THE VERSATILITY OF EPIDEMIOLOGY: ASSOCIATION OF CHRONIC DISEASES TO AGE-RELATED HEARING LOSS AND THE RISK OF CANCER WITHIN A COMMUNITY EXPOSED TO GASOLINE

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This dissertation demonstrates the versatility of epidemiology in public health research. The association between hearing sensitivity and diabetes, cardiovascular disease (CVD), and their risk factors was examined in a population of 2,049 adults within the Health, Aging, and Body Composition Study (mean age 77.5 ± 2.8 years; 37% black). CVD and diabetes may contribute to age-related hearing loss by affecting blood flow within the inner ear via macro- and micro-vascular changes. Clinical CVD was not associated with hearing sensitivity however; subclinical CVD measures were moderately associated with poorer auditory function in females. After controlling for age, race, and site, CVD risk factors positively associated with worse mid-frequency hearing thresholds in males were weight, insulin, glucose, triglycerides, and smoking and in females were heart rate and glucose. Risk factors associated with worse high frequency thresholds were weight, insulin, triglycerides, and smoking in males and heart rate, glucose, and smoking in females. Diabetes was associated with mid-frequency hearing loss upon adjustment for common hearing loss risk factors (OR=1.60; 95%CI: 1.26–2.02). The metabolic syndrome was associated with mid-frequency hearing loss in whites prior to excluding diabetics. These results suggest that diabetes, in conjunction with CVD, contributes to age-related hearing loss, particularly strial presbycusis, and independent of common hearing loss risk factors. Given the

high prevalence of hearing impairment among older adults, the identification of potentially modifiable risk factors for age-related hearing loss is of public health significance.

Epidemiology can also be utilized in more applied settings. A retrospective cohort study was conducted to determine if residents affected by an underground gasoline spill in Hazle Township/Hazleton, Pennsylvania were at increased risk for cancer from 1990-2000. A total of 663 individuals representing 275 households comprised the study population. Age-adjusted standard incidence ratios (SIRs) were calculated using Pennsylvania rates to determine expected numbers. The age-adjusted leukemia SIR for the gasoline affected area was 4.40 (95%CI: 1.09-10.24). These results suggest a possible association between chronic low-level benzene exposure and increased risk for leukemia in the residents living near the spill site. This project directly impacted the public health of residents and also demonstrated the importance of collaboration and surveillance.

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PREFACE

Epidemiology is the essential science of public health. Throughout the course of my graduate education I have been fortunate for the untraditional opportunity to use epidemiological methods and fundamentals in a variety of epidemiological disciplines including environmental, cardiovascular disease, aging, occupational, infectious, and lifestyle. For my dissertation, I chose to demonstrate my knowledge of epidemiology by presenting research from two different genres. The first area pertains to the contribution of chronic diseases to hearing sensitivity and the second area focuses on the association of chronic low-level benzene to risk of cancer within a community exposed to gasoline. Although these areas of research are quite different from one another, they represent the utility of epidemiology in diverse situations and its contribution to public health.

As I begin my career in public health I hope to continue to apply fundamental epidemiological skills to projects that more immediately impact the public's health regardless of the discipline. I am grateful for the education I have received at the University of Pittsburgh Graduate School of Public Health which has provided me with these skills and a foundation in public health research. In particular I would like to acknowledge the following persons for supporting me in various ways throughout my tenure in graduate school and also those persons who made this dissertation research possible.

I would like to express my gratitude to Dr. Evelyn Talbott for serving as my academic advisor and Dr. Kim Sutton-Tyrrell for providing me with a graduate research experience. Additional thanks are extended to my committee members who have shared their expertise as I conducted my research. This research would not have been possible without the staff and

participants of the Health ABC study and the Hazleton and Hazle Township Health Effects studies and I would like to express my genuine appreciation and gratitude to all of them for their contributions.

My friends and colleagues have been an integral part of my experience as a graduate student. To my friends, thank you for providing a social outlet and being so willing to listen to me as I expressed frustration and happiness during the roller coaster ride that is graduate school. I would especially like to acknowledge the girls of DSO and Vinay for providing me with never-ending support, understanding, and sources of fun. You all have made these the best years I have had in Pittsburgh and I consider myself fortunate to have friends like you. To my colleagues at the EDC and CDC thanks for helping me grow professionally, providing me with guidance on projects, and for introducing me to different aspects of public health.

Finally, I would like to express my sincere gratitude and appreciation towards my family – Mom, Dad, Sheral, and Sheran. You have been the source of my inspiration and without your continued love and encouragement this achievement would not be possible.

1. INTRODUCTION: ASSOCIATION OF CHRONIC DISEASES TO AGE-RELATED HEARING LOSS

Hearing impairment among older adults is of public health significance. Nearly 33% of Americans 70 years or older have some degree of hearing impairment[1]. The World Health Organization also ranks hearing loss as the 15th greatest cause of the burden of disease in disability-adjusted life years[2]. Not only does hearing difficulty affect communication processes, but it also has been shown to lead to a lower quality of life, decreased functional capacity, and poorer psychosocial functioning[3-7]. It is therefore important to better understand the causes of hearing loss so that more effective prevention methods can be developed.

While several causes of hearing loss have been identified, including environmental and occupational noise exposure, infectious diseases, hereditary diseases, and otosclerosis among others, the most common cause of hearing loss is presbycusis[8]. Presbycusis is defined as hearing loss due to age and has been characterized into four types based on the suspected cause and location of hearing loss. These types are sensory, neural, strial, and cochlear conductive presbycusis[9]. The precise etiology of presbycusis, however, is still unknown and is likely to be a combination of various factors. Among those factors are chronic diseases, such as cardiovascular disease (CVD) and diabetes. If associated with presbycusis, these diseases may offer insight into alternative prevention methods for hearing loss because they and their risk factors are potentially modifiable.

1.1. ASSOCIATION OF CARDIOVASCULAR DISEASE AND HEARING LOSS

Several epidemiological studies have been conducted to examine the hypothesis that cardiovascular disease and its risk factors are linked with hearing loss. The association between CVD and hearing loss is strongest among those with clinical CVD such as coronary heart disease, stroke, and intermittent claudication[10-14]. Several of these studies, however, suffer from limitations such as inadequate sample size and control populations, and lack of information on potential cofounders such as a history of a noisy occupation[10-13].

The association between hearing loss and several CVD risk factors such as blood pressure, hyperlipidemia, clotting factors, and smoking has also been examined although the results are in many instances conflicting. Hypertension has been found to be associated with poor auditory function in several different populations[10,14-16]. Literature also supports the role of hypotension and acute and chronic sensorineural hearing loss[17,18]. Low HDL levels were associated with worse auditory function particularly in women[14,19-21]. Smoking has been linked with hearing loss by exerting ototoxic effects on the cochlea via vasoconstriction[22,23]. Other risk factors such as cholesterol, heart rate, and fibrinogen among others, have not been consistently linked with worse hearing function in the literature[14,16,19,24,25].

Although individual CVD risk factors themselves may not lead to hearing loss, the overall CVD process may, particularly since hearing loss has been linked with clinical CVD. It is therefore of interest to examine the association between aspects of subclinical CVD, such as peripheral arterial disease and arterial stiffness, with hearing loss as well.

1.2. ASSOCIATION OF DIABETES AND THE METABOLIC SYNDROME WITH HEARING LOSS

The relationship between diabetes and hearing loss has been examined in several epidemiological studies with findings being equivocal[26-41]. While the majority of studies have found a positive association between diabetes and hearing loss[27,29-32,36,39-41], many suffer from limitations such as small sample size and lack of an appropriate control population[27,32,37]. Of the four population based studies to our knowledge that have examined the association of diabetes with hearing loss[14,36,40,42], two found a modest positive association [36,42]and one found a positive association among those diabetics who were not using insulin medications[40].

Metabolic syndrome is highly prevalent among persons with diabetes and is a risk factor for both diabetes and CVD. To date, no study has specifically addressed the role of the metabolic syndrome, a potential precursor of diabetes and CVD, with hearing sensitivity.

1.3. BIOLOGICAL MECHANISMS

The biological premise upon which the above epidemiological studies were conducted is described within this section. Cardiovascular disease can contribute to presbycusis via a number of mechanisms. One hypothesis, pertaining to strial presbycusis, is that systemic

cardiovascular disease, such as atherosclerosis, contributes to decreased blood flow within the capillaries of the inner ear and thickens capillary walls [43,44]. This in turn may impede transport of nutrients or ions within the inner ear, thereby affecting the chemical composition of endolymph, an inner ear fluid. Subsequently, the transduction of energy to the auditory neurons is altered and low-frequency hearing function is primarily affected.

Diabetes has also been linked with strial presbycusis through similar mechanisms. Histopathological studies of diabetic ears have observed microangiopathy, including basement membrane thickening of the stria vascularis, in both the peripheral and central auditory systems [45-47].

Alternative hypotheses whereby CVD and diabetes may contribute to hearing loss are associated with sensory presbycusis. Insufficient or disrupted blood flow to the stria vascularis as a result of systemic atherosclerosis, may lead to the degradation of hair cells; this in turn is directly related to a loss in hearing sensitivity, particularly at high frequencies[48,49]. Diabetes can also contribute to presbycusis by promoting atherosclerosis, thus acting via the same biological pathway.

Additional research has suggested that diabetes-promoted thickening of the endolymphatic sac may cause an accumulation of toxic waste products within the endolymph leading to subsequent hair cell dysfunction [30,50]. Neuropathy, particularly of the VIII cranial nerve which is involved in the central auditory pathway, is another means whereby diabetes can affect hearing function[46].

1.4. HYPOTHESES AND SPECIFIC AIMS

It is evident from biological and epidemiological studies that both CVD and diabetes may contribute to the development of presbycusis. The literature, however, is lacking with respect to examining these associations in population-based cohorts, particularly those comprised of different races. Additionally, no study has examined the association between subclinical cardiovascular disease and metabolic syndrome with hearing loss.

We hypothesize that CVD risk factors and clinical and subclinical CVD along with diabetes and the metabolic syndrome will be positively associated with hearing loss in a population of healthy, older black men and women. To specifically address these hypotheses and existing limitations in the literature, this dissertation research has the following specific aims:

1. To investigate whether hearing sensitivity is associated with cardiovascular disease risk factors (weight, cholesterol, lipids, glucose, blood pressure, and smoking status) independent of common hearing loss risk factors such as age and history of a noisy occupation.
2. To determine whether hearing sensitivity is associated with subclinical cardiovascular disease measures such as pulse-wave velocity and ankle-arm index independent of hearing loss risk factors.
3. To determine whether participants with clinical cardiovascular disease (coronary heart disease, myocardial infarction, and stroke) have worse hearing thresholds than those without.

4. To determine whether participants with diabetes have poorer hearing thresholds and a higher prevalence of hearing loss than those without diabetes after controlling for common hearing risk factors.
5. To determine whether participants with metabolic syndrome have poorer hearing thresholds than those without after controlling for common hearing risk factors.
6. To examine differences in the above associations by gender/racial groups.

2. HEARING LOSS: ASSOCIATIONS WITH CLINICAL AND SUBCLINICAL CARDIOVASCULAR DISEASE WITHIN THE HEALTH, AGING, AND BODY COMPOSITION STUDY

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2.1. ABSTRACT

Cardiovascular disease (CVD) and its precursors may play a role in the etiology of age-associated hearing loss by affecting blood flow to and within the inner ear. The association between hearing loss, clinical and subclinical CVD, and CVD risk factors was examined to explore this hypothesis using data from the Health, Aging, and Body Composition Study (Health ABC).

Audiometric puretone thresholds were obtained at the 4th annual follow-up visit of the Health ABC Study in 2,049 well-functioning adults (mean age = 77.5 ± 2.8 years; 37% Black). Puretone averages reflecting a mid (PTA_{mid}: 500, 1000, and 2000 Hz) and a high (PTA_{hi}: 2000, 4000, and 8000 Hz) frequency emphasis were calculated for each ear. History of a clinical CVD event was determined at the fourth annual follow-up visit as well. CVD risk factors, aortic pulse-wave velocity, and ankle-arm index were evaluated from baseline measures.

Aside from black women with a history of stroke, persons with a history of clinical cardiovascular disease did not have poorer hearing than those without a history. Age and white race were associated with higher PTAs and were subsequently adjusted for in regression analyses along with study site. Separate linear regression models for PTA were constructed for each cardiovascular risk factor. Risk factors independently and positively associated with an increase in PTA_{mid} were: weight, insulin, glucose, triglycerides, and history of smoking in males and heart rate and fasting glucose in women ($p<0.05$). For PTA_{hi}, similar results were obtained with the exception of smoking becoming significantly associated with poorer hearing in females and glucose no longer

being associated with hearing function in males. Additionally, an increase of 25 cm/s in PWV and presence of peripheral arterial disease, as assessed by ankle-arm index, were independently associated with worse hearing thresholds in women when using the better hearing ear as an outcome.

Collectively these results suggest that CVD may play a role in the development of hearing loss, particularly presbycusis (age-related hearing loss). This research marks a novel finding and is the first to evaluate subclincial CVD and its relationship with presbycusis in a population of blacks and whites. Further research should delineate how each of these factors relates to hearing loss and which of these factors may be modifiable.

2.2. INTRODUCTION

Approximately 33% of Americans age 70 years or older suffer from some level of hearing loss, most typically a sensorineural hearing loss(1). This type of hearing loss has a significant impact on quality of life, physical function, and psychosocial well-being and constitutes an important public health problem(2-6). While hearing loss may be attributed to several factors, the most common cause is presbycusis or hearing loss attributed to age(7).

The precise etiology of presbycusis is unknown and is likely to be a combination of various factors. The cardiovascular system may play a role in the causal pathway. Early studies conducted by Rosen et al.(8) within members of the Mabaan tribe of Central Africa attributed the absence of high frequency hearing loss to the absence of

elevated blood pressure in the tribe. Additional studies by Rosen et al. found that patients given a low-fat diet and with a lower prevalence of coronary heart disease had better hearing compared to a control group given a diet high in saturated fats(9, 10).

In contrast, other studies that have specifically looked at components of blood chemistry including lipids, glucose, and clotting factors among others, have found few if any associations with hearing level(11, 12). Most recently, the Framingham study has reported that only high systolic blood pressure in men and women and high glucose and low HDL in women alone were associated with hearing loss, particularly at low frequencies(13). However, prevalent clinical CVD was associated with higher odds of low-frequency hearing loss in the Framingham study, suggesting that the CVD process itself may impact hearing function as opposed to its individual risk factors.

Thus, there is evidence to suggest that CVD may play a role in initiating or exacerbating presbycusis. The purpose of this study is to further investigate the relationship between hearing sensitivity and CVD risk factors and clinical and subclinical CVD within a population of black and white community-dwelling older adults. Of special interest is the consideration of subclinical measures of CVD including the ankle-arm blood pressure index, a surrogate measure of peripheral occlusion, and aortic pulse-wave velocity, an indicator of central artery stiffness. Although risk factors for hearing loss have been examined in this cohort before(14), this report will be one of the first to examine the relationship of subclinical measures of CVD and hearing loss in a large community-based population of blacks and whites and may provide further insight into the pathophysiologic mechanism by which CVD or its precursors contribute to hearing loss.

2.3. METHODS

2.3.1. Study Population

The Health, Aging, and Body Composition (Health ABC) study is a population-based prospective cohort study designed to examine the impact of changes in weight and body composition on age-related physiological and functional changes. The cohort was established between March 1997 and July 1998. Participants aged 70-79 years of age were drawn from a random sample of Medicare beneficiaries residing in ZIP codes surrounding two metropolitan centers, Pittsburgh, PA and Memphis, TN. Eligibility criteria consisted of reporting twice before enrollment being able to walk a quarter of a mile without difficulty, being able to walk up a flight of stairs without difficulty, and having the ability to perform basic activities of daily living such as getting in and out of a bed or chair, bathing, dressing, and eating. In addition, they had to have no life threatening illness and no intention to move from their respective metropolitan area for 3 or more years.

The Health ABC baseline cohort consisted of 3,075 men (48%) and women (52%) with 42% of the cohort classified as Black. The present analysis utilized 2,203 members of the cohort with complete audiometric data obtained at their fourth annual follow-up examination. Persons with both ears completely obstructed were excluded from analysis (N=154). Thus our analysis sample consisted of 2,049 participants who were 52% female and 37% Black. The study protocol and informed consent forms signed by all participants have been approved by the institutional review boards of the University of Pittsburgh and University of Tennessee.

2.3.2. Audiometric Assessment

Audiometric evaluations were conducted in a sound-treated booth within a quiet examination room during the fourth annual Health ABC follow-up examination (2001-2002). Information on ear infections, tinnitus, ear surgery, use of hearing aids, limitations associated with hearing, and prior noise exposure was obtained. Prior to the audiometric examination, the ear canal was examined for evidence of occlusion due to cerumen. If both ears were completely obstructed, the participant was excluded from analysis.

Air conduction puretone thresholds were obtained for audiometric frequencies between 250-8,000 Hz using a portable puretone audiometer calibrated to current ANSI standards. Thresholds were measured using earphones and reported as hearing level in decibels (dB HL) using the American Speech and Hearing Association guidelines for puretone audiometry(15). Mid frequency puretone averages (PTA_{mid}) were calculated by averaging the hearing thresholds at frequencies of 500, 1000, and 2000 Hz. High frequency puretone averages (PTA_{hi}) were calculated by averaging hearing thresholds at frequencies of 2000, 4000, and 8000 Hz.

2.3.3. Pulse-Wave Velocity

Aortic pulse wave velocity was obtained using nondirectional transcutaneous Doppler flow probes by Parks Medical Electronics Inc. (model 810A, 9.0 – 10.0 MHz probes) during the baseline visit. All study personnel involved in the collection of PWV data

were trained and certified by the National Institute of Aging, Laboratory of Cardiovascular Science, Gerontology Research Center (Baltimore, MD). Pulsatile flow was measured from simultaneous flow signals obtained from the right carotid and femoral arteries. Data in the form of 10-second waveforms were recorded by customized programming for later analysis. Three separate pulsatile flow runs were ascertained for each participant. Distance between the carotid to femoral probes was measured above the surface of the body with a metal tape measure. Pulse wave velocity (PWV) was calculated as the time in seconds between the foot of the velocity signal at the carotid and femoral sites divided by the associated carotid to femoral distance in centimeters. Data from all usable runs was averaged and the resulting value was used for analysis. A faster PWV reflects a stiffer vessel.

2.3.4. Ankle-Arm Index and Blood Pressure

Two seated resting blood pressures were taken at each clinic visit using stethoscopes and sphygmomanometers and then were averaged. Ankle-arm blood pressure was collected at the baseline and third annual follow-up clinic visits. Blood pressures were measured on the right arm and both ankles using a hand-held 8 MHz Doppler probe with built-in speaker and mercury column sphygmomanometers. Ankle-arm index (AAI) was subsequently calculated as the average of two ratios between the tibial and brachial arteries. The lower of the left and right ankle-arm indices was used to classify the individual presence of lower extremity arterial disease, defined as an AAI of less than 0.9 based on the baseline AAI assessment.

2.3.5. Laboratory and Additional Clinic Data

Medical history was ascertained by questionnaire at each annual visit. Participants were asked whether a physician had informed them of specific health conditions, including stroke, myocardial infarction, or coronary heart disease. A participant was classified as having prevalent CVD if they reported any of the above outcomes at any of the five annual examinations, if they were taking medications specific to the disease at the baseline exam, or if they were hospitalized for a CVD event during follow-up. Smoking status and alcohol use were ascertained via questionnaire at the baseline visit. Medication history was assessed at each clinic visit with the exception of third annual follow-up visit.

Blood chemistries were analyzed using samples collected in the baseline Health ABC clinic visit. The following assays were carried out using a colorimetric technique on a Johnson and Johnson Vitros 950 analyzer: glucose, triglycerides, and HDL. HDL was determined after magnetic precipitation of LDL, VLDL, and chylomicrons. The Friedwald equation was used to estimate LDL values(16). Fasting insulin was assayed with a microparticle enzyme immunoassay.

Anthropometric measurements for height, weight, and girth were assessed at the baseline visit. Standing height was measured using a stadiometer and weight was measured with a standard balance-beam scale with the participant wearing lightweight clothing. For consistency, all risk factor measurements used in analysis, including those obtained from blood chemistry, were from the baseline visit, four years prior to the audiometric evaluation.

2.3.6. Statistical Analysis Techniques

Gender differences between risk factors were assessed with a t-test or a Wilcoxon signed rank test. Chi-square tests were used for categorical variables. The primary outcome measures were PTA_{mid} and PTA_{hi} in the worse ear. PTA_{mid} was log transformed in order to normalize its distribution.

All analyses were stratified by gender. Analysis of covariance was used to ascertain age and race-adjusted means for prevalent clinical CVD outcomes (history of stroke, coronary heart disease, myocardial infarction, and prevalent CVD) with hearing level in the worse ear (continuous PTA). Linear regression was used to assess the association between PTA and the continuous cardiovascular risk factors. A standardized estimate was calculated in order to compare the individual models and a p-value of <0.05 was considered statistically significant. All regression models were adjusted for age, site, and race. With the exception of site, these risk factors were selected as the primary confounders given their known relationship with hearing sensitivity. The models were stratified by gender since gender*risk factor interactions were significant. Race and risk factor interactions were tested to determine if an analysis stratified by race also was warranted. Only one race/risk factor interactions was statistically significant, weight in males; therefore the analysis was not stratified by race.

Lastly, the relationship between cardiovascular risk factors and hearing level also was evaluated using multivariable stepwise linear regression analysis. Baseline age, site, and race were forced into the models followed by those baseline risk factors that were significant at the $p<0.15$ level initially. Risk factors were then eliminated in a step down

procedure until all remaining independent predictors were significant at $p < 0.05$. All data were analyzed by SAS Statistical Software v8.2 (Cary, NC).

2.4. RESULTS

Risk factor data for the baseline cohort are presented in Table 1. Significant gender differences ($p<.05$) were noted for all variables with the exception of systolic blood pressure, fasting insulin, triglycerides, lower extremity arterial disease (AAI <0.9), history of stroke, and years of education. When stratified by race within gender, significant differences between black and white women were noted for all baseline risk factors with the exception heart rate, LDL, and total cholesterol. Black women had higher levels of weight, blood pressure, glucose, insulin, HDL, and pulse wave velocity and lower levels of triglycerides. Among males, black men had significantly higher blood pressure and HDL and lower triglycerides compared to white men.

Table 2 presents mean and median puretone averages for high and middle frequency ranges respectively. Due to the non-normal distribution of PTA_{mid}, median values are presented with the interquartile range. Men had a higher puretone average which translated into a higher prevalence of hearing loss. When stratified by race, black women consistently had the lowest puretone average in the worse ear (PTA_{mid}=28.3 PTA_{hi}=45.7) followed by black men (PTA_{mid}=28.3, PTA_{hi}=52.1), white women (PTA_{mid}=30.0, PTA_{hi}=52.0), and white men (PTA_{mid}=31.7, PTA_{hi}=63.4).

The prevalence of CVD (history of stroke, myocardial infarction, or coronary heart disease) in the population was 42.5% for men and 29.4% for women at the time of the hearing examination. Age, race, and site-adjusted mean hearing thresholds for mid-range and high-range frequencies were calculated for participants with a history of a CVD-related event and for those without (Table 3). No significant differences were noted between males and females who had a history of a clinical CVD condition and those without a history. However, black females with a history of stroke did have significantly higher hearing thresholds at higher frequencies compared to those without a history ($p<0.01$).

Mid-frequency and high-frequency hearing thresholds were highly correlated ($p<0.0001$) with age ($r_{mid}=0.197$, $r_{hi}=0.198$). Given that age and race have consistently been shown in the literature to be known risk factors, they were included as covariates in all models. Results of regression models for individual CVD risk factors that controlled for age, race, and site are presented in Tables 4 and 5 for middle and high frequency hearing thresholds in the worse ear respectively. Standardized estimates are presented so that comparisons across the individual risk factors can be more easily assessed.

The following risk factors were significantly associated with an increase in mid-frequency PTA in men: heavier weight, greater fasting insulin, fasting glucose, triglycerides, and history of smoking. For women, faster resting heart rate and higher fasting glucose were statistically significant. For high frequency PTA, similar results were noted with the exception of glucose no longer being associated in males and history of smoking in females becoming significant. These significant associations persisted upon further adjustment for occupational noise exposure.

Interactions between race and the individual risk factors also were tested within the above models. Significant interactions with race were only found for weight in men. White men who were heavier had poorer hearing whereas in black men, those who were heavier had better hearing.

The previous analyses were repeated using the puretone averages of the better ear as an outcome. Significant relationships were identical with a few exceptions. Within women, an ankle arm-index of less than 0.9, pulse-wave velocity, and a history of smoking also were significantly associated with PTA_{mid} and PTA_{hi}. History of smoking also was associated with worse mid-frequency hearing function in both men and women. Lastly, glucose was not associated with PTA_{mid} in men.

To assess multivariable model inclusion criteria, univariate regression models were created with each risk factor and hearing outcome. Risk factors significant at the $p<0.15$ level were entered into the linear regression model. For men, higher insulin continued to be associated with PTA_{mid} and triglycerides with PTA_{hi} and little else contributed to the model aside from history of a noisy job. For women, age, race, heart rate, and pulse-wave velocity remained in the model predicting PTA_{hi}. For PTA_{mid}, faster resting heart rate and smoking history were the only risk factors which contributed to the model after adjusting for age and race.

Table 2-1: Baseline Population Description by Gender

Characteristic	Male N=968	Female N=1081	p-value
Baseline characteristics			
Age (years)	73.6 ± 2.8	73.3 ± 2.8	0.011
Race (black)	310 (32.0%)	451 (41.7%)	<.001
Weight (kg)	81.5 ± 13.4	70.4 ± 14.4	<.001
Systolic blood pressure (mm Hg)	134.7 ± 19.8	135.9 ± 20.0	0.775
Diastolic blood pressure (mm Hg)	72.6 ± 11.3	69.8 ± 11.7	<.001
Heart rate (beats/minute)	62.0 (56.0 – 70.0)	65.0 (58.0 – 72.0)	0.006
Fasting glucose (mg/dL)	96.0 (89.0 – 108.0)	92.0 (85.0 – 101.0)	<.001
Fasting insulin (IU/mL)	6.7 (4.9 – 9.9)	7.0 (4.9 – 10.3)	0.463
Cholesterol (mg/dL)	192.5 ± 34.9	213.5 ± 38.1	<.001
LDL (mg/dL)	118.6 ± 32.3	125.2 ± 35.6	<.001
HDL (mg/dL)	45.0 (38.0 – 54.0)	58.0 (48.0-69.0)	<.001
Triglycerides (mg/dL)	119.0 (88.5 – 163.0)	120.0 (92.0 – 168.0)	0.297
Pulse-wave velocity (cm/s)*	831.0 (644.0 – 1083.3)	772.5 (608.0 – 986.0)	0.001
Ankle Arm Index < 0.9 (column %)	110 (11.9%)	128 (12.4%)	0.782
Current smoker (column %)	83 (8.6%)	84 (7.8%)	<.001
Past smoker (column %)	578 (59.8%)	364 (33.7%)	<.001
12 years education or above (column %)	736 (76.0%)	864 (79.9%)	0.037
History of noisy job or occupation (column %)	484 (50.2%)	133 (12.4%)	<.001
Characteristics at fourth annual follow-up visit			
History of CVD† (column %)	411 (42.5%)	318 (29.4%)	<.001
History of coronary heart disease (column %)	350 (36.2%)	245 (22.7%)	<.001
History of stroke (column %)	132 (13.6%)	121 (11.2%)	0.093
History of myocardial infarction	289 (29.9%)	189 (17.5%)	<.001

*N=784 & N=911
†Includes history of coronary heart disease, myocardial infarction, or stroke
Means presented with standard deviation and t-test p-values
Medians presented with interquartile range and Wilcoxon test p-values
Frequencies presented with N and chi-square p-values

Table 2-2: Median Mid-Frequency and Mean High-Frequency Hearing Levels by Gender

Characteristic	Male N=968	Female N=1081	p-value
Better ear mid-frequency PTA	23.3 (15.8 – 35.0)	21.7 (15.0 – 31.7)	<.001
Worse ear mid-frequency PTA	30.0 (21.7 – 43.3)	28.3 (20.0 – 38.3)	<.001
Better ear high-frequency PTA	51.0 ± 16.5	41.5 ± 15.3	<.001
Worse ear high-frequency PTA	59.8 ± 17.1	49.4 ± 16.3	<.001

Mid Frequency PTA defined as average of 500, 1000, and 2000 Hz hearing levels
High Frequency PTA defined as average of 2000, 4000, and 8000 Hz hearing levels

Table 2-3: Age, Race, and Site Adjusted Mean Levels of Hearing by Concurrent Disease Status

CVD outcome	N	PTA_{mid}	PTA_{hi}
MEN			
Cardiovascular disease			
No	557	33.2	59.5
Yes	411	34.0	60.1
P		0.437	0.568
Myocardial infarction			
No	679	33.8	59.9
Yes	289	32.8	59.5
P		0.381	0.727
Stroke			
No	836	33.5	60.0
Yes	132	33.7	58.7
P		0.909	0.400
Coronary heart disease			
No	618	33.7	59.8
Yes	350	33.3	59.7
P		0.725	0.897
WOMEN			
Cardiovascular disease			
No	763	30.5	48.9
Yes	318	31.7	50.5
P		0.204	0.137
Myocardial infarction			
No	892	30.7	49.4
Yes	189	31.5	49.5
P		0.506	0.912
Stroke			
No	960	30.7	49.1
Yes	121	32.2	51.9
P		0.297	0.06
Coronary heart disease			
No	836	30.7	49.2
Yes	245	31.5	49.9
P		0.444	0.594

PTA_{mid}: Puretone average of 500, 1000, and 2000 Hz hearing levels
PTA_{hi}: Puretone average of 2000, 4000, and 8000 Hz hearing levels

Table 2-4: Mid Frequency Hearing Thresholds and Baseline Risk Factors Adjusted* logPTA$_{mid}$ Standardized Regression Coefficients

Risk Factor	Male N=968		Female N=1081	
	Standardized β	*p-value*	*Standardized β*	*p-value*
Weight (kg)	0.079	0.012	0.027	0.392
Systolic Blood Pressure (mm Hg)	0.046	0.144	0.0001	0.996
Diastolic Blood Pressure (mm Hg)	0.024	0.467	-0.023	0.466
Heart Rate (beats/minute)	0.057	0.071	0.089	0.003
Fasting Glucose (mg/dL)	0.069	0.028	0.069	0.023
Fasting Insulin (Iu/mL)	0.080	0.015	0.003	0.929
Cholesterol (mg/dL)	0.039	0.221	-0.029	0.346
LDL (mg/dL)	0.012	0.705	-0.050	0.097
HDL (mg/dL)	-0.021	0.521	0.013	0.661
Triglycerides (mg/dL)	0.104	0.011	0.010	0.760
Pulse-Wave Velocity (25 cm/s) †	0.019	0.587	0.048	0.154
AAI < 0.9	0.030	0.370	0.027	0.387
Past Smoker	0.066	0.036	0.035	0.249

*Adjusted for age, race, and site

†Also adjusts for SBP, N= 784 (males) and 911 (females)

PTA$_{mid}$: Puretone average of 500, 1000, and 2000 Hz hearing levels

Table 2-5: High Frequency Hearing Thresholds and Baseline Risk Factors Adjusted* PTA_{hi} Standardized Regression Coefficients

Risk factor	Male N=968		Female N=1081	
	Standardized β	*p-value*	*Standardized β*	*p-value*
Weight (kg)	0.072	0.017	0.015	0.640
Systolic blood pressure (mm Hg)	0.010	0.732	0.009	0.769
Diastolic blood pressure (mm Hg)	-0.012	0.713	0.007	0.817
Heart rate (beats/minute)	0.035	0.247	0.074	0.012
Fasting glucose (mg/dL)	0.032	0.282	0.072	0.015
Fasting insulin (IU/mL)	0.074	0.019	0.013	0.667
Cholesterol (mg/dL)	0.015	0.627	-0.030	0.317
LDL (mg/dL)	0.001	0.967	-0.053	0.075
HDL (mg/dL)	-0.027	0.385	0.014	0.637
Triglycerides (mg/dL)	0.066	0.032	0.014	0.656
Pulse-wave velocity (25 cm/s)†	0.002	0.951	0.056	0.092
AAI < 0.9	0.018	0.570	0.026	0.391
Past smoker	0.080	0.008	0.060	0.046

*Adjusted for age, race, and site

†Also adjusts for SBP, N= 784 (males) and 911 (females)

PTA_{hi}: Puretone average of 2000, 4000, and 8000 Hz hearing levels

2.5. DISCUSSION

Presbycusis has a multi-factorial etiology. This paper considers the contribution of CVD and related risk factors to age-related hearing loss within a population of well-functioning black and white elderly adults. The primary findings of this analysis were that subclinical CVD, particularly in women, and selected CVD risk factors such as weight, triglycerides, insulin, and glucose, were related to poorer hearing whereas clinical CVD was not. These aspects of CVD may offer some insight into possible etiological mechanisms related to the development of presbycusis. They will be discussed below in the context of existing literature and hypotheses.

Significant relationships between selected CVD risk factors and poorer auditory function were detected for both men and women in the Health ABC cohort. Higher weight, triglyceride, glucose, and insulin levels along with a history of smoking were correlates of mid-frequency hearing in men, whereas higher glucose levels and faster resting heart rate were correlates in women. For the higher frequencies, higher weight, triglyceride, blood insulin levels, and history of smoking were associated with poorer hearing among men, while risk factors among women included faster heart rate, higher glucose, and a history of smoking. After race stratification, higher blood pressure was associated with poorer mid-frequency hearing among white men as were higher triglycerides, glucose, and weight. In black women heart rate was associated with worse mid-frequency hearing. No risk factors were significantly related to mid-frequency hearing thresholds in black males or white females. For high frequencies the race-stratified results were similar with the exception of history of smoking being significantly

associated with worse hearing thresholds in white males and females along with glucose in black females and insulin in white females.

It is difficult to draw conclusions with respect to the mechanisms whereby each of these factors operates individually. Several authors have suggested that smoking contributes to hearing loss by affecting antioxidative mechanisms in the auditory system or by affecting the vasculature of the inner ear(17, 18). With respect to the other CVD risk factors–viewed collectively, they may be suggestive of a pre-diabetic state.

The relationship between diabetes and hearing impairment is equivocal. Of those studies where diabetic status was found to be correlated with hearing impairment, all suggested that the diabetic condition led to microvascular dysfunction within the inner ear (19-24). The markers of diabetes significant in our study, may be important because of individual effects on hearing or because they may act through the metabolic syndrome or full-blown diabetes. If so, these same CVD precursors could contribute to presbycusis by affecting the microvasculature of the inner ear, primarily the stria vascularis. The stria vascularis is a rich bed of membrane capillaries that supplies nutrients to cochlear components. Insufficient nutrient supply as a result of capillary constriction leads to hair cell damage and death resulting in subsequent hearing impairment.

The Framingham study is one of few studies that have also examined the association between CVD, CVD risk factors, and hearing loss in a large population of community-dwelling elderly adults. In the Framingham study population, significant associations between hypertension and poor hearing were found. Although not discussed by the authors, hypertension, along with insulin resistance, has been hypothesized to be a consequence of microvascular dysfunction (25, 26). Within Framingham women, a

significant positive relationship between blood glucose level (β= 0.0287, p=0.001) and age-adjusted low-frequency hearing level as well as a significant inverse relationship with HDL were also observed. Absence of a hearing sensitivity/lipid relationship in our study may reflect our cohort's better lipid profile.

Because Framingham defined low-frequency hearing thresholds as the pure tone average of 250, 500, and 1000 Hz, we repeated our analysis using this definition as well. Triglycerides, heart rate, and fasting glucose in men were significantly associated with low frequency hearing threshold after controlling for age, race, and site. Weight, insulin, and a history of smoking were borderline significant ($p<0.07$) in males. In women, fasting glucose and heart rate were significantly associated with low frequency hearing threshold consistent with our results using mid-frequency hearing thresholds.

Although the Framingham investigators found few other significant relationships between hearing sensitivity and CVD precursors, they did find a significant difference in age-adjusted mean levels of hearing by prevalent clinical CVD conditions. This is in contrast to our study where few differences were noted between hearing levels in persons with and without clinical CVD outcomes. Differences were confined to the general prevalent CVD classification in women for mid-frequency hearing thresholds in the better ear only.

The Framingham cohort was established when participants were less than 35 years of age. The Health ABC cohort on the other hand recruited healthy individuals at an older age (70-79). Therefore selection and survival bias may be operational within our cohort and account for the differences with the Framingham study. The inclusion of race as a confounder was also considered as a possible explanation for the disparate findings

in our population. However, upon repeating the analyses stratified by race and gender, a statistically significant difference between mean hearing level and clinical CVD was confined to stroke and high frequency auditory function in black females alone (those with stroke had worse hearing). It should also be noted the while CVD is extremely common among older adults it is also highly variable.

The Framingham study has suggested that rather than the CVD risk factors themselves impacting hearing it is the CVD process which impacts it. Thus far in our study, we have found that certain CVD risk factors are correlated with hearing impairment but that presence of clinical CVD is not. In order to provide some clues as to whether or not these risk factors act as part of the CVD process or act independently in a separate etiologic pathway, we chose to analyze the relationship between subclinical CVD measures and hearing sensitivity.

Atherosclerosis has been hypothesized to be responsible for hair cell and neuronal degeneration within the cochlea by affecting blood flow to the inner ear via stiffening or constriction of the internal auditory artery. Improper blood flow to the cochlea can cause a disruption in the chemical balance of the inner ear fluid, endolymph. This in turn affects the electrical activity of the hair cells and subsequently activation of the auditory nerve. In our population, two surrogate measures of atherosclerosis were evaluated. Both pulse-wave velocity, a measure of arterial stiffness, and peripheral arterial disease as assessed by ankle-arm index were significantly associated with poorer hearing levels in women when utilizing the better ear. These measures serve as intermediary indicators of the CVD disease process and may provide more direct evidence that macrovascular disease perhaps promoted by CVD risk factors such as weight, insulin, and glucose,

affects hearing loss. These risk factors were also found to be correlated with both pulse wave velocity and ankle arm index independently and after adjustment for age and systolic blood pressure (pulse wave velocity only).

The finding that subclinical CVD may be associated with auditory function in women but not men is curious. One explanation is that women are of lesser risk for exposure to sociocusis and noise-induced hearing loss. Therefore, the relationships between CVD and presbycusis are more easily observed. Alternatively, different pathophysiologic mechanisms possibly influenced by hormones may be in place(27). Finally, survival bias may again come into play since females have a higher life expectancy than males.

Since our findings are consistent for low and high frequencies, the supposition that CVD affects sensory presbycusis, a consequence of hair cell loss, and metabolic presbycusis, a consequence of strial atrophy, is supported. Without repeated epidemiological and histopathological studies it is difficult to assess for certain the mechanisms by which CVD or its precursors impact auditory function. Limitations of the present analysis are its cross sectional design and limited history of prior noise exposure. However, the study population has several strengths including its size and racial composition. As the cohort continues to be followed, a longitudinal component can be added to assess causal relationships particularly between subclinical CVD measures and deterioration of hearing.

In conclusion, the finding that subclinical CVD measures in women and CVD risk factors such as weight, insulin, and glucose are significantly related, to hearing impairment above and beyond well known hearing risk factors is of significant public

health interest. Upon further confirmation, CVD prevention and the modification of its risk factors may also be used as a means to slow the progression of presbycusis in older adults without traditional hearing loss risk factors.

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3. HEARING LOSS: ASSOCIATIONS WITH DIABETES AND THE METABOLIC SYNDROME WITHIN THE HEALTH, AGING, AND BODY COMPOSITION STUDY

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3.1. ABSTRACT

OBJECTIVE:

To evaluate the association of NIDDM and metabolic syndrome with hearing loss in a population of well-functioning, community dwelling blacks and whites.

RESEARCH DESIGN and METHODS:

Data from the Health, Aging, and Body Composition Study were used for the analyses. Audiometric puretone thresholds were obtained at the fourth annual follow-up visit in 2049 well-functioning adults (mean age = 77.5 ± 2.8 years; 37% Black). Puretone averages reflecting an average (PTAavg: 500, 1000, 2000, and 4000 Hz), mid (PTAmid: 500, 1000, and 2000 Hz) and a high (PTAhi: 2000, 4000, and 8000 Hz) frequency emphasis were calculated for the worse hearing ear. Participants were classified as being diabetic through self-report of doctor diagnosis, fasting glucose levels ≥ 126 mg/dL, or use of diabetic medication at any of the annual examinations.

RESULTS:

Diabetes was associated with mid frequency hearing loss, particularly in white males, white females, and black females. The odds of hearing loss among diabetic participants were 1.60 (95% CI: 1.26-2.02) upon adjustment for age, Health ABC site, race, gender, history of ear surgery, and history of a noisy job. The metabolic syndrome was associated with average and middle frequency hearing loss in white males and females prior to controlling for diabetic status. Upon excluding the 436 diabetics from the analysis, metabolic syndrome was only associated with average and middle frequency hearing loss in white females.

CONCLUSIONS:

This study found an association between NIDDM and mid-frequency hearing loss which suggests that diabetes may contribute to the development of presbycusis.

3.2. INTRODUCTION

Nearly 34% of elderly Americans report some degree of age-related sensorineural hearing impairment, or presbycusis(1). The precise etiology of presbycusis is unknown, however chronic diseases such as cardiovascular disease and diabetes appear to contribute to its development(2-4). Understanding the mechanisms by which these diseases result in hearing loss may provide insight into the causal pathway of presbycusis.

We have previously reported on the association of cardiovascular disease and hearing sensitivity in a cohort of elderly, well functioning, black and white men and women(5). Our primary results suggested that cardiovascular disease risk factors such as weight, insulin, glucose, and subclinical cardiovascular disease were associated with poorer hearing sensitivity. These same risk factors have also been linked with diabetes and the metabolic syndrome.

Diabetes may impact auditory function via both macro- and micro-vascular pathways. From a macrovascular perspective, diabetes may aid in the development of atherosclerosis, which subsequently affects blood flow through the internal auditory artery. Microvascular disease related to diabetes may result in hearing loss by altering

the capillaries of the stria vascularis or by causing neuronal degeneration within the auditory system(6, 7).

The results of previous studies on the relationship between diabetes and hearing loss have been equivocal(4, 6, 8-24). While the majority of studies have found a positive association between diabetes and hearing loss severity(4, 6, 9, 11-13, 17, 19-22, 24), many suffer from limitations such as small sample size and lack of an appropriate control population(6, 9, 13, 17). Additionally few studies used population-based samples and to our knowledge, none of the previous studies included older blacks (2, 4, 20, 24).

The purpose of this research is to assess the relationship between diabetes, specifically non-insulin dependent diabetes, and auditory function in a community based population of black and white males and females. In our previous research, we found an association between hearing loss and selected components of the metabolic syndrome(5). Since the metabolic syndrome is highly correlated with diabetes, the current investigation will also consider the possibility of an association between hearing loss and the metabolic syndrome taken as a whole. This study improves on previous research in several ways. It will be the first community-based study to consider the metabolic syndrome in relationship to hearing loss as well as one of the first to evaluate the association between diabetes and hearing loss within blacks.

3.3. METHODS

3.3.1. Study Population

The Health, Aging, and Body Composition (Health ABC) cohort was established between March 1997 and July 1998 in order to examine the impact of changes in weight and body composition on age-related physiological and functional changes. Participants were recruited from a random sample of Medicare beneficiaries ages 70-79 residing in ZIP codes surrounding two metropolitan centers, Pittsburgh, PA and Memphis, TN. All participants had to meet eligibility criteria which included an ability to perform basic activities of daily living, no difficulty in climbing 10 steps or walking one quarter of a mile, no affliction with a life threatening illness, and an intention to remain in their respective metropolitan area for 3 or more years.

The total Health ABC baseline cohort consisted of 3,075 men (48%) and women (52%) with 42% of the cohort classified as black. Hearing exams were completed in 2,203 members of the cohort. The present analysis excluded 154 persons due to impacted cerumen in both ear canals. This resulted in a total of 2,049 participants (52% females and 37% black) within our analysis sample. These participants did not differ from those excluded in the analysis with respect to risk factor characteristics. The institutional review boards of the University of Pittsburgh and University of Tennessee approved the study protocol and informed consent was obtained from all participants.

3.3.2. Audiometric Assessment

The Health ABC audiometric evaluation was conducted during the fourth Health ABC follow-up examination (2001-2002). Assessments were carried out under soundproof conditions according to American Speech-Language and Hearing Association guidelines(25). Prior to testing, a series of questions related to ear infections, tinnitus, ear surgery, use of hearing aids, limitations associated with hearing, and prior noise exposure were asked. Otoscopy was performed prior to testing to rule out cerumen impaction of the external ear canals.

Pure-tone air-conduction hearing thresholds were obtained at 250, 500, 1000, 2000, 4000, and 8000 Hz using a Maico MA-40 audiometer that was calibrated according to current ANSI standards (26). Auditory function was based on three pure-tone averages (PTA) using the worse-hearing ear; PTA_{avg} (mean of 500, 1000, 2000, and 4000 Hz), PTA_{mid}(mean of 500, 1000, and 2000 Hz), and PTA_{hi} (mean of 2000, 4000, and 8000 Hz). Hearing loss for each frequency range was defined as a PTA of greater than 25 dB HL (hearing level in decibels).

3.3.3. Definition of Diabetes and the Metabolic Syndrome

Participants were classified as having diabetes if they met any of the following criteria during any of their Health ABC clinic visits: self-report of doctor diagnosed diabetes, use of diabetic medication, or fasting glucose greater than or equal to 126mg/dL at their

baseline or third follow-up Health ABC examination. Duration of diabetes was categorized into three groups: <5 years, 5-15 years, and 15+ years.

Participants were asked during their baseline visit their age at time of diabetes diagnosis. This age was subtracted from their age at the time of audiometric evaluation to determine years of diabetes duration. Participants with incident diabetes during follow-up were classified in the <5 year category. Five participants with suspected insulin-dependent diabetes (age at diagnosis < 20 years) were categorized as not having diabetes since our focus was on non-insulin dependent diabetes (NIDDM).

Metabolic syndrome (MS) was defined using the Adult Treatment Panel III criteria(26). Briefly, a participant was classified as having MS if they had any three of the following components: waist circumference >102 cm in men and > 88 cm in women, triglycerides > 150 mg/dL, HDL < 40 mg/dL in men and <50 mg/dL in women, high blood pressure (≥130/85 mmHg), or high fasting glucose (≥110 mg/dL). Because all five components of MS were only simultaneously measured at the baseline clinic visit, MS status was defined at baseline. If a participant had missing values for the components of metabolic syndrome they were classified as missing metabolic syndrome status unless they were positive on 3 or more of their non-missing criterion in which case they were still classified as having MS.

3.3.4. Clinic and Laboratory Data

Medical history was ascertained by questionnaire at each annual visit. Participants were asked whether a physician had informed them of a particular health condition. A

participant was classified as having prevalent CVD if they reported stroke, myocardial infarction, or coronary heart disease at any of the five annual examinations, if they were taking medications specific to the disease at the baseline exam, or if they were hospitalized for a CVD event during follow-up. Smoking status was also ascertained via questionnaire at the baseline and fourth annual follow-up visits. Medication history was inventoried at each of the annual visits with the exception of the third Health ABC follow-up evaluation.

Anthropometric measurements for height, weight, and girth were assessed at the baseline visit and weight also was assessed at each subsequent follow-up visit. Standing height was measured using a stadiometer and weight was measured with a standard balance-beam scale with the participant wearing lightweight clothing. Body mass index was calculated as weight divided by the baseline height in meters squared. Waist circumference was measured at the maximum circumference in the region of the umbilicus using a flexible tape measure.

Two seated resting blood pressures were taken at each clinic visit and averaged. Ankle-arm blood pressures were measured using standard blood pressure cuffs and a Doppler ultrasound probe to detect systolic blood pressure. The Ankle Arm Index (AAI) was calculated as the ankle blood pressure divided by the brachial artery blood pressure. If this ratio was less than 0.9 a participant was classified as having a low AAI. Methods for determining aortic pulse wave velocity at the baseline visit have been described previously(5, 27). Stiffer vessels are characterized by faster PWV.

Blood chemistry was analyzed using samples collected in the baseline Health ABC clinic visit and the 3rd Health ABC follow-up visit. Triglycerides, HDL, LDL, and

fasting insulin were only assayed in the baseline clinic visit. Glucose, total cholesterol, fasting glucose, and hemoglobin A1c were measured at both the baseline and 3rd follow-up visits. Details of the assays for glucose, triglycerides, HDL, LDL, and fasting insulin have been described previously(5). Hemoglobin A1c, a measure of glycemic control, was determined using a Biorad Variant high-performance liquid chromatography assay. Lastly, baseline homeostasis model assessment (HOMA), an index of insulin resistance, was calculated as (fasting glucose x fasting insulin)/22.4. Data on the following risk factors were available from the baseline visit only: heart rate, fasting insulin, LDL cholesterol, HDL cholesterol, triglycerides, creatinine, pulse-wave velocity, HOMA, and metabolic syndrome.

3.3.5. Statistical Analysis Techniques

Differences between diabetic participants and non-diabetic participants were assessed with a t-test or a Wilcoxon signed rank test. Chi-square tests were used for categorical variables. The primary continuous outcome measures were PTA_{mid} and PTA_{hi} in the worse hearing ear. PTA_{mid} was log transformed in order to normalize its distribution. For logistic regression binary outcomes of hearing loss were used. These included hearing loss of at least 26 dB HL for average, middle, and high frequency ranges.

Analysis of covariance was used to ascertain age– and site– adjusted means for hearing level by diabetes and metabolic syndrome status in the overall sample and among race/gender strata.

Lastly, the relationship between hearing loss and diabetic status or metabolic syndrome presence was also evaluated using multivariable logistic regression analysis to adjust for possible confounders and covariates. Age, site, and history of ear surgery were forced into the models followed by those baseline risk factors that were significant at the $p<0.15$ level initially. Risk factors were then eliminated using backwards selection until all remaining independent predictors were significant at $p<0.05$. Exact methods were also employed when more appropriate.

The final models adjusted for age, Health ABC site, and history of ear surgery. Race and gender were controlled for in the models for the total population. The models for the total population and males were adjusted for history of a noisy occupation as well. All data were analyzed by SAS Statistical Software v8.2 (Cary, NC).

3.4. RESULTS

3.4.1. Diabetes and Hearing Sensitivity

A description of the population by diabetes status is presented in Table 1. Wherever possible, data from the clinic visit closest in date to the hearing examination was presented. Significant differences were noted between diabetic and non-diabetic participants for all risk factors except age, LDL cholesterol, history of smoking, and history of ear surgery. Aside from diastolic blood pressure, cholesterol, and education, diabetics had more adverse levels of the presented risk factors. It is especially interesting

to note that diabetic participants were more likely to be black, had a higher prevalence of peripheral arterial disease and arterial stiffness, as assessed by AAI and PWV respectively, and were more likely to meet the criteria for the metabolic syndrome.

Figure 1 presents adjusted mean hearing levels for the whole population as well as race and gender subgroups by diabetic status for each frequency range. For all frequency ranges, white male diabetic participants and black female diabetic participants had significantly higher hearing thresholds than non-diabetics upon adjustment for age and Health ABC site. These differences persisted upon further adjustment for history of a noisy job and history of ear surgery.

In order to assess whether diabetes was independently associated with hearing loss, logistic regression analyses were performed. These results are presented in Table 2. With the exception of black males, diabetes was significantly associated with hearing loss in the middle frequencies (500–2000 Hz) for all subgroups and the total population.

Using a backward selection technique, we also assessed whether additional risk factors not included in the original model should also be controlled for among the subgroups and total population. No other risk factors significantly contributed to the multivariable model except within white males. Within white males, weight and education also significantly contributed to the model predicting middle frequency hearing loss (OR=1.74, 95% CI: 1.10–2.74).

The OR for high frequency hearing loss in the total population was 1.47 (95% CI: 0.86–2.51) upon adjustment for age, site, race, gender, history of ear surgery, and history of a noisy job. When attempting to model the association between high frequency hearing loss and history of diabetes within each of the racial and gender subgroups it was

observed that in all instances at least 89% of individuals had high frequency hearing loss and less than 3% of those with diabetes did not have high frequency hearing loss. In exploratory exact logistic regression analyses, resulting confidence intervals were insignificant and large, most likely a result of these small cells. Due to the foreseen instability and variability of estimates, we chose not to model the association of high frequency hearing loss and diabetes within the racial and gender subgroups. Unadjusted differences in the proportion of diabetics with high frequency hearing loss versus those without were significant only in black females with diabetics having a higher proportion of hearing loss (Fishers's exact p-value=0.024). The analysis was also repeated using a less conservative cut-off for high frequency hearing loss (>40 dB), however this did not impact the results or add to the stability of the logistic models.

The contribution of duration of diabetes and glycemic control, as measured by HgA1c at the third follow-up examination, to hearing loss also was assessed in separate multivariable logistic regression models. Within all diabetics, neither duration of diabetes ($OR_{5\text{-}15years}$=0.76, p=0.332; $OR_{15+years}$=0.58, p=0.859) nor glycemic control (OR=0.89, p=0.149) were statistically associated with average frequency hearing loss after adjustment for age, site, gender, race, history or ear surgery, and history of a noisy job. Similar findings were observed when considering the association between duration of diabetes and glycemic control with middle and high frequency loss.

3.4.2. Metabolic Syndrome and Hearing Sensitivity

The overall prevalence of metabolic syndrome in our study population was 37.8% (n=765). Figure 2 shows the age and site adjusted mean PTA_{mid} and PTA_{hi} hearing levels for the whole population as well as race and gender groups by presence of metabolic syndrome. For both middle and high frequencies, white males and females with MS had higher hearing thresholds than those without MS. Additional analyses considered whether a trend was observed with the number of components of metabolic syndrome (0-5) and hearing thresholds; no trend was observed.

Multivariable-adjusted models of hearing loss based on MS status are presented in Table 3. The metabolic syndrome was significantly associated with average and middle frequency hearing loss in white males and females upon adjustment for age, Health ABC site, history of ear surgery, and in males, history of a noisy job as well.

The odds for high frequency hearing loss among individuals with MS was 1.40 (95% CI: 0.91-2.17) after adjusting for these same risk factors and race and gender. Separate models for high frequency hearing loss and race and gender subgroups were not constructed because of reasons matching those described earlier for the diabetes analysis. However, black females with metabolic syndrome were more likely to have high frequency hearing loss compared to those without MS (Fisher's exact p-value=0.045).

Since the metabolic syndrome was so prevalent among the diabetics we sought to further examine the association between metabolic syndrome and hearing loss without this potential confounder (Table 3). After excluding diabetic participants from the analysis, metabolic syndrome was significantly associated with average and middle

frequency hearing loss only among white females. The odds for high frequency hearing loss in non-diabetic participants with metabolic syndrome were 1.32 (95% CI: 0.77-2.25).

Table 3-1 Population Description by Diabetic Status (N=2,049)

Characteristic	Non-diabetic N=1,613	Diabetic N=436	p-value
Age (years)	73.4 ± 2.8	73.5 ± 2.7	0.699
Black race	548 (34.0%)	213 (49.0%)	<0.001
Female	876 (54.3%)	205 (47.0%)	0.007
BMI (kg/m^2)*	26.9 ± 4.8	28.9 ± 5.0	<0.001
Weight (kg)*	74.1 ± 14.6	81.2 ± 15.3	<0.001
Systolic blood pressure (mm Hg)*	134.5 ± 20.2	138.9 ± 22.3	0.027
Diastolic blood pressure (mm Hg)*	71.0 ± 10.9	69.2 ± 11.3	0.033
Heart rate (beats/minute)	63.9 (57 – 70)	68.0 (59.0 – 76.0)	<0.001
Fasting glucose (mg/dL)*	92.0 (86.0 – 98.0)	137.3 (108 – 154)	<0.001
Fasting insulin (IU/mL)	6.6 (4.7 – 9.6)	8.3 (5.9 – 12.4)	<0.001
Hemoglobin A1c*	5.3 (5.1 – 5.6)	6.7 (6.0 – 7.6)	<0.001
HOMA	27.1 (18.9-40.9)	48.7 (30.5 – 77.8)	<0.001
Creatinine (mg/dL)	1.0 (0.9 – 1.1)	1.0 (0.9 – 1.2)	0.012
Cholesterol (mg/dL)*	192.1 ± 36.4	186.5 ± 39.2	0.006
LDL (mg/dL)	122.3 ± 33.8	121.0 ± 35.6	0.558
HDL (mg/dL)	53.0 (43.0 – 64.0)	47.0 (39.0 – 56.0)	<0.001
Triglycerides (mg/dL)	116.0 (87.0 – 159.0)	137.0 (100.0 – 186.0)	<0.001
Metabolic syndrome	8.6%	42.0%	<0.001
Pulse-wave velocity (cm/s)†	778.0 (609.0 – 1008.7)	858.3 (689.4 – 1110.3)	<0.001
Ankle arm index < 0.9	164 (10.6%)	74 (18.2%)	<0.001
Current smoker	106 (6.6%)	20 (4.6%)	0.253
Past smoker	763 (47.6%)	218 (50.2%)	0.253
History of CVD	538 (33.4%)	191 (43.8%)	<.001
12 years education or above (column %)	1290 (80.0%)	310 (71.1%)	<.0001
History of noisy job or occupation (column %)	455 (28.4%)	162 (37.3%)	0.001
History of ear surgery	75 (4.7%)	23 (5.3%)	0.591

Means presented with standard deviation and t-test p-values
Medians presented with interquartile range and Wilcoxon test p-values
Frequencies presented with column % and chi-square p-values

*Risk factors were collected at the third (glucose, HgA1c, cholesterol, AAI) or fourth (blood pressure, weight) annual Health ABC follow-up visit
†N=1,343 non-diabetic and N=352 diabetic

Figure 3-1: Mean Levels of Hearing by Diabetic Status adjusted for age and Health ABC site

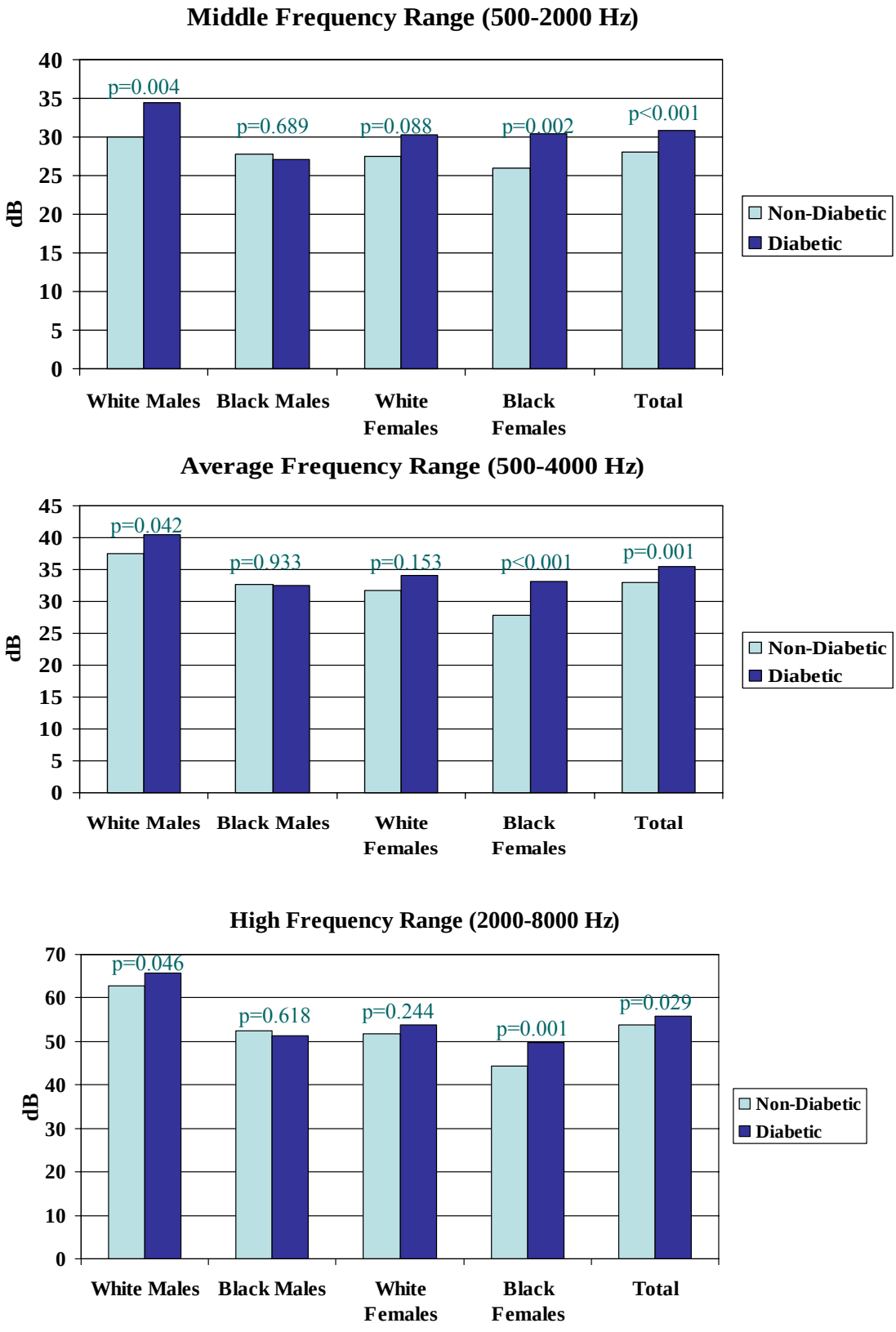

Table 3-2: Adjusted Odds of Hearing Loss and Diabetes

	Average Frequency Loss		Middle Frequency Loss	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Total Population[*]	1.27 (1.00-1.61)	0.054	1.60 (1.26-2.02)	<.001
White Males[†]	1.37 (0.83-2.25)	0.223	1.99 (1.27-3.11)	0.003
Black Males[†]	0.81 (0.48-1.36)	0.427	0.99 (0.59-1.64)	0.955
White Females[‡]	1.53 (0.92-2.53)	0.099	2.00 (1.20-3.33)	0.008
Black Females[‡]	1.48 (0.95-2.31)	0.087	1.69 (1.08-2.65)	0.022

[*]Adjusted for age, race, gender, site, history of ear surgery, and history of noisy job
[†]Adjusted for age, site, history of ear surgery, and history of noisy job
[‡]Adjusted for age, site, and history of ear surgery

Average Frequency Hearing Loss = PTA_{avg} (500, 1000, 2000, 4000) ≥ 26 dB HL
Middle Frequency Hearing Loss = PTA_{mid} (500, 1000, 2000) ≥ 26 dB HL

Figure 3-2: Mean Levels of Hearing by Presence of Metabolic Syndrome adjusted for age and Health ABC site

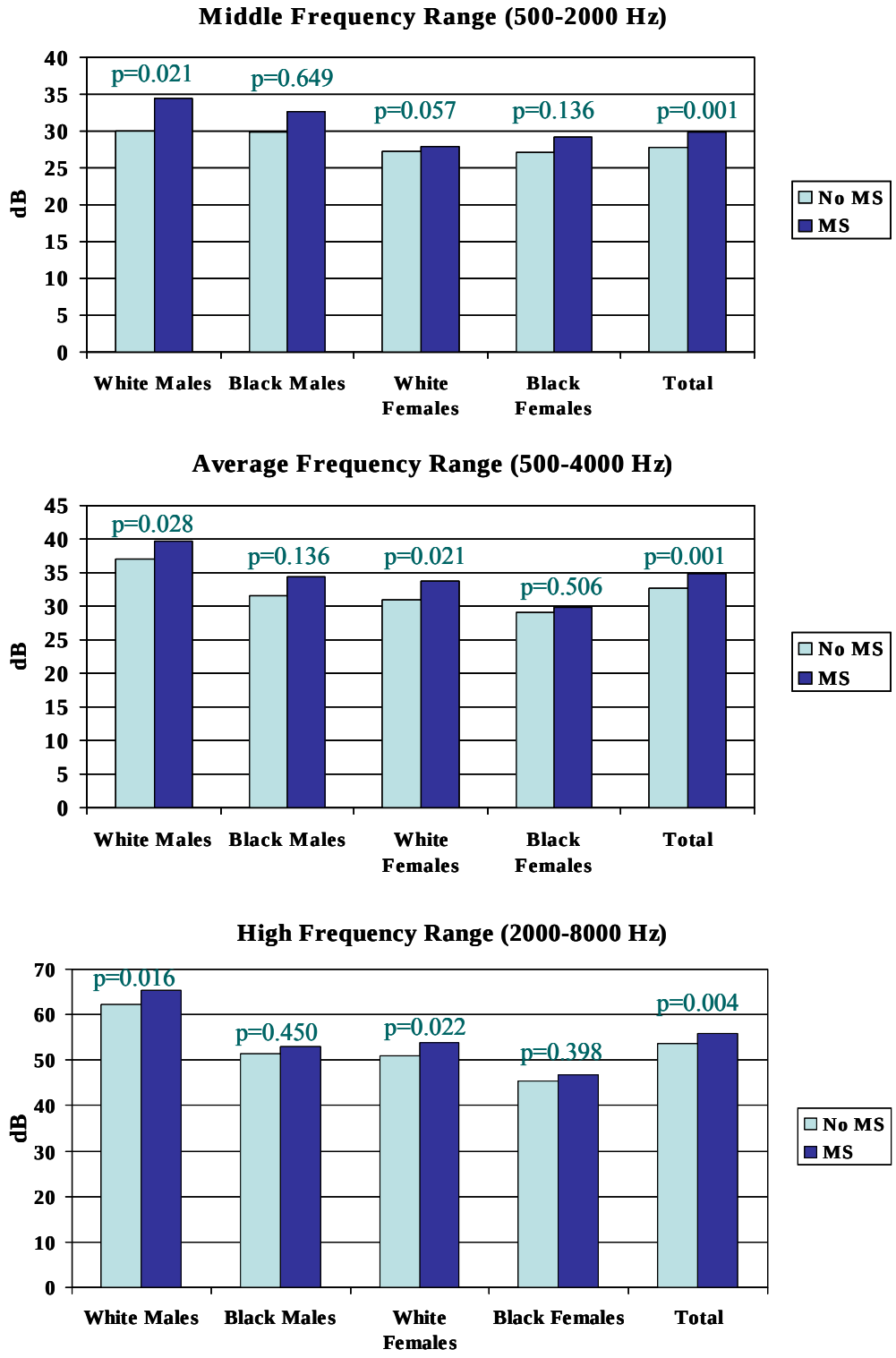

Table 3-3: Adjusted Odds of Hearing Loss and Metabolic Syndrome

N=2,049 – Full Study Population				
	Average Frequency Loss		Middle Frequency Loss	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Total Population*	1.30 (1.06-1.59)	0.011	1.38 (1.14-1.68)	0.001
White Males†	1.53 (1.01-2.30)	0.043	1.43 (1.01-2.02)	0.046
Black Males†	1.25 (0.74-2.10)	0.407	0.84 (0.51-1.40)	0.510
White Females‡	1.52 (1.07-2.14)	0.018	1.69 (1.20-2.37)	0.003
Black Females‡	0.88 (0.59-1.31)	0.514	1.35 (0.90-2.02)	0.142

N=1,613 – Excluding Diabetic Participants				
	Average Frequency Loss		Middle Frequency Loss	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Total Population*	1.21 (0.95-1.55)	0.127	1.16 (0.92-1.46)	0.214
White Males†	1.32 (0.81-2.16)	0.258	1.00 (0.66-1.51)	0.998
Black Males†	1.41 (0.65-3.06)	0.390	0.78 (0.38-1.61)	0.495
White Females‡	1.53 (1.04-2.25)	0.033	1.54 (1.05-2.24)	0.026
Black Females‡	0.64 (0.38-1.08)	0.093	1.01 (0.60-1.68)	0.986

*Adjusted for age, race, gender, site, history of ear surgery, and history of noisy job
†Adjusted for age, site, history of ear surgery, and history of noisy job
‡Adjusted for age, site, and history of ear surgery

Average Frequency Hearing Loss = PTA_{avg} (500, 1000, 2000, 4000) ≥ 26 dB HL
Middle Frequency Hearing Loss = PTA_{mid} (500, 1000, 2000) ≥ 26 dB HL

3.5. DISCUSSION

The purpose of this analysis was to characterize the association between hearing loss and diabetes and the metabolic syndrome among healthy older black and white men and women. The primary findings of this analysis were that diabetes was associated with at least a 60% increase in the odds of mid frequency hearing loss, particularly in white males, white females, and black females. The metabolic syndrome was associated with average and middle frequency hearing loss in white males and females prior to adjustment for diabetic status.

The finding that diabetes was associated with hearing loss at middle frequencies as opposed to higher frequencies suggests that it may play a role in the development of strial presbycusis. Strial presbycusis is characterized as an atrophy of the stria vascularis, a rich bed of capillaries, within the inner ear cochlea (28). The stria dictates the chemical composition of the endolymph which is responsible for the electrochemical potential that powers cochlear function.

Several histopathological studies have confirmed that diabetes leads to basement membrane thickening of the capillaries (6, 7, 29, 30). Diabetic microangiopathy has also been shown to lead to impairment of longitudinal flow within the endolymphatic sac. Narrowed pores or absent endothelial within the endolymphatic sac would limit the migration of macrophages and lymphocytes into or out of the sac. Thus, waste products may accumulate in the endolymph and impose toxic effects on the hair cells (6, 31).

Macrovascular disease has also been suggested as causing disturbances in the cochlear microvasculature. Fukui et al. found a relationship with carotid plaque score

and diabetic patients with idiopathic sudden hearing loss (32). Makishima also found narrowing of the lumen within the internal auditory artery(29, 33). Such changes in arterial structure as well as vascular lesions promoted by diabetes have the potential to alter blood flow to and within the cochlea. Low frequency hearing can be affected by any disturbance in blood flow since the blood supply of the cochlea is most distal at the apex of the cochlea where low frequency sounds are transduced. In our population diabetic participants had a higher prevalence of macrovascular disease characteristics such as peripheral arterial disease and stiffer vessels, as determined by PWV.

We repeated the analysis using a pure tone average of hearing thresholds at 250, 500, and 1000) Hz to calculate PTA_{low} and low frequency hearing loss (defined as $PTA_{low} \geq 26$ dB). Similar results were found except within white females where diabetes was not associated with low frequency hearing loss.

This study did not find an association with diabetes and high frequency hearing loss, although diabetic white males and black females did have significantly worse high-frequency hearing thresholds. This contrasts a previous study by Axelsson which did find an association(14). Possible explanations for the difference in these results may be our larger sample size, different population characteristics such as age and racial composition, or an unaccounted higher prevalence of noise-induced hearing loss within the Axelsson study which would have a greater impact on high frequency hearing loss.

To our knowledge this is the first population based study in the literature which has examined the association between diabetes and hearing loss in blacks and whites. Within the Beaver Dam cohort (N=3,571), a population of white men and women, a modest association between average frequency hearing loss and NIDDM was detected

upon excluding those with hearing loss inconsistent with presbycusis. Their models also adjusted for smoking status, education, and hypertension. While these risk factors have been linked with hearing loss in the literature (34, 35), they were not significantly related to hearing loss in our population. Glycemic control was not associated with hearing loss in the Beaver Dam population as well.

Within the Framingham Heart Study, no association between diabetes or impaired glucose tolerance was found (2). However, an association between higher blood glucose and higher (e.g. worse) low frequency hearing thresholds in women was observed. This is in agreement with previous findings in our population (5). Within Mexican Americans examined in the Hispanic Health and Nutrition Examination Survey, self-reported diabetics had higher hearing thresholds only at 500 Hz after adjustment for age, gender, marital status, and employment status. Among those diabetics who did not use insulin, hearing thresholds were higher than non-diabetics, suggesting that insulin use may be protective of diabetic hearing impairment. In our study, use of insulin medication was not associated with hearing thresholds or hearing loss.

The Beaver Dam study along with others examined diabetic neuropathy in conjunction with hearing loss. Neuropathy has also been linked with hearing loss via numerous mechanisms such as lesions on the cranial nerves, hypotension, tissue effects via the polylol pathway, and loss of peripheral nerve elements (17, 19, 29). Data collected on the Health ABC participants was limited to peripheral neuropathy and thus diabetic neuropathy could not be evaluated in this analysis but may be considered for future follow-up examinations.

The observation that black males with diabetes did not have significantly higher odds of hearing loss was curious. Melanin has been hypothesized as having a protective effect on hearing function although this would not fully explain why we did not observe similar odds among black females (36-38). Hearing function in females has been linked with hormones such as estradiol. Higher levels of estradiol have been linked with better hearing function (39). After the menopausal transition, however, levels of estradiol decrease and thus it is plausible that the effects of presbycusis become even more evident in females (40).

In order to distinguish whether diabetes itself or risk factors collectively associated with insulin resistance were associated with hearing loss we chose to examine the relationship between the metabolic syndrome and hearing loss. The prevalence of metabolic syndrome in our population was greater than that of national estimates (26). Metabolic syndrome was associated with hearing loss at average, middle, and low frequencies, particularly in white males and females.

Upon excluding diabetic participants from the metabolic syndrome analysis, however, MS was no longer significantly associated with hearing loss at any frequency range with the exception of average and middle frequency hearing loss in white females. This implies that diabetes is driving the association with metabolic syndrome and hearing loss. It is interesting to note that the metabolic syndrome was not associated with hearing loss in blacks, who overall have a lower prevalence of hearing loss than whites. Future research may focus on elucidating whether components of the metabolic syndrome act differently within whites compared to blacks.

Other opportunities for future research that would aid in addressing limitations of the present analysis include conducting a longitudinal study which would examine the temporal relationship between diabetes and incident hearing loss. To help determine the biological mechanism whereby diabetes affects hearing it may also be helpful to collect data on diabetic neuropathy, microvascular disease, and hormones. A detailed hearing history including job history, recreational activities, diseases of the ear, and ototoxic medication use among others would aid in delineating the effects of presbycusis alone. Additional research, whether cross-sectional or longitudinal, is also necessary in order to confirm our findings within blacks and women.

In summary, a positive association between diabetes and middle frequency hearing loss was observed in a population of well-functioning community dwelling blacks and whites. Middle frequency hearing loss is comparatively least affected by the effects of sociocusis and thus may serve as a better measure of the effects of presbycusis. Diabetes can exert its effect on hearing function via several pathways including those associated with strial presbycusis, macrovascular disease, and neuropathy. The metabolic syndrome was not found to be associated with hearing loss after excluding diabetic participants. Given that incidence rates for diabetes continue to increase, an even higher proportion of elderly may eventually suffer from some degree of hearing impairment. It is therefore of public health importance to confirm these findings through additional research so that appropriate prevention strategies can be designed.

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4. DISCUSSION: ASSOCIATION OF CHRONIC DISEASES TO AGE-RELATED HEARING LOSS

Given the high prevalence of hearing loss within older adults and subsequent impacts on quality of life, it is of public health importance to determine potentially modifiable causes of age-related hearing loss. Because cardiovascular disease and diabetes are preventable diseases with modifiable risk factors, this research sought to explore the association of these diseases and their risk factors with hearing sensitivity in a population of older black men and women.

Specifically, two separate analyses were conducted to assess the association of cardiovascular disease with hearing sensitivity and the association of diabetes with hearing sensitivity. Both analyses used data from the Health, Aging, and Body Composition (Health ABC) cohort. In this section the results of these studies are summarized and general conclusions are drawn. Additionally, the results will be discussed in the context of study limitations and existing literature. Finally, recommendations for future research will be made.

4.1. CARDIOVASCULAR DISEASE AND HEARING SENSITIVITY

In the first analysis it was hypothesized that clinical and subclinical cardiovascular disease (CVD) along with CVD risk factors would be associated with poorer hearing sensitivity. Upon adjustment for age, race, and Health ABC site, differences in hearing level were not observed between individuals with clinical CVD and those without. Positive associations between hearing thresholds in the better ear and the subclinical CVD measures of ankle-arm index and pulse wave velocity were observed in women only, although this was restricted to hearing thresholds in the better ear.

CVD risk factors which were associated with elevated mid-frequency hearing thresholds independent of age, race, and site were heavier weight, higher insulin, higher glucose, higher triglycerides, and a history of smoking in males and faster resting heart rate and fasting glucose in females. For high frequencies, heavier weight, higher insulin, and higher triglycerides were associated with worse hearing thresholds in males and faster heart rate, higher fasting glucose, and a history of smoking were associated with worse hearing in females, again independent of age, race, and site.

Literature which has specifically looked at the relationship between CVD and hearing sensitivity is sparse. Of the studies which have examined clinical CVD and hearing loss, three find a consistent positive association between presence of CVD and poorer hearing thresholds[11,13,14,51]. Although two of these studies were population-based[14,51], none had a significant sample of blacks within the study population. Our findings that clinical CVD was not associated with hearing may be the combination of selection bias and the fact that CVD prevalence is highly variable within older adults.

The literature is less consistent with respect to the association of various CVD risk factors with hearing function. This may be in part due to differences in sample size, population composition, and methods of measurement and analysis. In particular the following risk factors have been shown to be linked with hearing sensitivity in the literature: smoking[22,23,52], cholesterol[12,53,54], HDL[14,21], blood pressure[10,16]. However other studies have provided conflicting results [14,19,24].

Cholesterol and HDL have been linked to hearing sensitivity by promoting systemic atherosclerosis and vasoconstriction within the cochlear vessels. Systemic atherosclerosis has the potential to disturb blood flow within the inner ear, thus affecting auditory function. Smoking acts through similar mechanisms, in particular nicotine has been suggested as a cause of anemia of the cochlea via vasoconstriction[55].

Although CVD risk factors are not always associated with poor hearing thresholds, the significant associations observed with clinical CVD and hearing sensitivity suggest that perhaps the CVD process itself affects auditory function rather than risk factors alone. To date no study has specifically addressed other aspects of the CVD process such as subclinical disease. Our findings with respect to the relationship of subclinical disease and hearing function in women, while interesting, remain to be confirmed in other populations.

4.2. DIABETES AND HEARING SENSITIVITY

The second analysis focused on the association of diabetes and the metabolic syndrome with hearing sensitivity and loss. Based on existing literature, it was hypothesized that diabetes and the metabolic syndrome would be positively associated with hearing loss. Diabetes was primarily associated with mid frequency hearing loss in white males, white females, and black females after controlling for age, race, Health ABC site, history of ear surgery, and history of a noisy job (in men only). It is interesting that an association between diabetes and hearing loss was not observed in black males. This observation may help to explain why black men have a lower prevalence of hearing impairment compared to white men (i.e. auditory function in black men is not influenced by diabetes) or may simply be the result of selection bias. Diabetes was not associated with high frequency hearing loss although age-adjusted mean high frequency hearing thresholds were higher in diabetic white males and black females.

The metabolic syndrome was associated with average and middle frequency hearing loss in white males and females independent of age, site, history of ear surgery, and history of a noisy job (males only). However, after excluding diabetics from the analysis, metabolic syndrome was only associated with average and middle frequency hearing loss in white females.

Several studies have looked at the association between diabetes and hearing loss from both a histopathological and epidemiological perspective. Histopathological studies aid in helping to explain biological effects, however suffer from sample size limitations[30,45-47,56]. The results of epidemiology studies are equivocal. Of the four

largest and population-based studies examining the association of diabetes and hearing loss, three found modest positive associations[36,40,42] and the other found only an association with higher levels of glucose and low-frequency hearing loss in women[14]. Each of these studies, however, considered different covariates and definitions of hearing loss. Additionally, the studies were predominately restricted to one racial/ethnic group.

The metabolic syndrome is a strong risk factor for diabetes and cardiovascular disease and has been associated with microvascular disease as well [57-62]. Thus, it is plausible that the metabolic syndrome may also be associated with presbycusis. To my knowledge, no study has specifically evaluated the potential association of metabolic syndrome with hearing sensitivity.

4.3. GENERAL DISCUSSION

This portion of the dissertation focused on the contribution of chronic diseases and their components to hearing sensitivity and loss. The findings suggest that both the cardiovascular disease process and diabetes may play a role in the etiology of presbycusis via a number of related mechanisms.

CVD and diabetes are known comorbidities making it difficult to distinguish the effects of each separate from one another. Yet, when analyzing the association of CVD risk factors with hearing sensitivity, it was evident that those risk factors most commonly associated with diabetes and the insulin resistance syndrome were also associated with poorer hearing sensitivity. These risk factors include weight, triglycerides, glucose, and

insulin. Even heart rate has been suggested as a marker of insulin resistance since increased insulin levels stimulate the sympathetic nervous system resulting in an increase in heart rate[63]. Upon excluding diabetics from the CVD risk factor analysis, the following findings were observed. Within males, insulin and glucose were no longer significantly associated with puretone averages at middle (PTA_{mid}) and high (PTA_{hi}) frequencies and within females glucose was no longer associated with PTA_{mid} or PTA_{hi}.

Diabetics have significantly higher levels of each of these risk factors (glucose, insulin, weight, heart rate, triglycerides) and thus we suspect that they are in fact driving the observed associations. Diabetics have also been shown to have a higher prevalence of atherosclerosis[64]. Atherosclerosis has the potential to cause disturbances within inner ear blood flow[44,49,65]. Furthermore, diabetics are known to have a greater extent of microvascular disease and neuropathy, both of which can also impact auditory function[30,45,46].

Strial presbycusis is characterized by atrophy of the stria vascularis and a subsequent decline in middle frequency hearing sensitivity. Atrophy of the stria vascularis can be due to a variety of factors foremost among them microvascular disease. Diabetes was associated with higher odds of middle frequency hearing loss, not high frequency hearing loss. This suggests that diabetes contributes to strial presbycusis more so than sensory presbycusis. Sensory presbycusis is characterized to a certain extent by a loss of hair cells as a result of an insufficient supply of blood and nutrients possibly due to systemic cardiovascular disease.

Sample sizes were not sufficient to detect whether or not diabetics with clinical CVD had higher hearing thresholds than those without but our hypothesis is that those

diabetics with clinical CVD would have the highest prevalence of hearing loss. Based on the research conducted within this cohort, it can be concluded that diabetes plays a role in the etiology of presbycusis to a greater degree than CVD alone. Additionally, diabetes and CVD may contribute to the etiology of presbycusis to different degrees within certain race and gender groups. Further research is needed to confirm our conclusions and to understand differences between specific race and gender populations. Opportunities for future research are discussed in the following section.

4.4. FUTURE RESEARCH

The primary limitations of the present study include a cross-sectional study design and lack of information on other hearing loss risk factors such as noisy activities and hobbies, familial history, and ear-related diseases such as chronic otitis media, otosclerosis, and Meniere's disease. In order to address limitations of the present analysis and to confirm our findings in other populations the following research is proposed.

Firstly, within this cohort detailed hearing information has been collected on a sub-sample of individuals. It would be ideal to collect this information on the whole cohort and also offer a repeat audiometric evaluation which includes measurements of otoacoustic emissions. This would add a longitudinal component to our outcome measure and also add additional longitudinal information to independent predictors. Additionally, the inclusion of otoacoustic emissions would allow for a better assessment of the integrity of outer hair cells which are more susceptible to vascular disease.

However, the utility of a longitudinal study such as the one proposed in an older population is questionable. It would be more interesting to look at incidence of hearing impairment versus prevalent hearing impairment particularly in younger populations. To further investigate whether the macrovascular or microvascular component of diabetes plays more of a role in presbycusis we suggest additional measures of each. To examine microvascular disease we suggest adding retinal photography measures and neuropathy measures. The current neuropathy measures within Health ABC are limited to peripheral measures such as monofilament testing, assessment of leg cramps, vibration perception threshold, and peroneal motor nerve conduction. To investigate macrovascular disease it would also be helpful to look at intima-media thickness and plaque amounts within larger arteries.

Further research is also recommended to better characterize the association of metabolic syndrome and impaired glucose tolerance on hearing loss. These symptoms are highly correlated with diabetes. If impaired glucose tolerance and metabolic syndrome are significantly associated with diabetes in other populations this may further support hearing loss prevention methods which incorporate control of diabetic risk factors. In this study the metabolic syndrome was not associated with hearing loss in the total population after excluding diabetics. However, this may be influenced by the fact that metabolic syndrome was defined four years prior to the evaluation of hearing function.

Future research also needs to focus on confirming these findings in other populations, particularly in blacks, females, and in younger persons. Our study found slightly different results among each of the race/gender subgroups. The differences

among these groups can be explained by a variety of factors each of which need additional studies to confirm. The next section describes proposed hypotheses as to why differences exist between hearing thresholds in men and women and blacks and whites and also suggests additional research that would aid in explaining race/gender disparities.

4.5. RESEARCH FOCUSING ON GENDER AND RACE DIFFERENCES

In these analyses differences were observed between the various race and gender subgroups. With respect to CVD and hearing loss, subclinical disease measures were associated with poorer hearing function in women but not in men. One explanation is that men are more prone to the effects of noise-induced hearing loss and thus factors which contribute to presbycusis are more evident in females. However, upon controlling for history of a noisy job we still did not observe an association between subclinical and clinical CVD in men. Thus it is likely that other factors such as hormones may play a role in this observation.

As with any occurrence when gender differences are observed, hormones serve as a common explanation. With respect to hearing loss, few studies have been conducted on the relationship of male hormones to hearing sensitivity. However, several studies have been conducted on the association of estradiol with hearing sensitivity. Postmenopausal women with higher levels of estradiol were found to have a lower incidence of hearing loss compared to women with lower levels of estradiol[66-69].

Additional studies have considered the effects of masculinity and hearing sensitivity. Studies which have considered otoacoustic emissions (OAEs) and auditory evoked potentials (AEPs) in females with opposite-sex co-twins or who are homosexual or bisexual have found that they exhibit masculinized or lower numbers of OAEs and AEPs similar to males[70,71]. The author proposes that prenatal exposure to high levels of androgens are responsible for the decreased OAE and AEP measures when compared to heterosexual females and women without male twins.

Aside from research focusing on hormones, the differential effects of medicinal drugs on hearing loss within males and females has also been studied. While several classes of drugs such as loop diuretics, salicylates, and antimalarials are known to be ototoxic, many other common classes of medicinal drugs have also been shown to be associated with hearing loss[72,73]. Given that our population was elderly and likely to be treated for other health complications this may offer another explanation.

Within the Health ABC cohort, participants who reported use of loop diurectics at the time of audiometric evaluation did not differ in hearing sensitivity compared to those not taking such drugs. Previous research has indicated that drugs classified as beta adrenergics, calcium channel blockers, and antihistamine or cold preparations potentially had ototoxic effects as well. Within our population, only those females who were using beta adrenergic medications had poorer hearing than those not using beta adrenergics consistent with a prior report[74].

Genetics has also been implicated as having a role in hearing sensitivity. In a familial aggregation study, Gates et al. found that aggregations for strial presbycusis

phenotypes were stronger in women than in men[75]. He suggests a genetic effect on inheritance of presbycusis within women and a mixed, genetically acquired cause in men.

Although, several hypotheses exist as to why differences in hearing sensitivity exist between the sexes, more studies are needed to help explain these gender disparities in age-related hearing loss. Additionally, more studies are needed to understand the difference in hearing sensitivity between blacks and whites.

In national surveys blacks consistently have a lower prevalence of hearing impairment compared to whites at all age levels[76]. This difference exists even after adjusting for traditional hearing loss risk factors such as age and a history of a noisy occupation. Several studies including this one have sought to understand why these differences in race exist. Based on the present results, metabolic syndrome may also help to explain the greater prevalence in whites but is only one factor in a myriad of others.

Possible alternative explanations include differences in occupational history, socioeconomic status, education, bone mineral density, and melanin. In this population only bone mineral density helped to explain the racial differences aside from MS[77]. Humans and animals with greater amounts of melanin have been shown to have better hearing[78-80]. Melanin may exert its protective effects by acting as a regulator of enzyme activity. Thus it is not unlikely that blacks have better hearing by virtue of their melanin levels.

4.6. SUMMARY

In summary this research found a positive association between diabetes and mid-frequency hearing loss within a population of healthy, well-functioning, older blacks and whites. Hearing loss at middle frequencies is most often associated with strial presbycusis, a result of atrophy of the stria vascularis. Atrophy of the stria vascularis is a combination of microvascular disease and macrovascular disease both of which are promoted by diabetes and in many instances are constituents of CVD. Significant associations between hearing sensitivity and clinical CVD were not observed. However, certain CVD risk factors and subclinical CVD in women were associated with hearing sensitivity. Thus, CVD may act synergistically with diabetes in contributing to age-related hearing impairment.

4.7. PUBLIC HEALTH IMPLICATIONS

Hearing loss is a common problem that leads to poor quality of life and many other complications. In order to address this problem we must seek to find ways to prevent age-related hearing loss. This research suggests that diabetes in conjunction with CVD may contribute to hearing loss. However, further research is needed to confirm these findings particularly in blacks and women. Screening for hearing impairment for diabetics may be warranted and control of diabetic risk factors is recommended.

5. INTRODUCTION: THE RISK OF CANCER WITHIN A COMMUNITY EXPOSED TO GASOLINE

The environment pervades our health in an infinite number of ways and is an essential component of the epidemiological triad. The last manuscript presented as part of this dissertation focuses on an exposure within the natural environment and its impact on community health. Specifically, it utilizes environmental epidemiology to assess the association between chronic low-level benzene exposure and cancer within a community exposed to gasoline vapors.

Gasoline is a complex mixture of more than 150 chemicals of which benzene constitutes 1-2% by volume in the United States[1,2]. Benzene in the environment sources from gasoline, industry, and cigarette smoke among other sources. Based on several animal and epidemiological studies, the US Environment Protection Agency has given benzene a weight of evidence classification of Category A, a "known" human carcinogen for all routes of exposure[3]. Exposure to benzene is therefore of significant public health concern.

Benzene toxicity primarily targets the hematopoetic system[4]. Thus, benzene is most directly associated with cancers of this system such as leukemia. The majority of studies which have examined the association between benzene and cancer have done so in an occupational setting. Although many of these studies have found a positive association between benzene exposure and leukemia and have strengths such as detailed

exposure histories and long follow-up times to account for cancer latency, they suffer from biases that make their conclusions difficult to apply to community exposures[5-8]. These biases include a healthy worker effect and exposures which are either acute or chronic at higher levels than experienced by communities. Increasingly, however, occupational studies are also reporting on the health effects of benzene at much lower levels than previously examined. The results from these studies are equivocal but a growing body of evidence supports the association of low-level benzene exposure with negative health effects such as decreased blood counts and leukemia[9-12].

Of the research conducted in a non-occupational setting, the study design most often chosen is ecological[13-19]. While these studies considered exposures that affected larger populations and were lower than those experienced in occupational cohorts, they too suffered from bias, namely ecological fallacy. The literature is deficient with respect to studies which examine the relationship between low-level chronic exposure to benzene and risk of cancer in community-based cohorts.

Our study seeks to address this deficiency by utilizing a retrospective cohort design to assess the health risks within a community exposed to chronic low-level benzene as a result of leaking underground gasoline storage tanks. Given the high prevalence of underground storage tanks, this exposure is unlikely to be an isolated occurrence. Aside from using traditional epidemiological methods, we also sought to employ a systems based approach in our investigation. This approach has become increasingly popular in environmental health and lends itself well to most public health investigations.

5.1. SYSTEMS THEORY

Systems theory was first proposed by Ludwig von Bertalanfy in the 1940s. He described systems theory as a general science of "wholeness" where the "whole is more than the sum of its parts"[20]. Many public health issues can be viewed as a system with dynamic components interacting with one another to achieve a goal[21,22]. Using all the components of a system, one can not only identify what contributed to a disease (the agent), but also why the agent entered the system, and finally how to take action so that the exposure does not occur again.

Specific to our example, benzene can be considered the agent or input of the system. Leaking storage tanks, groundwater, and sewer lines can be viewed as the processes within the system or why the agent entered the system. Lastly, the results from our study along with the results of environmental investigations from the Pennsylvania Department of Environmental Protection and Environmental Protection Agency will be considered so that recommendations for prevention can be made. Upon presentation of our health study and its results, the utility of the systems based approach in strengthening our project will be discussed along with recommendations for prevention and future research.

5.2. SPECIFIC AIMS

The specific aims of this portion of the dissertation are as follows:

1. To characterize the cancer experience of residents within the Tranguch spill area by calculating standard incidence ratios.
2. To assess the prevalence of other health conditions within resident of the Tranguch spill area.
3. To utilize a systems-based approach towards risk assessment of the Tranguch Spill Site by synthesizing the results of other environmental and epidemiological studies within the area.

6. COMMUNITY EXPOSURE TO GASOLINE VAPORS AND RISK OF CANCER

Submitted to the Archives of Environmental Health

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6.1. ABSTRACT

The Tranguch Fuel Spill was characterized as a leakage of 50,000-900,000 gallons of gasoline from underground storage tanks in Hazle Township and Hazleton, Pennsylvania. As a result, residents within the Environmental Protection Agency-defined remediation area were potentially exposed to chronic low levels of benzene since at least 1990. A retrospective cohort study was conducted to determine if affected residents were at increased risk for cancer from 1990-2000 compared to the Pennsylvania populace. A total of 663 individuals representing 275 households comprised the study population. Age-adjusted standard incidence ratios (SIRs) were calculated using Pennsylvania rates to determine expected numbers. The age-adjusted SIR for the gasoline affected area was 4.40 (95%CI: 1.09-10.24) for leukemia. These results suggest a possible association between chronic low-level benzene exposure and increased risk for leukemia in the residents living near the spill site.

6.2. INTRODUCTION

Leaking underground petroleum storage tanks are a frequent and serious problem. Petroleum leaking from these tanks contaminates surrounding soil and groundwater causing both environmental and health risks. In an effort to address the growing problem of leaking underground tanks, the United States Congress created the Leaking Underground Storage Tank Trust Fund to assist with cleanup efforts. Since the inception of this program in 1986 until September 30, 2004, the United States Environmental Protection Agency (EPA) estimated 447,233 releases had been identified and only 71% of these releases had a cleanup completed(1).

Given the prevalence of such releases, and the fact that nearly half of the US population depends upon groundwater as their primary drinking water source, it is highly probable that many communities continue to face potential health effects as a result of volatile organic compounds from these leaking petroleum sources(2). The public health effects of such leakages, however, have not been well documented or studied. This paper seeks to address this scarcity by reporting on the health effects of one community's exposure to gasoline leaked from underground storage tanks.

In response to several odor complaints by residents of Hazle Township and the city of Hazleton, both situated in northeastern Pennsylvania, the Pennsylvania Department of Environmental Protection (PADEP) began a series of investigations in 1991 that would later become known as the Tranguch Gasoline Spill. The spill was characterized as a leakage of approximately 50,000 to 900,000 gallons of gasoline from underground storage tanks. A plume of groundwater contamination was detected and

upon further investigation, consequent filtration into the sanitary sewer system was identified. It is believed that for at least 10 years, residents within the Tranguch spill area have been chronically exposed to low levels of benzene, a known carcinogen, and other organic solvents as a result of the leaking gasoline.

Within the United States, it has been estimated that the benzene content in gasoline is approximately 1-2% by volume(3). Global average benzene exposure estimates range from 5 μg /m^3 for outdoor levels to 15 μg /m^3 for personal levels(4-6). The majority of workplace exposures are of higher concentration and shorter duration than those experienced by the general population.

Previous epidemiological studies have found elevated standardized incidence ratios for leukemia among large occupational cohorts exposed to benzene concentrations greater than 200 ppm-years(7-9) . This is equivalent to or greater than a crude average of 10 ppm benzene exposure over the course of a 20 year working lifetime within one job. Hayes, et al. also found an increased risk of all hematologic cancers at levels below an average of 10 ppm in a cohort of benzene exposed workers(10).

Several occupational studies have also documented hematotoxic effects at much lower levels of benzene, such as less than 1 ppm(11-14). Glass et al. found evidence for an increased risk of leukemia among Australian petroleum workers whose highest intensity job exposure to benzene was as low as 0.8 ppm(14). Unlike previous occupational cohorts, this cohort provided evidence for risk of leukemia associated with cumulative exposure to benzene at any level above zero, with no obvious threshold. Moreover, Lan et al. recently demonstrated a significant depression (~15%) in white cell count within Chinese shoe factory workers with less than 1 ppm benzene job exposure

(11). This further corroborates the plausibility of adverse hematopoietic effects as a result of low-level exposure to benzene.

Ecological studies have also found increased risks for leukemia in areas with greater concentrations of environmental benzene in the air or greater car density and subsequent gasoline exposure. Such studies typically suffer from ecological fallacy, deficiencies in case ascertainment, and crude exposure estimates(15-21). However, they aid in the identification of high-risk areas which can then be studied in more detail.

The literature is limited with respect to community exposures such as experienced by Hazleton and Hazle Township residents. This exposure was low-level (in the range of parts per billion) and was long term. The Hazleton/Hazle Township exposure is also unique in that its geology and typography, consisting of underground coal mining and shallow bedrock, may have facilitated pooling of gasoline below the surface of the affected area thus increasing subsequent migration into groundwater and sewer systems and the probability of exposure. In a similar situation, Lindstrom et al. found benzene concentrations of 0.8 - 1.7 ppm (758-1670 μg /m^3) within the shower stall of a household using gasoline-contaminated groundwater(22). No link however, was made between exposure and health outcomes in that report. The focus of this research was to determine if Hazleton and Hazle Township residents of the Tranguch spill affected area were at increased risk for cancer compared to standard reference populations and to assess the prevalence of additional health outcomes within the residents.

6.3. METHODS

6.3.1. Benzene Exposure Estimates

Prior to EPA remediation efforts, the PADEP tested the indoor air of a subset of homes for the concentration of volatile organic compounds (VOCs). The sampling device used was a Hnu photo ionization detector (PID) which does not measure individual species of VOCs such as benzene. Sampling took place in 43 homes over the course of 72 days (49 sampling days) in 1993. The concentration of total VOCs measured by the Hnu PID ranged from 0-202 ppm with an estimated benzene concentration range of 0-42 ppm (0-136 mg/m^3)(23).

Area exposure assessments of benzene within the groundwater of the Tranguch Spill Site were estimated by the EPA and US Army Corps of Engineers through exposure-modeling conducted between 1994 through 1996. Groundwater estimates of benzene ranged from 200 $\mu g /m^3$ to 2500 $\mu g /m^3$ (23). Using these surveys and taking into consideration possible vapor migration through the sanitary sewer system, the EPA defined a remediation or "affected" area of 366 households within the Hazle Township and Hazleton municipalities potentially exposed to gasoline fumes as a result of the Tranguch fuel spill.

In late 2000 and January 2001, the EPA sampled approximately 366 residential properties for concentrations of indoor benzene using Summa canisters. Results from these samples were provided to investigators by approximately 20% of home owners.

Benzene levels ranged from non-detectable (<8.3 μg /m^3) to 140 μg /m^3 in the sample of homes for which owners released their results. However, cumulative benzene exposure among Hazleton/Hazle Township residents, cannot be adequately estimated due to the lack of comprehensive historical data on air and groundwater concentrations of benzene and duration of exposure. Therefore, exposure to benzene from the leaking tanks was defined by residence within the EPA defined remediation area.

6.3.2. Study Design, Area, and Target Population

A retrospective cohort study design was employed. This design was chosen because: the exposure took place years before study commencement, the health endpoints being observed were rare and had long latencies (e.g. cancer), and it optimized the small sample size. The cohort was constructed from tax records, municipal lists, and residential histories of persons living for at least six months within the EPA remediation or "affected" area from January 1, 1990 through December 31, 2000. A total of 366 properties were within the boundaries of the defined affected area.

Upon validation of properties eligible for study inclusion, 17 were identified as non-residential and thus excluded from the target population. The overall current property owner response rate was 80%. Of the 72 households that did not participate, 42 owners refused participation and 30 were unable to be contacted after multiple attempts.

Additionally, 72 properties had changed ownership within the study period. Several attempts were made to contact the 62 past owners of these 72 properties; 3 agreed to participate in the study.

6.3.3. Data Collection

Due to funding mechanisms of local municipalities, data collection and analysis for Hazleton and Hazle Township were conducted independently using the same methodology. A study-specific questionnaire was developed to assess demographics, and primary and secondary health outcomes. Questions dealt with residential, employment, medical, reproductive, and smoking history, education level, and symptom experiences. Participants were also asked to complete a medical record release form in order to obtain confirmation of self-reported cancers through participants' physicians. The study and data collection materials were reviewed and approved by the University of Pittsburgh Biomedical Institutional Review Board.

Data was collected in the summer of 2001 for Hazle Township properties and the summer of 2002 for Hazleton properties. Within each household, all individuals aged 18 years and older interested in participating were asked to read and sign the consent form, sign the medical release form, complete the questionnaire, and finally return the forms to the University of Pittsburgh in a pre-addressed stamped envelope. Parents or guardians were asked to complete the questionnaire for children under the age of 18. Proxy interviews from next of kin were conducted for persons unavailable or unable to complete the forms. Death certificates were requested for all deceased individuals. For individuals who did not respond to the initial mailing of study materials, follow-up telephone calls were made and reminder postcards were sent. To accommodate participants with little time for completion of a full study-questionnaire, an abbreviated questionnaire was constructed which addressed gender, race, marital status, date of birth,

occupation, vital status, smoking and residential history, and history of cancer, diabetes, and other chronic diseases for all household members on a single form.

The primary outcome, incident cancer, was identified via the questionnaires. For all self-reported cancers, the participant's attending physician was contacted for verification of the cancer diagnosis and to request the release of participant's medical records. In addition, a request was made to the Pennsylvania Department of Health for the confirmation of all self-reported cancers using data from the Pennsylvania Cancer Registry. Cancers were classified in a manner similar to that of the PA Cancer Registry employing ICD-O codes.

Information was also obtained on those persons who died during the eleven-year period of whom we were able to obtain next of kin interviews and a death certificate. The information on death certificates was ascertained from the Pennsylvania Department of Vital Statistics.

6.3.4. Statistical Analyses

Descriptive population statistics such as frequencies, means, and medians, were generated using SPSS v12.0 for Windows. The unit of analysis for the cancer incidence measures was the person-year. SAS v8.0 was used to determine the number of person-years contributed by each individual. Individuals residing within the study area from January 1, 1990 to December 31, 2000 contributed 11 person-years. Other individuals who moved into or out of the area within this time period contributed varying person-

years on the basis of their residential history. Individuals no longer accumulated person years once they were diagnosed with cancer or identified as deceased.

To characterize the cancer experience of Hazle Township/Hazleton residents, standard incidence ratios (SIRs) were calculated. SIRs were based on self-reported, physician- and Pennsylvania Cancer Registry-verified, cancer diagnoses from 1990-2000 and the expected number of cancers derived from indirect age-adjustment using Pennsylvania average annual cancer incidence rates. Confidence intervals (CI) were determined using exact methods, specifically employing Poisson tables in the Documenta Geigy(24). Statistical significance was defined as $p < 0.05$.

6.4. RESULTS

In total, 663 persons representing 275 households participated in the study. Over 63% of participants completed the full questionnaire with the remaining completing the abbreviated version. The population can be described as 99% Caucasian. The population was comprised of 343 (51.7%) females and 320 (48.3%) males. The mean age of the population alive at time of interview (N=625) was 49.2 ± 22.1 years and the mean years of residence within Hazleton or Hazle Township was equivalent to 36.7 ± 21.9 years (Table 1). The majority of residents were married with at least a high school education. Over 36% of males and 27% of females reported a history of smoking. Fifty-four percent of participants were employed with the remainder comprised of retirees, students, and unemployed persons. Twelve residents reported prior employment at a gasoline station.

There were a total of 38 persons in participating households who were deceased at time of interview but lived in the study area between 1990 and 2000. Information for these individuals was obtained by proxy interview. The causes of death for these individuals included cardiovascular disease (N=14), cerebrovascular disease (N=2), chronic obstructive pulmonary disease (N=2), pneumonia (N=2), cancer (N=13), and other diseases (N=5).

Forty-three incident primary cancers were reported within the cohort and verified by the Pennsylvania Cancer Registry for the period of January 1, 1990 thru December 31, 2000. These are listed by site and gender in Table 2. Of the four leukemia cases, two were acute myeloid in cell type, one was chronic myeloid, and one was chronic lymphocytic. The two acute myeloid leukemia cases also bordered the projected gasoline plume. The four leukemia cases did not have a history of working in a benzene-exposed occupation and did not report a parental history of cancer. Two of the leukemia cases had a history of smoking.

The SIRs for all cancers are presented in Table 3. The SIR for all cancer sites was 0.88, which indicated no increased risk for all-site cancer in the Hazleton/Hazle Township Tranguch remediation area. This result was not statistically significant. The SIR for leukemia was 4.40 (95% CI: 1.09-10.24) and was statistically significant. The SIRs for all other cancer sites were not statistically significant although the SIRs for Non-Hodgkin's Lymphoma, bladder, brain, stomach, breast, cervix, and prostate were greater than one.

The prevalence of health effects other than cancer was also assessed. With the exception of diabetes, prevalent disease/disorder information was only available for 69%

of the study population, those that completed the full questionnaire. Among the 456 individuals who were asked about prevalent disease/disorders other than cancer, 135 (20.4%) reported having diagnosed hypertension, 68 (10.3%) reported a diagnosis of cardiovascular disease other than stroke, and 16 (2.4%) reported a history of stroke. Additionally, 44 (6.6%) reported a doctor diagnosed thyroid problem and 44 (6.6%) reported diagnosed anemia. Diabetes information was available for 659 participants of which 46 (6.9%) reported having the disease. These data in particular must be interpreted with caution since they were self-reported and not verified. Due to the lack of a suitable control population, comparisons between the prevalence of health effects/outcomes other than cancer in our affected community and a non-affected community could not be made.

Table 6-1: Age Distribution of Population Alive at Time of Data Collection with Mean Age and Mean Years of Residence within Hazleton/Hazle Township by Age Group

	Males			Female			Total		
Age Group	N	Mean Age ± STD	Mean Years of Residence ± STD	N	Mean Age ± STD	Mean Years of Residence ± STD	N	Mean Age ± STD	Mean Years of Residence ± STD
<18	40	11.0 ± 4.7	10.1 ± 4.9	30	11.5 ± 4.0	10.0 ±4.3	70	11.3 ± 4.4	10.0 ± 4.6
18-34	63	26.3 ± 5.1	22.3 ± 7.3	47	27.3 ± 4.8	23.9 ±6.8	110	26.7 ± 5.0	23.0 ± 7.1
35-44	37	40.7 ± 2.9	33.9 ± 12.6	42	40.5 ± 2.6	30.8 ± 13.6	79	40.6 ± 2.8	32.2 ± 13.1
45-54	38	49.8 ± 2.7	32.9 ± 17.2	47	50.5 ± 3.3	33.3 ± 16.3	85	50.2 ± 3.0	33.1 ± 16.6
55-64	37	59.5 ± 3.1	40.4 ± 17.5	54	60.3 ± 3.0	43.6 ± 16.5	91	60.0 ± 3.1	42.3 ± 16.9
65-74	49	69.9 ± 3.2	50.9 ± 17.8	57	70.1 ± 3.1	50.0 ± 20.4	106	70.0 ± 3.1	50.4 ± 19.2
75+	30	79.6 ± 3.4	56.4 ± 25.6	54	79.4 ± 3.3	61.8 ± 23.6	84	79.4 ± 3.3	59.9 ± 24.3
Total	294	46.0 ± 22.4	34.3 ± 21.0	331	52.1 ± 21.3	38.8 ± 22.5	625	49.2 ± 22.1	36.8 ± 21.9

Table 6-2: Distribution of Residents by Years of Residence within Hazleton/Hazle Township

Years of Residence	Males	Females	Total
<5	14	12	26
5-9	14	19	33
10-19	53	41	94
20+	200	254	454
Total	281	326	607

Table 6-3: Number of Incident Cancer Cases by Gender 1990-2000

CANCER	Males	Females	Total
Leukemia	1	3	4
Non-Hodgkin's Lymphoma	1	1	2
Trachea, Bronchus, Lung, & Pleura	2	3	5
Colon	1	2	3
Urinary Bladder	2	1	3
Brain	2	0	2
Stomach	1	0	2
Female Breast	--	12	12
Cervix	--	1	1
Prostate	9	--	9
All Cancer Sites	20	23	43

Table 6-4: Standard Incidence Ratios for Affected Population of Hazleton and Hazle Township PA compared to the State of Pennsylvania

CANCER	Observed Cases	Expected Cases	Standardized Incidence Ratio	95% Confidence Interval
Leukemia	4	0.91	**4.40**	**1.09 – 10.24**
Non-Hodgkin's Lymphoma	2	1.62	1.23	0.15 – 4.46
Trachea, Bronchus, Lung, & Pleura	5	7.47	0.67	0.22 – 1.56
Colon	3	4.60	0.65	0.13 – 1.91
Urinary Bladder	3	2.35	1.28	0.26 – 3.73
Brain	2	0.55	3.64	0.44 – 13.13
Stomach	2	1.12	1.79	0.21 – 6.45
Female Breast	12	7.89	1.52	0.79 – 2.66
Cervix	1	0.38	2.63	0.08 – 14.66
Prostate	9	7.12	1.26	0.58 – 2.40
All Cancer Sites	43	49.1	0.88	0.64 – 1.18

6.5. DISCUSSION

In order to address the health concerns of a community exposed to low levels of benzene as a result of an underground gasoline spill, a health effects study was conducted. The primary objective of this study was to determine if residents within the Tranguch gasoline spill affected area were at an increased risk for cancer when compared to a standard reference population.

Within the Tranguch gasoline affected area, a total of 43 incident cancers from 1990-2000 were identified via self-report and subsequent physician and cancer-registry verification. While the age-adjusted all-cause cancer SIR was not statistically significant, the SIR of 4.40 (95% CI: 1.09-10.24) for leukemia was significant. Leukemia, particularly of the acute myeloid cell type, has been linked with benzene exposure(7, 25, 26). Our findings are consistent with other literature and suggest that long-term exposure to low-levels of benzene, a constituent of gasoline, may be associated with increased risk of hematopoietic malignancies(14, 20, 27).

These results are also consistent with a similar report by the Pennsylvania Department of Health (PADOH) which considered cancer incidence within the Tranguch gasoline affected area from 1985 to 2002(28). The PADOH study population comprised of all households (N=359) within the EPA-defined remediation area. The total number of residents (N=899) within the PADOH population was ascertained through a review of 1990 U.S. Census block-group data and by a PADOH door-to-door enumeration in 2001 of households not identified in the census. Incident cancer cases were identified using geo-coding and data from the Pennsylvania Cancer Registry as well as cases reported through self-report and those identified through the University of Pittsburgh study.

To calculate SIRs, the PADOH applied three sets of age-specific incident cancer rates for Pennsylvania (1985-1989, 1990-1994, and 1995-2002) to the study population in order to obtain the expected number of cancer cases. The expected numbers from each of the three time periods were summed to determine the total expected number of cancer cases within the affected area for the entire 18-year period and confidence intervals for the SIRs were calculated using the Poisson distribution. A total of 134 cancer cases were identified in the PADOH study. The SIR for all causes of cancer was 1.31 and was statistically significant. Additionally, seven incident cases of leukemia were observed resulting in a SIR of 3.63, also statistically significant. Of these seven cases, three were acute-myeloid in cell type and two were chronic myelocytic.

Despite different methods of ascertaining person-years, results from both our analysis and from the PADOH study suggest that an association between low-level chronic benzene exposure and leukemia risk might exist within the Tranguch Spill site. However, these findings should be interpreted in the context of study limitations. The exposure that occurred as a result of the Tranguch Gasoline Spill, is not well characterized. Upon identification of the spill, attempts were made by the PADEP and EPA to assess the volatile organic compound (VOC) and benzene exposure. However, the exact commencement date of the spill as well as the concentration and extent of benzene exposure remains largely unknown.

Of the available exposure data, the results from PADEP testing of indoor air within 43 homes during 1993-1994 best approximate VOC concentration prior to remediation. While PADEP readings were taken over the course of 10 weeks, the frequency and duration of each exposure within a home was not well documented. The sampling device used, a Hnu photo ionization detector, measured total VOCs and did not differentiate benzene. Based on initial benzene concentrations extrapolated from PADEP VOC measurements, the Agency for Toxic

Substances and Disease Registry (ATSDR) recently estimated that the maximum level of benzene exposure was approximately 42 ppm with an average level equivalent to 0.16 ppm(23). For a three- year period, this translates to 2 ppm-years for a maximum exposure and 0.03 ppm-years for an average exposure(23). ATSDR concluded that prior to remediation these benzene exposures might have been high enough to produce adverse health effects(23).

The EPA conducted additional sampling within all households in the remediation area in 2000-2001 using more sophisticated sampling techniques such as summa canisters. These samples however, were taken at one point in time and only in one or two locations within the home and potentially years after peak exposure. Thus, they may not reflect the actual exposure concentration over time nor do they adequately reflect historical levels of benzene prior to remediation efforts.

The remediation area was defined on the basis of a combination of groundwater sampling and exposure estimation models. These groundwater samples were also taken at least five years after the suspected commencement of the spill and therefore may underestimate the original extent and concentration of benzene exposure. Given the lack of historical benzene exposure data and the necessity to identify an objective exposure area for a health effects study, the EPA defined remediation area was chosen as our definition of "exposed". Inherent with the limitations of the exposure assessment, this area may over or under-estimate the true gasoline exposed population. Additional limitations of our study were a lack of an appropriate control population to adjust for confounders and compare the frequency of cancer risk factors and other health complications such as anemia, hypertension, and others.

In summary, this research provides potential evidence of an increase in hematopoietic cancer risk as a result of longer-term exposure to low concentrations of benzene. Although the

benzene exposure was not well characterized at an individual level, this research did not suffer from the ecological fallacy observed in other community studies investigating gasoline/benzene exposure and leukemia(15-21). The results are in agreement with occupational studies which have documented hematopoetic risk at similar low levels of benzene(11-13).

Within a population of 250 Chinese workers exposed to benzene, even as low as < 1 ppm in the air, white blood cell, granulocyte, lymphocyte, B cell, and platelet counts were depressed compared to unexposed controls. Such effects may lead to more serious hematopoietic consequences such as leukemia. Although an increase in the risk of leukemia as a result of exposure to low-level benzene remains equivocal(7, 29-32), our study provides support for the growing body of evidence suggesting a causal link(14, 17, 21).

Several recommendations were made to address the health concerns of residents affected by the Tranguch spill. The first recommendation was to continue surveillance of cancer, particularly leukemia as well as its precursors, within the Hazleton/Hazle Township municipalities until 2010. Continued surveillance will capture any latent cancers and also help stabilize incidence rates and narrow the confidence interval for SIR calculations. Data from the PA Cancer Registry alone will not suffice in capturing additional health effects caused by benzene such as aplastic anemia and myelodysplastic syndrome.

As part of this surveillance effort, a combination of active and passive reporting of specific medical conditions, including leukemia, anemia and myelodysplastic syndrome, would be instituted. Complete blood counts and other medical testing determined to be appropriate would also be conducted every six months or annually. Surveillance might also include screening for biomarkers of hematologic disease susceptibility (xenobiotic enzyme polymorphisms), biomarkers of early hematological effects of benzene exposure (chromosomal aberrations), and

evidence of environmental benzene exposure (glycophorin A, benzene-related DNA adducts, and urinary excretion products)(33-36). A further recommendation is to continue systematic surveillance over a longer follow-up period for individuals considered to be potentially at the greatest risk for leukemia such as children, the elderly, individuals with co-morbidities, and residents living over or adjacent to the projected gasoline plume boundary. ATSDR has also supported systematic surveillance for cancer in the affected area(23).

This research makes an important contribution to the literature, as it is one of very few studies to extensively investigate exposures to gasoline/benzene in a community setting. Given the high prevalence of leaking underground gasoline tanks in the United States, this exposure is far from unique. It is therefore important for communities and public health agencies to partner in order to assess and address health effects potentially resulting from such leakages.

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7. DISCUSSION OF ENVIRONMENTAL EPIDEMIOLOGY RESEARCH

7.1. SUMMARY OF OBJECTIVES AND FINDINGS

This investigation was an excellent example of applied epidemiology. In response to community health concerns stemming from exposure to gasoline fumes, a health effects study was carried out. This study had several objectives. The primary objective was to determine whether residents within the gasoline spill remediation area were at increased risk for cancer compared to a standard reference population, the Pennsylvania populace. A secondary objective was to characterize the prevalence of other health effects. The last objective was to employ the systems based approach in our investigation and interpretation.

A total of 43 incident cancers within the gasoline affected area were identified via self-report and subsequent physician and cancer-registry verification. The age-adjusted standard incidence ratio (SIR) for all-site cancer was not statistically significant (SIR=0.88, 95% CI=0.64-1.18). However, the age-adjusted SIR for leukemia of 4.40 (95% CI: 1.09-10.24) was significant. As had been discussed previously, leukemia, particularly of the acute myeloid cell type, has been linked with benzene exposure[8,23,24]. The age-adjusted SIR for all hematopoetic cancers (leukemia and Non-Hodgkin's lymphoma) was also elevated but not statistically significant (SIR= 2.37; 95% CI: 0.87-5.16). These results are consistent with other literature and

suggest that long-term exposure to low-levels of benzene, a constituent of gasoline, may be associated with increased risk of hematopoietic malignancies, particularly leukemia [12,18,25].

The prevalence of health effects other than cancer was also assessed in this study. Without an adequate control population of similar demographics, it is difficult to make comparisons with respect to these health effects. Additionally, prevalent disease/disorder information was only available for less than 70% of the entire study population. Therefore, sound conclusions with respect to the contribution of benzene exposure to disease prevalence within this population could not be drawn.

Despite these limitations it is interesting to note that 6.6% of residents reported having some form of anemia. This percentage is high compared to national survey data[26], however, the type of anemia in our population was not characterized nor verified via blood tests or physicians. Within the National Exposure Benzene Subregistry, benzene has been shown to be linked with an increased incidence of anemia in comparison to a similar population within the National Health Interview Survey[27].

7.2. THE SYSTEMS BASED APPROACH

In order to interpret these results in a broader public health context and make subsequent health recommendations, it was necessary to use a systems based approach to our investigation. As presented in the introduction, this approach encourages multidisciplinary collaboration among various agencies and sectors of public health. Modifying the traditional epidemiological triad of host, agent, and environment, by replacing host with epidemiology and agent with laboratory a public health triad is formed. Each of these elements had several strengths and limitations but viewed collectively they allowed us to draw better conclusions from which recommendations could be made to the community. We discuss each of the components and their limitations below in more detail.

7.2.1. Epidemiology Component

The epidemiology component was carried out by both the University of Pittsburgh and the Pennsylvania Department of Health (PADOH). Epidemiology was necessary in order to determine whether or not residents within the gasoline affected area were at increased risk for cancer compared to a standard population. Although the epidemiological methods employed by the University of Pittsburgh and the Pennsylvania Department of Health were slightly different, they both yielded a statistically significant SIR for leukemia (4.40 vs. 3.63).

The University of Pittsburgh study population consisted of residents who lived within the affected area from 1990-2000. Detailed residential histories for these individuals were

ascertained, which included any time spent away from the exposed area. We were unable to contact 72 households and 62 prior owners and their households to determine the number of person years they would contribute to our denominator. Although we attempted to contact those individuals who moved out of the area, only 3 returned any information. Thus the expected number of cases for our SIR calculation may have been underestimated. At the same time we were also unable to determine if additional incident cancers occurred within these individuals or those who moved out of the area.

If we were to estimate an average of 2.5 persons (the average number of persons within participating households) within each of the 62 prior owner households and 72 non-respondent households, we would have missing data on approximately 350 persons. Taking a conservative approach and overestimating the number of person-years by assuming each person contributed 11 person years to the denominator and proportioning these person years to the age groups based on the current study population's age-distribution, the following SIRS were calculated: 2.63 (95% CI: 0.85-6.13) for leukemia and 4.92, $p<0.05$ for acute myeloid leukemia. These SIRs are conservative, however, since the leukemia experience of these subjects is undetermined; if only one additional leukemia case developed within these nonparticipants, the results would most likely be significant.

The PADOH conducted a similar study but employed different methods with respect to person-year attainment and their length of follow-up[28]. The PADOH considered incident cancer cases from 1985-2001. In terms of person-year attainment, the PADOH determined their study population based on the 1990 census and an additional enumeration of 119 households in 2001. They considered that all persons within these households contributed 11 person-years to the denominator which most-likely overestimates the number of expected cancer cases and

subsequently helps to explain the smaller SIR of 3.63 for leukemia. Additionally, persons who developed cancer continued to accrue person years in the PADOH study. This is in contrast to our study, whereby, once a participant developed cancer, they no longer accrued person years.

Aside from the differences in person-year ascertainment and limitations inherent in each method, both studies suffered from limitations which are intrinsic to several environmental epidemiology studies. These include lack of exposure data (both population-based and personal), small sample sizes, and lack of an adequate control population. In instances where the sample size is dictated by an environmental exposure it is difficult to meet criteria for sufficient statistical power; thus the large confidence intervals for the SIRs in our study. However, continued surveillance would increase the number of person years and provide more stable estimates of SIRs. This recommendation along with other opportunities for future research will be discussed in a later section.

7.2.2. Environmental Component

Both epidemiological studies were dependent on environmental data from other agencies such as the Pennsylvania Department of Environmental Protection (PADEP) and the Environmental Protection Agency (EPA). In particular results from these investigations were necessary to define the gasoline affected population. The environmental investigation was designed to determine historical and present exposures of benzene as well as to assess exposure routes. A concise description of the PADEP and EPA sampling and remediation activities can be found in the ATSDR Tranguch Workgroup Report[29].

In brief, the PADEP sampled 43 homes prior to remediation efforts in 1993 with Hnu photo ionization detector meters. Volatile organic compounds (VOCs) adversely impacted more than 65% of these homes. In 1996, the EPA evaluated indoor air quality in 53 properties using more sophisticated detection methods, a real-time Trace Atmospheric Gas Analyzer (TAGA). Groundwater sampling and monitoring also took place during this time. In 2000, additional SUMMA canister sampling took place in a larger subset of homes including those with sewer vent traps already installed. Sampling took place in both basement and first floors of homes and 81% of the homes sampled had benzene levels less than the action limit of 8.3 $\mu g/m^3$. Based on the monitoring conducted above and additional investigation by the U.S. Army Corps of Engineers, a Tranguch Affected Area was defined by the EPA and PADEP.

Remediation activities included removal of leaking gasoline tanks from the Tranguch property, installation of sewer vent traps, carbon-filtration units, and radon-type units, and construction of a groundwater collection and soil-vapor extraction system which also entailed the replacement and repair of portions of the sanitary and sewer systems. These remediation efforts are described in detail within EPA's document the 22nd Street Cleanup Summary Report[30].

Limitations with the environmental portion of the investigation included an inability to define historical levels of benzene, an inefficient means of sampling, and in many instances a lack of effective communication with the public which led to community distrust with EPA representatives. With respect to sampling, the instrument used to measure benzene prior to remediation was only able to capture total VOCs. When SUMMA Canister sampling began, many homes were already undergoing remediation. The strict protocol for taking these samples within the homes was established after the initial round of sampling. Additionally, the samples are not representative of potential seasonal variations in concentration. These limitations make it

difficult to establish the historical level of benzene. Despite these limitations, the ATSDR still concluded based on available information that preremedial indoor air levels posed an indeterminate health hazard[29].

7.2.3. Laboratory Component

The laboratory portion can be considered an extension of the environmental portion in terms of analyzing the air samples for benzene and other VOC concentrations. However, the laboratory portion also encompassed blood work carried out by the PADOH.

The PADOH offered residents of the affected area free Complete Blood Count (CBC) tests from 2001 to the present. Data from only 389 of more than 700 persons in the affected area were available for analysis by the PADOH. The data from these blood tests are reported in the ATSDR report as mean values. No standard deviation, minimum, or maximum is reported and thus it is difficult to draw conclusions with respect to the impact of exposure on blood constituents despite the fact that each of the mean values falling within the normal laboratory limits. Chronic low level benzene has been shown to be associated with adverse blood effects such as depressed white cell counts[9-11].

7.3. RECOMMENDATIONS AND CONCLUSIONS

Each of the components, epidemiology, environmental, and laboratory, provides a more complete overall investigation and assessment of the Tranguch Fuel Spill study. Despite the various limitations there were several strengths. In particular the cancer experience of the population was well characterized and it was evident that the concentration of benzene at the time of the spill was likely to have posed a health risk.

Several measures have already been taken to "fix the system" by removing the potential for system input (benzene exposure via leaking gasoline), addressing the processes whereby benzene poses a health risk (remediation efforts), seeking to prevent output (early detection of hematopoetic malignancies), and providing feedback (community forums, reports, and recommendations).

Based on the University of Pittsburgh epidemiological investigation and other components of the systems-based investigation we propose the following primary recommendations.

1. Continue systematic surveillance of the cancer experience of residents within the Tranguch area until 2010. This would capture the latency effect for most hematopoetic malignancies.
2. Conduct more extensive and longer term surveillance among residents living directly over or adjacent to the projected gasoline plume since they are at highest risk for leukemia and related malignancies. This surveillance could include monitoring for precursors of disease such as myelodysplasia and aplastic anemia.

3. Continue monitoring the gasoline-contaminated groundwater plume and to conduct additional air-sampling monitoring within homes directly above or adjacent to this plume. Sewer-vent traps and other remediation-related devices should not be removed from homes until there is sufficient data to ensure that benzene levels remain consistently below the action limit.

Future research may wish to consider the utility in screening for biomarkers of hematologic disease susceptibility, early hemtaologic effects of benzene exposure, and evidence of environmental benzene exposure. Additionally, we suggest that this investigation be used to establish an environmental health assessment protocol that would aid in future occurrences of a similar nature.

In summary, evidence of increased risk to leukemia was found within the Hazleton/Hazle Township population exposed to low levels of benzene. The approach used in this investigation highlighted strengths of public health infrastructure including sound surveillance and cooperation between various public health agencies and institutions. Given the prevalence of leaking underground storage tanks, this investigation will serve as an important contribution to the literature and to the public's health.

APPENDIX A

ASSOCIATION OF CARDIOVASCULAR DISEASE AND DIABETES TO MID-FREQUENCY HEARING LOSS IN THE CARDIOVASCULAR HEALTH STUDY COHORT

The contribution of diabetes and cardiovascular disease to age-related hearing loss remains debatable. In order to add to existing literature and evidence, an analysis was conducted using data from the Cardiovascular Health Study (CHS). A summary of the methodology and results of this research is presented within this appendix.

METHODOLOGY

Study Design

The Cardiovascular Health Study is a population-based longitudinal cohort study designed to examine factors related to the onset of coronary heart disease (CHD) and stroke in adults aged 65 years and older. The following specific objectives have been identified[1]:

1. To quantify associations of conventional and hypothesized risk factors with coronary heart disease, stroke, and subclinical disease.

2. To assess the association of indicators of subclinical disease with the incidence of CHD and stroke.
3. To characterize the natural history of CHD and stroke and identify factors associated with clinical course.
4. To describe the prevalence and distribution of risk factors, subclinical cardiovascular disease, and clinically diagnosed CHD and stroke.

The CHS cohort has been followed for 11 years in the clinic. Annual visits consisted of an examination of psychosocial factors, medical care, resting blood pressure, anthropometric measurements, functional status, neurological function, and resting ECG. Additional data collected at baseline and at each subsequent three-year examination period consisted of ankle-arm indices, physical examination, physical activity assessment, dietary intake, ambulatory ECG, spirometry, blood chemistry, ultrasonography, and echocardiography.

Study Population and Eligibility Criteria

The CHS cohort was established between June 1989 and June 1990. Participants aged 65 years or older were recruited from four communities: Forsyth County, North Carolina, Sacramento County, California, Washington County, Maryland, and Pittsburgh, Pennsylvania. Recruitment procedures utilized a random sample of persons from Medicare eligibility lists maintained by the Health Care Financing Administration. Individuals who were institutionalized, anticipated leaving the community within three years following the baseline examination, were in hospice or under active treatment for cancer, could not communicate in the language of the interviewer,

were confined to a wheelchair at home, or could not cognitively sign an informed consent were ineligible for study enrollment.

Audiometric data was collected as part of an ancillary study within the Pittsburgh cohort alone. Thus, the analysis is restricted to participants who completed an audiometric evaluation. The present study population consists of 544 persons (58.5% female and 41.5% male). African Americans comprised 21.9% of the population.

Hearing Assessment

Audiometry was conducted in the year 11 CHS Pittsburgh cohort. The protocol first involved a visual examination of the ear to note serous, purulent, or sanguineous discharges. If present, the ear was not examined. An AudioSpec ear speculum (Audiometer model 23300) was used to ascertain pure-tone thresholds. Mid frequency pure-tone averages (PTA) were calculated as the mean of hearing thresholds at frequencies of 500, 1000, and 2000 Hz. Hearing thresholds were also measured at 250, 4000, and 8000 Hz. Hearing impairment was defined as a PTA in the worst ear greater than 25 dB HL.

Diabetes and Clinical and Subclinical Cardiovascular Disease

A participant was classified as having diabetes if they used insulin or oral hypoglycemics or if glucose levels exceeded 126 mg/dL. Clinical CVD was identified through self-report with verification by medical records on an annual basis. For this analysis, a participant was classified as having a history of clinical CVD if they reported a history of angina, coronary heart disease,

congestive heart failure, stroke, transient ischemic attack, myocardial infarction, or intermittent claudication.

An aggregate measure of subclinical disease in multiple vascular beds was defined for the CHS cohort by Kuller et al.[2]. This measure consists of carotid intima-media thickness, pulse-wave velocity, ankle-arm indices, echocardiograms, and results from the Rose questionnaire. The methodology to ascertain these subclinical disease measures has been described previously[1,3]. Criteria for subclinical cardiovascular disease are as follows: an ankle/arm index less than or equal to 0.9, internal carotid wall thickness greater than the 80th percentile of the baseline cohort, carotid stenosis greater than 25%, major electrocardiographic abnormalities, Rose questionnaire claudication positive, or Rose questionnaire angina positive.

Additional measurements

Lipids, cholesterol, glucose, insulin, and other blood chemistries were ascertained at the year 11 clinic visit. The methods to ascertain these chemistries has been described in previous reports[1]. Home interviews collected information on demographics, occupational history, illnesses, medication use, and medical history including the Rose questionnaires for angina pectoris and pulmonary symptoms[4]. Sitting blood pressure was measured twice in the right arm of participants. Anthropometric measurements for height, weight, and waist and hip circumference were measured using standard procedures.

Statistical Analyses

SPSS v12.0 for Windows was used for all analyses and statistical significance was defined as $p < 0.05$. Frequencies and means were generated for the description of the population. Discrete variables were compared suing chi-square tests and continuous variables were compared using t-tests. Multivariable logistic regression was performed in order to calculate adjusted odds of hearing loss. All independent variables were entered into the model in one step.

RESULTS AND DISCUSSION

The mean age of the population was 80.1 ± 4.2 years. Caucasians and males had a higher prevalence of hearing impairment at any frequency range compared to African-Americans and females. The prevalence of mid-frequency hearing loss among women was 56.0% and among men was 54.0%. Table 1 presents a description of the study population by hearing loss status and stratified by gender. In general those with hearing loss did not differ in characteristics compared to those without hearing loss. A few exceptions were noted. Black females were less likely to be characterized as having hearing loss. A higher proportion of males with hearing loss had subclinical CVD or a history of congestive heart failure.

Table 2 presents the results of logistic regression analyses examining the odds of hearing loss among participants with diabetes, subclinical CVD, and clinical CVD independent of age, race, and sex. Only primary hearing loss risk factors were adjusted for because participants with

hearing loss did not differ with respect to other potential risk factors such as smoking. Participants with diabetes or CVD did not have higher odds of hearing loss.

These results are not surprising considering the age of the population and the inherent survival bias. While the CHS study did not collect specific information on noisy occupation it did collect occupational history. Even after adjustment for potential noisy occupations, the results are unlikely to change. This cohort did however provide an opportunity to investigate unique subclinical CVD measures and their association with hearing loss. Further analyses could consider the association of electron bean tomography measures of calcification with hearing loss or focus more specifically on intima media thickness and hearing loss. The utility of such analyses is questionable and it is recommended that future research be conducted in younger populations.

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Table A-1: Description of Population by Gender and Hearing Loss Status

	Males N=226			Females N=318		
Population Characteristic	*PTA < 25*	*PTA ≥ 25*	*p-value*	*PTA < 25*	*PTA ≥ 25*	*p-value*
Age	79.0 ± 3.2	81.7 ± 4.9	<.001	78.2 ± 3.3	80.9 ± 4.1	0.003
% Black	24 (23.1%)	23 (18.9%)	0.435	43 (30.7%)	29 (16.3%)	0.002
% Diabetes	17 (16.5%)	18 (14.9%)	0.738	18 (12.8%)	21 (11.8%)	0.793
% Subclinical Cardiovascular Disease	51 (49.0%)	90 (73.2%)	<0.001	72 (51.1%)	102 (57.0%)	0.291
% Coronary Heart Disease	34 (32.7%)	41 (33.3%)	0.789	27 (19.1%)	48 (26.8%)	0.108
% Congestive Heart Failure	8 (7.7%)	23 (18.7%)	0.016	7 (5.0%)	16 (8.9%)	0.172
% Intermittent Claudication	5 (4.8%)	10 (8.1%)	0.315	4 (2.8%)	4 (2.2%)	0.732
%Myocardial Infarction	13 (12.5%)	24 (19.5%)	0.154	14 (9.9%)	23 (12.8%)	0.417
% Stroke	7 (6.7%)	6 (4.9%)	0.549	4 (2.8%)	12 (6.7%)	0.115
% Ever Smoker	68 (65.4%)	85 (69.7%)	0.686	83 (59.3%)	93 (53.8%)	0.588
Weight (lbs)	172.7 ± 26.4	168.2 ± 27.5	0.462	147.9 ± 28.9	142.9 ± 27.8	0.861
Cholesterol (mg/dL)	181.9 ± 33.8	183.1 ± 36.6	0.171	210.2 ± 38.5	209.6 ± 35.2	0.433
Systolic Blood Pressure (mmHg)	135.0 ± 23.0	131.0 ± 18.3	0.062	132.8 ± 23.4	135.0 ± 21.0	0.420
Diastolic Blood Pressure (mmHg)	69.9 ± 11.1	68.5 ± 10.5	0.365	68.0 ±11.1	67.1 ± 10.6	0.852

Table A-2: Odds of Mid-Frequency Hearing Loss for Participants with diabetes, or cardiovascular disease adjusted for age and race

	Males		Females	
	OR	95% CI	OR	95% CI
Diabetes	1.12	0.52 – 2.40	0.79	0.38 – 1.65
Any Subclinical CVD	0.40	0.23 – 0.72	0.98	0.61 – 1.59
Any Clinical CVD	0.86	0.49 – 1.52	0.68	0.40 – 1.15

APPENDIX B

PRINCIPLES OF AUDIOLOGY

Anatomy and Function of the Outer, Middle, and Inner Ear

The anatomy of the ear is commonly separated into three distinct portions, the outer, middle, and inner ear (Figure B-1). The outer ear, primarily made of cartilage, consists of the visible part of the ear known as the pinna and the external auditory canal leading to the eardrum. Its primary function is to amplify and localize incoming sound waves. Additionally the external ear provides protection for the eardrum (tympanic membrane) against the environment and foreign bodies.

The middle ear is bounded by the tympanic membrane and the promontory, a bony wall forming the outer boundary of the inner ear. Within the middle ear cavity are three small bones, ligaments, muscles, and the Eustachian tube which connects to the nasopharynx. The tympanic membrane is attached to the three middle ear bones or ossicles known as the malleus, incus, and stapes. Collectively these bones are referred to as the ossicular chain. Two muscles are also present within the middle ear, the tensor tympani and the stapedial muscle.

Acoustic stimuli can be transmitted through the middle ear to the inner ear by the air in the middle cavity or via the ossicular chain, a more effective method. For the ossicular chain to

effectively transmit vibrations to the inner ear, the middle ear cavity must be able to maintain pressure equalized to atmospheric conditions. The Eustachian tube is responsible for pressure equalization in the middle ear. Another function of the middle ear, particularly of the ossicular chain, is to vibrate the oval window membrane of the inner ear. Vibrations of this membrane cause fluid within the inner ear to move. Thus, when more pressure is required to stimulate fluid movement, force from the tympanic membrane activates a lever-like action of the ossicular chain. The middle ear muscles assist with the reduction of transmission of pressure through the ossicular chain along with helping to limit distortion. Many of the middle ear structures also provide sources of impedance for sound transmission to the inner ear fluids.

The inner ear has the most complicated structure and function of the peripheral ear. It consists of three primary components all residing in the temporal bone: the semicircular canals, the vestibule, and the cochlea. The semicircular canals, superior, posterior, and lateral, open into the vestibule. The vestibule contains the structures (ultricle and saccule) related to sense of balance. The cochlea contains the primary auditory organ of the ear and resembles a tightly coiled tube of decreasing diameter. Two membranes (basilar and Reissner's) divide the cochlea into three sections: the scala vestibuli, scala media, and scala tympani.

The scala tympani and scala vestibuli contain a fluid known as perilymph. Perilymph, unlike other extracellular fluids, is highly positive in its ionic concentration. The helicotrema connects these two scala. Fluid within the scala tympani and vestibuli shifts as a result of increased pressure on the oval window. Subsequent fluid displacement is allowed via the round window causing a wave within the cochlear fluids and a displacement of the scala media (Figure B-2).

The scala media or cochlear sac contains endolymph and is surrounded by a dense layer of blood capillaries and specialized cells known as the stria vascularis. The stria vascularis provides the nutrient source for the cells of the cochlea. Within the scala media also lays the organ of Corti, the end organ of hearing. The organ of Corti is divided into an inner and outer portion by rods. These rods form a tunnel which is filled with cortilymph and is lined with haircells and their supporting cells. It is these haircells that serve as the biological transducer for the auditory system through their cilia and associated nerve endings.

Essentially the general function of the cochlea is to translate the mechanical vibrations of sound into neural responses. The mechanical actions of the stapes and the vibration of inner ear fluids cause the basilar membrane and subsequently the cilia of haircells to move. The bending of the cilia provokes a neural potential which is sent to the auditory nerve and translated into neural information via the central auditory pathway (Figure B-3).

It is evident that the cochlea is a highly sensitive organ that plays one of the most critical roles in human hearing. Any disruptions to the nutrient supply of the cochlea, including its blood supply, may have an impact on hearing via numerous mechanisms.

Figure B-1: Cross-section of the human ear

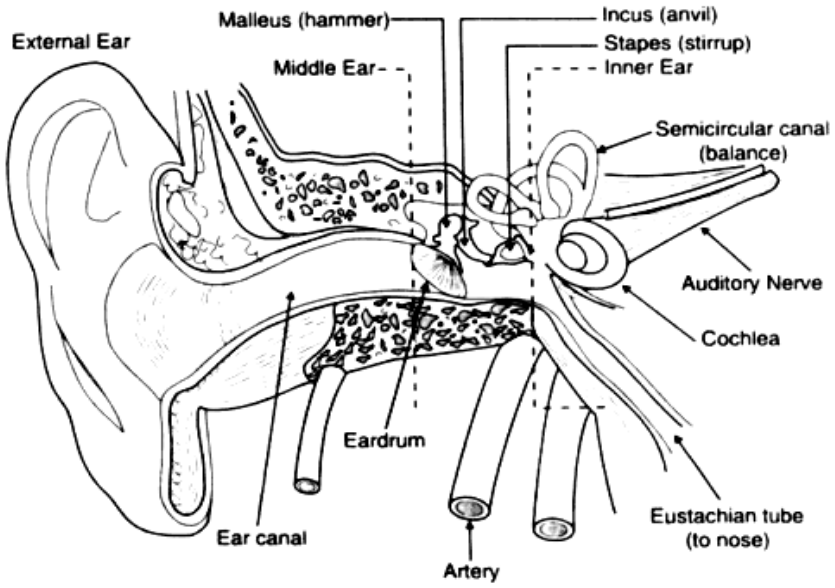


Figure B-2: Movement of Fluid within the Cochlea

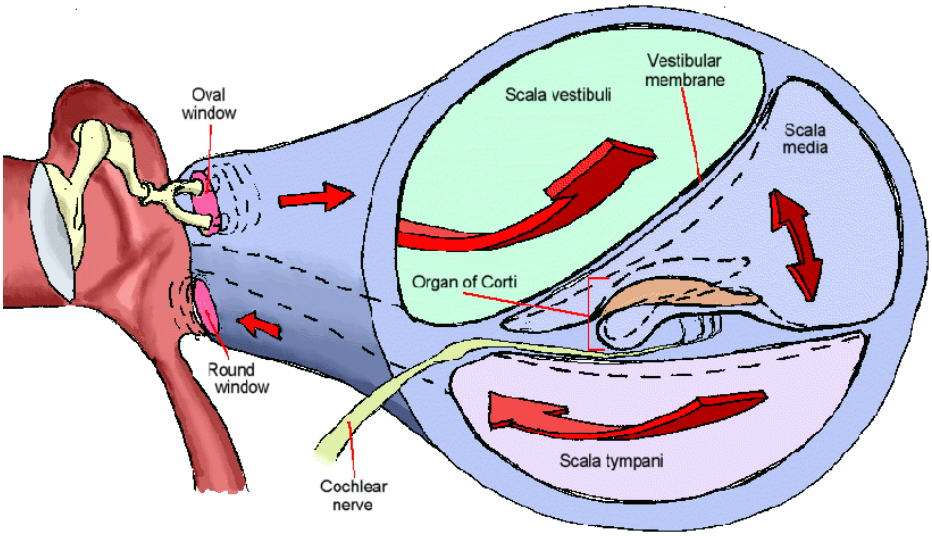
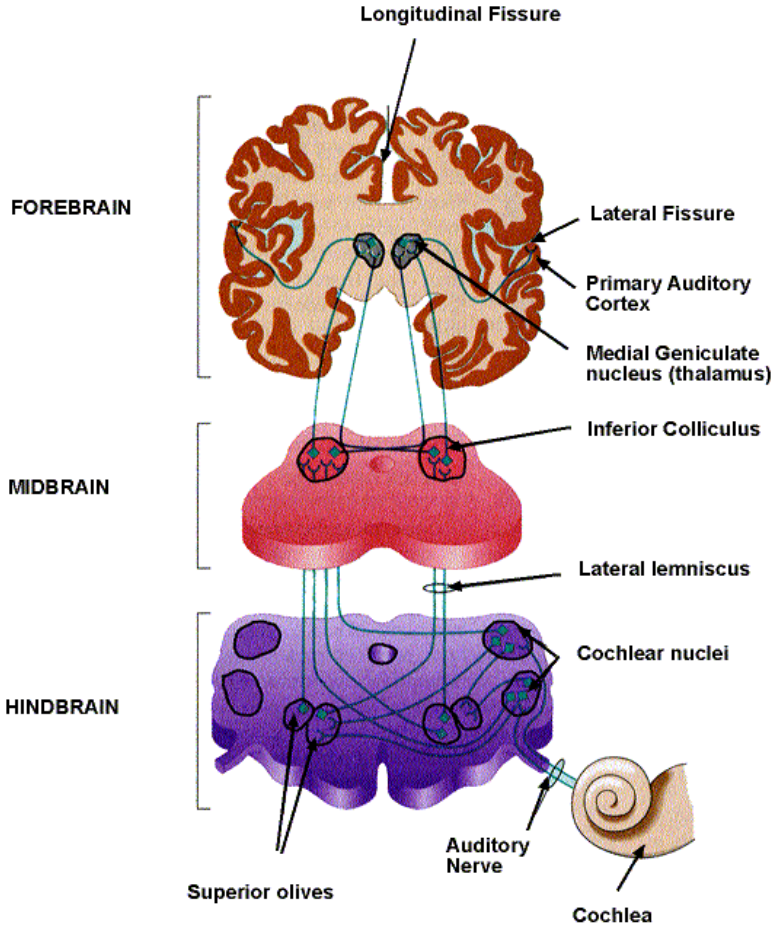


Figure B-3: The Central Auditory Pathway



Audiology and Audiometric Assessment

The science of audiology seeks to study hearing and evaluate abnormalities. Hearing loss can be divided into two major categories, conductive and sensorineural. In conductive hearing loss, a barrier in the outer or middle ear results in sound attenuation. Disturbances in the inner ear or auditory nerve are primarily responsible for sensorineural hearing loss or impaired bone conduction. Mixed hearing loss is the result of problems which occur in the conductive and sensorineural mechanisms simultaneously.

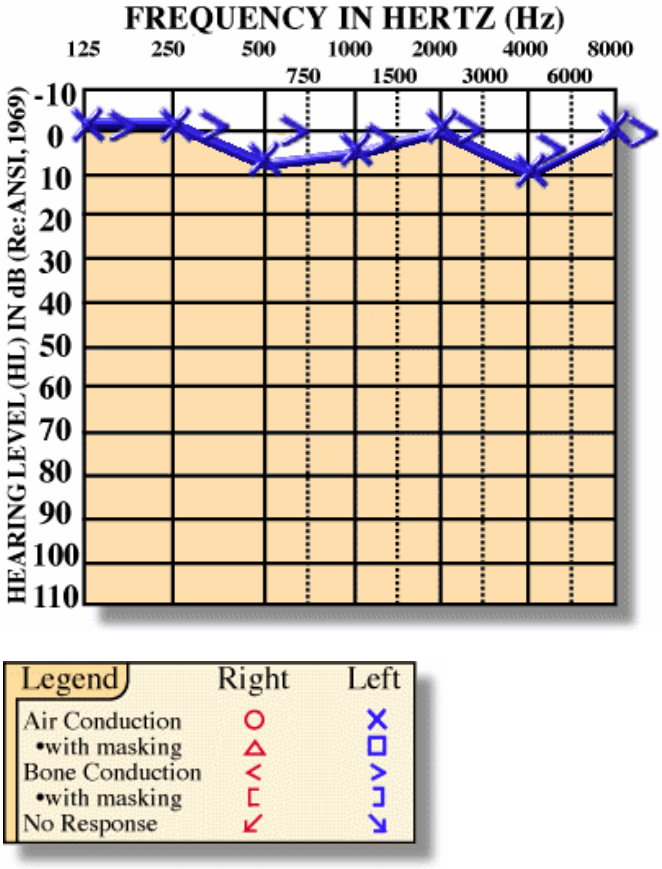
In order to measure hearing and to characterize abnormalities, audiologists can employ a battery of tests. To establish hearing thresholds audiologists begin with pure-tone audiometry whereby a range of puretones can be administered at various frequency and intensity levels. Results of air (stimuli transmitted through earphones) and bone conduction (stimuli transmitted via a bone vibrator) audiometry can both be recorded on an audiogram (Figure B-4). Auditory tests for site of lesion are employed to distinguish between sensory lesions within the cochlea and lesions beyond the cochlea which are neural. Examples of such tests measure loudness recruitment, differential intensity discrimination, and acoustic immittance among others. Additional tests utilizing spondaic words, word-recognition lists, high-frequency emphasis lists, and others can be used to test speech audiometry. For a survey of hearing loss in the general population, air conduction tests are the most commonly employed.

The procedure for air conduction tests using pure-tone audiometry is well-established. The audiometer is the primary instrument used for testing. Most audiometers consist of a frequency selector, a presentation button which presents the tone to a listener, a hearing level dial which controls tone intensity, an output selector (which determines which ear the sound is presented to), and a dial for masking level to be presented to the nontest ear if necessary.

An audiogram is used to plot pure-tone air thresholds. This chart plots hearing level in decibels against frequency in Hz. Standard symbols displayed in the audiogram key are used within the plot (Figure B-4). To obtain thresholds, the hearing examination most always takes place in a sound-treated room or a quiet room designated for hearing examination. Patients are instructed to respond to pure-tone signals no matter how soft the tone is and also to respond as quickly as possible during the presentation of the sound. The most common form of response is a simple raising or lowering of a hand.

Threshold testing begins with a presentation of a 1000 Hz pure-tone at 30 dB. If the participant does not respond to this level, the signal is increased by 20 dB and presented again. If the response is positive at the initial 30 dB, the intensity is decreased in 10 dB steps until the listener does not respond. An ascending technique is then employed to identify the precise threshold whereby a listener responds to a given tone positively at least 50% of the time. The technique employs 5 dB increments. Once the threshold is ascertained at 1000 Hz, the procedure is repeated for the higher test frequencies (2000-8000 Hz), then repeated at 1000 Hz once again for validity, and finally conducted at 500 and 250 Hz last.

Figure B-4: Audiogram



Hearing & Aging

It is well established that hearing ability declines with age. The aging auditory process is known as presbycusis. Studies seeking to characterize presbycusis in the inner ear and auditory nerve posed a challenge to investigators. The results of a number of studies were synthesized by Schuknecht in 1974[1]. He proposed four classifications of presbycusis: sensory, neural, strial, and cochlear conductive. Sensory presbycusis results from the degeneration of hair cells particularly within the basal region of the cochlea. The mechanism whereby these cells senesce is thought to be related to a decrease in enzymatic activity with subsequent accumulation of lipofuscin sometimes referred to as the "senile" pigment. Alternatively insufficient blood flow within the inner ear may also lead to hair cell degeneration causing a subsequent loss of hearing.

Strial presbycusis refers to atrophy of the stria vascularis in the middle and apical turns of the cochlea. This category of presbycusis may be the most directly related to the cardiovascular system. Systemic cardiovascular disease such as atherosclerosis may contribute to decreased blood flow within the capillaries and thickened capillary walls. This in turn may impede transport of nutrients or ions thereby affecting the chemical composition of the endolymph and subsequently altering the transduction of energy to the auditory neurons.

Neural presbycusis is characterized by loss of neurons within the cochlea that results in poor speech discrimination. The last category of presbycusis, as defined by Schuknecht, is cochlear conductive presbycusis. Alterations within the spiral ligament and supportive tissues may affect the mechanics of the cochlear duct thus leading to sensorineural hearing loss.

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APPENDIX C

MAGNITUDE OF THE PROBLEM – LITERATURE REVIEW

Prevalence & Public Health Significance

Hearing loss affects a high proportion of adults worldwide. Data collected from the 1999 National Health Interview Survey showed that 16% of the adult United States population experienced hearing difficulty (defined as a little trouble, a lot of trouble, or deaf)[1]. Among adults aged 65-74 years of age 28.8% reported some degree of hearing difficulty. This increased to 45.6% for persons aged 75 years and over. Males in all racial and ethnic groups reported a higher prevalence of hearing difficulty compared to females. The higher proportion of hearing difficulty in males has been primarily attributed to occupational and recreational noise exposure. The prevalence of self-reported hearing difficulty also varied by race and sex. Asian and Black or African American adults had a lower prevalence (7.8% and 7.4% respectively) of hearing difficulty than Whites or American Indians (17.2% and 20.1% respectively). The difference in racial prevalence rates has not been sufficiently explained.

The high prevalence of self-reported hearing impairment is of public health significance. Not only does hearing impairment affect communication processes, but it also has been shown to lead to poor psychosocial functioning, a lower quality of life, and decreased functional

capacity[2-6]. Hearing impairment and deafness thus contributes to considerable societal cost[7]. It is essential to characterize auditory function in populations to assist with the development of more effective prevention and rehabilitation tools.

Framingham Cohort

A population study of hearing in the elderly was conducted as a component of the Framingham Heart Study. The Framingham Heart Study recruited 5,209 individuals free of cardiovascular disease from a population-based sample of individuals living in Framingham, MA. The first clinical examination took place in 1952 with biennial examinations of cardiovascular and other disease outcomes taking place thereafter. Because hearing loss is a common chronic disability, the authors sought to examine the extent of the hearing decline in a population of elderly.

The study population consisted of 1,662 members of the original Framingham cohort (41% male)[8]. The average age of the subgroup was 73 years. Study procedures were divided into two parts, A and B. Part A was administered to all 1,662 subjects and consisted of a brief questionnaire, otoscopy, immitance measures, pure-tone thresholds (250 Hz – 8 kHz), and word recognition at conversational level. Part B consisted of additional word recognition tests and ipsilateral acoustic reflex thresholds. A total of 1,026 participants free of middle ear disease, prior ear surgery, or asymmetrical thresholds underwent Part B procedures. Pure tone averages were calculated by averaging thresholds at 0.5, 1.0, and 2.0 kHz. A four-frequency pure tone average (PTA_3) was calculated by adding the threshold at 3.0 kHz. Three definitions for hearing impairment were developed for analytic purposes: 1) as a binary variable with normal equated to

a pure-tone average (PTA) <26 dB, 2) as a continuous variable derived as a percentage score from 1.5 x (PTA_3 – 25), and 3) as a binary variable using the American Medical Association handicap score of >15% as classification of hearing impairment.

Forty-one percent (n=683) reported hearing loss either due to noise exposure (n=128), age (n=230), infection (n=89), injury (n=13), or unknown causes (n=223). Multivariable analysis of variance with age as a covariate found that self-reported hearing loss varied significantly ($p<0.0001$) with increasing age, self-reported cause, and male gender. Tinnitus was reported by 279 (16.8%) of the subjects. Results from pure-tone threshold testing confirmed prior research, with increasing age there was a trend for worsening of thresholds particularly in higher frequencies. The mean pure tone threshold in men was 22.0 ± 0.52 compared to a mean threshold of 20.4 ± 0.42 in women. An audiometric notch was present in 40% of the women and 66% of the men.

Word recognition tests were performed in 1,294 subjects in part A who had a PTA of <50 dB HL or no evidence of middle ear abnormality. Women performed better on the word recognition and maximum word recognition tests compared to men ($p=0.0001$). The apparent gender difference diminishes when one considers that a greater proportion of men had sharply falling high-frequency loss audiograms. However, the decline in word-recognition scores with age was statistically different between genders (8.6% per decade for men and 5.6% per decade for women).

The results of the immitance tests found only 5% of subjects with tympanometric abnormalities. Middle ear pressure was consistent among genders and age groups. Middle ear compliance did however decrease significantly with age although the magnitude of the effect was small.

Defining hearing loss as a PTA of >26 dB HL in the better ear, 29% of the cohort (32.5% of the males and 26.7% of the females) was classified as having a hearing impairment. Males were more likely to have a hearing problem (χ^2 p=0.013). The mean hearing handicap score of the cohort was 9.2 ± 0.64% with a median of 4%. Consistent with the PTA hearing impairment findings, males had significantly higher handicap scores than females (13.7 ± 0.9% for males vs. 6.2 ± 0.86% for females). An analysis of variance for handicap scores by age and gender was also statistically significant (p=<0.0001). Using a criterion of a handicap score of ≥15%, 35% of the cohort was classified as hearing impaired. These subjects were significantly older, had higher pure-tone averages, and lower word recognition scores.

A history of hearing aid use was reported by 10.3% of the cohort. The hearing handicap score of the current hearing aid users was dramatically higher than non users (52% vs. 4%).

The results of this study provided a better understanding of the epidemiology of hearing loss and measures to assess and classify hearing sensitivity. Self-reported history of hearing loss was 41%. Using a definition of PTA of 26 dB HL or greater, 29% of the cohort was classified as hearing impaired. Other definitions of hearing loss resulted in a prevalence closer to self-report (PTA_3 46%, Word Recognition score 46%, AMA handicap score 41%). A greater proportion of men had hearing loss compared to women for all classifications of hearing loss. This observation is most likely related to occupational history of noise exposure. Word recognition ability also declined with age and was in part related to the observed audibility in the cohort. Results from the immitance measures did not suggest stiffening of the middle ear mechanism with age. Abnormal middle ear function was uncommon in the cohort. Finally, hearing aid use was lower than expected given the results of audiological testing.

Biases inherent in this study are self-reported hearing loss, retrospective exposure to noise, and composition of the study population. There were many strengths of the study including its large sample size and methodology.

In an associated report, Cooper et al. examined the prevalence of central auditory disorders in the Framingham Cohort[9]. Three indices of Central Auditory Process Disorders (CAPD) were used, the Central Institute for the Deaf W-22 lists, the Synthetic Sentence Identification tests with ipsilateral competing message (SSI-ICM), and the Staggered Spondaic Word test. In brief, abnormal results on any one of the three indices occurred in 22.6% of the subjects and the overall prevalence of CAPD in the cohort was lower than suggested by prior studies. Additionally, age accounted for no greater than 15% of the variability within each of the three indices. When correlated with pure tone averages, the performance-intensity function rollover index (RO) and the PB-SSI score (calculated as the difference between the maximum word recognition score and synthetic sentence identification test) persisted to be independent of hearing loss. A high r^2 was found between the staggered spondaic word test and PTA. However, the clinical relevance of such a finding is uncertain given a lack of biological plausibility.

Longitudinal Analysis of Hearing Decline

Longitudinal analyses have numerous advantages over cross-sectional designs. The primary advantage is that longitudinal analyses aid in the determination of factors attributed with disease etiology. Serial examinations within a single cohort also allow one to more accurately assess

change in a dependent variable due to age. A longitudinal analysis of hearing ability was conducted within the Framingham cohort previously described[10].

Eligible participants included those who volunteered for audiometric testing at biennial examinations 15 (1978-1979) and 18 (1983-1985). The resulting sample size was equivalent to 1,475. The age range for the subjects was 58-88 at exam 15 and 64-94 at exam 18. The methods for the audiometric testing have been discussed in the above Gates publication. Differences between the methodology employed in the biennial 15 and biennial 18 examinations were limited to the type of audiometer used. Change scores were calculated for each individual test frequency, for the averages of the thresholds 0.5-2.0 kHz (PTA), and for the averages of the thresholds at 4, 6, and 8 kHz (PTA_{4-8}). Changes were compared within and between gender and ears (left and right). Considering Studebaker's test-retest variability, the criterion for clinically significant change was chosen to be greater than 10 dB.

Mean differences in pure-tone thresholds for each ear by gender were 2.9±0.25 and 4.7±0.26 for the right and left ears of the men and 3.6±0.21 and 5.3±0.2 in the right and left ears of the women. For PTA_{4-8}, the mean difference was 5.7±0.32 and 6.9±0.35 in the right and left ears of the men and 8.0 ± 0.28 and 8.8 ± 0.28 dB in the right and left ears of the women. The PTA worsened in 8.5%, 13.5%, and 4.1% of the subjects' right, left, and both ears respectively. The proportion of individuals with worse PTA_{4-8} was higher. For the right and left ears respectively the PTA_{4-8} declined in 31.1% and 35.3% of subjects and declined in both ears for 18.7% of participants. The average age of individuals who experienced a decline in PTA hearing function was significantly higher than the rest of the population (69.3 vs. 66.7 years, $p<0.0001$).

ANOVAs were calculated to determine whether the rate of threshold change varied with age after considering the effects of age, ear, gender, and frequency on the amount of change. For

the lower frequencies, age was a main effect predictor of change. For the higher frequencies, gender and ear were significantly confounding the main effects of age. Linear trends were analyzed with regression techniques. The 6 year rate of change increased in both genders for frequencies less than 2 kHz. Between 4 and 6 kHz the rate of hearing loss in women continued to increase with age whereas in men the threshold change slowed with increasing age. At 8 kHz the rate of hearing loss slowed in both genders. Initial PTA did not an effect on change in PTA. However, initial PTA did have an effect on threshold change for PTA_{4-8}. For every 7dB increase in the initial PTA_{4-8}, the difference in PTA_{4-8} was lowered by 1 dB. The rate of decline was significantly higher in men than women.

The primary results of this study were that hearing decline occurred primarily at 6 and 8 kHz frequencies. Although age had a significant effect upon rate of change in lower frequencies it only accounted for 9% of the variability. Therefore, it is suggested that other factors which covary with age should be considered. Significant gender differences in rates of change were not observed. Rate of change increases in low frequencies and slows in high frequencies although the magnitude of change is higher in the higher frequencies. Interestingly initial hearing does not have an impact on rate of change in lower frequencies but does in higher frequencies. This suggests that two different processes affect age-related hearing dysfunction. For the higher frequencies, prior cochlear damage and haircell degeneration may have more of role. These factors do not adequately explain the observations for the lower frequencies. The authors suggest that strial atrophy may provide one pathophysiological explanation.

To investigate whether audiologic change varied in persons with audiometric notches a separate analysis was conducted within the Framingham cohort. Audiometric notches between the 3-6 kHz region of an audiogram are usually indicative of noise damage. The 15 year change

in audiometric thresholds was examined in 203 men from the cohort who had measurements at the 15th and 22nd biennial examinations. They were divided into three groups on the basis of their audiograms – no notch, small notch (an elevation of 15-34 dB in the 3-6 kHz region), and large notch (an elevation of >35 dB in the 3-6 kHz region). Threshold change in the notch region was not as pronounced as in frequencies less than 2 kHz.

Subjects classified in the large notch group experienced a greater decline in thresholds in the lower frequencies as compared to the other two groups. Subjects in the small notch group experienced a greater decline in threshold at the 8 kHz frequency. Changes at the lower frequencies were independent of initial hearing loss (at the 15th biennial exam). In contrast, changes at the higher frequencies were influenced by hearing level at the initial visit. Conclusions from this study are that the noise-damaged ear ages at a different rate than the non-noise damaged ear and perhaps via a different mechanism.

Limitations with the study were that data on potential confounders such as ototoxic drug use, recreational noise, and history of certain ear diseases were not collected. Additionally, data on noise exposure that occurred between the two examination periods was not available. Given the age of the population, it is unlikely that a high proportion of individuals were exposed to continued noise exposure in either an occupational or recreational setting. This research does provide further support for the necessity of prevention against noise-induced hearing loss. The auditory notch does have interesting implications for clinical practice and may in the future serve as a surrogate measure of prior noise damage.

Beaver Dam Studies

The Epidemiology of Hearing Loss Study is a population-based cohort study designed to assess the descriptive epidemiology of hearing loss in older adults of Beaver Dam, Wisconsin[11]. The study population was pulled from a population-based cohort established in 1987-1988 for the Beaver Dam Eye Study. A total of 4,926 persons aged 43-84 years completed initial eye examinations for the eye study. Those persons who were alive as of March 1, 1993 were invited to participate in the hearing study (N=4,541). A total of 3,753 participants actually enrolled in the hearing study. The mean age of the study population was 65.8 years with 57.7% being women and all participants classified as non-Hispanic whites.

The study visit comprised of an otoscopic examination, a screening tympanogram, and pure-tone air (250-8,000 Hz) and bone (500 and 4,000 Hz) conduction audiometry. Additional information on medical history, noisy hobbies and occupation, family history, and self-perceived hearing function was collected via questionnaire. Hearing loss was defined as a PTA (500, 1000, 2000, and 4000 Hz) greater than 25 dB in the worse ear and classified as mild (> 25 dB and <40dB), moderate (>40 dB and <60 dB), and marked (>60 dB) based on this definition. Presence of an air-bone gap of 15 dB or greater in the ear with worse hearing constituted conductive hearing loss.

Prevalence of hearing loss was 45.9% in the whole cohort. Of persons with hearing loss, 58.1% were classified as having mild loss, 30.6% moderate loss, and 11.3% marked loss. The primary results of this study found hearing sensitivity to decline with age and higher frequencies. Logistic regression modeling predicted that with each 5-year increase in age, hearing loss increased by nearly 90%. Hearing loss was also more prevalent among men (OR=4.42, 95% CI:

3.73-5.24). Women were nearly four times less likely to have hearing impairment (OR=1.88, 95% CI: 1.80-1.97).

The prevalence of persons reporting a hearing handicap increased steadily for each hearing loss group (5.5% no hearing loss, 19.7% mild, 47.5% moderate, and 71.4% marked). This population had a low prevalence of conductive hearing loss and abnormal middle-ear function.

Aside from age and sex, education and income level were inversely related to hearing loss. Occupational noise exposure was also a significant predictor of hearing loss (OR=1.31). This epidemiological survey of hearing loss in a community-based sample resulted in estimates similar to that already reported in the literature.

Popelka et al.[12] further examined hearing aid use within the EHLS cohort and found that there was a low prevalence of hearing aid use among those with some level of hearing loss. In total only 14.6% of the study population were currently using hearing aids although the overall hearing loss (defined as a PTA of >25 dB) was approximately 46%. As expected, hearing aid use increased with age ($p>0.001$). Hearing aid use was also positively correlated with severity of hearing loss, word recognition scores, self-reported hearing loss, self-perceived hearing handicap, and history of military noise exposure. Participants with a higher education level (>16 vs. <12 years) and self-reported hearing loss were more likely to use hearing aids (OR=3.20, 95% CI: 1.68-6.07 and OR=4.87, 95% CI: 2.05-11;.56 respectively) after adjusting for age, sex, severity of loss, education, word recognition score, Hearing Handicap Inventory for the Elderly score, and self-reported loss.

Additional research from the EHLS study has shed light on risk factors such as smoking[13], non-insulin dependent diabetes[14], and recreational fire-arm use[15] as well as the relationships between cataracts[16] and age related maculopathy[17] and hearing loss.

Alameda County Study[18]

Other studies have been also assessed the prevalence of hearing impairment using questionnaire data alone. Hearing function was measured in the Alameda County Study, another large population based cohort study. Hearing impairment was assessed via self-report after asking two questions, "Do you have trouble hearing (even with a hearing aid)?" or "Have you ever had trouble hearing (even with a hearing aid)?" If yes, "Have you had it in the last 12 months?" Age-adjusted prevalence rates were calculated for each survey period (1965, 1974, 1983, and 1994) and included 5108 participants who responded in any one of the four periods. Incidence of hearing loss was examined among those reporting no hearing impairments in 1974 and who participated in the 1994 survey. Data on risk factors for hearing impairment were collected in the 1974 survey and included occupational data and exposure to ototoxic drugs as measured by symptoms related to their use.

Hearing impairment prevalence increased steadily from 1965 to 1994 in both men and women although rates were consistently higher among men. The overall prevalence increased from 9.2% in 1965 to 18.0% among all participants aged 50 and older. Those under the age of 70 experienced the greatest percentage increase in hearing impairment from 1965 to 1994. Results from the incidence analysis revealed significant age, ethnicity, gender, and income

adjusted odds ratios for persons reporting an occupation of craftsman, operative, or foreman (OR=1.45 95% CI: 1.01-2.08), admittance to a hospital in the last 8 years (OR=1.42, 95% ci:1.09-1.78), operation requiring hospital stay in the last 8 years (OR=1.34, 95% CDI: 1.05-1.78), any medical symptom potentially related to ototoxic drug use (OR=1.34, 95% CI: 1.01-1.79), and exercise (OR=0.69, 95% CI: 0.54-0.88).

This study demonstrated the public health significance of hearing impairment. However, it did suffer from several limitations related to methodology. Questionnaire data alone does not sufficiently suffice to determine hearing loss – this rate could be either under or over-reported. Based on previous literature, self-reported hearing loss is most often under-reported. Data related to the risk factors was also fairly weak especially with regard to potential exposure to ototoxic drugs.

Conclusion

In the two prospective cohorts reviewed, the prevalence of hearing impairment ranged from 46% in the Beaver Dam Study (mean age=66) to 29% in the Framingham Study (mean age=73). Hearing loss was significantly more prevalent among men and in older adults. The literature is deficient with respect to examining the prevalence of hearing impairment in non-white populations. While definitions of hearing impairment varied, the above studies still demonstrate the extent to which hearing impairment is of public health significance.

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APPENDIX D

RELATIONSHIP OF HEARING LOSS WITH CARDIOVASCULAR DISEASE AND ITS RISK FACTORS LITERATURE REVIEW

The inner ear is a sensitive organ comprised of numerous minute vessels and specialized hair cells. A single end artery, the internal auditory artery, supplies the inner ear with nutrients. Blood flow is concentrated within the stria vascularis of the inner ear. Cochlear blood flow is hypothesized to be modulated by a combination of vessel permeability, systemic or extrinsic factors, and local or intrinsic factors.[1] Disturbances in blood flow may lead to an alteration of the chemical composition of endolymph or degeneration of hair and nerve cells within the cochlea, subsequently leading to hearing loss. It is therefore plausible that disturbances and disease processes in the cardiovascular system as a whole may have the potential to affect hearing.

While most audiology texts implicate vascular disease as having a causal role in the etiology of presbycusis, few studies have actually specifically addressed this area. In this appendix, the literature on hearing loss and cardiovascular disease and its risk factors is critically reviewed. Studies which looked at cardiovascular disease as a whole are first reviewed followed by those which specifically consider hypotension and hearing loss, blood chemistry and viscosity and hearing loss, and biological studies related to arteriosclerosis and hearing function.

Cardiovascular Disease and Hearing Loss

Research examining the potential role of cardiovascular disease and its risk factors with presbycusis began as early as the late 1950s. Rosen et al.[2] studied a population of Sudanese known as the Mabaans in order to examine the effect of aging on hearing without environmental confounders that exist in populations of modern civilization. The general sound level of the village was less than 40 dB on a C scale of a sound level meter. A total of 541 persons aged 10 to 90 were examined using audiometric tests, physical and neurological measures, and blood pressure measurements.

Details of the physical and neurological measures were not outlined in the methodology; however the investigators did report three cases of total deafness, two with significant hearing loss, three with unilateral hearing impairment, and two with poor hearing since childhood on the basis of these exams. Chronic diseases such as high blood pressure, coronary artery disease, asthma, and others were unknown in the tribe.

Determination of age proved to be more difficult than in modern societies. Sociocultural methods were employed to estimate chronological age. Since Mabaans look younger than their chronological age, age was most often underestimated.

Blood pressure findings in the Mabaans were compared to healthy persons in the United States[3]. Interestingly, blood pressures within the Maabans remained fairly constant with increasing age. Additionally, Maaban males had consistently lower blood pressures than Maaban females, unlike the US population.

The hearing study utilized battery operated and portable audiometers which were calibrated twice daily. Participants were instructed to raise their hand once they heard a tone and

lower it when the sound ceased. Median hearing thresholds for male Mabaans below the age of 40 were negative up to a frequency of 2000 Hz (threshold at 2000 Hz = -2.1 dB). Hearing thresholds at 2000 Hz for participants aged 50 and above were 2.9 dB. With higher frequencies and age, the thresholds increased steadily. Similar observations were found in Mabaan females although hearing thresholds within the younger participants were slightly higher than in males (thresholds of -2.1 dB for 2000 Hz for those aged 20 and below). Comparisons with populations in the United States showed that older Mabaan men and women had superior hearing especially at higher frequencies. Differences in hearing thresholds at frequencies of 4000 Hz and 6000 Hz among Mabaans and US populations ranged between 40 and 50 dB.

The primary conclusions from this study link the absence of elevated blood pressure in Mabaans with the absence of high tone loss in aging Mabaans. This suggests that underlying cardiovascular disease may play a role in hearing loss. Possible biological explanations suggest that atherosclerosis may impede the transport ability of capillaries within the inner ear.

A critical appraisal of this study must take into consideration its sociocultural context. As such it was difficult to ascertain age and complete medical histories. Biases as a result of sociocultural inferences include an underestimation of chronological age and a potentially false assumption that participants were free of existing cardiovascular disease. For those persons that were identified as having hearing impairments it was unclear as to whether or not they were included or excluded in the overall analysis. Given the small number of participants with hearing disorders it is unlikely that inclusion would bias the overall results to a significant extent.

The methodology for the audiometry was not presented in great detail making it difficult to determine its appropriateness. Statistical tests of significance were not performed to determine the extent of observed differences. Finally, the cross sectional design and ecological

comparisons of the study make it difficult to conclude that the relationship between blood pressure, a surrogate marker of cardiovascular disease, and hearing function is causal. The study does however, provide impetus for further investigations into the observed association.

Rosen et al.1965 also hypothesized that coronary heart disease, if viewed as a nutritional disease, may be related to hearing loss and an increased air-bone gap (characteristic of conductive hearing loss)[4]. To test their hypothesis the investigators established control and experimental groups among mental patients ages 40-49 (N=39 experimental and 37 control) and ages 50-59 (N=97 experimental and 106 control) in Finland. The experimental group was provided a diet with less saturated fats and more polyunsaturated acids. The control group was fed a typical Finnish diet containing large quantities of saturated fat derived mainly from whole milk and butter. After three years of diet, the experimental group had significantly lower cholesterol levels and a longer coagulation time. Chi-square analysis found that incident cases of CHD were also lower in the experimental group ($p<0.02$). Results of the hearing tests found better air conduction means and smaller air-bone gaps in the experimental group. The authors conclude that the difference in coronary heart disease among the two groups parallels the difference in hearing between the groups.

After conclusion of the five year diet trial, the investigators reversed the diets for four years[5]. Similar findings were observed, the now low-fat hospital had improved hearing when compared to the now high-fat hospital population. A limitation in this analysis is that the authors chose to analyze their data at a population rather than individual level. This factor in conjunction with the relatively small sample size may render the results less supportive of a causal association since chance and ecological fallacy may play a significant role.

Given more modern methods it would be prudent to further validate the preceding conclusion. A quantitative analysis of serum cholesterol in conjunction with hearing function would strengthen the observed association. At the same time potential confounding factors, such as prior noise exposure, prior cardiovascular disease events and/or risk factors should also be assessed.

Results from a cross-sectional analysis of hearing function in the aged conducted by Rubinstein supported Rosen's prior conclusions. Rubinstein et al. found more superior hearing in a control group of 23 patients as compared to 23 patients aged 65 and older with appreciable cardiovascular disturbances with signs of impaired peripheral circulation [6]. The analysis suffered from a small sample size along with inadequate definitions of the study groups. The authors did not assess prior history of CVD in the control population nor did they sufficiently define the "exposed" group.

Another study conducted in 1975 by Drettner et al. investigated potential associations between cardiovascular risk factors and hearing loss in 1,000 fifty-year old men[7]. Risk factors examined included blood pressure, heart rate, serum cholesterol and triglycerides, uric acid, hematocrit, glucose tolerance, smoking habit, and noise exposure. Hearing was tested with a pure-tone audiometer at frequencies of 500, 1000, 2000, 3000, 4000, and 6000 Hz bilaterally. Additional covariates such as history of ear disease, noise exposure, and smoking habits were collected via questionnaire. Individuals reporting a positive history of ear inflammation and/or disease were excluded from the correlation analysis (N=238). The results of the correlation analysis showed no significant associations between risk factors and hearing loss with the exception of smoking habits. A prospective study designed to look at smoking in conjunction

with cardiovascular disease and cardiovascular risk factors had been proposed by the authors to further support their findings.

The most recent study to specifically address CVD and hearing loss was ancillary to the Framingham Heart Study[8]. The study population consisted of 676 men with a mean age of 72.7 years and 986 women with a mean age of 73.0 years. Hearing tests consisted of pure-tone audiometry and suprathreshold tests (word recognition and synthetic sentence identification). Pure tone averages were calculated for the lower frequencies (250, 500, and 1000 Hz) and higher frequencies (4000, 6000, and 8000 Hz) separately. The mean pure-tone average (PTA) of frequencies between 250-8000 Hz in the better ear was 22.2±13.4 dB HL in men and 20.7±13.1 in women. Independent variables were divided into CVD measures and CVD risk factors. Prevalent CVD was defined as having any one of the following measures: coronary heart disease, stroke, or intermittent claudication. CVD risk factors which were examined in relation to hearing level were blood pressure and prevalent hypertension, diabetes mellitus, smoking, weight, and triglyceride, cholesterol, and lipid levels. The occurrence of cardiovascular events was evaluated at each examination. Diagnoses were verified by three physicians and a participant was classified as having prevalent CVD if any one of the following events, CHD, heart attack, stroke, or intermittent claudication occurred prior to the audiologic examination.

With respect to CVD events and age-adjusted hearing thresholds, both men and women with a history of stroke, CHD, or intermittent claudication (IC) had statistically significant higher hearing thresholds at the low range frequencies. Women with a history of the above disease measures also had increased hearing thresholds at the high range frequencies. Odds ratios (OR) predicting threshold elevations of 40 dB hearing loss reflected the above results. The OR for a PTA_{lo} of 40dB HL in women with prevalent CVD was equivalent to 3.06 (95% CI: 1.84, 5.10).

In men this OR was lower, 1.75 (95% CI: 1.01-3.03). Threshold elevation at high frequencies was related to total CVD only within women (OR=1.49 95% CI: 1.02-2.17).

The results of the cardiovascular risk factor and hearing loss analysis found a statistically significant relationship (though of small magnitude) between hypertension/blood pressure and age-adjusted hearing thresholds. Additionally, an inverse relation of age-adjusted HDL and PTA_{lo} was observed in women.

CVD events were not correlated with maximum recognition scores in the study population. For women with heart attacks and stroke, the synthetic sentence identification (SSI) test scores were significantly reduced in both ears. For men, no association was found between CVD events and SSI results

The authors suggest that since a relationship was found between CVD events instead of CVD risk factors, that the CVD process may affect hearing. Additionally, the results suggest that the pathophysiological mechanisms of hearing loss may be gender specific with potential relationships to premenopausal estrogen levels, nosocusis, or sociocusis. Although the results of this study can be interpreted as exploratory in nature, they do suggest that CVD may play a role in low-frequency presbycusis particularly in women.

The study had several strengths including a large sample size and excellent hearing measures. Despite the cross-sectional nature of the present analysis, the Framingham cohort does offer the opportunity to look at changes in risk factors and prevalent hearing loss. Some limitations of the study were that potential confounding factors such as ototoxic drug use and history of occupational and recreational noise exposure were not addressed. Additionally, the population consisted of all Caucasian individuals which did not permit for the evaluation of racial/ethnic differences.

Preliminary analysis from the Epidemiology of Hearing Loss Study in Beaver Dam, WI supports the findings from Gates et al. In their study of 2,626 men and women aged 52-97 years of age, self-reported cardiovascular disease was identified via questionnaire. Individuals with a history of cardiovascular disease were 1.54 times (95% CI: 1.04-2.95) more likely to have abnormal cochlear function (defined as a distortion product otoacoustic emission/noise ratio as <+9dB for an average of 2, 3, and 4 kHz or no single frequency over +9dB) even after adjustment for age, gender, hunting, and activity level[9]. An OR of 1.77 (95% CI 1.03-3.06) was obtained when comparing individuals with a myocardial infarction to those without. When stratified by sex, this relationship was even stronger in women (OR=2.69, 95% CI: 1.19-6.07).

Hypotension and Sensorineural Hearing Loss

Systemic hypotension has been hypothesized to play a role in the etiology of gradual and acute sensorineural hearing loss (SHL). Pirodda, et al. conducted an investigation of hypotension and SHL within a young population free of additional vascular risk factors[10]. The sample was selected from the original "Brisighella Study", an epidemiological investigation on chronic diseases of social impact begun in 1972 and now housed under the WHO's Risk Factors and Life Expectancy study. Eligibility criteria for the study group included a blood pressure of ≤ 60 mm Hg diastole and/or ≤105 mm Hg systole and aged 50 years or less. A total of 20 hypotension subjects were recruited. The control population (N=100) met similar age criteria and was selected from the same region as cases.

The otological evaluation consisted of an otoscopic examination, audiometric evaluation including both bone and air conduction testing, and a questionnaire to assess previous history of audiological, vestibular, or otological diseases and familial or neonatal hearing impairments. Hearing impairment was defined as having a bone conduction threshold of ≥ 25 dB HL at two consecutive frequencies.

The primary results of this study found 35% of hypotension subjects to have a hearing impairment versus 3% of control subjects (χ^2 p=<0.0001). The authors propose that hypotension's role in the pathogenesis of SHL involves a "protracted condition of haemodynamic imbalance" that leads to an insufficiency of transient systems. This in turn may affect nutrient supply to cochlear receptors.

A later study conducted by Pirodda et al.[11] confirm the above results, further supporting their theory of hypotension's role in the pathogenesis of acute and chronic sensorineural hearing loss. Additional research is needed from longitudinal analyses in larger populations to substantiate the author's mechanistic hypotheses.

Blood Chemistry and Hearing Loss

Since the inner ear is supplied by an end artery, cardiovascular risk factors within blood chemistry may provide insight into the relationship between CVD and hearing loss. Lee et al. conducted a comprehensive examination of blood chemistry and hearing loss[12]. A total of 89 females and 128 males aged 60 to 82 years without a history of middle ear disease were recruited for the study. Pure-tone audiometry was conducted to assess hearing thresholds. Subjects were

classified into one of three groups based on their combined pure-tone average thresholds (PTA) in both ears at frequencies of 500, 1000, 2000, and 4000 Hz. Normal to mild hearing was defined as a PTA of < 20 dB HL, mild to moderate hearing was defined as a PTA ≥20 and ≤40 dB HL, and moderate to severe hearing was defined as a PTA > 40 dB HL.

Blood samples were taken after a minimum 8 hour fast. Blood chemistry tests were divided into 1) an electrolyte panel consisting of CO_2, chloride, potassium, sodium, calcium, creatinine, glucose, magnesium, and urea nitrogen, 2) a hematology panel consisting of white and red blood cells, hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, hematocrit, platelets, red cell distribution width (RDW), and mean platelet volume, 3) a lipid profile consisting of total cholesterol and low and high density lipoproteins, immunglobins (IgA, IgE, IgG, and IgM), and 4) thyroxine.

The study population had hearing thresholds similar to the 25th percentile of the ISO standard for the 70-year old otologically normal population. With the exception of glucose, white blood cells, IgA, total cholesterol, and LDL, the mean blood chemistry results for the study population fell within the normal range of values as defined by the Department of Pathology and Laboratory Medicine at the Medical University of South Carolina.

Univariate correlations resulted in only three statistically significant relationships between blood chemistry and PTAs, all within women. The red cell distribution width, chloride, and magnesium had significant correlations although the authors caution that the findings may be due to chance as a result of the number of correlations performed. Multiple regression analyses adjusting for sample size did not result in any significant relationships.

Factor analysis was employed to reduce the number of variables within the blood chemistry data. Factor analysis resulted in two to four factors being extracted from each blood

chemistry panel. Four factors accounted for 81% of the variance within the hematological panel of both men and women. Similarly 69% and 70% of the variance was explained by the four factors in the electrolyte panel of men and women respectively. Two factors were established for the serum lipids. The total % of variance for the lipid factors was greater than 83% for both men and women suggesting that the lipids were highly correlated. Factor analysis for the immunoglobins had the lowest % of variance suggestive of a low degree of correlation among these blood components. The discriminant analysis failed to add higher classification rates than the factor analysis. Canonical analysis was performed to maximize the correlation between two sets of variables by generating new variables through linear transformation of the original variables. Wilk's lambda was used to test statistical significance of the canonical analysis r-squares. None of the r-squares were statistically significant.

The final set of analyses performed was nonlinear and utilized a LDL/HDL ratio. Women with high LDL/HDL ratios (a high risk condition for coronary heart disease) had PTAs between 10 and 30 dB HL. This is in contrast to women with low LDL/HDL ratios which had a larger range of PTAs (between 0 and 80 dB HL). Participants were grouped into four quadrants on the basis of their PTA and LDL/HDL ratio. A chi-square test of the resultant contingency table was significant at the 0.05 level suggesting that there was a comparable difference between women with high LDL/HDL ratios and women with low LDL/HDL ratios and PTAs. Results for the men were non-significant as the data was scattered randomly throughout all four quadrants.

The primary findings of this study were as follows: with the exception of serum chloride, magnesium, and RDW in women, none of the blood chemistry measures were significantly associated with hearing loss. The most notable finding was the relationship between low LDL/HDL ratios and hearing loss. These conclusions would be strengthened by a larger

longitudinal study. Limitations of the study were primarily related to the number of multiple comparisons leading to a higher Type II error.

Several other reports have specifically focused on examining the relation between hyperlipidemia/hyperlipoproteinemia and hearing disorders. Lipoproteins are involved in the atherogenic process and thus may be a mediator of hearing loss and vascular disease. A review of existing literature on hyperlipoproteinemia and presbycusis supports the hypothesis that vascular disease or hyperlipoprotenemia (HLP) and hearing loss are related either as independent predictors or as intermediary factors between noise exposure and hearing loss[13]. Due to deficiencies in study design (small sample size, inadequate controls, and inadequate adjustment for confounders among others), the results of these studies should be interpreted with caution. A study not addressed in the Ray 1991 review is briefly summarized below.

Suzuki et al. conducted a cross-sectional investigation in 607 men and 317 women aged 40-59 years of age in Japan[14]. The analysis divided the study population into two groups, a high and a low based on a mean lipid concentration of less than or greater than or equal to 1 standard deviation of the mean. Hearing levels at 2000 and 4000 Hz were better in men classified in the high-level HDL-C group. The authors hypothesize that their findings in men alone were related to greater exposure to noise. Their conclusions suggest that low HDL levels are associated with atherosclerotic related circulatory disturbances in the vasculature of the cochlea. In order to support their statement additional research is needed, perhaps in populations with a known greater exposure to noise.

Blood Viscosity and Sudden Hearing Loss

Three commonly accepted causes of sudden hearing loss are viral infections, immunopathological mechanisms, and vascular disturbances. The latter cause relates to blood viscosity and flow. Browning et al. considered blood viscosity as a factor of sensorineural hearing loss in two groups of patients[15]. Patients were excluded if they had a history of occupational noise exposure, conductive defect, middle ear disease, or a pathological increase in blood viscosity, acute infection within the preceding four weeks, or were currently on drug therapy. Blood, plasma, and relative blood viscosity were determined for 49 adults and hematocrit and serum protein and albumin were available for 92 adults. The primary findings from this study were that the more viscous the plasma, the better the hearing thresholds particularly in higher frequencies. However, increased high-shear blood viscosity was predictive of poorer sensorineural hearing loss. When corrected for hematocrit and divided by plasma viscosity, high shear blood viscosity can serve as a surrogate for red-cell rigidity. One hypothesis is that red cells with less rigidity could lead to poorer blood flow within the stria vascularis.

The above study was replicated in a larger population (N=342) pulled from the Caerphilly Collaborative Heart Disease Study[16]. Of the 342 individuals with available data a subset of 124 participants with similar eligibility criteria as the Browning report was created. Comparisons between these two groups revealed few differences aside from higher hearing thresholds in the selected subjects especially at higher frequencies. There were no significant correlations between plasma viscosity and hearing thresholds. Whole-blood viscosity was however correlated with hearing thresholds at all frequencies, suggestive of red-cell properties.

As a follow-up to these findings, Gatehouse and Lowe conducted an additional study incorporating red cell filterability as a predictor of hearing impairment[17]. Ninety-three individuals between the ages of 50 and 75 years were recruited. Plasma, whole blood, and relative viscosity along with red cell filterability were measured. Air-conduction thresholds were obtained for frequencies between 250-8000 Hz. After adjustment for age, sex, and socioeconomic group, whole blood viscosity at high shear rate was correlated with higher hearing thresholds for lower frequencies (250-2000 Hz). At frequencies of 4000 and 8000 Hz, red cell filterability was associated with raised hearing thresholds after adjustment for the same three demographic variables listed previously. Differences in these associations were noted when the population was stratified by age. Within the older age group, high shear viscosity was related to hearing impairment at frequencies of 250 and 500 Hz only, yet red cell filterability was associated with higher hearing thresholds for frequencies between 1000 and 8000 Hz. These results suggest that the individual cell-based measure (red-cell filtration) plays a larger role in sensorineural hearing loss than measures of bulk blood flow or viscosity.

Another determinant of blood viscosity is fibrinogen. Suckfüll et al. conducted a cross-sectional study investigating hyperfibrinogenemia as a risk factor for sudden hearing loss (SHL)[18]. Fifty-three patients who had experienced SHL within a five day period were age and gender matched to a control population with no history of SHL or sensorineural hearing loss. The primary results of the study found that patients with SHL had significantly ($p<0.05$) higher plasma viscosity (1.31 ± 0.13 mPa/s vs. 1.26 ± 0.08 mPa/s), erythrocyte aggregation (27.3 ± 5.6 vs. 20.9 ± 8.5), and fibrinogen (343 ± 98 mg/dL vs. 303 ± 69 mg/dL) levels. The results of this study are consistent with others that have also found a correlation between increased whole blood viscosity and hearing loss and/or higher hearing thresholds. It is unlikely that fibrinogen

alone affects SHL. It would be interesting for investigators to evaluate this relationship in a prospective manner taking into account additional cardiovascular risk factors and potential confounders related to hearing loss in general.

Biological Studies

Johnson and Hawkins examined the microvascular pathology of the ear to assess whether it was related to metabolic presbycusis[19]. Temporal bones from 150 cases aged newborn to 90 years were examined. General observations were that with aging there was a gradual loss of capillaries in the stria vascularis, thickened arterial walls with narrower lumens, and atrophy of the spiral ligament. All cases with hair cell loss in the cochlea had corresponding strial atrophy. The authors conclude on the basis of their observations that arteriosclerosis may play a role in strial atrophy which consequently leads to a degeneration of hair cells.

Makishima (1978) conducted a histopathological study of the temporal bones, brains, kidneys, and other arteries in 40 patients over the age of 50[20]. The purpose of his study was to relate audiometric records to the morphologic findings, in particular angiosclerotic changes, within the bones and organs of the study patients. Severity of arteriosclerosis of the aorta and arteries of the Willis circle was evaluated by the Gore method. Lumen narrowing was evaluated as the ratio of arterial wall thickness to arterial lumen diameter. Audiograms for each of the cases were divided into three grades of hearing (normal, moderate hearing loss, and severe hearing loss). The results of the study found a close relationship between lumen narrowing of the internal auditory artery and hearing loss. In addition, a positive correlation was found

between the degree of lumen narrowing within the artery, the degree of spiral ganglion atrophy, and the degree of hearing loss. The author concludes that presbycusis may be the result of arteriosclerosis and subsequent spiral ganglion atrophy thus affecting auditory function.

Discussion

A review of the literature investigating the relationship between cardiovascular disease and its risk factors with auditory function suggests that vascular disease plays a role in presbycusis. Studies suggest that cardiovascular outcomes such as myocardial infarction, intermittent claudication, stroke, and coronary heart disease are related to poorer hearing function[4,7-9]. The most consistent relationship has been observed in two separate populations between coronary heart disease and hearing loss[4,8]. Since the pathogenesis between these outcomes and hearing loss is undetermined, researchers have sought to investigate whether CVD risk factors play mediating roles.

Aside from lipids, smoking, and factors related to blood viscosity, the majority of CVD risk factors within blood chemistry showed essentially no relation with hearing loss. How these risk factors are involved in hearing loss is under considerable debate. Most studies argue that the etiology behind hyperlipidemia and hearing loss is vascular in nature[6,13,21]. Lipoproteins, particularly LDL, have been shown to be involved in the development of atherosclerosis. Since CVD is systemic it is biologically plausible that lipoproteins may also affect the microvasculature of the stria vascularis in a similar manner as they affect larger vessels. The

observation that HDL offers a protective effect on hearing loss also warrants further investigation.

Blood viscosity is an integral component of local blood flow. Increased fibrinogen has been associated with increased blood viscosity. Increased viscosity impacts oxygen exchange and transport within vessels and contributes to the subsequent development of micothrombi and endothelial damage. Another manner in which blood viscosity and its components may impact inner ear blood flow is via decreased red-cell rigidity.

Although these studies do support the theory that the vascular system plays a role in the etiology of presbycusis, it is evident that the literature is deficient with respect to repeatability, observations in populations of various ethnic and racial makeup, and study design. More physiological research is needed to understand how the stria vascularis changes with respect to increasing systemic atherosclerosis. Additional epidemiological research is required to understand if the relationships observed are consistent in populations of similar demographic makeup and if these relationships exist in populations of varying ethnic and racial groups. Finally, epidemiological studies are needed to address which aspect of cardiovascular disease is involved in the etiology of presbycusis. At the time of this review, no studies have looked at subclinical cardiovascular disease and hearing loss in a systematic manner. The proposed study seeks to address some of these deficiencies and contribute to this growing area of the literature.

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CHAPTERS 5 AND 7

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