cohort (continued)

		Mean ± SD	
Fasting Blood Glucose (FBG)		137 ± 54.1	
HbA1c		6.995 ± 1.5124	
Body Mass Index (BMI)		31 ± 5.8	
Waist Circumference (in cm)		100.8 ± 12.7	
Total Cholesterol		178 ± 40.2	
LDL Cholesterol		94 ± 31.3	
Cholesterol/HDL Ratio		3.5 ± .899	
Triglycerides		162 ± 107.1	
Diabetes Self-Care Activities at time of test (n=131)			
		n	%
Perform SMBG test		86	65.6%
Follow a diet for diabetes		79	60.3%
Diabetes Medications by self-report and home audit at time of test (n=405)			
No diabetes medication		128	31.6%
Oral diabetes medication only		222	54.8%
Non-oral diabetes medication only		27	6.7%
Combination oral and non-oral diabetes medication		28	6.9%
Selected Medications by self-report and home audit at time of test (n=405)			
		n	%
Antihypertensives	Yes	315	77.8%
Statins	Yes	182	44.9%
Ototoxic Drug Use	Yes	161	39.8%
Loop Diuretic Use	Yes	57	14.1%
Hearing Variables			
Use a hearing aid at baseline	Yes	31	7.9%
Difficult to converse in crowded room	Yes	85	21.5%

Results of Part 1 Analysis

Prevalence of Hearing Loss in Diabetes

The prevalence of any hearing loss (> 25 dB) at low-mid frequencies and high frequencies in the worse and better ear is presented in Table 3. While 81.2% of those with diabetes had low-mid frequency hearing loss in the worse ear compared to 77.1% of those without diabetes, this difference was not significant (χ^2(*df*) = 2.213(1), *p* = .138). Similarly, 69.4% of those with diabetes had low-mid frequency hearing in the better ear compared to 64.4% of those without diabetes, this difference was also not significant (χ^2(*df*) = 2.402(1), *p* = .121). High frequency hearing loss was nearly universal in this population at the > 25 dB level. Comparing those with diabetes, 99.5% had hearing loss in high frequencies in the worse ear compared to those without diabetes having a prevalence of 97.1% hearing loss in high frequencies in the worse ear. This difference between those with diabetes and those without was significant in the worse ear (χ^2(*df*) = 6.172(1), *p* = .013; Cramer's V = .086). For high frequency hearing loss in the better ear, 96.3% of those with diabetes had hearing loss compared to 93.3% of those without diabetes (χ^2(*df*) = 3.530(1), *p* = .061). This difference did not reach statistical significance using the continuity corrected chi-square that is appropriate for two-by-two crosstabulations.

Due to the high prevalence of hearing loss > 25 dB in this population, calculation of prevalence for moderate-severe hearing loss (> 40 dB) at each frequency level and in each ear was performed (See Table 4). Comparing those with diabetes to those without, 37.3% vs. 34.9% had moderate-severe mid-low

frequency hearing loss in the worse ear. This difference was not statistically significant (χ^2(*df*) = .505(1), *p* = .477). For the better ear, 21% of those with diabetes had moderate-severe mid-low frequency hearing loss compared to 19.7% without diabetes (χ^2(*df*) = .186(1), *p* = .666). At high frequencies in the worse ear, 82.2% of those with diabetes had moderate-severe hearing loss compared to 76.8% of those without diabetes. This difference was statistically significant (χ^2(*df*) = 3.992(1), *p* = .046). The better ear difference, however, failed to reach significance (χ^2(*df*) = 3.042(1), *p* = .081).

Table 3

Prevalence Crosstabulation of Diabetes Status and Any Hearing Loss (>25 dB)

Low-mid frequency > 25 dB HL worse ear			
	Diabetes		
Low-mid frequency HL worse ear	No	Yes	Totals
No	134	76	210
Yes	451	329	780
Totals	585	405	990
Low-mid frequency > 25 dB HL Better ear			
	Diabetes		
Low-mid frequency HL better ear	No	Yes	Totals
No	208	124	332
Yes	377	281	658
Totals	585	405	990
High frequency > 25 dB HL Worse ear			
	Diabetes		
High frequency HL worse ear	No	Yes	Totals
No	17	2	19
Yes	568	403	971
Totals	585	405	990
High frequency > 25 dB HL Better ear			
	Diabetes		
High frequency HL better ear	No	Yes	Totals
No	39	15	54
Yes	546	390	936
Totals	585	405	990

Table 4

Prevalence Crosstabulation of Diabetes Status and Moderate-Severe Hearing Loss (>40 dB)

Low-mid frequency > 40 dB HL worse ear			
	Diabetes		
Low-mid frequency HL worse ear	No	Yes	Totals
No	381	254	635
Yes	204	151	355
Totals	585	405	990
Low-mid frequency > 40 dB HL Better ear			
	Diabetes		
Low-mid frequency HL better ear	No	Yes	Totals
No	470	320	790
Yes	115	85	200
Totals	585	405	990
High frequency > 40 dB HL Worse ear			
	Diabetes		
High frequency HL worse ear	No	Yes	Totals
No	136	72	208
Yes	449	333	782
Totals	585	405	990
High frequency > 40 dB HL Better ear			
	Diabetes		
High frequency HL better ear	No	Yes	Totals
No	198	115	313
Yes	387	290	677
Totals	585	405	990

Age, Gender and Diabetes

Prior to model building, nonparametric bivariate correlations (r_s) between diabetes, age, gender, history of stroke, hypertension, ototoxic drug use (current and prior), loop diuretic use (current and prior) and hearing loss for the full cohort (N=990) were determined. Results are shown in Table 5. In bivariate analysis, diabetes was weakly but significantly correlated with moderate-severe high frequency hearing loss in the worse ear, but not in the better ear. Diabetes was not correlated with low frequency hearing loss in either ear. Age, however, was moderately and significantly correlated with moderate-severe high frequency hearing loss in both the worse and the better ear. Age was also significantly correlated with low frequency hearing loss in either ear but at a lesser magnitude than for high frequency loss. Gender has a slightly lower magnitude correlation than age in either ear and was negative indicating females are less likely to have hearing loss. Stroke was weakly but significantly correlated with hypertension and ototoxic drug use, including loop diuretics, but was only significantly correlated, weakly, with low frequency hearing loss in the better ear but not significantly in the worse ear. Stroke history had no significant correlation to high frequency hearing loss. Hypertension was not significantly correlated with any type of hearing loss. Loop diuretic use was weakly correlated with high frequency loss in either ear but the broader category of any ototoxic drug use was not. Prior loop diuretic use was very strongly correlated with current loop diuretic use indicating persistence in use of this type of medication among a subset of the

sample. Current ototoxic drug use was highly correlated with prior use but at a smaller magnitude than for loop diuretics.

The large significant correlations between both low frequency hearing loss for better and worse ear and then for high frequency hearing loss in the better and worse ear are indicative of the lack of independence of these results. Those with low frequency loss in one ear are likely to suffer loss in the other ear and those with high frequency loss in one ear are also likely to suffer high frequency loss in the other ear. The lack of a one-to-one correlation between the ears is reflective of mild asymmetry that is commonly seen in hearing loss; however, the asymmetry did not reach the clinical criteria for asymmetric hearing loss in the high frequencies except in a small number of individuals (21). The criteria for asymmetric hearing loss in high frequencies is 30 dB difference at the 3000, 4000, and 6000 Hz frequencies (American Academy of Otolaryngology - Head and Neck Surgery [AAO-HNS], 1997). The correlations of low frequency loss and high frequency loss in either the worse or better ear is moderate and significant while reflecting lower magnitude than the same frequency level loss between the two ears.

Table 5

Correlations between Diabetes, Age, Gender, Stroke, Hypertension, Ototoxic Drug Use, and Hearing Loss

N=990	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Diabetes	1.0	-.043	-.070*	.117**	.212**	.130**	.097**	.157**	.132**	.025	.016	.066*	.058
2. Age at hearing test		1.0	.017	.065*	.072*	.146**	.113**	.150**	.087**	.276**	.248**	.308**	.346**
3. Gender			1.0	-.012	.040	.040	.087**	.039	.031	-.252**	-.245**	-.240**	-.295**
4. Stroke				1.0	.121**	.202**	.075*	.188**	.100**	.061	.074*	.041	.043
5. Hypertension					1.0	.147**	.150**	.169**	.163**	.047	.033	.057	.059
6. Loop diuretic use						1.0	.449**	.812**	.237**	.031	.034	.091**	.072**
7. Any ototoxic drug use							1.0	.361**	.529**	-.011	-.024	.022	.019
8. Prior loop diuretic use								1.0	.293**	.044	.040	.098**	.076*
9. Prior ototoxic drugs									1.0	.018	-.001	.033	.016
10. M-S LF HL worse										1.0	.673**	.370**	.413**
11. M-S LF HL better											1.0	.253**	.326**
12. M-S HF HL worse												1.0	.758**
13. M-S HF HL better													1.0

* $p < .05$. ** $p < .01$. *** $p < .0005$

Logistic Regression Modeling of Age and Diabetes as Predictors of Hearing Loss

To explore hearing loss by frequency levels, separate logistic regression analyses were done for each type of hearing loss (low-mid frequency in the worse ear and the better ear, and high frequency in the worse ear and better ear). Model 1 includes age and diabetes as predictors of hearing loss for each hearing outcome. Each model was significant in predicting the hearing loss outcome included in the analysis (See Table 6 and Table 7). Age was a consistent significant predictor of hearing loss at each frequency level and in each ear with Odds Ratios (OR) for hearing loss ranging from 1.105 to 1.172 for each year of age over age 65. Diabetes was a significant predictor of high frequency hearing loss in both the worse and the better ear when controlling for age with OR of 1.538 (95% CI: 1.099-2.153) in the worse ear and 1.431 (95% CI: 1.065-1.922) in the better ear. Diabetes did not significantly predict hearing loss in the low-mid frequency ranges.

Table 6

Logistic Regression Model 1 Fit: Age and Diabetes as Predictors of Hearing Loss

Model 1	χ^2	*df*	*Sig.*	-2 Log likelihood	% Variance	Correctly Classified
Low-mid worse	81.323	2	<.0005***	1210.825	7.9-10.8	67.8%
Low-mid better	67.978	2	<.0005***	928.339	6.6-10.5	79.5%
High worse	111.919	2	<.0005***	905.980	10.7-16.6	79.6%
High better	139.679	2	<.0005***	1095.727	13.2-18.5	69.4%

*** $p < .0005$.

Table 7

Model 1: Logistic Regression Prediction Model of Age and Diabetes for Hearing Loss

Model 1 N=990						Odds	95% C.I for Odds Ratio	
	B	S.E.	Wald	*df*	*Sig.*	Ratio	Lower	Upper
Low-Mid Frequency Worse Ear					Model Fit: $\chi^2(df) = 81.323(2)$, $p < .0005$***			
Age	.100	.012	72.852	1	<.0005***	1.105	1.080	1.131
Diabetes	.175	.141	1.548	1	.213	1.191	.904	1.569
Constant	-8.282	.906	83.565	1				
Low-Mid Frequency Better Ear					Model Fit: $\chi^2(df) = 67.978(2)$, $p < .0005$***			
Age	.105	.013	63.186	1	<.0005***	1.111	1.082	1.140
Diabetes	.159	.167	.908	1	.341	1.172	.845	1.627
Constant	-9.500	1.037	83.866	1				
High Frequency Worse Ear					Model Fit: $\chi^2(df) = 111.919(2)$, $p < .0005$***			
Age	.159	.017	83.747	1	<.0005***	1.172	1.133	1.212
Diabetes	.431	.171	6.302	1	.012*	1.538	1.099	2.153
Constant	-10.601	1.271	69.537	1				
High Frequency Better Ear					Model Fit: $\chi^2(df) = 139.679(2)$, $p < .0005$***			
Age	.153	.015	107.273	1	<.0005***	1.166	1.132	1.200
Diabetes	.358	.151	5.657	1	.017*	1.431	1.065	1.922
Constant	-10.808	1.100	96.600	1				

** $p < .05$. ***$p < .0005$.*

Logistic Regression Modeling of Age, Diabetes, and Gender as Predictors of Hearing Loss

Model 2 includes age and diabetes as in Model 1 with gender added as an additional predictor of hearing loss. Each model was significant in predicting the hearing loss outcome included in the analysis (See Table 8 and Table 9). The addition of gender explained more variance in the hearing loss outcomes and resulted in more cases correctly classified than did Model 1 with only age and diabetes in the model. ORs for age slightly increased with gender in the model. ORs for diabetes decreased and failed to reach significance with gender in the model. In high frequency hearing loss in the worse ear, however, the significance level was less than 1/100th over .05 and it was less than .10 in the better ear.

Table 8

Logistic Regression Model 2 Fit: Age, Diabetes and Gender as Predictors of Hearing Loss

Model 2	χ^2	*df*	*Sig.*	-2 Log likelihood	% Variance	Correctly Classified
Low-mid freq worse ear	149.538	3	<.0005***	1142.610	14-19.2	69.9%
Low-mid freq better ear	130.893	3	<.0005***	865.424	12.4-19.5	80.9%
High freq worse ear	180.957	3	<.0005***	905.980	16.7-26	80.0%
High freq better ear	246.332	3	<.0005***	989.074	22-30.9	74.5%

*** $p < .0005$.

Table 9

Model 2: Logistic Regression Prediction Model of Age, Diabetes & Gender for Hearing Loss

Model 2 N=990						Odds	95% C.I for Odds Ratio	
	B	S.E.	Wald	*df*	*Sig.*	Ratio	Lower	Upper
Low-Mid Frequency Worse Ear					Model Fit: $\chi^2(df) = 149.538(3)$, $p < .0005$***			
Age	.108	.012	77.018	1	<.0005***	1.115	1.088	1.142
Diabetes	.099	.146	.460	1	.498	1.104	.829	1.470
Gender	1.182	.146	65.371	1	<.0005***	3.262	2.449	4.345
Constant	-9.387	.964	94.785	1				
Low-Mid Frequency Better Ear					Model Fit: $\chi^2(df) = 130.893(3)$, $p < .0005$***			
Age	.113	.014	66.521	1	<.0005***	1.119	1.089	1.150
Diabetes	.081	.173	.218	1	.640	1.084	.772	1.523
Gender	1.344	.175	59.132	1	<.0005***	3.836	2.723	5.403
Constant	-10.704	1.099	94.778	1				
High Frequency Worse Ear					Model Fit: $\chi^2(df) = 180.957(3)$, $p < .0005$***			
Age	.173	.018	88.866	1	<.0005**	1.188	1.147	1.232
Diabetes	.350	.179	3.828	1	.050	1.419	.999	2.016
Gender	1.574	.208	57.200	1	<.0005***	4.824	3.209	7.254
Constant	-12.092	1.354	79.710	1				
High Frequency Better Ear					Model Fit: $\chi^2(df) = 246.332(3)$, $p < .0005$***			
Age	.175	.016	115.398	1	<.0005**	1.191	1.154	1.230
Diabetes	.271	.160	2.857	1	.091	1.311	.958	1.794
Gender	1.706	.179	90.510	1	<.0005***	5.507	3.875	7.826
Constant	-12.953	1.224	111.952	1				

$p < .0005$.$p < .0005$.

Additional Potential Predictors of Hearing Loss: Loop Diuretic Use, History of Stroke, and Hypertension

Loop diuretic use, history of stroke, and hypertension were added to the logistic regression models for each hearing outcome. The models for each hearing outcome remained significant with these additional predictors added but none of these new predictors reached significance of <.05 for any of the hearing outcomes. Stroke history in the better ear was just above the cut-off (OR: 1.571; 95% CI: .999-2.47, p =.0505). The model with the additional predictors was not a better fitting model based on a Chi-square goodness of fit statistic on the difference in -2 Log Liklihood for the two models ($\chi^2(df) = 4.706(3)$, $p = .195$). No significant changes in model fit or odds ratios were achieved with the removal of loop diuretic use and hypertension (model results not shown). For moderate-severe high frequency hearing loss in the worse ear, loop diuretic use approached significance (OR: 1.947; 95% CI: .904-4.194, p =.089). This model with the additional predictors, however, was a better fitting model based on a Chi-square goodness of fit statistic on the difference in -2 Log Liklihood for the two models ($\chi^2(df) = 72.882(3)$, $p < .0005$). No significant changes in model fit or odds ratios were achieved with the removal of stroke history and hypertension (model results not shown).

Gender Differences in Hearing Loss

To further explore differences in gender-related high frequency hearing loss, diabetes and age were included in separate models by gender. Model 3 includes age and diabetes stratified by gender (See Table 10 and Table 11). Age

remains significant for males and females in either ear. The ORs for high frequency loss in males due to age are higher than they are for females. Diabetes did not reach significance as a predictor of high frequency loss for males but was significant for females in the worse ear with an OR of 1.646 (95%CI: 1.101-2.461).

Table 10

Logistic Regression Model 3 Fit: Age and Diabetes as Predictors of High Frequency Hearing Loss by Gender

Model 3	χ^2	*df*	*Sig.*	-2 Log likelihood	% Variance	Correctly Classified
			Males			
High freq worse ear	38.858	2	<.0005***	202.605	9.3-20.5	90.9
High-mid freq better ear	38.639	2	<.0005***	295.078	9.3-16.3	85.1
			Females			
High freq worse ear	85.630	2	<.0005***	628.576	13.4-19.2	72.5%
High freq better ear	115.896	2	<.0005***	693.951	17.8-23.8	67.6

*** $p < .0005$.

Table 11

Model 3: Logistic Regression Prediction Model of Age and Diabetes for Hearing Loss by Gender

Model 1 N=990							95% C.I for Odds Ratio	
	B	S.E.	Wald	*df*	*Sig.*	Odds Ratio	Lower	Upper
High Frequency Worse Ear – Males				Model Fit: $\chi^2(df) = 38.858(2)$, p <.0005***				
Age	.252	.051	24.666	1	<.0005***	1.287	1.165	1.421
Diabetes	-.157	.369	.181	1	.670	.855	.414	1.763
Constant	-15.937	3.593	19.672	1				
High Frequency Better Ear – Males				Model Fit: $\chi^2(df) = 38.639(2)$, p <.0005***				
Age	.180	.034	27.707	1	<.0005***	1.197	1.119	1.280
Diabetes	.238	.299	.630	1	.427	1.268	.705	2.280
Constant	-11.588	2.472	21.980	1				
High Frequency Worse Ear – Females				Model Fit: $\chi^2(df) = 85.630(2)$, p <.0005***				
Age	.159	.020	64.258	1	<.0005***	1.172	1.127	1.218
Diabetes	.498	.205	5.888	1	.015*	1.646	1.101	2.461
Constant	-11.109	1.467	57.335	1				
High Frequency Better Ear – Females				Model Fit: $\chi^2(df) = 115.896(2)$, p <.0005***				
Age	.173	.019	87.589	1	<.0005***	1.189	1.147	1.233
Diabetes	.283	.189	2.239	1	.135	1.328	.916	1.925
Constant	-12.852	1.394	84.991	1				

*p < .05. ***p < .0005.

Summary of Part 1 Analysis Findings

The prevalence of hearing loss in those with diabetes is greater than in those without diabetes but is only significantly different for high frequency loss in the worse ear. Diabetes was not a significant predictor for hearing loss in low-mid frequencies. Therefore, no further analysis was conducted on low-mid frequency hearing loss in Part 2 of the analysis. Diabetes is a predictor for high frequency hearing loss in both worse and better ears when controlling for age but not when gender is added to the model. However, diabetes remains a predictor of high frequency hearing loss for females when analysis is stratified by gender, controlling for age. Due to the significance level for high frequency hearing loss being less than .10 even when gender is in the model and due to the association reported in the published literature (Bainbridge et al., 2008) both worse and better ear analysis for high frequency hearing loss were carried forward in to Part 2 analysis. The addition of other possible predictors, stroke, hypertension, and loop diuretics only resulted in a better fitting model in the worse ear and none of the added predictors were significant. Loop diuretic use, however, had $p < .10$.

Results of Part 2 Analysis

Part 2 analysis was done on a diabetes sub-cohort, the subset of participants who had a diagnosis of diabetes at the time of their hearing test (n=405). The analysis was conducted in six stages, one to answer each research questions posed.

Part 2 Analysis: Diabetes Signs and Symptoms

To answer question 1) Are selected signs and symptoms of diabetes, such as neuropathic, vascular and diabetes-specific symptoms associated with and predictive of high frequency hearing loss?, a factor analysis was conducted on the 35-item diabetes signs and symptoms questionnaire that was included in the home visit interview at the time the hearing test was conducted. Factors from this analysis were then entered into a logistic regression model.

Factor Analysis of Diabetes Signs and Symptoms

A previously performed exploratory factor analysis of diabetes signs and symptoms was carried out by the SALSA Principal Investigator. Factor analysis for validation was repeated for the present study on the subset of SALSA participants who had diabetes at the time of their hearing test (n=405). Several different factor solutions were evaluated, including those with between four and eight factors that were then rotated using Varimax orthogonal rotation with Kaiser normalization in SPSS v.15. A scree plot was created based on the initial Eigenvalues of the unrotated factors (see Figure 2).

Eight factors had Eigenvalues > 1. As can be seen in the Scree plot (Figure 2), the slope of the line continues to decline to or even beyond factor eight. However, when theoretical considerations were employed, both the six and the seven factor solutions were more interpretable and theoretically consistent than the four, five, or eight factor solutions. Varimax orthogonal rotation with Kaiser normalization was employed for both the six and seven factor solutions.

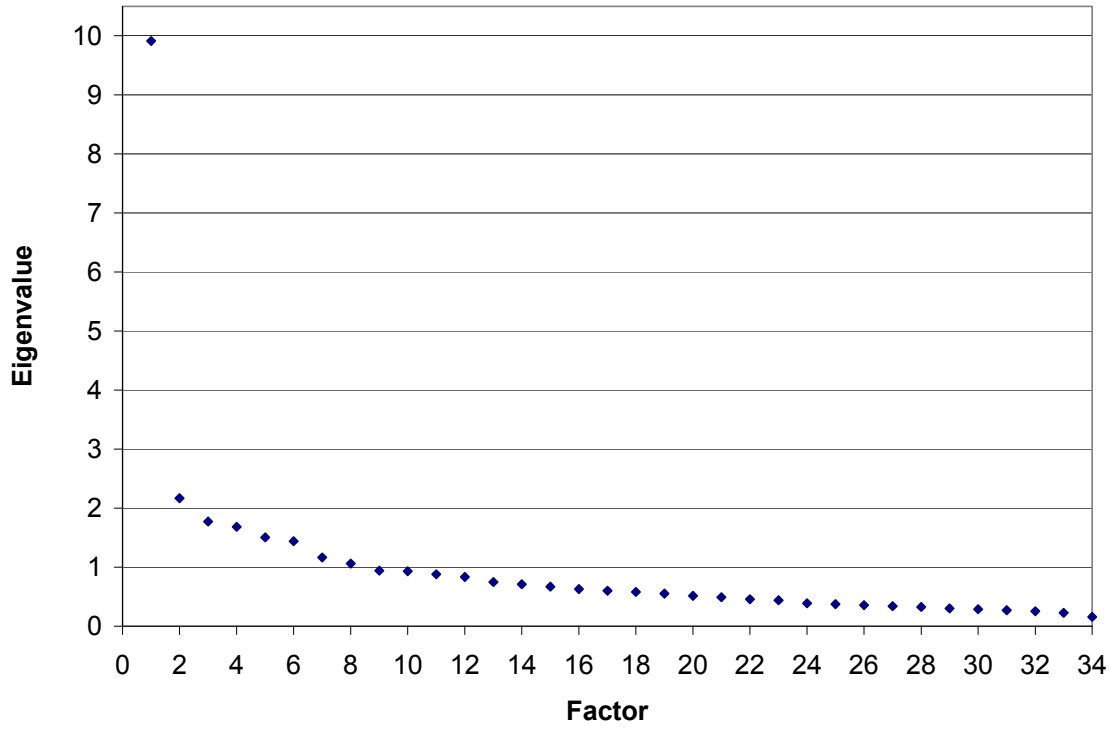

Figure 2: Diabetes Signs and Symptoms Unrotated Factors Scree Plot

The loadings of the six factor rotated component solution are presented in Table 12. Factor 1 (10 items) relates to lower extremity symptoms and peripheral neuropathy in both upper and lower extremities with Cronbach's α = .84. Factor 2 (5 items) relates to energy and fatigue with Cronbach's α = .83. Factor 3 (5 items) contains all symptoms of visual difficulty with Cronbach's α = .85. Factor 4 (5 items) contains items related to mood and concentration with Cronbach's α = .74. Factor 5 (4 items) has symptoms of cardiac and/or pulmonary origin with Cronbach's α = .71. Factor 6 (4 items) is consistent with hyperglycemia and contains the symptoms known as the "polys" with Cronbach's α = .69. These reliability coefficients are acceptable for the exploratory nature of this study

(Nunnally & Bernstein, 1994). Therefore, each of the factors was treated as a subscale in analysis.

Table 12

Factor Loadings from Diabetes Signs and Symptoms Factor Analysis

Item	Factor					
Factor 1: Extremity and neuropathic symptom loadings						
	1	2	3	4	5	6
Aching calves when walking	**.652**	.306	.134	.049	-.027	.094
Numbness (loss of sensation) in the feet	**.542**	.235	.087	.095	.148	.070
Numbness (loss of sensation) in hands	**.521**	.128	.153	.152	.164	.080
Tingling sensations in the limbs at night	**.514**	-.013	.154	.312	.155	.199
Burning pain in the calves at night	**.691**	.156	.080	.054	.044	.086
Shooting pains in the legs	**.661**	.188	.099	.145	.132	.150
Burning pain in the legs	**.710**	.167	.096	.070	.036	.176
Tingling/prickling sensations hands or fingers	**.533**	-.019	.173	.161	.167	.169
Odd feelings in legs/feet touching each other	**.348**	.213	.117	-.041	.291	-.056
Tingling or prickling sensations in legs or feet	**.562**	.034	.127	.355	.209	.171
Factor 2: Energy and fatigue						
	1	**2**	3	4	5	6
Lack of strength (energy)	.207	**.751**	.171	.099	.071	.079
An overall sense of fatigue	.232	**.760**	.130	.121	.160	.155
Sleepiness or drowsiness	.149	**.541**	.222	.227	.115	.180
Increasing fatigue during course of day	.219	**.723**	.186	.226	.113	.135
Fatigue in the morning when getting up	.118	**.734**	.060	.190	.149	.118

Factor Loadings from Diabetes Signs and Symptoms Factor Analysis (continued)

Factor 3: Visual difficulties						
	1	2	**3**	4	5	6
Persistently blurred vision (also with glasses on)	.194	.140	**.798**	.088	.087	.033
Deteriorating vision	.152	.152	**.836**	.065	.109	.040
Flashes or black spots in field of vision	.231	.065	**.473**	.169	.136	.163
Fluctuating clear and blurred vision	.114	.174	**.831**	.059	.064	.165
Sudden deterioration of vision	.128	.146	**.821**	.131	.109	.068
Factor 4: Mood and concentration						
	1	2	3	**4**	5	6
Difficulty concentrating	.183	.307	.153	**.365**	.078	.184
Moodiness	.122	.169	.084	**.795**	.057	.142
Irritability just before a meal	.166	,166	.065	**.650**	.103	-.057
Easily irritated or annoyed	.127	.161	.113	**.806**	.076	.054
Difficulty staying attentive	.204	.232	.141	**.446**	.144	.215
Factor 5: Cardiac and pulmonary symptoms						
	1	2	3	4	**5**	6
Shortness of breath at night	.222	.134	.117	.018	**.476**	.055
Palpitations or pains in chest or heart region	.072	.086	.094	.126	**.878**	.812
Pains in the chest or heart region	.105	.077	.104	.129	**.860**	.058
Shortness of breath during exercise	.198	.227	.086	.145	**.422**	.133
Factor 6: Hyperglycemic symptoms						
	1	2	3	4	5	**6**
Very thirsty	.137	.186	.071	.025	.040	**.812**
Dry mouth	.224	.157	.122	.147	.167	**.580**
Frequent urination	.193	.202	.187	.110	.036	**.444**
Drinking a lot (all sorts of beverages)	.155	.063	.045	.067	.077	**.826**

The seven factor rotated solution differed from the six factor solution mainly in its ability to discriminate between lower extremity symptoms that may be due to peripheral vascular disease (PVD) instead of or in addition to peripheral neuropathy. Specifically, the factors (and their loadings) that loaded onto a separate seventh factor were: aching calves when walking (.738), burning in the calves at night (.735), shooting pains in the legs (.635), and burning pain in the legs (.694). However, with the exception of aching calves when walking, the other symptoms could easily be due to lower extremity neuropathy rather than, or in addition to, PVD. Due to the ambiguity of the origin of these symptoms, the six factor rotation was used to develop subscales of signs and symptoms to be used in further analysis.

The six diabetes signs and symptoms factors identified from factor analysis had a number of moderate to strong positive correlations with each other and with duration of diabetes (results not reported). Only two of the factors, Factor 2 (energy and fatigue) and Factor 4 (Mood and concentration) correlated significantly with high frequency hearing loss. These weak correlations were negative and only in the better ear (See Table 13).

Table 13

Correlations (r_s) Between Diabetes Signs and Symptoms Factors, Diabetes Duration and Moderate-Severe (M-S) High Frequency (HF) Hearing Loss (HL)

Factors	1	2	3	4	5	6	Dur.
M-S HF HL worse ear	-.007	-.043	-.039	-.040	.030	-.051	-.051
M-S HF HL better ear	-.011	-.133**	-.065	-.102*	.036	-.090	-.079

*$p < .05$. ** $p < .01$.

Descriptive statistics for those participants who reported the presence of any of the signs and symptoms associated with the determined diabetes signs and symptoms factors is reported in Table 14. Neuropathic symptoms were reported the most frequently, followed by energy/fatigue and hyperglycemic symptoms. Neuropathic symptoms also were the highest reported in severity with the highest mean and standard deviation and greatest range. Cardiac/pulmonary symptoms were reported the least frequently with the lowest mean of symptom severity.

Table 14

Descriptive Statistics of Diabetes Signs and Symptoms Factors

Factor	n	%	Range	Mean	*SD*
Factor 1: Peripheral Neuropathy	233	57.5%	1-41	10.70	9.12
Factor 2: Energy and Fatigue	210	51.9%	1-24	8.01	5.53
Factor 3: Visual Difficulty	173	42.7%	1-24	7.74	5.59
Factor 4: Mood and Concentration	196	48.4%	1-25	6.53	4.61
Factor 5: Cardiac/pulmonary	111	27.4%	1-19	5.23	3.82
Factor 6: Hyperglycemic symptoms	209	51.6%	1-17	5.41	3.85

A multicollinearity analysis revealed shared variance for the six Factors relating to the hearing loss outcome ranging between the lowest of 27.7% for Factor 1 and highest of 53.4% for Factor 5. This level of shared variance was expected due to the nature of the questionnaire as all questions related to signs and symptoms associated with diabetes. According to Hosmer and Lemeshow (2000), when multicollinearity appears to be a problem, the standard errors in the logistic regression results should be examined for aberrantly large values that suggest the multicollinearity is significantly affecting results.

All diabetes signs and symptoms factors were entered into logistic regression models for the worse and better ears with moderate-severe high frequency hearing loss as the outcome. The standard errors were small, consistent with stable results not unduly affected by the collinearity found. Therefore, no variables in this logistic regression model were removed.

Only the logistic regression model with moderate-severe high frequency hearing loss in the better ear as the outcome was significant (See Table 15). Factors 2 (energy and fatigue) and 5 (cardiac/pulmonary) were significant predictors of moderate-severe high frequency hearing loss in the better ear. The model predicted 71.9% of the moderate-severe high frequency hearing loss cases correctly and explained approximately 4.4 to 6.3% of the variance in hearing loss (χ^2(*df*) = 18.073(6), *p* = .006). A logistic regression model of the diabetes signs and symptoms factors in the worse ear did not reach significance. In that model, Factor 5 (cardiac/pulmonary) had a *p* value of .082 (model results not shown).

Table 15

Logistic Regression Prediction Model of Diabetes Signs and Symptoms Factors for Moderate-Severe High Frequency Hearing Loss in the Better Ear

	B	S.E.	Wald	*df*	*Sig.*	Odds Ratio	95%CI
Factor 1	.025	.018	1.807	1	.179	1.025	.989 – 1.063
Factor 2	-.066	.026	6.272	1	.012*	.936	.889 –.986
Factor 3	.001	.025	.002	1	.966	1.001	.953 – 1.052
Factor 4	-.054	.030	3.162	1	.075	.948	.894 – 1.005
Factor 5	.105	.049	4.665	1	.031*	1.111	1.010 – 1.223
Factor 6	-.037	.035	1.122	1	.289	.964	.900 – 1.032
Constant	1.203	.158	58.124	1			

**p* < .05.

Factors representing energy and fatigue (Factor 2) and cardiac/pulmonary symptoms (Factor 5) were brought forward into the composite model of predictors of high frequency hearing loss.

Part 2 Analysis: Clinical Indicators

To answer the research question 2) Are selected clinical indicators (duration of diabetes, hypertension, metabolic syndrome, BMI, waist circumference, ototoxic drugs, smoking (pack years), and ETOH use (in years) associated with and predictive of high frequency hearing loss?, the selected clinical indicators were entered into separate logistic regression models for moderate-severe high frequency hearing loss in the better ear and in the worse ear.

Two of the clinical indicators, BMI and duration of diabetes were modeled as continuous variables. BMI for the subsample is relatively normally distributed without significant skewness or kurtosis. Duration of diabetes, however, is positively skewed with the skewness statistic greater than twice its standard error (1.446, SE .121). Kurtosis was also high at 2.186. Therefore, nonparametric correlations are evaluated for these variables. Pearson Product Moment Correlation of BMI with duration of diabetes broken into ordinal categories (by 5 year groupings) (r =.034, n.s.) was not different than the nonparametric correlation (r_s) so the nonparametric values are reported in Table 16.

Table 16

Correlations (r_s) of Clinical Indicators

	1	2	3	4	5	6	7	8
1. Diabetes duration	1.0	.144**	.063	.031	.029	.029	-.071	-.278**
2. Hypertension		1.0	.137**	.056	.057	.132**	-.144**	-.136**
3. Metabolic Syndrome			1.0	.381**	.584**	.070	-.017	-.212**
4. BMI				1.0	.629**	.110*	-.040	-.089
5. At risk Waist circumference					1.0	.136**	-.080	-.166**
6. Ototoxic drug use						1.0	.017	-.028
7. Current smoking							1.0	.239**
8. Alcohol								1.0

*$p < .05$. **$p < .01$.

Duration of diabetes was weakly but significantly positively correlated with hypertension and had a weak but negative correlation with alcohol intake. Hypertension was weakly but significantly positively correlated with metabolic syndrome and ototoxic drug use and weakly negatively associated with current smoking and alcohol use. Metabolic syndrome at SALSA study baseline was moderately positively correlated with BMI and strongly correlated with having at risk waist circumference. Metabolic syndrome was weakly negatively correlated with alcohol intake. BMI had a strong positive correlation with waist circumference, and a weak correlation with ototoxic drug use. In addition to the correlations described above, at risk waist circumference had a weak positive correlation with ototoxic drug use and a weak negative correlation with alcohol use. Smoking was weakly to moderately correlated with alcohol use.

Ototoxic drug use was characterized in two ways in analysis: any ototoxic drug use at time of the hearing test and loop diuretic use at time of the hearing test. Any ototoxic drug use was not significant in the models that included other clinical indicators (results not reported); loop diuretic use was significant, so models including that characterization are reported.

Analysis for multicollinearity revealed significant collinearity present between the clinical indicators. Between 42.1% and 86.1% of the variance of any one variable was shared with the others (See Table 17).

Table 17

Multicollinearity and Shared Variance between Clinical Indicators

	Collinearity Statistic Tolerance	% Shared Variance for M-S HF HL outcome
Duration of diabetes	.898	80.6%
Hypertension	.914	83.5%
Metabolic Syndrome	.880	77.4%
BMI	.649	42.1%
Waist Circumference	.625	39.1%
Loop diuretics	.869	75.5%
Smoking	.928	86.1%
Alcohol intake	.856	73.3%

Simple logistic regression models for each Clinical Indicator were fit for moderate-severe high frequency hearing loss in the worse ear and in the better ear. Waist circumference risk models were significant in both the worse ear ($\chi^2(df) = 4.845(1)$, $p = .028$) and the better ear ($\chi^2(df) = 10.650(1)$, $p = .01$).Loop

diuretic use models were also significant in both the worse ear (χ^2(*df*) = 4.253(1), *p* = .039) and the better ear (χ^2(*df*) = 4..168(1), *p* = .041) while alcohol use was only significant in the better ear (χ^2(*df*) = 6.768(1), *p* = .009). Subsequently, logistic regression models were developed with these three clinical indicators as predictors and moderate-severe high frequency hearing loss as the outcome variable. Models were run for both the worse and the better hearing ears. In the subsequent logistic Regression models, the optimally weighted combination of these three clinical indicators were significant in both the worse ear explaining approximately 2.7 to 4.5% of the variance in moderate-severe hearing loss with 82% of cases correctly classified; and in the better ear explaining approximately 5.4 to 7.8% of the variance in moderate-severe hearing loss with 71.2% of cases correctly classified (See Table 18).

Of the clinical indicators evaluated in the group clinical indicators model, at risk waist circumference and loop diuretic use remained significant predictors of moderate-severe high frequency hearing loss in the worse ear and in the better

Table 18

Logistic Regression Prediction Model of Clinical Indicators for Moderate-Severe High Frequency Hearing Loss

	B	S.E.	Wald	*df*	Sig.	Odds Ratio	95%CI
Worse Ear			Model Fit: $\chi^2(df) = 10.815(3)$, $p = .013$*				
Waist Circumference	-.600	.298	4.056	1	.044*	.549	.306 – .984
Loop Diuretics	1.022	.497	4.230	1	.040*	2.780	1.049 – 7..365
Alcohol Intake	.121	.088	1.898	1	.168	1.129	.950 – 1.342
Constant	1.630	.291	31.332	1			
Better Ear			Model Fit: $\chi^2(df) = 21.742(3)$, $p < .0005$***				
Waist Circumference	-.736	.254	8.417	1	.004*	.004	.292 – .788
Loop Diuretics	.907	.381	5.673	1	.017*	.017	1.174 – 5.229
Alcohol Intake	.198	.076	6.683	1	.010*	.010	1.049 – 1.416
Constant	.999	.246	16.546	1			

* $p < .05$. *** $p < .0005$.

Of the clinical indicators, waist circumference, loop diuretic use, and alcohol intake was brought forward into the composite model of predictors of high frequency hearing loss.

Part 2 Analysis: Indicators of Microangiopathy

To answer research question 3) Are clinical indicators of microangiopathy (fasting glucose, HbA1c, Semmes-Weinstein Monofilament Test and/or Vibration

Threshold testing, glomerular filtration rate, and diabetic retinopathy) associated with and predictive of high frequency hearing loss?, selected clinical indicators that represent proxies for microangiopathy were evaluated and entered in logistic regression models.

GFR and duration of diabetes. Duration of diabetes was categorized into ordinal categories (<5 years, 5<10, 10<15, 15<20, >20). GFR values were categorized into 3 ordinal categories (>90, 60<90, <60). Duration of diabetes diagnosis and GFR were significantly associated in the subset of SALSA participants who had diabetes at the time of their hearing test ($\chi^2(8, n=391) = 22.5$, $p = .004$). As duration of diabetes increased, GFR was more likely to be lower.

Semmes-Weinstein Monofiliment results. Results of the Semmes-Weinstein Monofilament (SWM) test done on multiple sites on both feet (described in the methods section) were collapsed into one variable to reflect the number of insensate sites present on the feet. A SWM tested site was computed as insensate if both trials of the SWM at that site were not felt by the participant. The total number of sites meeting this criteria were then summed (See Table 19).

Table 19

Semmes-Weinstein Monofiliment Testing Results

Full cohort (N=990)			Diabetes cohort (n=405)		
Insensate Sites	Frequency	%	Insensate Sites	Frequency	%
0	812	82.0	0	332	82.0
1	30	3.0	1	11	2.7
2	22	2.2	2	10	2.5
3	9	.9	3	3	.7
4	14	1.4	4	5	1.2
5	13	1.3	5	3	.7
6	8	.8	6	3	.7
7	3	.3	7	0	0
8	8	.8	8	2	.5
9	4	.4	9	2	.5
10	16	1.6	10	6	1.5
Missing	51	5.2	Missing	28	6.9

There was no significant difference in the prevalence of insensate sites via SWM testing for those with diabetes compared to those without (χ^2(*df*) = 1.359(1), n=939, n.s.). For the diabetes sub-cohort, duration of diabetes in 5 year groupings (<5, 5<10, 10<15, 15<20, $\geq$20) did not predict having insensate sites via SWM testing (χ^2(*df*) = 5.413(4), n=377, n.s.).

Vibration Threshold Testing. Vibration Threshold (VTE) testing results from each foot were collapsed into a single variable indicating reduced or absent vibration sense in one or both feet (see Table 20). VTE results did differ by

diabetes status. Those with diabetes were more likely to have reduced or absent vibration sense in either or both feet than those without diabetes ($\chi^2(df)$ = 7.009(1), n=924, p = .008).

Table 20

Vibration Threshold Frequencies

	No diabetes	Diabetes	Totals
VTE intact	279 30.2%	152 16.5%	431 60.2%
VTE reduced or absent	277 30%	216 23.4%	493 39.8%
Totals	556 46.6%	368 53.4%	924 100%

Peripheral neuropathy was further analyzed after collapsing the SWM and VTE results into a single variable. The new peripheral neuropathy variable discriminated between those with or without diabetes. If diabetes was present, insensate sites and/or abnormal VTE were more likely to occur ($\chi^2(df)$ = 4.379(1), n=881, p = .036).

Nonparametric correlations (r_s) between the microangiopathic indicators were evaluated (see Table 21). Fasting blood glucose was strongly and significantly correlated with HbA1c and weakly but significantly correlated with retinopathy. HbA1c was a little more strongly correlated with retinopathy than was fasting blood glucose and was weakly but positively correlated with both peripheral neuropathy and GFR. Peripheral neuropathy was mildly but negatively

correlated with GFR and weakly positively correlated with retinopathy. GFR was the only microangiopathic indicator that correlated with hearing loss in either ear with weak negative correlations. This indicates that as GFR is reduced (indicative of worse kidney function), hearing loss is more likely.

Table 21

Correlations between Microangiopathic Indicators (r_s)

	1	2	3	4	5	6	7
1. FBG	1.0	.598**	.035	.051	.182**	.043	.022
2. HbA1c		1.0	.072*	.074*	.242**	.019	.016
3. Peripheral Neuropathy			1.0	-.070*	.066*	-.039	-.035
4. GFR				1.0	-.052	-.141**	-.134**
5. Diabetic Retinopathy					1.0	.025	.002
6. M-S HF HL worse ear						1.0	.758**
7. M-S HF HL better ear							1.0

Logistic regression models for worse and better ears moderate-severe high frequency hearing loss were developed with all microangiopathic indicators (glucose, HbA1c, peripheral neuropathy, GFR, and diabetic retinopathy) as predictors. The model for the worse ear was not significant (χ^2(*df*) = 7.697(5), n=314, *p* = .174). The model for the better ear also was also not significant (χ^2(*df*) = 9.925(5), n=314, *p* = .077). GFR approached significance (*p* = .059) for the better ear only (see Table 22) and is below the .10 significance level chosen to select predictors to move forward to the composite model.

Table 22

Logistic Regression Prediction Model of Microangiopathic Indicators for Moderate-Severe High Frequency Hearing Loss

Moderate-Severe High Frequency Hearing Loss Worse Ear							
Model Fit	$\chi^2(df)$ = 7.697(5), n=314, p = .174						
	B	S.E.	Wald	*df*	Sig.	Odds Ratio	95%CI
Fasting Glucose	.004	.004	1.076	1	.300	1.004	.997 – 1.011
HbA1c	-.198	.122	2.618	1	.106	.821	.646 – 1.043
Periph. Neuropathy	-.387	.329	1.385	1	.239	.679	.357 – 1.293
GFR	-.009	.006	2.375	1	.123	.991	.980 – 1.002
Retinopathy	-.211	.404	.273	1	.601	.810	.367 – 1.788
Constant	3.553	.854	17.324	1			
Moderate-Severe High Frequency Hearing Loss Better Ear							
Model Fit	$\chi^2(df)$ = 9.925(5), n=314, p = .077						
	B	S.E.	Wald	*df*	Sig.	Odds Ratio	95%CI
Fasting Glucose	-.003	.003	1.364	1	.243	.997	.991 – 1.002
HbA1c	.034	.101	.111	1	.739	1.034	.848 – 1.262
Periph. Neuropathy	-.417	.273	2.339	1	.126	.659	.386 – 1.124
GFR	-.010	.005	3.554	1	.059	.990	.980 – 1.000
Retinopathy	-.539	.337	2.553		.110	.583	.301 – 1.130
Constant	2.332	.715	10.652				

When logistic regression models were run evaluating any high frequency hearing loss (>25 dB), a significant model was found in the better ear (χ^2(*df*) = 11.241(5), n=313, *p* = .047) (see Table 23). This model explained between 3.5 and 13.4% of the variance in hearing loss in the better ear. None of the individual predictors reached significance; however, GFR again approached significance with *p* = .054. This model correctly classified 96.5% of the participants on hearing loss in the better ear, more than any previous models developed. The worse ear model failed to converge to a solution as there were not sufficient numbers of individuals with no hearing loss in this ear to serve as a comparison group for the analysis (results not shown). GFR was brought forward into the final composite regression model predicting high frequency hearing loss.

Table 23

Logistic Regression Prediction Model of Microangiopathic Indicators for any High Frequency Hearing Loss in the Better Ear (>25 dB)

	B	S.E.	Wald	*df*	Sig.	Odds Ratio	95%CI
Model Fit	χ^2(*df*) = 11.241(5), n=313, *p* = .047						
Fasting Glucose	-.004	.006	.550	1	.458	.996	.985 – 1.007
HbA1c	-.273	.218	1.566	1	.211	.761	.496 – 1.167
Periph. Neuropathy	-.252	.712	.125	1	.723	.777	.193 – 3.138
GFR	-.020	.010	3.701	1	.054	.980	.961 – 1.000
Retinopathy	-.651	.736	.782	1	.376	.521	.123 – 2.208
Constant	8.277	1.741	22.600	1			

Part 2 Analysis: Macroangiopathic Indicators

To answer research question 4) Are clinical indicators of macroangiopathy (coronary artery disease, peripheral vascular disease, cerebrovascular disease, blood lipids) associated with and predictive of high frequency hearing loss?, logistic regression models using macroangiopathic indicators as predictors of moderate-severe high frequency hearing loss in the worse and the better ears were developed.

Nonparametric correlations (r_s) of macroangiopathic indicators and moderate-severe high frequency hearing loss in both the worse and better ear were determined (see Table 24). History of coronary artery disease (CAD) was weakly positively correlated with cerebrovascular disease (CVD) and weakly to moderately correlated with peripheral vascular disease (PVD). CAD was also weakly positively correlated with Total cholesterol/HDL ratio but not significantly correlated with individual blood lipids. CVD was the only macroangiopathic indicator significantly correlated with moderate-severe high frequency hearing loss, in the better ear only. The correlation was weak and positive. Total cholesterol was highly positively correlated with LDL cholesterol and moderately to strongly correlated with HDL/cholesterol ratio and triglycerides. LDL cholesterol, in addition to correlations mentioned above, was strongly positively correlated with Total cholesterol/HDL ratio and weakly positively correlated with triglycerides. Total cholesterol/HDL ratio was also strongly positively correlated with triglycerides.

History of coronary artery disease (CAD), cerebrovascular disease (CVD), peripheral vascular disease (PVD), and blood lipid variables at the time of the hearing test (total cholesterol, LDL, Total cholesterol/HDL ratio) were entered into the logistic regression model. The model was not significant in predicting moderate-severe high frequency hearing loss in either ear (Worse ear: $\chi^2(df)$ = 7.441(7), n=377, p =.384; Better ear: $\chi^2(df)$ = 6.706(7), n=377, p = .460) (see Table 25).

To verify that multicollinearity between macroangiopathic indicators was the reason for the non-significance of the model, multicollinearity of the macroangiopathic indicators was assessed. CAD, PVD, and total cholesterol shared between 83-86% of their variance with all other macroangiopathic indicators in predicting moderate-severe high frequency hearing loss while LDL, Total cholesterol/HDL ratio and triglycerides had almost no shared variance. However, when simple binary logistic regression models for each macroangiopathic indicator with moderate-severe high frequency hearing loss in both the worse and better hearing ears were developed, none were significant predictors (results not shown). Multicollinearity was not the cause of the non-significance of macroangiopathic indicators in predicting moderate-severe high frequency hearing loss. Therefore, none of the macroangiopathic indicators was brought forward into the final composite model of predictors for high frequency hearing loss.

Table 24

Correlations (r_s) between Macroangiopathic Indicators and Moderate-Severe High Frequency Hearing Loss

	1	2	3	4†	5†	6†	7†	8	9
1. CAD	1.0	.152**	.248**	.005	.024	.135**	.064	.025	.001
2. CVD		1.0	.084	.002	-.007	.022	.032	.064	.117*
3. PVD			1.0	.019	.008	.002	.018	.002	.047
4. TC †				1.0	.854**	.471**	.442**	-.076	-.033
5. LDL -C†					1.0	.524**	.144**	-.047	-.029
6. TC/HDL†						1.0	.613**	-.018	.000
7. TG†							1.0	-.042	-.002
8. M-S HF HL worse ear								1.0	.668**
9. M-S HF HL better ear									1.0

TC=Total Cholesterol; TG=Triglycerides. †n=377 for these variables

Table 25

Logistic Regression Prediction Model of Macroangiopathic Indicators for High Frequency Hearing Loss

n=377							95% C.I for Odds Ratio	
	B	S.E.	Wald	*df*	*Sig.*	Odds Ratio	Lower	Upper
High Frequency Worse Ear				Model Fit : χ^2(*df*) = 7.441(7), n=377, *p* =.384				
CAD	-.153	.201	.256	1	.613	.859.	476	1.549
CVD	.234	.380	.379	1	.538	1.263	.600	2.659
PVD	.428	.300	2.039	1	.153	1.534	.853	2.759
TC	-.012	.015	.609	1	.435	.988	.959	1.018
LDL	.006	.022	.088	1	.766	1.006	.965	1.050
TC/HDL	.306	.404	.576	1	.448	1.358	.616	2.995
TG	.000	.004	.006	1	.938	1.000	.992	1.007
Constant	1.917	1.422	1.818	1				
High Frequency Better Ear				Model Fit : χ^2(*df*) = 6.706(7), n=377, *p* = .460				
CAD	.069	.255	.074	1	.785	1.072	.651	1.766
CVD	-.004	.305	.000	1	.989	.996	.548	1.811
PVD	.136	.245	.307	1	.580	1.146	.708	1.854
TC	-.015	.014	1.156	1	.282	.985	.959	1.012
LDL	.015	.019	.620	1	.431	1.015	.978	1.055
TC/HDL	.186	.353	.279	1	.598	1.205	.603	2.405
TG	.001	.003	.139	1	.710	1.001	.995	1.008
Constant	1.165	1.235	.889	1				

Part 2 Analysis: Work-related Exposures and High Frequency Hearing Loss

To answer research question 5) Are work-related exposures associated with and predictive of high frequency hearing loss?, a logistic regression model was fit to include selected work-related exposures. Nonparametric correlations (r_s) of work-related exposures with each other and with moderate-severe high frequency hearing loss in both the worse and better ears were determined (See Table 26). Exposures to pesticides, lead, cadmium, other heavy metals, solvents, dusts, fumes, high levels of heat and noise were significantly moderately to highly correlated with each other.

Several work-related exposures correlated significantly with moderate-severe high frequency hearing loss. Pesticides, solvents, dusts, fumes, loud noise, and heat exposure were all positively correlated in the better ear while only pesticides and fumes were correlated in the worse ear.

Of the 140 farm/fishing/forestry workers in the full study cohort for which there is exposure data, 103 (73.6%) of them reported both noise and pesticides exposure. In the diabetes sub-cohort, of the 64 farm/fishing/forestry workers for which there is exposure data, 45 (76.3%) report both exposures. Some of these workers within the diabetes sub-cohort exposed to both noise and pesticides also reported other known and suspected ototoxic exposures: loop diuretics (8), solvents (12), lead and other heavy metals (4), and high levels of heat (46).

To further evaluate the potential impact of the significant correlations between the work-related exposures, a multicollinearity assessment was conducted with all the work-related exposures with moderate-severe high

frequency hearing loss as the outcome. All work-related exposures were determined to have significant multicollinearity for the outcome of moderate-severe high frequency hearing loss in both the better and worse hearing ears (see Table 27). Between 13% and 42% of variance was shared between the exposures. Pesticides, solvents, and cadmium had the most amount of shared variance with the other exposures while noise and high levels of heat exposures had the least amount of shared variance.

Table 26

Correlations of Work-Related Exposures and Moderate-Severe High Frequency Hearing Loss

	1	2	3	4	5	6	7	8	9	10	11
1. Pesticides	1.0 n=392	.226** n=385	.169** n=385	.237** n=387	.135** n=387	.512** n=391	.526** n=391	.452** n=391	.500** n=391	.143** n=391	.144** n=391
2. Lead		1.0 n=386	.564** n=382	.424** n=384	.625** n=385	.342** n=386	.347** n=386	.301** n=386	.257** n=386	.096 n=386	.079 n=386
3. Cadmium			1.0 n=386	.362** n=384	.533** n=385	.254** n=386	.269** n=386	.214** n=386	.208** n=386	.025 n=386	.022 n=386
4. Solvents				1.0 n=388	.503** n=387	.466** n=388	.454** n=388	.392** n=388	.366** n=388	.115* n=388	.064 n=388
5. Other HM					1.0 n=388	.318** n=388	.322** n=388	.301** n=388	.251** n=388	.092 n=388	.081 n=388
6. Dusts						1.0 n=392	.665** n=392	.622** n=392	.646** n=392	.168** n=392	.082 n=392
7. Fumes							1.0 n=392	.639** n=392	.637** n=392	.164** n=392	.121** n=392
8. Loud Noise								1.0 n=392	.745** n=392	.123** n=392	.091 n=392
9. Heat									1.0 n=392	.123** n=392	.097 n=392
10. HF HL Better ear										1.0 n=405	.738** n=405
11. HF HL Worse ear											1.0 n=405

*$p < .05$. **$p < .01$. ***$p < .0005$.

Table 27

Multicollinearity and Shared Variance between Work-Related Exposures

	Collinearity Statistic Tolerance	% Shared Variance for M-S HF HL outcome
Pesticides	.646	42%
Lead	.509	26%
Cadmium	.611	37%
Solvents	.613	38%
Other Heavy Metals	.505	26%
Dusts	.424	18%
Fumes	.423	18%
Loud Noise	.371	14%
High Levels of Heat	.359	13%

Due to the significant multicollinearity between the work-related exposures, simple binary logistic regression models for each work-related exposure on hearing loss in both the worse or better ear were developed. Pesticides exposure was significant in both the worse and better ear. Lead, Solvents, Dusts, Fumes, Noise, and High Levels of Heat exposure models were significant in only the better ear (see Table 28).

Table 28

Logistic Regression Model Fit of Work-Related Exposures for Hearing Loss

	χ^2	*df*	*Sig.*	-2 Log likelihood	% Variance	Correctly Classified
Pesticide Exposure						
worse ear	9.351	1	.002*	355.060	2.4-3.9%	82.4%
better ear	8.606	1	.003*	456.062	2.2-3.1	71.9%
Lead Exposure						
worse ear	2.786	1	.095	359.670	.7-1.2%	82.1%
better ear	3.910	1	.048*	457.429	1-1.4%	71.5%
Cadmium Exposure						
worse ear	.206	1	.650	362.250	.1%	82.1%
better ear	.248	1	.619	461.092	.1%	71.5%
Solvent Exposure						
worse ear	1.672	1	.196	361.569	.4-.7%	82.2%
better ear	5.478	1	.019*	457.200	1.4-2.0%	71.6%
Other Heavy Metals						
worse ear	2.897	1	.089	360.344	.7-1.2%	82.2%
better ear	3.592	1	.058	459.085	.9-1.3%	71.6%
Dusts Exposure						
worse ear	2.637	1	.104	362.162	.7-1.1%	82.4%
better ear	11.180	1	.001**	454.148	2.8-4%	71.9%
Fumes Exposure						
worse ear	5.982	1	.014*	358.817	1.5-2.5%	82.4%
better ear	10.988	1	.001**	454.340	2.8-4%	71.9%
Noise Exposure						
worse ear	3.206	1	.073	361.593	.8-1.3%	82.4%
better ear	5.885	1	.015*	459.443	1.5-2.1%	71.9%
High Levels of Heat Exposure						
worse ear	3.720	1	.054	361.079	.9-1.6%	82.4%
better ear	5.923	1	.015*	459.405	1.5-2.2%	71.9%

*$p < .05$. **$p < .01$.

Based on the significance of the correlations and multicollinearity that confounds the relationships, different models utilizing exposures that were significant in simple binary logistic regression were evaluated to determine the best fit (results not reported). The best fitting model for predicting moderate-severe high frequency hearing loss from work-related exposures included pesticides, solvents, and noise (Worse ear: $\chi^2(df) = 9.540(3)$, n=387. $p = .023$; Better ear: $\chi^2(df) = 11.677(3)$, n=387, $p = .009$) (see Table 29). In this refined work-related exposure model, only pesticides exposure is significant in the worse hearing ear and none of the variables are significant in the better hearing ear the model's overall significance. Based on a 10% change in beta as the determinant of a confounder, noise confounds the relationship between pesticide exposure and high frequency hearing loss. Therefore, both of these work-related exposures were brought forward into the final composite hearing loss model.

Table 29

Logistic Regression Prediction Model of Work-related Exposures for Moderate-Severe High Frequency Hearing Loss

n=387							95% C.I	
	B	S.E.	Wald	*df*	*Sig.*	Odds Ratio	Lower	Upper
High Frequency Worse Ear			Model Fit : χ^2(*df*) = 9.540(3), n=387. *p* = .023*					
Pesticides	1.039	.448	5.377	1	.020*	2.827	1.175	6.805
Solvents	.200	.376	.282	1	.595	1.221	.584	2.553
Noise	.073	.306	.057	1	.812	1.076	.590	1.959
Constant	1.272	.186	46.575	1				
High-Frequency Better Ear			Model Fit : χ^2(*df*) = 11.677(3), n=387, *p* = .009**					
Pesticides	.653	.340	3.688	1	.055	1.922	.987	3.745
Solvents	.464	.322	2.079	1	.149	1.591	.846	2.989
Noise	.153	.265	.335	1	.563	1.165	.694	1.957
Constant	.620	.161	14.746	1				

*$p < .05$. **$p < .01$.

An interesting finding not related to the research questions under study was discovered during the course of this analysis when selected exposures were entered into a logistic regression model for the SALSA participants who did not have diabetes (n-585). Logistic regression models with pesticides and noise exposure were significant in the worse ear (χ^2(*df*) = 9.069(2), n=575. *p* = .011) with noise exposure OR 1.746, significant at *p* = .005 and pesticides exposure

not significant. The model for the better ear was also significant (χ^2(*df*) = 7.608(2), n=575. *p* = .022) with noise exposure OR 1.873, significant at *p* = .009 and pesticides exposure not a significant predictor of hearing loss for those without diabetes. This finding in light of the results of pesticides exposure for those with diabetes suggests an interaction between diabetes and pesticides exposure.

To further explore possible interaction effects between diabetes and pesticides exposure, logistic regression models for the full cohort with exposure data available (n=966) for worse ear and then better ear were developed with diabetes at the time of test, pesticides exposure, noise exposure and two interaction terms (diabetes by noise and diabetes by pesticides) in the models. Significant models were found in both the worse ear and the better ear (See Table 30). For the entire cohort, noise is a significant predictor of hearing loss. The negative coefficient for the diabetes by noise interaction indicates that this effect is mostly seen in those without diabetes, although it falls shy of statistical significance. For the full cohort, pesticides is not a predictor for hearing loss but the significant diabetes by pesticides interaction in the worse ear indicates that the effect of pesticides on hearing loss depends on whether or not someone has diabetes. With the interaction terms in the model, diabetes no longer reaches significance on its own.

In order to determine if a more parsimonious model fit the data better, a second set of interaction logistic regression models were developed with the diabetes by noise interaction term removed from the analysis. This model was

not a significantly different fit to the data in the worse ear (χ^2(*df*) = 3.643(1), *p* = .534) or the better ear (χ^2(*df*) = 1.659(1), *p* = .759). The model including the diabetes by noise interaction was retained. To determine if there was an additional interaction between pesticides and noise exposure, a pesticides by noise exposure interaction term was added to the models both with and without other interaction terms included and was not found to be a significant predictor of high frequency hearing loss in any model.

Table 30

Logistic Regression Prediction Model of Interaction Effects Between Diabetes and Work-Related Exposures for Hearing Loss

n=966						Odds	95% C.I for Odds Ratio	
	B	S.E.	Wald	*df*	*Sig.*	Ratio	Lower	Upper
High Frequency Worse Ear					Model Fit : $\chi^2(df) = 28.7(5)$, $p < .0005$***			
Diabetes	.434	.228	3.614	1	.057	1.544	.987	2.416
Noise	.864	.240	12.991	1	<.0005***	2.372	1.483	3.795
DMxNoise	-.713	.374	3.643	1	.056	.490	.236	1.019
Pesticides	-.396	.292	1.834	1	.176	.673	.379	1.194
DM x Pesticides	1.455	.534	7.417	1	.006*	4.283	1.503	12.203
Constant	.847	.133	40.537	1				
High Frequency Better Ear					Model Fit : $\chi^2(df) = 29.2(5)$, $p < .0005$***			
Diabetes	.331	.203	2.666	1	.103	1.392	.936	2.071
Noise	.723	.205	12.413	1	<.0005***	2.061	1.378	3.082
DMxNoise	-.416	.323	1.661	1	.198	.660	.350	1.242
Pesticides	-.107	.255	.176	1	.675	.899	.545	1.481
DM x Pesticides	.794	.424	3.519	1	.061	2.213	.965	5.076
Constant	.308	.123	6.245	1				

*$p < .05$. *** $p < .0005$.

The discrepancy of different exposures predicting hearing loss for those with diabetes versus those without led to an examination of the exposure history to verify that this result was not due to disparate exposures between the two

groups. There was no significant difference in pesticides exposure between those with or without diabetes (χ^2(*df*) = .316(1), n=966, n.s.). There was also no significant difference in noise exposure between the two groups (χ^2(*df*) = .602(1), n=989, n.s.). Differences in exposures do not explain this discrepancy in findings.

Part 2 Analysis: Final Composite Model Results

To answer research question 6) Of the variables found to be predictive of high frequency hearing loss in individual model analysis conducted in Part 2 analysis questions 1-5, what is the relative contribution of these variables in predicting high frequency hearing loss in those with type 2 diabetes?, composite logistic regression models for each ear were developed. Variables from each grouping of variables (demographics, diabetes symptom factors, clinical indicators, microangiopathic indicators, macroangiopathic indicators, and work-related exposures) that reached a cut-off level of *p* = .10 significance or better in their logistic regression group model were brought forward to the final composite logistic regression model. The specific variables that made this cut-off for inclusion (by group) were:

Demographics: age and gender

Diabetes Symptom Factors: Energy/Fatigue (Factor 2) and Cardiac/Pulmonary (Factor 5)

Clinical indicators: waist circumference, loop diuretics, ETOH use

Microangiopathic Indicators: GFR

Macroangiopathic Indicators: none

Work-Related Exposures: pesticides and noise

The final composite logistic regression model was significant in both ears (See Table 31). Age and gender remain significant predictors of hearing loss in both ears so remain in the final composite model as adjustment. All the other Odds Ratios within the model are adjusted for all other variables in the model.

Results in the better and the worse ears are not the same (See Tables 33 and 34). Diabetes Symptom Factor 2 (energy/fatigue) and Factor 5 (cardiac/pulmonary) are significant predictors of hearing loss in the better ear but not in the worse ear. Similarly, pesticide exposure is a significant predictor of hearing loss in the worse ear but not the better ear. Noise exposure was not a significant predictor of hearing loss in either ear but is left in the model due to the confounding effect it has on pesticide exposure. At risk waist circumference, loop diuretic use, mean alcohol intake and GFR did not reach significant in either ear in the composite model.

Table 31

Logistic Regression Composite Model Fit of Predictors for Hearing Loss in Diabetes

n=368	χ^2	*df*	*Sig.*	-2 Log likelihood	% Variance	Correctly Classified
Worse ear	56.830	10	<.0005***	292.410	14.3-23.3	80.4%
Better ear	79.561	10	<.0005***	362.326	19.4-27.8	75.3%

****p* < .0005.

Table 32

Logistic Regression Composite Model of Predictors of Moderate-Severe High Frequency Hearing Loss, Worse Ear

n=368							95% C.I for Odds Ratio	
	B	S.E.	Wald	*df*	*Sig.*	Odds Ratio	Lower	Upper
	High Frequency Worse Ear				Model Fit: $\chi^2(df) = 56.830(10)$, $p < .0005$***			
Age	.162	.034	23.201	1	<.0005***	1.175	1.101	1.255
Gender	.819	.386	4.505	1	.034*	2.268	1.065	4.831
Factor 2	-.020	.028	.503	1	.478	.980	.927	1.036
Factor 5	.068	.061	1.246	1	.264	1.070	.950	1.205
Waist @ risk	-.230	.353	.426	1	.514	.794	.398	1.586
Loop diuretics	.596	.544	1.201	1	.273	1.814	.625	5.267
Mean Alcohol	.053	.104	.261	1	.610	1.054	.861	1.292
GFR	-.005	.007	.553	1	.457	.995	.982	1.008
Pesticides	1.177	.502	5.502	1	.019*	3.244	1.213	8.670
Noise	-.196	.333	.346	1	.556	.822	.428	1.580
Constant	-10.340	2.622	15.555	1				

*$p < .05$. *** $p < .0005$.

Table 33

Logistic Regression Composite Model of Predictors of Moderate-Severe High Frequency Hearing Loss, Better Ear

n=368						Odds	95% C.I for Odds Ratio	
	B	S.E.	Wald	*df*	*Sig.*	Ratio	Lower	Upper
	High Frequency Better Ear				Model Fit: $\chi^2(df) = 79.561(10)$, $p < .0005$***			
Age	.143	.027	27.173	1	<.0005***	1.154	1.093	1.217
Gender	1.173	.339	11.981	1	.001**	3.232	1.663	6.279
Factor 2	-.057	.025	5.182	1	.023*	.945	.900	.992
Factor 5	.110	.051	4.603	1	.032*	1.116	1.010	1.234
Waist @ risk	-.190	.305	.389	1	.533	.827	.455	1.503
Loop diuretics	.473	.431	1.201	1	.273	1.604	.689	3.736
Mean Alcohol	.102	.091	1.248	1	.264	1.107	.926	1.324
GFR	-.003	.006	.244	1	.621	.997	.986	1.009
Pesticides	.608	.384	2.510	1	.113	1.836	.866	3.894
Noise	-.096	.297	.104	1	.747	.909	.508	1.626
Constant	-9.917	2.201	20.302	1				

*$p < .05$. **$p < .01$. ***$p < .0005$.

Summary of Part 2 Analysis Findings

A six factor structure of the diabetes signs and symptoms questionnaire resulted from factor analysis. Two of these factors, energy/fatigue and cardiac/pulmonary symptoms were significant in their group model and remained significant in the better ear in the final composite model. The clinical indicators that were significant in the group model, at risk waist circumference, loop diuretics, and alcohol intake, did not remain significant in the final composite model. GFR, the only microangiopathic indicator approaching significance in its group model, did not reach significance in the final composite model. No macroangiopathic indicators reached significance in their group model and were, therefore, not included in the final composite model. Pesticides exposure was significant in its group model and was confounded by noise exposure. Pesticides exposure remained significant in the worse ear final composite model.

For individuals with diabetes in this sample, age and gender were significant predictors of moderate-severe hearing loss in both ears while energy/fatigue and cardiac/pulmonary symptom factors were significant predictors only in the better ear with pesticides exposure a predictor in the worse ear. Subsequent analysis of the full cohort revealed the presence of an interaction between diabetes and pesticides. The effect of pesticides on hearing loss depended on whether or not a participant had diabetes.

Chapter 5: Discussion

Hearing Loss and Diabetes in a Sample (N=990) of Older Mexican Americans

Prevalence of Hearing Loss in Older Mexican Americans

Prevalence of low-mid frequency hearing loss did not differ for those with diabetes compared to those without diabetes in this study. This finding is consistent with the published literature in which diabetes has not been found to be a predictor of low-mid frequency hearing loss in an older cohort (Bainbridge et al., 2008). The lower prevalence of hearing loss at these frequencies in both those with or without diabetes compared to the prevalence at high frequencies suggests that low-mid frequencies are less susceptible to damage from any cause than are the higher frequencies (Sataloff & Sataloff, 2005c).

The prevalence of high frequency hearing loss among those with diabetes in this sample was only slightly but significantly higher than in those without diabetes in the worse hearing ear. This may be due to the small effect size that diabetes exerts on hearing loss. This small effect size is probably responsible for the conflicting results of many previous studies that have been conducted on hearing loss and diabetes cited by Fowler and Jones (1999). Bainbridge et al. (2008) had a much larger sample than other studies and therefore had more power to detect the effect of diabetes on hearing. The current study partially confirms the Bainbridge study with a smaller sample size as the findings in the worse ear are consistent with their results.

Hearing loss prevalence is known to vary by ethnicity (Campbell, Crews, Moriarty, Zack, & Blackman, 1999). The current study only sampled Mexican

American elders and found a much higher prevalence of hearing loss than was found in Hispanic American elders in the NHIS study. It is possible that unique characteristics of the current sample led to the high prevalence of hearing loss. Among these are the generally low socioeconomic status of the sample, the high proportion of laborers with probable noise exposure, in addition to the high prevalence of diabetes and vascular diseases. Additional research is needed to explore how sample characteristics affect prevalence of high frequency hearing loss. Findings from the current study are only generalizable to older Mexican Americans with similar characteristics to those of participants in this study.

Predictors of Hearing Loss in Older Mexican Americans

Diabetes is a significant predictor of moderate-severe high frequency hearing loss in both the better and worse hearing ears when only age and diabetes are in the predictive model. However, the effect of diabetes on hearing loss is no longer significant for the better hearing ear when gender is added to the model. Although gender differences in hearing loss were not a part of the original aims of this study, stratifying by gender did reveal that high frequency hearing loss in females was significantly more affected by diabetes than in males. These results suggest that the effect of diabetes on hearing loss in this cohort is explained by female gender and that females may be at greater risk of hearing loss if they have diabetes. Additional research is needed to confirm this finding. It is possible that noise and other environmental exposures more common in men obscured the effect of diabetes. The current study cannot

determine if noise and other exposures obscured the effect of diabetes on hearing loss in men and additional research is needed.

Diabetes and General Health Status Rating in Older Mexican Americans

In this study, participants' rating of their general health significantly differed by whether or not they had diabetes. Higher percentages of participants without diabetes rated their health as excellent, very good or good compared to those with diabetes. Diabetes is known to affect individuals' self-report of general health status (Centers for Disease & Prevention, 2006). Hearing loss also has an effect on quality of life for older adults (Dalton et al., 2003). To this writer's knowledge, the potentially synergistic effect of these two conditions on perceived health status has not been studied. The perceived general health status of an individual with diabetes may be mediated by the level of diabetes signs and symptoms that are present and the presence and severity of diabetes complications. The added effect of hearing loss to this mix is unknown. Data from the SALSA study database could be used to explore this research question.

Discussion of Relationships between Diabetes and Hearing Loss

Age and Gender as Predictors of Moderate-Severe High Frequency Hearing Loss in Diabetes

Age and gender were contributors to high frequency hearing loss in diabetes consistent with the previously reported literature (Bainbridge et al., 2008). In the sub-cohort of participants with diabetes (n=405), all participants were aged 65 and over at the time of their hearing test. This study supports the impact of age on hearing loss continuing to accrue throughout the lifespan as

with each year of aging beyond age 65, SALSA participants with diabetes were between 9 and 25% more likely to have moderate-severe high frequency hearing loss in one or both ears. This effect of aging on hearing does not appear to wane in later years. Life presents many ototoxic experiences that accumulate over time. How much of presbycusis is a result of various environmental and metabolic insults throughout the lifespan is not fully known. Determining the relative impact of all of these different ototoxic drug exposures is beyond the scope of most research studies. The results of the current study do add to the understanding of some of those lifetime exposures.

It is possible that the effect of this sample's exclusively elderly population obscured the effects of other contributors to hearing loss in diabetes. The age of this population may have the impact of dampening the magnitude of findings due to the high prevalence of hearing loss found. It would have been ideal to compare those with no hearing loss to those with mild hearing loss and to those with moderate to severe hearing loss. There were not sufficient numbers of participants with no hearing loss in this sample to make a meaningful comparison group. The necessity of grouping those with no hearing loss together with those having mild hearing loss to compare to those with moderate-severe hearing loss most likely masked the effects or reduced the magnitude of the effects found. A sample that included younger participants with and without diabetes in addition to the older participants is indicated to further evaluate predictors of hearing loss.

The effect of male gender on hearing loss is also large and may obscure other effects on hearing loss. Men had higher odds of moderate-severe high

frequency hearing loss compared to women in both ears in the diabetes sub-cohort of this sample just as they did in the full cohort. It is generally supposed that the difference between hearing loss in men and women is due to differing environmental exposures between men and women over the lifespan, including more noise exposure for men. When common work-related exposures were considered in this study, noise exposure was a confounder for predicting hearing loss in diabetes but was not significant in the model including both of these exposures for those with diabetes. The possible reasons for the disparate findings relating to work-related exposures between those with diabetes compared to those without diabetes will be discussed in more detail in the work-related exposures section of this discussion.

Diabetes Signs and Symptoms Factors as Predictors of Moderate-Severe High Frequency Hearing Loss

The factor analysis conducted within this study on the diabetes signs and symptom questionnaire was theoretically consistent. Each factor's items related to a subset of known diabetes signs and symptoms that were internally consistent as evidenced by the Cronbach's α for each factor. Factor 6 relating to hyperglycemic symptoms had the lowest Cronbach's α of the factors which may have been related to the relatively good glycemic control in this sample resulting in less report of these symptoms. Additionally, aging and longer duration of diabetes can blunt the experience of hyperglycemic symptoms which would also result in lower reporting of hyperglycemic related symptoms that make up the factor.

The factor solution used in this study was done only with the diabetes sub-cohort and it differed from the factor solution determined in the previous factor analysis done with data from the entire SALSA cohort. This finding is expected and theoretically consistent because many of the individual symptoms on the questionnaire can be found in disease processes other than diabetes. This fact would likely lead to a different factor structure depending on what disease processes were represented in the full SALSA cohort.

Within the diabetes signs and symptoms factor analysis, Factor 2, related to energy and fatigue appeared to have a mildly protective effect in the better hearing ear. This means that the more an individual was bothered by energy or fatigue related symptoms, the less likely they were to have hearing loss. Having more difficulty with energy or fatigue does not make theoretical sense as a protective factor. Additional study would need to be done to rule out the possibility that this finding is spurious or due to measurement issues with the diabetes signs and symptoms questionnaire that was used for determining the factor structure. Fatigue and energy levels are very individually perceived and are not likely to be consistently rated from one individual to another with similar levels of the symptoms.

The Factor relating to cardiac/pulmonary symptoms predicting slightly increased odds of moderate-severe high frequency hearing loss in the better hearing ear is interesting. Several possible mechanisms may underlie the predictive relationship of cardiopulmonary symptoms and hearing loss. It is possible that cardiac/pulmonary symptoms are a sensitive indicator of

microangiopathic process that could lead to hearing loss. It is also possible that cardiac/pulmonary symptoms are due to large vessel disease in the heart and are related to hearing loss through shared pathology with large vessel disease. However, this latter possibility is less likely considering that no macroangiopathic indicators were significantly related to hearing loss. A combination of micro- and macroangiopathic effects may contribute to hearing loss in diabetes. Further discussion of these possibilities will be covered in the micro- and macroangiopathy sections of this discussion.

Hearing loss in this population was slightly asymmetrical as it commonly is, although this asymmetry did not reach the level (≥30 dB) that is deemed significant except in a small number of participants (American Academy of Otolaryngology - Head and Neck Surgery [AAO-HNS], 1997). This observed asymmetry, however, may have contributed to the disparate findings for each ear. The effect of Factor 5, cardiac/pulmonary symptoms, was only seen in the better hearing ear which may represent the presence of early pathological changes due to diabetes that are not seen in the other ear because of the overwhelming effects of age and gender in the worse hearing ear.

Microangiopathic Indicators as Predictor of Any High Frequency Hearing Loss

The model that included microangiopathic indicators as predictors of any high frequency hearing loss (>25 dB) in the better hearing ear was significant despite the lack of significance for individual predictors within the model. As a group, these indicators were significant for high frequency hearing loss in diabetes. This finding is consistent with the theory that microangiopathic

processes contribute to hearing loss in individuals with diabetes. The model for microangiopathic indicators as predictors of moderate-severe hearing loss was not significant. Individual microangiopathy indicators used may have been insufficiently sensitive to demonstrate the effect in this model. Also, the fact that those with no hearing loss were grouped together with those with mild hearing loss diluted the effect of microangiopathy on hearing loss. Additional research is indicated to determine in what other ways microangiopathy could be modeled to better understand its potential contribution to hearing loss.

Cardiac autonomic neuropathy (CAN) due to diabetes is considered to be a microangiopathic process. Factor 5 cardiac/pulmonary symptoms previously discussed may be due to CAN (Boulton et al., 2005; Edwards et al., 2008). If the signs and symptoms that make up this factor are the result of cardiac autonomic neuropathy, this finding may represent a common pathway for hearing loss and CAN. According to Edwards et al, (2008), CAN is present in most individuals with diabetes due to vagus nerve damage resulting from diabetes. The neural structures of the ears responsible for hearing may suffer a similar damaging effect from diabetes, leading to high frequency hearing loss. Additional research would be needed to determine if a common pathological pathway is present. Based on the odds ratio, this factor has a small effect size related to hearing loss. A larger sample would be needed to further evaluate the effect of CAN on hearing loss in diabetes.

Work-Related Exposures as Predictors of Moderate-Severe High Frequency Hearing Loss

Noise and Hearing Loss. A significant body of knowledge exists regarding excessive noise exposure leading to high frequency hearing loss (Henderson et al., 2002; Morata & Little, 2002; Sataloff & Sataloff, 2005c). Noise exposure was not a significant predictor of moderate-severe high frequency hearing loss in those with diabetes in this study. However, noise exposure did confound the relationship between pesticides exposure and hearing loss so was included in the final conceptual model.

Many occupations involve multiple environmental exposures that occur together so the potential for confounding must be considered. Confounding occurs when a variable distorts the relationship between two or more other variables under study due to the strong association between the confounding variable and the other variable(s). Controlling for multiple exposures is difficult when there is high correlation consistent with confounding between the exposures as in the present study. Determining the individual effects of each exposure becomes problematic. As Pearce, Checkoway and Kriebel state: “The decision to control for a presumed confounder can certainly be made with more confidence if there is supporting prior knowledge that the factor is predictive of disease, independently of its association with exposure” (2007, p. 566). As noise is known to be a predictor of high frequency hearing loss in the absence of pesticide exposure, it qualifies as a potential confounder of the relationship between pesticides and hearing loss by this definition.

Pesticides and Hearing Loss. Pesticides exposure was a significant predictor of hearing loss in the worse hearing ear only. As previously noted, it was not a significant predictor for those without diabetes despite the fact that pesticides exposure did not differ significantly between these two groups. When an interaction effect between diabetes and pesticides exposure was tested in the full cohort, it was found to be a significant predictor. This suggests the possibility that those with diabetes are more neurologically susceptible to the negative effects of toxic pesticides exposures due to their compromised health status as a result of diabetes and/or oxidative stress. The present study cannot determine if this is the pathway leading to high frequency hearing loss; however, it makes sense that those with diabetes who are both neurologically compromised and have increased oxidative stress due to the disease would be more prone to the neurotoxic and oxidative stress effects of pesticides exposure. From this perspective, the study findings can be said to support theories of hearing loss related to neuropathic changes and/or oxidative stress. The concept of increased neurologic susceptibility as a mechanism for hearing loss requires further research. An alternate explanation might be that pesticides exposure increases the likelihood of developing diabetes. Additional research will be needed to determine the temporal relationship of this interaction and the mechanism of action leading to hearing loss in diabetes.

For the farm workers included in this sample, noise and pesticide exposure often occurred together. Many of these farm workers also reported other work-related exposures in lesser numbers. To adequately test the effects of

these multiple exposures, including interaction effects, a larger sample size would be needed.

An evaluation of pesticides use and reports of pesticides poisoning in California reported that nearly one third of all pesticides used are known to be toxic. Although California is thought to have among the best reporting structures for pesticides abuse in the world, Reeves and Schafer (2003) report that it is still inadequate to protect the health of farm workers. The state's Pesticide Use Reporting system and its Pesticide Illness Surveillance Program address only acute effects of pesticides. Chronic effects are usually not reported. Additionally, multiple barriers have been identified to adequate reporting of even acute poisoning incidents. Among these are: misdiagnosis by health care practitioners, workers preference for receiving care across the border in Mexico, and fear of job loss or retaliation by employers for reporting health problems. The evaluators of pesticides reporting in California further indicate that most poisonings go unreported and factors that lead to underreporting are increasing (Reeves & Schafer, 2003).

In the current study, there are no details available on which pesticides workers were exposed to. However, organophosphate pesticides have historically been commonly used on major crops in the Sacramento Valley, including almonds (Brodt et al., 2004). Organophosphate pesticides are among the most toxic pesticides. They have been targeted by the Federal Food Quality Protection Act for reduction in residue on food products. This law provides public protection but does little to nothing to reduce potential exposure to farm workers

or their children as it specifically excludes direct exposure to farm workers to field pesticides residue from its coverage (Reeves & Schafer, 2003).

There are laws intended to provide protection to farm workers from pesticides exposure. The Worker Protection Standard enacted in 1995 at the federal level mandates posting requirements and field reentry rules following pesticides use. Additionally, the Standard requires worker training, the use of protective equipment, and emergency medical care access in the event of exposure. Analysis conducted by Reeves and Schafer (2003) found violations of this Standard to be common. Among the violations noted are: lack of provision of personal protective equipment (PPE), inadequate decontamination and washing facilities, lack of information provided to farm workers about pesticides used. These evaluators' analysis of the data collected by California agencies responsible revealed that 88% of the violations specific to PPE for pesticides was due to employer negligence rather than worker failure to use available equipment.

The current study has no detailed data on the compliance to mandated postings about pesticides, worker training, use of PPE by workers that were exposed to pesticides, or access to medical care. However, given the generally inadequate compliance with these protective measures overall in California, it is fair to assume that workers in this study who had pesticides exposures had inadequate protections provided, increasing the potential for negative health effects.

The pervasive poverty that most farm workers live in increases the risks associated with potential pesticides exposure. Dinham and Malik state that "poverty drains the ability of those affected to take action" (2003, p. 40). When workers exposed to pesticides have inadequate access to bathing and laundering facilities, the recommendation to bathe after work and don clean clothes at the beginning of each work day (washed separately from the family wash) becomes problematic. The poverty-level wages and fear of job loss are powerful incentives for workers to remain working when ill, even when the illness is a result of their work. Reeves and Schafer (2003) report that "many farm workers consider the symptoms they experience simply part of the job" (p. 37).

Other Chemical Exposures and Hearing Loss in Diabetes. Solvents and heavy metals exposures were not significant predictors of moderate-severe high frequency hearing loss in this sample. They have been found to be predictors in other studies (Fuente & McPherson, 2006; Gobba, 2003; Hodgkinson & Prasher, 2006; Rybak, 1992). There may have been insufficient power to detect an effect for lead, cadmium, and other heavy metals as 10.6%, 5.2% and 12.6% of the diabetes sub-cohort were exposed to these substances respectively. In the case of solvents, however, 22.2% of those with diabetes reported exposure. The dichotomous nature of the exposure data may be responsible for failure to detect an effect. There was no information available as to which solvents and in what quantities workers were exposed to. More precise exposure data would be needed to determine if an effect was present. Solvents failed to reach the level of confounding in this study with pesticides. This was most likely due to the

relatively small number of participants with diabetes who reported both exposures (9.6%).

Synergistic effects between the chemicals cannot be ruled out as contributing to moderate-severe high frequency hearing loss, particularly given the multi-collinearity that is present between exposures in this sample. To test multiple synergistic effects or interactions, a larger sample would be needed and possibly the use of sophisticated modeling techniques such as structural equation modeling that can test mediation and moderation simultaneously. Animal studies have confirmed that combinations of chemicals and noise exposure result in greater ototoxicity than noise alone (Morata, Dunn, & Sieber, 1994). Work by the NoiseChem research group and others may shed further light on the synergistic and interactive effects of various exposures in the future (Morata 2007; Prasher et al., 2002).

Discussion of Other Potential Predictors of Hearing Loss in Diabetes

Clinical Indicators and Hearing Loss. The three clinical indicators found to be significant in their group model that were subsequently included in the composite model: at-risk waist circumference, loop diuretic use, and mean alcohol use; were not significant for predicting moderate-severe high frequency hearing loss in either ear in the composite model. These negative findings may have several possible implications.

At-risk waist circumference is a measure of central adiposity that is associated with insulin resistance, a key feature of type 2 diabetes. Lack of its predictive ability in this study suggests that insulin resistance and body fat have

little to no role in contributing to hearing loss. Extending this line of thought, insulin and other hormones of glucose metabolism may not be candidates for biochemical pathways to hearing loss. Further study would be needed to confirm this hypothesis, particularly in light of the role of insulin failure being believed to be the end result of mitochondrial oxidative stress.

Loop diuretics, while significant in predicting hearing loss in the clinical indicators model of this study, did not retain significance in the final composite model. Of the participants with diabetes in this study, 57 (14%) were using loop diuretics at the time of the study and the correlation with prior use was very strong. Loop diuretics are known to be ototoxic (Brown, Henley, Penny, & Kupetz, 1985). Using the more inclusive category of any ototoxic drug use did not result in significance even at the level of the group model. These lack of signficant findings may be due to the minimal amount of information about these medications that was included in the analysis (yes/no dichotomous use). As multiple years of data on ototoxic drug use is available for this sample, a longitudinal analysis may reveal an effect that was not seen in the cross-sectional analysis.

Alcohol use also did not retain significance as a predictor of hearing logg when brought forward into the composite model. This lack of effect is most likely due to the relative modest alcohol ingestion among this sample and that years of alcohol ingestion was used as the measure since quantity ingested was only available for two study years. In research that has implicated alcohol in hearing loss, the level of ingestion is much higher than in this sample (Kovacic &

Somanathan, 2008). The fact that even modest alcohol ingestion was significant in the group model suggests the possibility of increased susceptibility to the oxidative stress effects of alcohol in diabetes. Modest alcohol ingestion was found to be protective in the study conducted by Sakuta et al. (2007). This discrepancy in findings is also interesting in light of what is known about alcohol. Modest intake is considered good for cardiovascular healthy while excess intake is known to be cardiotoxic. Additional research would be needed to determine the effect of alcohol ingestion on hearing loss in diabetes.

Glomerular Filtration Rate. GFR had approached significance in its microangiopathic model but failed to be a significant predictor of hearing loss in the composite model. The fact that none of the other microangiopathic indicators reached significance in their group model can be interpreted in several different ways. One is that microangiopathic pathology may not be the pathway of damage that leads to hearing loss in diabetes. The alternate explanation for their lack of predictive ability is that the indicators themselves are not sufficiently sensitive or specific measures of microangiopathy to find an effect if one is present or should be grouped together as one measure since they represent the same mechanism. Only additional research can shed light on these possible alternatives.

Macroangiopathic Indicators. Macroangiopathy is one theoretical cause of hearing loss proposed in the literature (Scuteri, Najjar, Morrell, & Lakatta, 2005). The failure of any of the macroangiopathic indicators to reach significance in their group model in this study suggests that macroangiopathic pathology is not the

mechanism of injury that leads to hearing loss in diabetes. CAD, CVD, and PVD are theoretically good indicators of macroangiopathic disease, so specificity of these measures to represent macroangiopathic processes in this case is unlikely.

The Factor 5 cardiac/pulmonary symptoms previously discussed could be linked to macroangiopathic processes. Additional research on these symptoms would be needed to clarify their origin as either microangiopathic or macroangiopathic.

Revised Conceptual Model for High Frequency Hearing Loss in Type 2 Diabetes

A revised conceptual framework was developed based on results of the analysis (See Figure 3). The model includes the demographic, diabetes signs and symptoms factors and the work-related exposures that were found to predict high frequency hearing loss in those with type 2 diabetes in the SALSA sample.

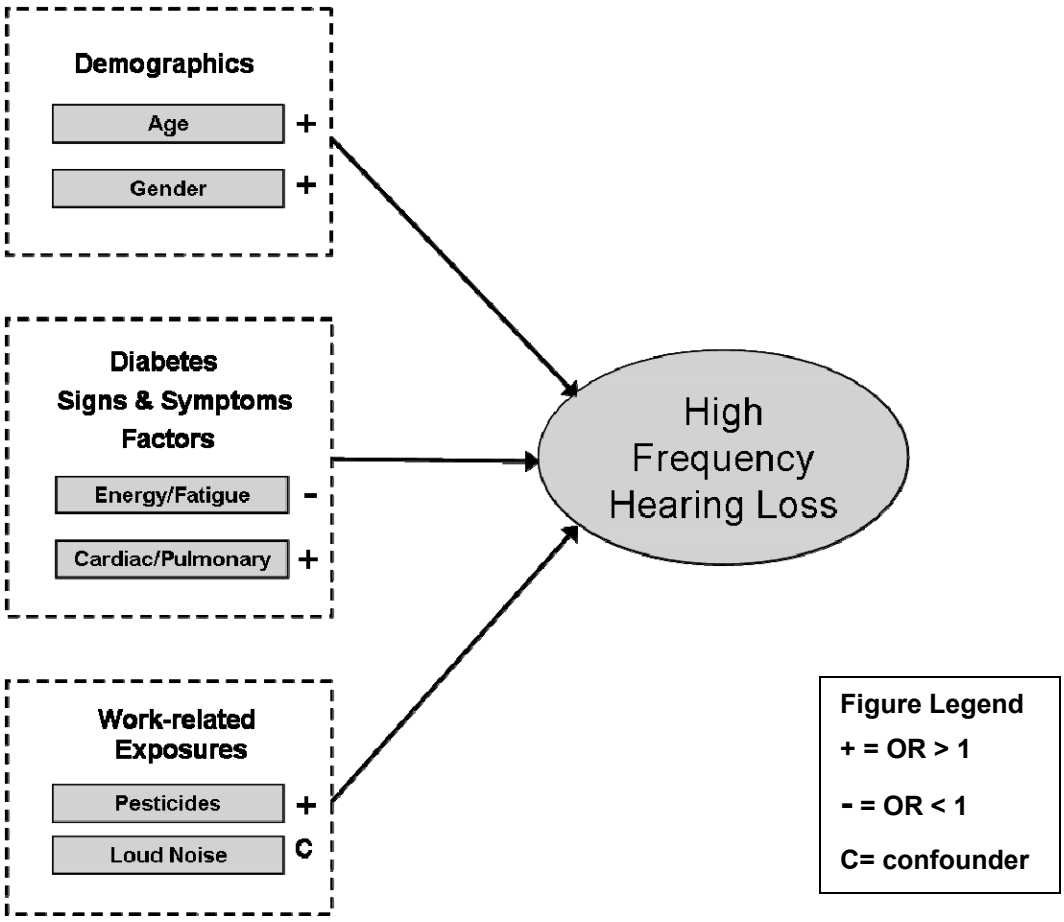

Figure 3 Revised Conceptual Framework for High Frequency Hearing Loss in Type 2 Diabetes

Implications for Nursing

Hearing loss has been shown to affect quality of life (Campbell, Crews, Moriarty, Zack, & Blackman, 1999; Strawbridge, Wallhagen, Shema, & Kaplan, 2000) and functional levels in older adults (Wallhagen et al., 2006; Wallhagen, Strawbridge, Shema, Kurata, & Kaplan, 2001). Diabetes has also been shown to affect quality of life (Holmes et al., 2000; U.K. Prospective Diabetes Study Group, 1999; Wexler et al., 2006), particularly in the presence of complications or

comorbidities. Both hearing loss and diabetes have also been associated with depression (Ciechanowski, Katon, & Russo, 2000; Davanipour et al., 2000). When diabetes and hearing loss are both present in an older adult, the potential for depression, decreased quality of life, and reduced functional capacity must be considered to be high. Evaluating older adults for these conditions and intervening with nursing measures as well as appropriate referrals for evaluation and care should be a part of routine nursing practice. Nursing measures for hearing loss include education to patients and families on adaptive strategies to practice and environmental modifications to employ that reduce the impact of hearing loss. Nursing measures can also include assessing readiness for hearing aid use and providing education on the potential benefits of hearing aids (Wallhage et al., 2006).

The effects of hearing aid technology on quality of life has been studied (Stark & Hickson, 2004). Hearing aid use was found to significantly reduce the negative quality of life impacts of hearing loss. Hearing aids are not covered under most insurance plans, including Medicare (HHS.gov, 2009) and their cost can be prohibitive for fixed-income or low-income individuals. This fact most likely contributes to the low rate of hearing aid use among the study sample. Nurses have potential to impact this through advocacy and participation in health care reform activities. In the current study, very few individuals reported using hearing aids at study baseline. Given the high prevalence of hearing loss in this sample, this is a very small number and suggests significant under-utilization of available treatment and rehabilitation. Coupled with the under-detection of hearing loss

reported by Bogardus and his colleagues that has been previously discussed (Bogardus et al., 2003), it is clear that the health needs of older adults with hearing loss are being inadequately met.

Nurses in all settings have ability to impact under-detection and under-treatment of hearing loss. Currently, audiometric screening is not a part of routine primary care. For those with diabetes, the recommendation for routine audiometric screening is just beginning to be employed due to the landmark study by Bainbridge et al. (2008). Implementation of simple screening to detect hearing loss can be done in nearly any health care setting and should always be included in routine physical examinations. Bagai and his collegues recommend asking all elderly individuals if they have difficulty hearing. If they admit to hearing impairment, they should be referred for audiometry. If they do not, they should be screened via the whispered voice test, properly administered. Those who fail this test should also be referred for audiometry (Bagai, Thavendiranathan, & Detsky, 2006). Bogardus and his colleagues caution that the whispered voice test may be inadequately sensitive to detect hearing loss. Use of the Hearing Handicap Inventory for the Elderly - Screening version (HHIE-S), which has been validated against pure tone audiometry and assesses functional impairment related to difficulty hearing, would be an even better screening tool to implement (Bogardus et al., 2003; Davanipour et al., 2000).

Implications for Occupational Health Nursing

Occupational Health Nurses have a professional obligation to protect the health and safety of workers in every setting in which they work (American

Association of Occupational Health Nurses, 2009). Additionally, this writer believes they have a moral obligation to work for the protection of all workers. This stance is consistent with the second statement in the AAOHN Code of Ethics: “Occupational and environmental health nurses, as licensed health care professionals, accept obligations to society as professional and responsible members of the community” (American Association of Occupational Health Nurses, 2009, p. 2).

The participants in the current study represent several vulnerable populations: farm workers, economically disadvantaged, older workers, and individuals with chronic disease that may increase their risks to work-related insults to health. Protecting worker health, particularly for the most vulnerable, can not be accomplished by Occupational Health Nurses alone. The combined efforts of professionals, regulatory agencies, governmental bodies, the community, and workers themselves are needed to advocate for workers to make the workplace a better place for workers.

To adequately protect the health and safety of working adults, there is a need to identify an action level for chemical exposures (with or without concurrent noise exposure) for inclusion in hearing conservation programs; to determine what training these workers should receive; to educate industry, professionals, unions and the public on the ototoxicity of chemicals and the health risks associated with these exposures (Morata 2007). Recent editions of the ACGIH TLVs and BEIs manual which serves as a resource for safety, environmental, and industrial hygiene professionals have only recently added

any information about the potential of chemical interaction with noise exposure (American Conference of Governmental Industrial Hygienists, 2006; 2007) and their recommendations barely scratch the surface of the need to evaluate these mixed exposures in workers. The NoiseChem research team is hoping that further study of the effects of chemicals on hearing and balance will result in a "paradigm shift in hearing conservation, refocusing attention away from noise to hearing" (Prasher et al., 2002, p. 8).

Morata (2007) suggests adding questionnaires to routine PTA screening performed in industry that focuses on detecting speech discrimination difficulty. When results of PTA are inconsistent with reported difficulties in hearing under certain circumstances, referral for additional testing is indicated. This expert also suggests that in work-related settings where workers are exposed to potentially ototoxic chemicals, tests that detect more central audiometric changes be employed. These tests would supplement PTA and include: sensitized speech tests, random gap detection tests, pitch and duration pattern tests, and evoked potential tests such as BAEP. The ideal testing battery would evaluate hearing from the cochlea all the way up to the portion of the brain responsible for interpreting sound. Additional research is needed to determine the appropriate test battery and the feasibility of incorporation into hearing conservation programs.

Agriculture remains a predominant occupation in the modern world as nearly 50% of all workers worldwide are engaged in various aspects of agricultural production (Maroni, Fanetti, & Metruccio, 2006). Pesticides have

been increasingly used in recent decades to improve production and enhance food quality. Legislative protection for agricultural workers has lagged behind the protection provided to workers in other occupations. Maroni and his colleagues assert that current technology is available to provide adequate protection to farm workers from the negative health effects from pesticides exposure. They further assert that to do so will be “economically rewarding” for both the individual farm worker and the community at large. Appropriate risk assessment and risk management are essential aspects of preventing hazardous exposure to pesticides.

Protecting workers from the effects of toxic exposures is the responsibility of Occupational Health professionals in compliance with OSHA’s general duty clause mandating a safe and healthy work environment as well as an important protection of human rights that is the joint responsibility of government, corporations, and the community (Dinham & Malik, 2003; Reeves & Schafer, 2003).

Riggs and Waples (2003) reported on a conference conducted in 2002 to provide market communication on sustainable agriculture. Their panel of experts asserts that current pesticides use is unnecessary to maintain adequate food production worldwide. They further assert that the use of chemicals at current rates is degrading the ability of the planet to continue to grow food. They outline a future of ecologically-based approaches to the management of crop pests that will not only ensure adequate future food supply but also provide needed protection to farm workers and the community from toxic pesticides. They call for

improving social awareness of both the health and environmental impact of pesticides use.

All 62 U.S.-produced pesticides that contain carbon disulfide have had their registrations cancelled, which theoretically means they will no longer be used (PAN Pesticides Database, 2009). Organophosphate pesticides use has also decreased in recent years in California (Reeves and Shafer, 2003). Additional progress has been made as the organic food movement has gained momentum. Organically-grown food is theoretically free of pesticides. Growth of this movement may be due to consumer awareness about the dangers of pesticides and thus, provides a market incentive for pesticides-free food. However, much remains to be done to protect vulnerable populations from the ill effects of pesticides use.

Future Research

Consistent with the recommendations of reviewers Fowler and Jones (1999), future studies on diabetes and hearing loss would be improved by longitudinal design, large sample sizes, well-matched controls from the same population, inclusion of all age groups, and control for important confounding variables. The SALSA participants met criteria for large sample size and controls (though not matched) from the same population. However, to control for all confounders, a larger sample would be needed. The SALSA sample only included elders. Hearing tests were not done multiple times over a prolonged time period. A longitudinal study that included all adults with large enough subsamples from various work types with differing exposures would help

determine causative factors as well as allow for determining synergistic effects of differing exposures. The interaction of work-related chemical exposures and noise could be studies in such a large study as well. Following the recommendations of the NoiseChem research team for analysis of multiple exposures would be important to include in the study design (Morata & Little, 2002).

The interaction of pesticides and diabetes found in the current study should also be further explored through longitudinal studies that have sufficient sample size to control for multiple possible confounders. Use of techniques such as structural equation modeling or other latent variable methods would help in understanding the potential multiple mediators and moderators that may be involved in hearing loss in diabetes with pesticides exposure.

The potential role of microangiopathic pathways to hearing loss in diabetes deserves further study. A first step would be to determine improved ways to model microangiopathy. The occurrence of cardiac autonomic neuropathy, as measured by heart rate variability and other physiologic measures, would be one important way to evaluate microangiopathy to determine if a relationship exists with hearing loss. Positive findings in such a study would point to a shared metabolic pathway for CAN and hearing loss in diabetes.

Strengths and Limitations of the Study

This study was not affected by the Healthy Worker effect that many studies of occupational exposures are prone to (Pearce et al., 2007). Participants

were recruited from the community regardless of their current working status and history of work-related exposures was gathered on all participants. There was a minimal amount of missing data in the exposure information.

An additional strength of this study is that participants with diabetes and those without came from the same regional and ethnic population. This is important for generalizability as well as confidence in the research findings.

Information for the parent SALSA study was collected in a systematic manner with many variables collected at regular intervals (every 12-15 months) throughout the study. The job and exposure information was collected at study baseline and the hearing test was administered at a subsequent follow-up visit. This reduced the potential for differential recall regarding work-related exposures as many possible outcome variables were under study and; therefore, it was unlikely that participants tailored their report of exposures based on beliefs about their risk status for hearing loss. This sequence of data collection procedures controlled for differential misclassification of exposures, a potential study threat (Pearce et al., 2007).

The current study was also potentially affected by exposure misclassification related to the outcome under study, hearing loss. The effect of exposure and disease misclassification in occupational epidemiology studies was discussed by Pearce, Checkoway and Kreibel (2007). Misclassification of disease status or occupational exposures leads to bias. The two types of misclassification, differential or nondifferential, are not equal in terms of leading to bias, however. Differential misclassification occurs when an error in exposure

classification is more likely given the disease state being studied. It also occurs when classification of the disease state is different in exposed or unexposed participants. If either of these misclassification errors occurs, the results will be biased. This type of situation is likely if there is motivation to report specific exposures such as belief that a particular exposure is related to the disease state being studied. Bias can be toward or away from the null value depending upon the individual circumstances of the misclassification.

How much misclassification of exposure or disease occurs is never definitively known in studies. However, study design and assessment of the study implementation can control for these biased effects. Studies should be conducted in such a way that the independence of exposure and disease misclassification can be supported and that the misclassification of both is non-differential. In the current study, nondifferential misclassification of exposures was more likely than differential misclassification due to the methods of data collection previously described. Also, important for the present study of diabetes and hearing loss, a nondifferential misclassification of a confounding variable may produce bias away from the null due to lack of control of the confounder (Pearce et al., 2007). A confounder is defined by the presence of three conditions: the confounder is predictive of the outcome under study in the absence of the exposure of interest; an association must exist between the confounder and the exposure of interest in the population under study; the confounder is not a mediator in the pathway between the exposure and the disease (Pearce et al., 2007). For noise and pesticides exposure in this study,

noise was a confounder for pesticides exposure in those with diabetes. Noise exposure is known to be predictive of hearing loss. However, the potential for noise to mediate the pathway between pesticides exposure and hearing loss was not found (results not shown). Additional research is needed to determine if such a relationship exists within the context of diabetes.

Self-report is frequently the only measure available to assess chemical, noise, and other work-related exposures when systematic industrial hygiene monitoring has not been done. As with all self-report measures, this method has significant limitations that potentially impact the current study. Benke et al. (2001) compared three different methods of determining occupational exposures to common chemicals: self-report, job-exposure matrices, and expert assessment; and found that for some exposures, notably pesticides, self-report was in close agreement with the panel of Industrial Hygiene experts. Self-report consistently underestimated the prevalence of other occupational exposures compared to expert panel. The underestimation of exposures was noted by the authors to result in attenuation of any Odds Ratios of exposure for a given outcome. Applying this literature to the current study, self-report of pesticides exposure is likely to be relatively accurate, adding to the confidence in the current study's findings; noise exposure is likely to be underestimated by self-report. The impact of underestimation of noise exposure in the current study may be that noise is a predictor of high frequency hearing loss for those with diabetes in addition to being a predictor for those without diabetes. Additional research with more

precise exposure data would clarify the contribution of these and other work-related exposures to high frequency hearing loss.

Conclusion

The current study looked at diabetes and hearing loss in older Mexican Americans and evaluated the potential contribution of multi-faceted potential predictors of hearing loss. Despite the fact that most of the participants were no longer working, their life-time exposure histories were valuable to consider for understanding hearing loss in diabetes. This study's findings support the concept that there are multiple physiologic and environmental reasons why individuals with diabetes are prone to high frequency hearing loss. These multiple reasons include aging, gender, physiologic processes associated with diabetes, and environmental exposures in the workplace. Age is the predominant and most important predictor of hearing loss. Gender and work-related environmental exposures are also important predictors. When these factors are combined with having diabetes, there is an even greater risk of hearing loss.

The graying of America represents a demographic shift that is unprecedented in the history of the United States. The largest population cohort in history is reaching late middle age and contemplating retirement. At the same time, the concurrent decrease in the birth rate is leading to an inevitable insufficiency in the numbers of workers for the jobs that need to be done. Corporate America will soon need the talents (and labor) represented by the "sixty-something" generation (Dychtwald, Erickson, & Morison, 2006). As Americans live longer and a segment of the population has the financial need to

continue working to a greater age than their parents or grandparents, the presence of chronic disease and its impact on ability to work will become increasingly important.

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Appendices

Appendix 1: Variables and Measures

Variable*	Measurement/Computation	Variable Type
Hearing Variables – Dependent Variables**		
Low-mid frequency hearing loss >25 dB worse ear	Created from raw pure tone audiometry 500-2000 Hz	Yes/No Dichotomous
Low-mid frequency hearing loss >25 dB better ear	Created from raw pure tone audiometry 500-2000 Hz	Yes/No Dichotomous
High frequency hearing loss >25 dB worse ear	Created from raw pure tone audiometry 3000-8000 Hz	Yes/No Dichotomous
High frequency hearing loss >25 dB better ear	Created from raw pure tone audiometry 3000-8000 Hz	Yes/No Dichotomous
Low-mid frequency hearing loss >40 dB worse ear	Created from raw pure tone audiometry 500-2000 Hz	Yes/No Dichotomous
Low-mid frequency hearing loss >40 dB better ear	Created from raw pure tone audiometry 500-2000 Hz	Yes/No Dichotomous
High frequency hearing loss >40 dB worse ear	Created from raw pure tone audiometry 3000-8000 Hz	Yes/No Dichotomous
High frequency hearing loss >40 dB better ear	Created from raw pure tone audiometry 3000-8000 Hz	Yes/No Dichotomous
Variables for Sample Description and Independent Variables		
Demographics		
Age	Years from date of birth	Continuous
Gender**	Male/Female	Dichotomous

Diabetes Signs and Symptoms Factors		
Diabetes Signs and Symptoms	35 item interview	Yes/No
(individual items)	questionnaire at home visit	Dichotomous
F1: Extremity & Neuropathy	Six created variables from summation of questions on subscales developed from factor analysis of 35 item Diabetes Signs & Symptoms	Count
F2: Energy & Fatigue		Count
F3: Visual Difficulties		Count
F4: Mood & Concentration		Count
F5: Cardiac & Pulmonary		Count
F6: Hyperglycemic Symptoms		Count
Work Exposures		
Pesticides**	Self-reported primary job	Yes/No Dichotomous
Lead**	Self-reported primary job	Yes/No Dichotomous
Cadmium**	Self-reported primary job	Yes/No Dichotomous
Solvents**	Self-reported primary job	Yes/No Dichotomous
Other heavy metals**	Self-reported primary job	Yes/No Dichotomous
Dusts**	Self-reported primary job	Yes/No Dichotomous
Fumes**	Self-reported primary job	Yes/No Dichotomous
Loud noise**	Self-reported primary job	Yes/No Dichotomous
High levels of heat**	Self-reported primary job	Yes/No Dichotomous
Other occupational exposures**	Self-reported primary job	Yes/No Dichotomous

Clinical Indicators		
Type 2 diabetes	Diagnosis by fasting glucose >125 mg/dL, HbA1c > 6.5%, self-report of physician diagnosis or the use of any medication for diabetes	Yes/No Dichotomous
Diabetes Duration	Calculated from self-reported baseline duration; incidence during study	Continuous
Diabetes Duration categories	Created from categorization of continuous diabetes duration variable: <5 years; >5<10, >10<15, >15<20, >20	Categorical, ordered
Hypertension	Self-reported or by use of antihypertensive medication	Yes/No Dichotomous
Metabolic Syndrome**	Computed from: waist circumference serum triglycerides HDL cholesterol blood pressure blood glucose	Yes/No Dichotomous
Body Mass Index (BMI)	Computed from height and weight	Continuous
Waist Circumference	Measured at home visit	Continuous
At Risk Waist Circumference	Collapsed variable from measured waist circumference; at risk for males >102 cm; females >88 cm	Yes/No Dichotomous

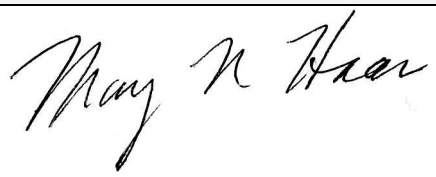
Medication Use		
Antihypertensive use	Self-reported and medication audit at home visit	Yes/No Dichotomous
Statin use	Self-reported and medication audit at home visit	Yes/No Dichotomous
Medication us for PVD/CVD	Self-reported and medication audit at home visit	Yes/No Dichotomous
Ototoxic drug use, current	Self-report and medication audit at home visit	Yes/no Dichotomous
Ototoxic drug use, previous	Self-report and medication audit at home visit	Yes/no Dichotomous
Loop diuretic drug use, current	Self-report and medication audit at home visit	Yes/no Dichotomous
Loop diuretic drug use, previous	Self-report and medication audit at home visit	Yes/no Dichotomous
Lifestyle Variables		
Current smoking status**	Self-reported at home visit interview	Yes/No Dichotomous
Alcohol (ETOH) use	Any alcohol use in study years to time of test; number of drinks at baseline	Count

Microangiopathic Indicators		
Fasting Blood Glucose	Lab report of sample taken at home visit	Continuous
HbA1c	Lab report of sample taken at home visit	Continuous
Semmes Weinstein Monofiliment (SWM) test***	Computed number of foot insensate sites from raw test data	Count
Semmes Weinstein Monofiliment (SWM) dichotomized***	Collapsed number of insensate sites into none/one or more	Yes/No Normal Dichotomous
Vibration Threshold Test (VTE)***	Computed variable from raw test data	Ordinal
Vibration Threshold Test (VTE) dichotomized***	Collapsed from VTE variable (present vs. reduced/absent)	Yes/No Normal Dichotomous
Peripheral Neuropathy	Computed variable from VTE dichotomous and SWM dichotomous variables	Yes/No Dichotomous
Glomerular Filtration Rate (GFR)**	*Calculated*	Continuous
Glomerular Filtration Rate (GFR) categories**	Collapsed from Continuous GFR into categories: Normal GFR $\geq$ 90 Mild decrease in GFR 60-89 Moderate decrease GFR 30-59; Severe decrease in GFR < 30	Categorical Ordered
Diabetes Retinopathy	Self-reported at interview	Yes/No Dichotomous

Macroangiopathic Indicators		
Coronary Artery Disease	Created variable from Myocardial Infarction &/or Angina Pectoris self-reported at home visit	Yes/No Dichotomous
Peripheral Vascular Disease	Created variable from intermittent claudication and/or Ankle-Arm Index <.9	Yes/No Dichotomous (
Cerebral Vascular Disease	History of stroke by self-report at any time	Yes/No Dichotomous
Total Cholesterol	Laboratory report of sample taken at home visit	Continuous
LDL***	Laboratory report of sample taken at home visit	Continuous
Cholesterol/HDL ratio	Laboratory report of sample taken at home visit	Continuous
Triglycerides	Laboratory report of sample taken at home visit	Continuous
General Health Status		
General health rating	Self-reported at home visit interview	Ordinal
Health compared to others	Self-reported at home visit interview	Ordinal

*Except where noted, all variables were collected at the time of the hearing test.
**Collected at baseline. ***Data used that was collected closest to time of hearing test.

Appendix 2: Self-Certification of Exemption from the University of California San Francisco Committee on Human Research (CHR) approval

Principal Investigator:		
Name and degree **Mary N. Haan, DrPH, MPH**	Institution **University of Michigan**	Department **Epidemiology**
Mailing Address M5174 SPH II; 109 Observatory St, Ann Arbor, Michigan	Phone Number (734) 646 4049	E-mail Address mnhaan@umich.edu
Study/Grant Title/Award No.:		
Sacramento Area Latino Study on Aging (SALSA)		
Conditions that must be met for the coded private information (data) or biological specimens:		
1. The coded private information or specimens were not collected specifically for the current proposed research project, 2. and one or more of the following apply. Check all that apply: _____ a. The key to decipher the code is destroyed before researcher begins. _X__ b. PI and holder of the key enter into an agreement prohibiting the release of the key under any circumstances. _____ c. There are IRB-approved written policies for the repository or data management that prohibit the release of the key.		
Principal Investigator's Certification: I certify that the information provided in this application is complete and correct.		
 **Principal Investigators Signature**		**Date: March 23. 2009**

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Author Signature Date