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RISK FACTORS FOR HEARING IMPAIRMENT IN TYPE 1 DIABETES

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Abstract

Objective: Studies have demonstrated that glycated hemoglobin (HbA1c) is a significant predictor of hearing impairment in type 1 diabetes. We identified additional factors associated with hearing impairment in participants with type 1 diabetes from the Diabetes Control and Complications Trial and its observational follow-up, the Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study.

Methods: A total of 1,150 DCCT/EDIC participants were recruited for the Hearing Study. A medical history, physical measurements, and a self-administered hearing questionnaire were obtained. Audiometry was performed by study-certified personnel and assessed centrally. Logistic regression models assessed the association of risk factors and comorbidities with speech- and high-frequency hearing impairment.

Results: Mean age was 55 ± 7 years, duration of diabetes 34 ± 5 years, and DCCT/EDIC HbA1c $7.9 \pm 0.9\%$ (63 mmol/mol). In multivariable models, higher odds of speech-frequency impairment were significantly associated with older age, higher HbA1c, history of noise exposure, male sex, and higher triglycerides. Higher odds of high-frequency impairment were associated with older age, male sex, history of noise exposure, higher skin intrinsic fluorescence (SIF) as a marker of tissue glycation, higher HbA1c, nonprofessional/nontechnical occupations, sedentary activity, and

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

lower low-density-lipoprotein cholesterol. Among participants who previously completed computed tomography and carotid ultrasonography, coronary artery calcification (CAC >0) and carotid intima-medial thickness were significantly associated with high- but not speech-frequency impairment.

Conclusion: Consistent with previous reports, male sex, age, several metabolic factors, and noise exposure are independently associated with hearing impairment. The association with SIF further emphasizes the importance of glycemia—as a modifiable risk factor—over time. In addition, the macrovascular contribution of CAC is novel and important.

Clinical Trials Registration Numbers: [NCT00360893](#), [NCT00360815](#)

Keywords

diabetes complications; type 1 diabetes; epidemiology; hearing impairment; risk factors; glycemia

INTRODUCTION

Hearing is a critical function for perceiving environmental signals and for effective communication between individuals. Loss of hearing may result in adverse consequences, including social isolation, depression, and reduced health-related quality-of-life (1–3). The impact of hearing loss in the U.S. includes an estimated 3 billion dollars annually in direct medical costs for those aged 65 years and older and considerable loss of productivity due to disability (4). Over half of U.S. adults aged 60 to 69 years have at least a mild deficit in hearing sensitivity in the range of tones most important for the perception of speech (5). Many factors associated with hearing loss have been suggested or identified, such as older age, male sex, and exposure to loud noise. Data from the National Health and Nutrition Examination Survey (NHANES) have suggested that diabetes is also an important risk factor for hearing impairment (6). Among individuals with diabetes, identifying additional risk factors for hearing impairment may provide caregivers an opportunity to manage this disability through lifestyle and other preventative strategies.

The Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Hearing Study demonstrated no difference in the prevalence of hearing impairment between participants with type 1 diabetes (T1D) and a group of spousal controls without diabetes (7), in contrast to the association found in the NHANES investigation, which did not specify diabetes by type (6). However, among participants with T1D, higher mean glycosylated hemoglobin (HbA1c) over the duration of the DCCT/EDIC study was associated with hearing impairment. The DCCT/EDIC study provides an opportunity to identify additional risk factors for hearing impairment in a large, well-characterized cohort of participants with T1D followed for over 30 years. This is the first cohort study of adults with long-standing T1D to assess factors associated with hearing loss using standardized audiometric testing.

METHODS

Participants with T1D

Detailed descriptions of the DCCT clinical trial and EDIC observational follow-up study have been published (8,9). Briefly, between 1983 and 1989, 1,441 participants with T1D, ages 13 to 39 years, were randomized into the DCCT, a multicenter, controlled clinical trial designed to compare the effects of intensive and conventional diabetes therapy on the development and progression of diabetes-related complications. During the DCCT, intensive therapy consisted of 3 daily insulin injections or use of an external insulin infusion pump, with dose adjustments based on 4 daily self-monitored blood glucose measurements. Glucose targets were 70 to 120 mg/dL before and <180 mg/dL after meals. The HbA1c goal was <6.05% (43 mmol/mol), two standard deviations above the nondiabetic mean. Conventional therapy employed 1 to 2 daily injections of insulin, with the goal of freedom from symptoms of hyperglycemia and hypoglycemia.

After an average of 6.5 years of follow-up (range, 3 to 9 years), the DCCT was stopped 1 year early (1993) after demonstrating the benefit of intensive glycemic therapy on the development and progression of microvascular complications. Participants in the conventional group were instructed in intensive therapy, and all participants were referred back to their own health care providers for ongoing diabetes care. In 1994, 1,375 (96%) of the 1,428 surviving cohort agreed to participate in the subsequent, ongoing EDIC observational study (9), and after an additional 22 years of follow-up, 1,214 (94% of 1,297 surviving) participants continued to be followed at the time of this study. All surviving DCCT/EDIC participants were invited to participate in the DCCT/EDIC Hearing Study, and 1,150 (89% of the 1,297 surviving) participants were enrolled. The study was conducted across 27 EDIC clinical centers during EDIC years 20 to 22 (2013–2015).

EDIC Evaluations

Each annual EDIC visit included a detailed medical history of demographic and behavioral risk factors, medication use, and medical outcomes, and a physical examination with measurements of height, weight, sitting blood pressure, and pulse rate (9). Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, documented hypertension, or the use of antihypertensive medications. Hyperlipidemia was defined as a low-density lipoprotein (LDL) cholesterol ≥ 130 mg/dL or the use of lipid-lowering medications. Insulin doses were self-reported and expressed as the average total daily dose in units per kilogram of body weight.

Blood samples were assayed centrally for HbA1c, using high-performance ion-exchange liquid chromatography. The DCCT and EDIC updated HbA1c means represent the running averages during DCCT and EDIC, respectively. The time-weighted DCCT/EDIC mean HbA1c represents the total glycemic exposure during DCCT/EDIC, with weights of 0.25 and 1 for quarterly DCCT and annual EDIC values, respectively, from enrollment (1983–1989) to the date of the audiologic exam. Fasting lipids (triglycerides, total, and high-density lipoprotein [HDL] cholesterol) were measured in alternate years and evaluated centrally. LDL cholesterol was calculated using the Friedewald equation (10).

Skin intrinsic fluorescence (SIF), a measure of advanced glycation end products (11–14), was obtained from the skin on the underside of the left forearm near the elbow using the SCOUT DS skin fluorescence spectrometer (VeraLight, Inc, Albuquerque, NM). SIF was excited with light-emitting diodes centered at 375 nm and detected over the emission range of 435 to 655 nm, with k_x set to 0.6 and k_m set to 0.2. The resulting intrinsic fluorescence, f_{xm} , was integrated over the 435- to 655-nm spectral region and multiplied by 1,000 to give the SIF sum (13).

Retinopathy was assessed by standardized 7-field stereoscopic fundus photographs obtained every 6 months during DCCT and in one-fourth of the cohort each year during EDIC. Photographs were centrally graded with standardized methods using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale (15). Proliferative diabetic retinopathy (PDR) was defined as any ETDRS score ≥ 12 or scatter laser treatment during DCCT/EDIC, and clinically significant macular edema was defined as any score ≥ 20 or focal laser or anti-vascular endothelial growth factor treatment (16).

Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine measured annually during DCCT/EDIC. Albumin excretion rate (AER) was measured annually during DCCT and in alternate years during EDIC. Kidney disease was defined as any impaired eGFR (<60 mL/min/1.73 m²) on ≥ 2 consecutive visits during DCCT/EDIC, microalbuminuria (any AER ≥ 30 mg/24 hours on ≥ 2 consecutive visits during DCCT/EDIC), or macroalbuminuria (any AER ≥ 300 mg/24 hours during DCCT/EDIC). End-stage renal disease was defined as treatment with dialysis or transplantation for chronic renal failure.

In EDIC year 13/14, neurologic evaluations and nerve conduction studies were conducted using the same protocol as was used in the DCCT. Confirmed clinical neuropathy was defined as a combination of signs and symptoms consistent with distal symmetrical polyneuropathy and nerve conduction abnormalities involving two or more peripheral nerves among the median, peroneal, and sural nerves (17). Cardiovascular autonomic tests were conducted in EDIC year 16/17 and used to establish the presence of cardiovascular autonomic neuropathy, defined as an R-R variation <15 , or an R-R variation <20 in combination with a Valsalva ratio ≤ 1.5 , or a decrease of >10 mm Hg in diastolic blood pressure upon standing (18).

All cardiovascular disease (CVD) events were adjudicated and classified by a committee masked to treatment group assignment and HbA1c levels. CVD events were defined as any one of the following: cardiovascular death, nonfatal myocardial infarction (MI), nonfatal stroke, subclinical MI detected on an annual electrocardiogram, angina confirmed by ischemic changes with exercise tolerance testing or by clinically significant obstruction on coronary angiography, revascularization (with angioplasty or coronary artery bypass), or congestive heart failure (19).

Coronary artery calcification (CAC) was assessed at EDIC year 8 with computed tomography (20), and carotid intima-media thickness (IMT) was measured at EDIC year 12 with carotid ultrasonography (21).

DCCT/EDIC Hearing Study Protocol

Participants underwent a standard audiologic examination and completed a self-administered hearing questionnaire to assess exposure to loud noise over time and perceived hearing loss. In this study, noise exposure was based on chronic exposure to occupational, recreational, or environmental loud noises (e.g., firearm use, military equipment, steady and loud music, or environmental noises) with infrequent use (<50% of the time) of ear protection. Otoscopic examinations and audiometric testing were performed by study-certified audiologists. Hearing was measured in sound-treated booths using TDH-50P headphones or insert earphones when there was evidence of ear canal collapse. Pure-tone air-conduction thresholds were obtained at 500, 1,000, 2,000, 3,000, 4,000, 6,000, and 8,000 Hz, and bone-conduction thresholds were obtained at 500, 2,000, and 4,000 Hz (22,23). Masked thresholds were determined when necessary. De-identified audiometric exams were assessed centrally at the University of Wisconsin EpiSense Audiometry Reading Center. Readers were blinded to prior DCCT treatment assignment and other clinical information. Speech-frequency hearing impairment was defined as a pure-tone average (PTA) >25 dB hearing loss (HL) of thresholds measured at 500, 1,000, 2,000, and 4,000 Hz, and high-frequency hearing impairment was defined as a PTA >25 dB HL of thresholds measured at 3,000, 4,000, 6,000, and 8,000 Hz (6). Person-level variables were constructed for any hearing impairment (either ear) and bilateral hearing impairment (both ears).

Statistical Considerations

Candidate risk factors were grouped into 10 blocks (Table 1) consistent with previous risk factor evaluations of microvascular and cardiovascular complications in the DCCT/EDIC study (24–26). Covariates were measured at defined time points per the DCCT/EDIC protocol described above. For covariates obtained less than annually, the covariate measurement closest to the audiometric evaluation was used in the analyses. Differences in risk factors between groups were tested using the *t* test for continuous characteristics or the chi-square test for categorical characteristics. Separate logistic regression models were used to evaluate the association of speech- and high-frequency hearing impairment with each of the individual risk factors, both unadjusted and minimally adjusted for age and sex. Unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals are presented for risk factors that differed significantly between groups.

Multivariable logistic regression models were evaluated separately for speech- and high-frequency hearing impairment using similar model-building techniques previously described by the DCCT/EDIC study (24). Given the large number of risk factors, variables were entered into the logistic regression model one block at a time in the order displayed in Table 1, starting with the study design factors, then demographic, behavioral/environmental, etc. After each block was added, a variable was retained if it had a $P < .10$ or was included in the sub-model with the best (i.e., lowest) Akaike information criterion value, a measure of the relative model fit (27). After the last block was entered, an overall multivariable model was fit using the selected covariates, and variables significant at $P < .05$ were retained. Next, a sensitivity analysis was conducted, using a backward elimination modeling technique, where variables significant at $P < .10$ were retained at each step. A final combined multivariable logistic regression model was evaluated using all of the variables selected by each of the two

modeling techniques, and variables significant at $P < .05$ were kept in the final multivariable model. Finally, an additional model was examined among the subset of participants who participated in the carotid IMT and CAC studies ($n = 863$). The ORs and unsigned covariate Z-values are presented, the latter to differentiate covariate effects with $P < .0001$ (2-sided), equivalent to a $|Z| \geq 3.89$. Given the exploratory nature of our analyses, no adjustments for multiple testing were performed.

RESULTS

Speech-frequency hearing impairment in either ear was observed in 20% ($n = 227$) and high-frequency hearing impairment in 52% ($n = 595$) of participants. Table 2 presents the characteristics of the DCCT/EDIC participants at EDIC years 20 through 22 by categories of speech- and high-frequency hearing impairment in one or both ears, as well as the corresponding OR adjusted for age and sex. Risk factors that were significantly associated with a higher odds of speech-frequency hearing impairment included older age, male sex, less education, history of exposure to loud noise, greater height, weight, and waist circumference, history of hypertension, worse lipid levels (triglycerides, HDL, history of hyperlipidemia), higher HbA1c (current, EDIC updated mean, and DCCT/EDIC time-weighted mean), higher insulin dose, higher SIF, presence of complications (retinopathy, kidney disease, neuropathy, cardiovascular disease), and self-reported medication (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β -blockers, calcium channel blockers, lipid-lowering agents, diuretics) use (Table 2). Light to moderate alcohol use and higher total cholesterol levels were associated with lower odds of speech-frequency hearing impairment. After adjustment for age and sex, speech-frequency hearing impairment continued to be significantly associated with older age (adjusted only for sex), male sex (adjusted only for age), history of exposure to loud noise, greater waist circumference, higher triglycerides, lower HDL cholesterol, higher HbA1c (multiple measures), higher SIF, kidney disease (multiple measures), confirmed clinical neuropathy, and history of cardiovascular disease. The association of light to moderate alcohol use with lower speech-frequency hearing impairment also remained significant after adjustment for age and sex.

A similar set of risk factors was associated with higher odds of high-frequency hearing impairment (Table 2) but additionally included nonprofessional/nontechnical occupation, higher systolic blood pressure, lower LDL cholesterol, any PDR or worse, and any sustained microalbuminuria (AER ≥ 30 mg/24 hours). Light to moderate alcohol use, history of hyperlipidemia, and HbA1c (current and DCCT/EDIC time-weighted mean) were not significantly associated with high-frequency hearing impairment. After adjustment for age and sex, older age (adjusted only for sex), male sex (adjusted only for age), less education, nonprofessional/nontechnical occupation, history of exposure to loud noise, higher HbA1c (EDIC updated mean), higher SIF, retinopathy (multiple measures), any sustained microalbuminuria, confirmed clinical neuropathy, and a CAC score >0 remained significantly associated with higher odds of high-frequency hearing impairment.

Table 3 presents the final multivariable logistic regression models for speech- and high-frequency hearing impairment, with the covariates listed in the order of the unsigned

covariate Z-values and *P* values. Factors associated with higher odds of speech-frequency hearing impairment included older age (OR, 3.65 per 10 years; $Z = 9.18$; $P < .0001$), higher current HbA1c (OR, 1.28 per 1%; $Z = 3.40$; $P = .0007$), exposure to loud noise ($Z = 2.92$; $P = .0035$), female versus male sex ($Z = 2.48$; $P = .0132$), and higher triglycerides ($Z = 2.38$; $P = .0171$). For high-frequency hearing impairment, older age (OR, 3.24 per 10 years; $Z = 10.00$; $P < .0001$), sex (OR, 0.38 female vs. male; $Z = 6.59$; $P < .0001$), exposure to loud noise ($Z = 2.68$; $P = .0074$), SIF ($Z = 2.57$; $P = .0101$), and current HbA1c ($Z = 2.47$; $P = .0137$) were associated with higher odds. Lower odds of high-frequency hearing impairment were associated with professional/technical occupation ($Z = 2.22$; $P = .0264$), moderate or strenuous physical activity ($Z = 2.19$; $P = .0287$), and higher LDL cholesterol ($Z = 1.97$; $P = .0490$).

Table 4 presents two additional models that were evaluated among the subset of participants who participated in the carotid IMT and CAC studies ($n = 863$). After adjustment for all other risk factors identified in Table 3, CAC > 0 and IMT were significantly associated with high-frequency hearing impairment but not with speech-frequency hearing impairment (OR, 1.62 and OR, 0.21 per millimeter, respectively). For high-frequency hearing impairment, there was a significant interaction between sex and IMT ($P = .0193$). The association between IMT and high-frequency hearing impairment was only significant in males (OR, 0.11 per millimeter; $Z = 3.30$; $P = .0010$) and not females (OR, 3.11 per millimeter; $Z = 0.88$; $P = .3771$).

DISCUSSION

The DCCT/EDIC Hearing Study previously demonstrated a significant association between higher HbA1c and hearing loss in this well-phenotyped cohort of participants with T1D who have been extensively characterized for over 30 years (7). In these analyses, we assessed the associations of additional demographic, behavioral, physiologic, pathophysiologic, and environmental factors with hearing impairment.

In the final multivariable models, acute glycemic exposure, as measured by current HbA1c, was a significant risk factor for both speech- and high-frequency impairment. In addition, SIF, a noninvasive measure of advanced glycation end products, was significantly associated with high-frequency hearing impairment, after adjustment for all other factors. SIF has been associated with mean HbA1c as well as with the development of microvascular and cardiovascular complications in T1D (11,13). Interestingly, in both models, glycemia as measured by SIF and/or by current HbA1c was the most significant modifiable risk factor after chronic exposure to loud noise.

Measurements of carotid artery IMT and CAC among the subset of participants who completed the IMT and CAC studies were associated with high-frequency hearing impairment but not speech-frequency impairment in the final multivariable models. In addition, adjustment for both IMT and CAC in the final multivariable model for high-frequency hearing impairment did not materially change the associations for the other risk factors in the model, suggesting different potential mechanisms. While IMT and plaque have been associated with the incidence of hearing loss in middle-aged adults (25), we are

unaware of any studies with measurements of CAC and audiometry. Furthermore, it is interesting to note that none of the microvascular complications (retinopathy, kidney disease, neuropathy) were significantly associated with hearing impairment in the final multivariable models.

In the current analysis, elevated triglycerides were associated with speech-frequency hearing impairment, whereas LDL cholesterol was inversely associated with high-frequency hearing impairment. Other studies have demonstrated that triglycerides but not LDL levels are associated with prevalent hearing impairment (28,29). In previous reports, the DCCT/EDIC demonstrated that HbA1c is a significant correlate and predictor of longitudinal changes in several traditional CVD risk factors (body mass index, blood pressure, pulse rate, lipids), with the strongest longitudinal associations among lipid measurements and concurrent glycemia (30). Data from the NHANES (1999–2004) also examined various risk factor associations with hearing loss and demonstrated that lower HDL cholesterol was correlated with hearing impairment, as were a history of coronary heart disease, peripheral neuropathy, and poor general health (31).

Demographic and environmental factors associated with hearing impairment in the DCCT/EDIC Hearing Study included age, male sex, and exposure to loud noise. These results are consistent with previous studies of individuals with type 1 and type 2 diabetes and in the general population (32–35); however, conflicting evidence has been reported for the association between noise exposure and the development of hearing loss (35–38).

In addition, our findings suggest an association between various lifestyle factors and hearing impairment. Namely, participants with professional/technical occupations and those who reported moderate or strenuous physical activity were less likely to experience high-frequency hearing loss. Other studies have demonstrated similar associations between occupation, physical activity, and hearing loss (35,39). In the Blue Mountains Hearing Study, Mitchell et al (35) demonstrated that high occupational prestige was associated with a decreased incidence of hearing loss. In addition, Curhan et al (39) reported that higher physical activity was related inversely to the risk of self-reported hearing loss in women participating in the Nurses' Health Study.

Smoking and body mass index were not significant risk factors for hearing impairment in the DCCT/EDIC cohort, while evidence in the general population is conflicting. In a population based, cross-sectional study of 3,753 adults aged 48 to 92 years, individuals who smoked were 1.67 times more likely than nonsmokers to experience hearing loss, and passive smoking (living with a smoker) also was associated with hearing loss (40). In this same cohort, education, central adiposity, and poorly controlled diabetes were also associated with the 15-year cumulative incidence of hearing loss (41). Other longitudinal studies with shorter durations of follow-up have not demonstrated an association between smoking and the incidence of hearing loss (42). The low prevalence of smoking in the DCCT/EDIC cohort may have limited our ability to detect an association with hearing impairment.

Low eGFR based on measures of cystatin-C has been associated with increased risk of developing hearing impairment (43). In this study, microalbuminuria was associated with an

increased risk of speech-frequency hearing impairment. Previous studies have demonstrated that exposure to cytotoxic drugs, particularly aminoglycosides and cisplatin, is strongly associated with hearing loss; approximately 20% of individuals receiving aminoglycosides experience hearing loss (44,45). However, these specific medications were not assessed in our cohort. No significant associations were identified between hearing impairment and the prevalence of other autoimmune diseases (data not shown).

This study included a sizable cohort of individuals with T1D that has been followed for over 3 decades, with standardized data collection methods and continued participation of over 90% of the surviving original DCCT cohort. The association of acute and chronic glycemic control with hearing impairment, as well as with the microvascular and cardiovascular complications associated with T1D, reinforces the importance of striving for long-term glycemic control in reducing risk in this population. In addition, the factors associated with increased and decreased odds of hearing impairment identified in this study may encourage health care providers to inquire about hearing difficulties and suggest lifestyle and preventative strategies to reduce hearing impairment and other diabetes-related complications.

This study is limited by the absence of previous hearing assessments, preventing the ability to address longitudinal changes in hearing. Only individuals with T1D, aged 13 to 39 years at baseline, were evaluated, and the degree to which our results apply to individuals with other types of diabetes, or diabetes diagnosed in early childhood, is not clear. The mean age of our study population at the time of this study was 55 ± 7 years, and the effects of diabetes in a younger or older cohort may differ compared to this cohort. Finally, while this study identifies several potential risk factors associated with hearing loss in T1D, it does not provide insight into the pathogenesis of hearing impairment in this sample.

CONCLUSION

The longitudinal data available within the DCCT/EDIC Hearing Study afforded the opportunity to evaluate the contribution of various demographic, behavioral, environmental, clinical factors, and diabetes-related comorbidities to the risk of hearing impairment in a cohort of individuals with T1D studied for over 30 years. Many of the environmental, demographic, and diabetes-related comorbidities identified in this study are consistent with those identified in samples not selected for T1D. However, in this study, we also found that glycated end products, as measured by SIF, were significantly associated with hearing impairment, thus emphasizing the importance of glycemic control. In addition, the association of CAC with high-frequency hearing impairment is novel and important. Further study into these unique relationships with hearing impairment in T1D is warranted.

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Abbreviations:

AER	albumin excretion rate
CAC	coronary artery calcification
CVD	cardiovascular disease
DCCT/EDIC	Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications
eGFR	estimated glomerular filtration rate
ETDRS	Early Treatment Diabetic Retinopathy Study
HbA1c	glycated hemoglobin
HDL	high-density lipoprotein
IMT	intima-media thickness
LDL	low-density lipoprotein
NHANES	National Health and Nutrition Examination Survey
OR	odds ratio
SIF	skin intrinsic fluorescence
T1D	type 1 diabetes

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Table 1

Candidate Risk Factors by Block

Design	Treatment group, cohort
Demographic	Age, sex, race, education, occupation, marital status
Behavioral/Environmental	Cigarette smoking, alcohol use, physical activity, exposure to loud noise, hearing loss in parents
Physical	Height, weight, body mass index, waist circumference
Blood Pressure/Pulse	Systolic and diastolic blood pressure, pulse pressure, pulse rate
Lipids	Total cholesterol, triglycerides, HDL and LDL cholesterol
Diabetes-related	Duration of type 1 diabetes, HbA1c, insulin dose, hypoglycemia, skin-intrinsic fluorescence
Microvascular	Retinopathy, kidney disease, neuropathy
Macrovascular	Any cardiovascular disease, carotid IMT, CAC
Medications	ACE inhibitors, ARBs, β -blockers, calcium channel blockers, lipid-lowering agents, diuretics

Table 2

Association of Risk Factors With Odds of Speech- and High-frequency Hearing Impairment among DCCT/EDIC Participants

	Speech-frequency				High-frequency			
	Unadjusted			Age & Sex Adjusted	Unadjusted			Age & Sex Adjusted
	No	Yes			No	Yes		
	Mean $\pm$ SD or No. (%)		P value	Odds Ratio (95% CI)	Mean $\pm$ SD or No. (%)		P value	Odds Ratio (95% CI)
Design	923	227			555	595		
Treatment group (intensive)	476 (52)	118 (52)	0.9115		288 (52)	306 (51)	0.8752	
Cohort assignment (primary prevention)	463 (50)	109 (50)	0.9876		279 (50)	298 (50)	0.9497	
Demographic								
Age (years)	54 $\pm$ 7	59 $\pm$ 7	<.0001	1.12 (1.09, 1.15)	53 $\pm$ 7	58 $\pm$ 6	<.0001	1.13 (1.10, 1.15)
Sex (female)	466 (50)	83 (37)	.0002	0.59 (0.43, 0.81)	333 (60)	216 (36)	<.0001	0.38 (0.29, 0.49)
Race (non-Hispanic white)	865 (94)	217 (96)	.2824		520 (94)	562 (94)	.5850	
Education (college graduate)	596 (64)	129 (57)	.0304		374 (67)	351 (59)	.0032	0.71 (0.54, 0.92)
Occupation (professional/technical)	515 (56)	119 (52)	.3599		327 (59)	307 (52)	.0126	0.73 (0.56, 0.94)
Marital status (married/remarried)	504 (55)	121 (53)	.7245		294 (53)	331 (56)	.3660	
Behavioral/Environmental								
Cigarette smoker	92 (10)	21 (9)	.7453		48 (9)	65 (11)	.1951	
Alcohol use								
None	253 (27)	83 (37)	.0049		168 (30)	168 (28)	.6998	
Light to moderate	608 (66)	134 (59)		0.66 (0.47, 0.91)	350 (63)	392 (66)		
Heavy	62 (7)	10 (4)			37 (7)	35 (6)		
Moderate or strenuous physical activity	542 (59)	120 (53)	.1096		331 (60)	331 (56)	.1692	
Exposure to loud noise ^a	270 (29)	105 (46)	<.0001	1.72 (1.24, 2.38)	133 (24)	242 (41)	<.0001	1.59 (1.20, 2.12)
Hearing loss in parents	442 (48)	120 (54)	.1455		266 (48)	296 (50)	.5412	
Physical								
Height (cm)	171 $\pm$ 10	173 $\pm$ 9	.0027		170 $\pm$ 9	173 $\pm$ 9	<.0001	
Weight (kg)	84 $\pm$ 18	89 $\pm$ 21	.0021		83 $\pm$ 18	87 $\pm$ 19	<.0001	
Body mass index (kg/m ²)	29 $\pm$ 5	29 $\pm$ 6	.0844		29 $\pm$ 6	29 $\pm$ 6	.4656	
Waist circumference (cm)	93 $\pm$ 14	98 $\pm$ 15	<.0001	1.14 (1.02, 1.27)	92 $\pm$ 14	96 $\pm$ 15	<.0001	
Blood Pressure/Pulse								
Systolic (mm Hg)	122 $\pm$ 15	122 $\pm$ 16	.7758		121 $\pm$ 15	123 $\pm$ 16	.0100	

	Speech-frequency				High-frequency			
	Unadjusted			Age & Sex Adjusted	Unadjusted			Age & Sex Adjusted
	No	Yes			No	Yes		
	Mean $\pm$ SD or No. (%)		P value	Odds Ratio (95% CI)	Mean $\pm$ SD or No. (%)		P value	Odds Ratio (95% CI)
Diastolic (mm Hg)	70 $\pm$ 9	69 $\pm$ 9	.0497		70 $\pm$ 9	70 $\pm$ 10	.5479	
Any hypertension ^b	770 (83)	204 (90)	.0157		449 (80)	525 (88)	.0006	
Pulse rate (bpm)	71 $\pm$ 11	71 $\pm$ 12	.9166		71 $\pm$ 11	71 $\pm$ 11	.9186	
Lipids								
Total cholesterol (mg/dL)	176 $\pm$ 37	170 $\pm$ 33	.0144		178 $\pm$ 37	172 $\pm$ 36	.0030	
Triglycerides (mg/dL)	75 $\pm$ 56	84 $\pm$ 58	.0318	1.03 (1.01, 1.05)	72 $\pm$ 50	80 $\pm$ 63	.0237	
HDL cholesterol (mg/dL)	64 $\pm$ 20	59 $\pm$ 17	.0009	0.90 (0.82, 0.98)	65 $\pm$ 20	61 $\pm$ 19	.0019	
LDL cholesterol (mg/dL)	98 $\pm$ 30	94 $\pm$ 28	.1100		99 $\pm$ 31	95 $\pm$ 29	.0210	
Any hyperlipidemia ^b	627 (68)	170 (75)	.0417		371 (67)	426 (72)	.0810	
Diabetes-related								
Duration of diabetes (years)	34 $\pm$ 5	33 $\pm$ 5	.7029		34 $\pm$ 5	34 $\pm$ 5	.8816	
Current HbA1c (mmol/mol)	62.8 $\pm$ 12.3	65.1 $\pm$ 14.3			62.8 $\pm$ 12.9	63.6 $\pm$ 12.6		
Current HbA1c (%)	7.9 $\pm$ 1.1	8.1 $\pm$ 1.3	.0153	1.26 (1.10, 1.43)	7.9 $\pm$ 1.2	8.0 $\pm$ 1.2	.2824	
DCCT updated mean HbA1c (mmol/mol) ^c	64.5 $\pm$ 14.7	65.1 $\pm$ 14.8			64.8 $\pm$ 14.9	64.4 $\pm$ 14.4		
DCCT updated mean HbA1c (%) ^c	8.1 $\pm$ 1.3	8.1 $\pm$ 1.4	.5878		8.1 $\pm$ 1.4	8.0 $\pm$ 1.3	.6304	
EDIC updated mean HbA1c (mmol/mol) ^c	62.4 $\pm$ 10.4	65.3 $\pm$ 11.1			62.3 $\pm$ 10.9	63.7 $\pm$ 10.3		
EDIC updated mean HbA1c (%) ^c	7.9 $\pm$ 1.0	8.1 $\pm$ 1.0	.0002	1.41 (1.20, 1.65)	7.8 $\pm$ 1.0	8.0 $\pm$ 0.9	.0260	1.22 (1.07, 1.39)
DCCT/EDIC time-weighted mean HbA1c (mmol/mol) ^c	62.8 $\pm$ 9.9	65.3 $\pm$ 10.5			62.8 $\pm$ 10.1	63.8 $\pm$ 9.9		
DCCT/EDIC time-weighted mean HbA1c (%) ^c	7.9 $\pm$ 0.9	8.1 $\pm$ 1.0	.0010	1.43 (1.21, 1.69)	7.9 $\pm$ 0.9	8.0 $\pm$ 0.9	.0746	
Insulin dose (units/kg/day)	0.6 $\pm$ 0.2	0.7 $\pm$ 0.3	.0170		0.6 $\pm$ 0.2	0.6 $\pm$ 0.3	.0373	
Any hypoglycemia requiring assistance ^d	635 (69)	148 (65)	.2973		379 (68)	404 (68)	.8875	
Skin-intrinsic fluorescence (per SD)	22 $\pm$ 4	24 $\pm$ 5	<.0001	1.05 (1.01, 1.08)	22 $\pm$ 4	24 $\pm$ 5	<.0001	1.06 (1.03, 1.09)
Microvascular								
Retinopathy								
Any PDR or worse or scatter laser	230 (25)	69 (30)	.0919		125 (23)	174 (29)	.0094	1.43 (1.07, 1.93)

	Speech-frequency				High-frequency			
	Unadjusted			Age & Sex Adjusted	Unadjusted			Age & Sex Adjusted
	No	Yes			No	Yes		
	Mean $\pm$ SD or No. (%)		P value	Odds Ratio (95% CI)	Mean $\pm$ SD or No. (%)		P value	Odds Ratio (95% CI)
Any CSME or focal laser	256 (28)	83 (37)	.0090		134 (24)	205 (34)	.0001	1.42 (1.07, 1.88)
Kidney Disease								
Any sustained eGFR <60 mL/min/1.73 m ² or ESRD	49 (5)	28 (12)	.0001	2.00 (1.18, 3.39)	27 (5)	50 (8)	.0164	
Any sustained AER $\geq$ 30 mg/24 hours	263 (28)	79 (35)	.0625		145 (26)	197 (33)	.0096	1.62 (1.22, 2.16)
Any AER $\geq$ 300 mg/24 hours	89 (10)	36 (16)	.0070	2.01 (1.28, 3.15)	51 (9)	74 (12)	.0770	
Neuropathy								
Confirmed clinical neuropathy	276 (30)	108 (48)	<.0001	1.56 (1.14, 2.14)	136 (25)	248 (42)	<.0001	1.63 (1.23, 2.15)
Cardiovascular autonomic neuropathy	385 (42)	120 (53)	.0024		210 (38)	295 (50)	<.0001	
Macrovascular								
Cardiovascular								
Any history of cardiovascular disease	97 (11)	46 (20)	<.0001	1.54 (1.03, 2.33)	51 (9)	92 (15)	.0013	
Carotid intima-medial thickness (mm)	0.67 $\pm$ 0.13	0.73 $\pm$ 0.16	<.0001		0.66 $\pm$ 0.14	0.71 $\pm$ 0.13	<.0001	
Coronary artery calcification score $\geq$ 0	213 (26)	91 (43)	<.0001		89 (18)	215 (39)	<.0001	1.57 (1.14, 2.16)
Medications								
ACE inhibitors or ARBs	531 (58)	164 (68)	.0046		300 (54)	385 (65)	.0002	
β -blockers	119 (13)	45 (20)	.0075		64 (12)	100 (17)	.0106	
Calcium channel blockers	86 (9)	33 (15)	.0207		43 (8)	76 (13)	.0052	
Lipid-lowering agents	562 (61)	164 (72)	.0015		314 (57)	412 (69)	<.0001	
Diuretics	142 (15)	55 (24)	.0015		87 (16)	110 (18)	.2060	

Abbreviations: ACE = angiotensin-converting enzyme inhibitors; AER = albumin excretion rate; ARB = angiotensin II receptor blocker; CI = confidence interval; CSME = clinically significant macular edema; DCCT = Diabetes Control and Complications Trial; EDIC = Epidemiology of Diabetes Interventions and Complications; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease (dialysis or transplant); HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PDR = proliferative diabetic retinopathy.

Data are mean $\pm$ SD or No. (%) and odds ratios (95% CI) from adjusted logistic regression models (age and sex). Differences between groups (yes vs. no hearing impairment) were tested using the *t* test for quantitative characteristics or chi-square test for categorical characteristics. Odds ratios are only presented for risk factors that are significantly different between groups after adjustment for age and sex (*P* < .05).

^aExposure to loud noises is defined as having been exposed to loud noises due to firearm use, being near military equipment, having a noisy job, exposure to steady and loud music or environmental noises, all while wearing hearing protection no more than 50% of the time.

^bHypertension is defined as systolic blood pressure $\geq$ 140 mmHg, diastolic blood pressure $\geq$ 90 mmHg, documented hypertension, or the use of antihypertensive medications, and hyperlipidemia as LDL cholesterol $\geq$ 130 mg/dl or the use of lipid-lowering medications.

^cThe DCCT and EDIC updated mean HbA1c's represent the running averages during DCCT and EDIC, respectively. The time-weighted DCCT/EDIC mean HbA1c represents the total glycemic exposure during DCCT/EDIC with weights of 0.25 and 1 for quarterly DCCT and annual EDIC values, respectively.

^dSelf-reported occurrence of hypoglycemia documented quarterly during the DCCT and within three months of the annual visit during EDIC.

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Table 3

Final Multivariable Models for Speech-and High-frequency Hearing Impairment in One or Both Ears (n = 1,075)

	Odds Ratio (95% CI)	Z-value	P value
Speech-frequency			
Age (per 10 years)	3.65 (2.77, 4.81)	9.18	<.0001
Current HbA1c (per 1%)	1.28 (1.11, 1.47)	3.40	.0007
Exposure to loud noise (yes vs. no)	1.69 (1.19, 2.40)	2.92	.0035
Sex (female vs. male)	0.63 (0.44, 0.91)	2.48	.0132
Triglycerides (per 10% increase)	1.04 (1.01, 1.07)	2.38	.0171
High-frequency			
Age (per 10 years)	3.24 (2.57, 4.07)	10.00	<.0001
Sex (female vs. male)	0.38 (0.29, 0.51)	6.59	<.0001
Exposure to loud noise (yes vs. no)	1.52 (1.12, 2.07)	2.68	.0074
Skin-intrinsic fluorescence (per SD = 4.6773)	1.22 (1.05, 1.43)	2.57	.0101
Current HbA1c (per 1%)	1.17 (1.03, 1.32)	2.47	.0137
Occupation (professional/technical vs. no)	0.73 (0.55, 0.96)	2.22	.0264
Moderate or strenuous physical activity (yes vs. no)	0.73 (0.56, 0.97)	2.19	.0287
LDL cholesterol (per 10 mg/dL)	0.95 (0.91, 1.00)	1.97	.0490

Abbreviations: CI = confidence interval; HbA1c = glycated hemoglobin; LDL = low-density lipoprotein.

Data are odds ratios (95% CI) from multivariable logistic regression models. Covariates are listed in the order of significance as indicated by the Z-value.

Table 4

Final Multivariable Models for Speech-and High-frequency Hearing Impairment in One or Both Ears, Including Carotid IMT and Coronary Artery Calcification (n = 863)

	Odds Ratio (95% CI)	Z-value	P value
Speech-frequency			
Age (per 10 years)	3.39 (2.40, 4.78)	6.95	<.0001
Exposure to loud noise (yes vs. no)	1.94 (1.32, 2.85)	3.36	.0008
Current HbA1c (per 1%)	1.31 (1.11, 1.54)	3.19	.0014
Sex (female vs. male)	0.59 (0.38, 0.90)	2.47	.0135
Triglycerides (per 10% increase)	1.03 (0.99, 1.06)	1.47	.1407
Carotid intima-medial thickness (per 1 mm)	1.38 (0.38, 4.99)	0.50	.6190
Coronary artery calcification score >0 (yes vs. no)	1.09 (0.73, 1.64)	0.44	.6622
High-frequency			
Age (per 10 years)	3.37 (2.53, 4.50)	8.24	<.0001
Sex (female vs. male)	0.34 (0.24, 0.48)	6.28	<.0001
Coronary artery calcification score >0 (yes vs. no)	1.62 (1.11, 2.34)	2.53	.0114
Carotid intima-medial thickness (per 1 mm)	0.21 (0.06, 0.73)	2.46	.0140
Exposure to loud noise (yes vs. no)	1.54 (1.09, 2.17)	2.44	.0148
Current HbA1c (per 1%)	1.18 (1.03, 1.36)	2.33	.0197
Skin-intrinsic fluorescence (per SD = 4.6773)	1.21 (1.02, 1.44)	2.15	.0314
Occupation (professional/technical vs. no)	0.72 (0.53, 0.99)	2.05	.0401
LDL cholesterol (per 10 mg/dL)	0.95 (0.90, 1.00)	1.84	.0663
Moderate or strenuous physical activity (yes vs. no)	0.83 (0.60, 1.13)	1.20	.2293

Abbreviations: CI = confidence interval; HbA1c = glycated hemoglobin; IMT = intima-media thickness; LDL = low-density lipoprotein.

Data are odds ratios (95% CI) from multivariable logistic regression models. Covariates are listed in the order of significance as indicated by the Z-value.