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Association of type 2 diabetes mellitus with sensorineural hearing loss – A population-based analysis.

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Abstract

OBJECTIVE: To test the hypothesis that patients with poorly controlled type 2 diabetes mellitus are more likely to develop sensorineural hearing loss (SNHL) than non-diabetic patients.
STUDY DESIGN: Retrospective cohort study.
SETTING: TriNetX US Collaborative Network (2003-2022).
METHODS: Electronic medical record data from the TriNetX US Collaborative Network was queried for subjects without prior hearing loss, defined using medical billing codes (ICD-10, CPT, etc.), who were diagnosed with type 2 diabetes mellitus after January 2003. Patients were stratified by most recent HbA1c (8.0-13.9% or ≥14.0%) and by age at diagnosis (21-30, 31-40, 41-50, 51-60, 61-70, ≥71 years). Primary outcome was development of SNHL ≤20 years after diabetes diagnosis. Cohorts were propensity-score matched for age, gender, race, and hearing loss-related conditions, including vascular disease and tobacco/nicotine use. Hearing loss risk in each cohort were compared against age-matched non-diabetic subjects.
RESULTS: All diabetic patients had greater risk of SNHL compared to age-matched controls; having a higher HbA1c (≥14.0%) additionally associated with greater risk than a lower HbA1c (8.0-13.9%) for all age groups except 21-30 and 31-40 years. Furthermore, risk was higher for older patients of both HbA1c ranges, with patients ≥71 years at diagnosis having greatest risk. Patients ≥71 with HbA1c ≥14.0% (n = 3,870) had a 0.51% (95% confidence interval: 0.28-0.74, $p < 0.0001$) greater hearing loss risk, and patients with HbA1c 8.0-13.9% (n = 155,066) had 0.24% (0.22-0.27, $p < 0.0001$) greater risk.
CONCLUSION: Type 2 diabetes diagnosis appears to strongly associate with greater risk of developing SNHL, especially in older patients. Audiometric screening may be warranted.

Abbreviations:

SNHL	- Sensorineural Hearing Loss
T2D	- Type 2 Diabetes
T1D	- Type 1 Diabetes
EHR	- Electronic Health Record
HCO	- Healthcare Organization
PSM	- Propensity Score Matching

INTRODUCTION

Sensorineural hearing loss (SNHL) has long been postulated as a potential complication of type 2 diabetes mellitus (T2D). Multiple studies have reported a high prevalence of varying forms of hearing loss among diabetic patient populations, with estimates ranging from 21.3-85%, compared to 20.3-23% among the general US population (Bainbridge *et al.* 2010; Baiduc & Helzner, 2019; Shafiepour *et al.* 2022; Al-Rubeaan *et al.* 2021; Hosseini *et al.* 2020; Lin *et al.* 2011; Goman & Lin, 2016). However, there has been ongoing debate about the association between T2D and SNHL that is not better accounted for by confounding factors, such as older age and long patient history of diabetes, that may associate with hearing loss simply due to natural, progressive inner ear degeneration (Harner, 1981; de España *et al.* 1995; Dalton *et al.* 1998; Horikawa *et al.* 2013). Proponents of an SNHL-T2D association cite a physiological relationship between hearing loss and hyperglycemia-related microvascular damage, as is observed with other established diabetic complications (e.g., retinopathy, nephropathy, neuropathy) (Samocha-Bonet *et al.* 2021; Okhovat *et al.* 2011; Wang & Lo, 2018; Elangovan & Spankovich, 2019). It has been demonstrated in animal models that diabetes is associated with progressive intraluminal narrowing of the blood vessels supplying the inner ear, suggesting a direct relationship between magnitude of hyperglycemia and risk of change. This results in ischemic damage to critical internal ear structures including the basilar membrane, stria vascularis, outer hair cells, and spiral ganglion (Nakae & Tachibana, 1986; Fukushima *et al.* 2005; Raynor *et al.* 1995; Smith *et al.* 1995; Tsuda *et al.* 2016). Aladag *et al.* (2009) also observed a greater production of free radicals, due to dysregulated glucose metabolism, in diabetic patients with poor hearing compared to diabetic patients with normal hearing, suggesting that inner ear pathology in diabetics may be due to oxidative damage. It has therefore been proposed that better control of glycemic index should reduce the risk of early-onset SNHL which, if confirmed, would be valuable in the long-term management of patients with T2D.

While some studies have supported the association between poorer glycemic control and higher rates of hearing impairment, this relationship has not been consistently observed (Al-Rubeaan *et al.* 2021; Kakarlapudi *et al.* 2003; Kim *et al.* 2017). Moreover, limited attention has been given to the clinical implementation of routine audiometric screening for diabetic patients, a practice commonly performed for other microvascular complications such as retinopathy, nephropathy, and neuropathy (Al-Rubeaan *et al.* 2021; Spankovich & Yerraguntla, 2019; Mishra & Poorery 2019; Vesperini 2011). Previous investigations linking T2D with an increased incidence and severity of hearing loss have been constrained by factors such as small sample sizes, restricted age ranges, or the absence of non-diabetic control groups (Kim *et al.* 2017; Srinivas *et al.* 2016; Krishnappa & Khaja, 2014; Mozaffari *et al.* 2008; Samelli *et al.* 2017; Ren *et al.* 2009; Sakuta *et al.* 2006; Mitchell *et al.* 2009; Bamanie & Al-Noury, 2011; Dosemane *et al.* 2019). Furthermore, age, a significant confounding factor, has been inadequately addressed in many studies. The prevalence of T2D has steadily increased in the United States over six decades, highlighting the clinical importance of understanding the role of T2D in the development of SNHL (Klonoff, 2009; Cowie *et al.* 2018). Using the TriNetX US Collaborative Network database, this study aims to explore population-level data to determine the likelihood of developing SNHL based on glycemic control in T2D patients, stratified by decades of age. We hypothesize that patients across all age groups with poorly controlled T2D are more likely to develop SNHL than their age matched non-diabetic counterparts.

METHODS

This study utilized deidentified electronic health record (EHR) data available through the TriNetX US Collaborative Network (accessed on January 07, 2023), which encompasses approximately 95 million patients from 56 Health Care Organizations (HCOs) across the United States. TriNetX-LLC is a global federated live EHR research network and database. Thomas Jefferson University's Institutional Review Board deemed this study exempt from review.

Two overall populations were built, namely patients with or without T2D. Index events were defined separately for each population. For patients without T2D diagnosis, the index event was the earliest documented healthcare visit at any one of the participating HCOs within the US Collaborative Network between January 2003 and January 2023. For patients with T2D, the index event was the visit associated with initial diagnosis of T2D within the above time frame. This study time frame was selected as the TriNetX platform excludes patients who met index criteria over 20 years prior to the study date. Subjects with any of the following conditions were excluded: (1) under 18 years old at index, (2) have preexisting SNHL or other ear pathology that could impair hearing, (3) report exposure to damaging noise, use of ototoxic agents, or family history of hearing loss following their index event. This yielded $n = 73{,}874{,}851$ unique patients.

Populations were built such that control patients could not have a record of prediabetes, type 1 diabetes mellitus (T1D), or T2D, and must have had at least one reported HbA1c, with no reports surpassing 5.6% at any point during the study time frame [Figure 1], as defined by recorded ICD codes [Table 1]. Patients with T2D could not have a concomitant diagnosis of T1D

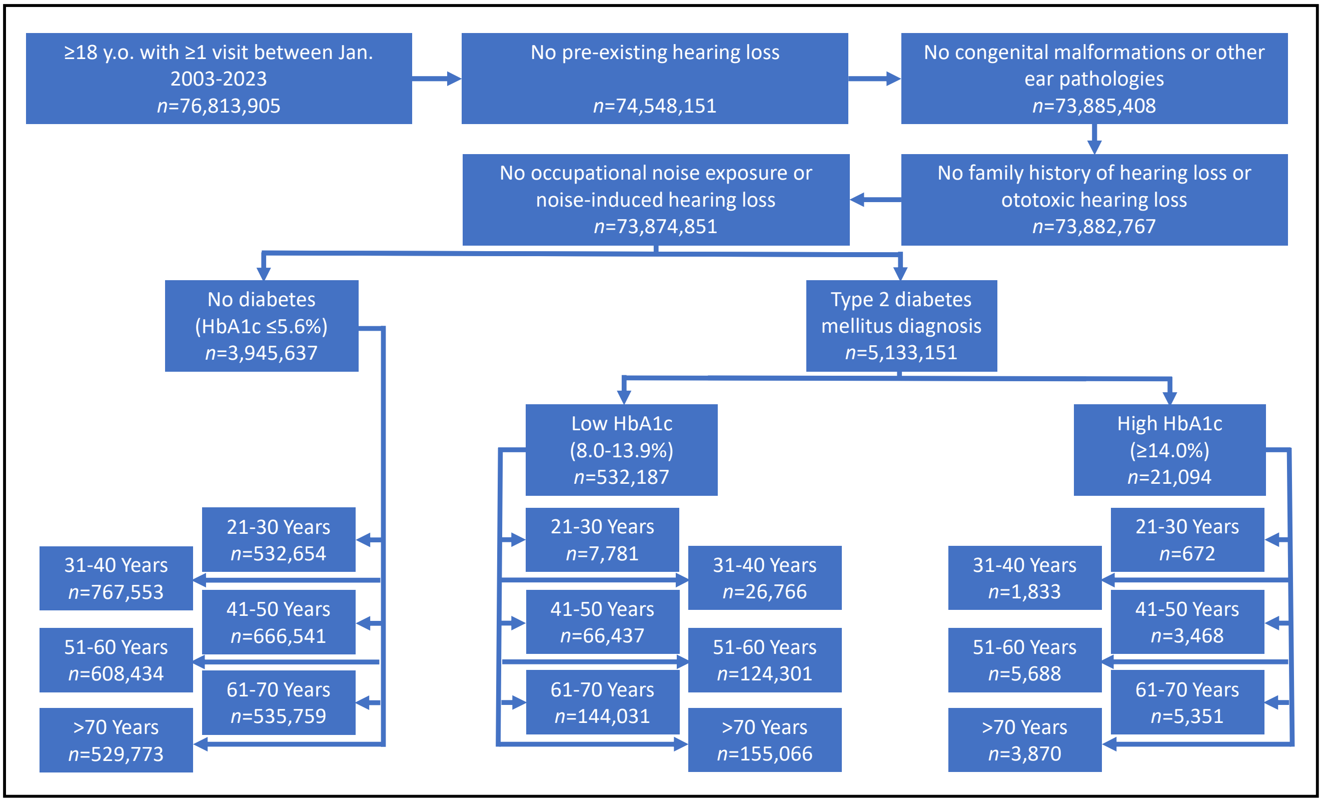

Fig. 1. Steps in cohort generation using TriNetX US Collaborative Network, and populations returned at each step including final cohort sizes.

Tab. 1. ICD codes used for cohort generation in the TriNetX US Collaborative Network database, and their corresponding definitions

ICD-10-CM Code	Definition
Exclusion/Inclusion	
E10	Type 1 diabetes mellitus
E11	Type 2 diabetes mellitus
H65.2	Chronic serous otitis media
H65.3	Chronic mucoid otitis media
H65.4	Other chronic nonsuppurative otitis media
H66.1	Chronic tubotympanic suppurative otitis media
H66.2	Chronic atticoantral suppurative otitis media
H66.3	Other chronic suppurative otitis media
H83.3	Noise effects on inner ear
H83.9	Unspecified disease of inner ear
H90	Conductive and sensorineural hearing loss
H91	Other and unspecified hearing loss
H91.0	Ototoxic hearing loss
H93	Other disorders of ear, not elsewhere classified
Q16	Congenital malformations of ear causing impairment of hearing
R73.03	Prediabetes
Z57.0	Occupational exposure to noise
Z82.2	Family history of deafness and hearing loss
Outcomes	
H90.3	Sensorineural hearing loss, bilateral
H90.4	Sensorineural hearing loss, unilateral with unrestricted hearing on the contralateral side
H90.5	Unspecified sensorineural hearing loss
H90.A2	Sensorineural hearing loss, unilateral, with restricted hearing on the contralateral side
H91.1	Presbycusis
Comorbidities	
F12	Cannabis related disorders
F17	Nicotine dependence
I10	Essential (primary) hypertension
I63	Cerebral infarction
I70	Atherosclerosis

and were further stratified as either high or low HbA1c sub-populations. High HbA1c was defined as a value of ≥14% at any point after diagnosis of T2D and at most recent evaluation. Low HbA1c included reported values between 8.0-13.9%. Finally, all control and diabetic patients were stratified by age at index (21-30, 31-40, 41-50, 51-60, 61-70, ≥71 years) to yield individual cohorts. These criteria resulted in n = 9,078,788 total patients across all cohorts.

The main outcome of interest was a diagnosis of SNHL. The proportion of patients who developed SNHL within the 20-year post-index event period for each diabetic cohort was compared to that of an age-matched control cohort, for a total of 12 comparisons of SNHL risk. For each comparison, the statistical significance of the difference in risk was determined using chi-square covariate analysis with 95% confidence intervals, with $\alpha = 0.05$. Given the large number of individual tests being conducted to identify an overall difference at the population level, we utilized the Bonferroni correction, such that individual tests required $0.05/12 \approx p < 0.0042$ to be considered significant, to minimize the risk of a Type I error due to random chance (Armstrong, 2014). Propensity score matching (PSM), a statistical method that simulates randomization in an observational study by matching control and experimental subjects with a similar propensity for an outcome based on preexisting covariates, was also performed (Kane *et al.* 2020). For each analysis, diabetic and control patients underwent 1:1 PSM for the following factors: current age, sex, race and ethnicity, use of nicotine and cannabis products, and comorbidities that have been linked to ischemic inner ear damage (essential hypertension, cerebral infarction, and atherosclerosis) (Przewoźny *et al.* 2015; Kuo *et al.* 2016; Tsuzuki *et al.* 2021; Ciccone *et al.* 2012; Lin *et al.* 2011). All outcomes before and after PSM were measured in this study. Additionally, each of the factors used for PSM were compared between diabetic and control cohorts to both further characterize these populations and assess the effectiveness of PSM. This was also done with chi-square analysis, where $p < 0.05$ was significant. Due to the high risk of a Type II error given the large number of statistical tests required for these covariate analyses, Bonferroni correction was not used here. All calculations were conducted using the built-in statistical tools offered by the TriNetX database. Any trial outcomes with 1-9 patients were automatically reported as 10 by TriNetX to maintain patient confidentiality.

RESULTS

All non-diabetic control cohorts contained more females than males (50.7-64.4%), whereas each diabetic cohort with high HbA1c was mostly male (47.6-62.9%) at all ages, except those ≥71 years old (48.5% male). For diabetic cohorts with low HbA1c, those under age 41 years old were mostly female (50.4-58.5%), while cohorts over 41 years old were mostly male (49.5-55.3%). The control population and low HbA1c sub-population were both predominantly Caucasian across all age groups (42.1-77.7%), followed by African American (10.0-31.4%) and Asian (1.5-4.8%). For the high HbA1c sub-population, the majority of each cohort over age 51 years were also Caucasian (43.7-58.0%), whereas the majorities under age 51 years were African American (41.5-44.9%). The average age at index for diabetic and control cohorts within each age group were similar and differed by ≤1.6 years. Time elapsed from index event to study query date for all cohorts ranged from 3.3-5.4 years. A full comparison of demographic characteristics is illustrated in Table 2.

We identified 5,133,151 patients with a diagnosis of T2D and 3,945,637 without. Among diabetics, 532,187 had low HbA1c (8.0-13.9%) and 21,094 had high HbA1c (≥14.0%) values. Following age stratification, the largest cohorts for each condition were 31-40 years (n = 767,553) for subjects without diabetes, ≥71 years (n = 155,066) for low HbA1c, and 51-60 years (n = 5,688) for high HbA1c. The smallest cohorts were ≥71 years (n = 529,773), 21-30 years (n = 7,781), and 21-30 years (n = 672), respectively.

Diabetic patients had greater prevalence of all five measured comorbidities than their age-matched non-diabetic counterparts ($p < 0.03$ for all comparisons). Additionally, the high HbA1c sub-population had higher rates of all comorbid conditions than the low HbA1c sub-population across all ages, except for essential hypertension in the 51-60 and ≥71 age ranges. The most prevalent comorbidity within the T2D population was hypertension, affecting 20.8-64.9% of each low HbA1c cohort, and 23.4-67.5% of each high HbA1c cohort, versus 3.4-39.6% of each non-diabetic cohort; for both populations, the prevalence of hypertension positively correlated with age. For the non-diabetic population, hypertension was also the most common comorbidity for cohorts ≥41 years old (13.2-39.6%), whereas nicotine dependence was the most common for cohorts 21-30 and 31-40 years old (5.0-7.6%). After PSM, differences in comorbidity rates between diabetics and non-diabetics were no longer statistically significant ($p \geq 0.1493$), except for select instances [Table 3].

A diagnosis of T2D, regardless of glycemic index, was associated with significantly greater risk of SNHL vs. age-matched control cohorts for all patients ≥41 years old at index ($p < 0.0001$ for all comparisons). For patients 21-30 and 31-40 years old, low HbA1c cohorts had greater risk of hearing loss than controls ($p < 0.0001$ for both age groups), whereas high HbA1c cohorts did not (21-30 years: $p = 0.9106$, 31-40 years: $p = 0.8772$). The number of non-diabetic patients who developed SNHL for each age group were 10 (Age: 21-30, 0.002%), 10 (31-40, 0.001%), 14 (41-50, 0.002%), 20 (51-60, 0.003%), 28 (61-70, 0.01%), and 35 (≥71, 0.01%). For diabetics with low HbA1c, these outcomes

Tab. 2. A comparison of demographic characteristics between diabetic and control cohorts at different decades of age

Variable	No Diabetes n(%)	Diabetes (Low A1c) n(%)	Diabetes (High A1c) n(%)
21-30 years			
Age Years±SD	26.0±2.9	26.4±2.8	26.1±2.9
Age at Index Years±SD	21.9±4.3	22.6±4.2	22.8±3.9
Female	343,208 (64.4)	4,552 (58.5)	279 (41.5)
Male	176,504 (33.1)	3,060 (39.3)	320 (47.6)
Hispanic/Latino	85,312 (16.0)	1,959 (25.2)	117 (17.4)
Not Hispanic/Latino	336,909 (63.3)	4,418 (56.8)	399 (59.4)
White	300,474 (56.4)	3,276 (42.1)	184 (27.4)
Black/African American	105,864 (19.9)	2,447 (31.4)	289 (43.0)
Asian	19,090 (3.6)	285 (3.6)	10 (1.5)
31-40 years			
Age Years±SD	35.5±2.9	36.4±2.8	36.2±2.9
Age at Index Years±SD	31.2±4.2	32.6±4.0	32.7±4.1
Female	491,931 (64.1)	13,485 (50.4)	633 (34.5)
Male	257,552 (33.6)	12,808 (47.9)	1,070 (57.4)
Hispanic/Latino	92,348 (12.0)	6,081 (22.7)	299 (16.3)
Not Hispanic/Latino	514,052 (67.0)	15,950 (59.6)	1,162 (63.4)
White	460,101 (59.9)	12,720 (47.5)	575 (31.4)
Black/African American	132,773 (17.3)	7,921 (29.6)	823 (44.9)
Asian	37,205 (4.8)	995 (3.7)	30 (1.6)
41-50 years			
Age Years±SD	45.3±2.9	46.1±2.8	45.9±2.9
Age at Index Years±SD	40.6±4.4	41.9±4.2	42.2±4.3
Female	395,933 (59.4)	29,876 (45.0)	1,237 (35.7)
Male	254,214 (38.1)	35,313 (53.2)	2,180 (62.9)
Hispanic/Latino	73,657 (11.1)	13,395 (20.2)	603 (17.4)
Not Hispanic/Latino	455,445 (68.3)	41,253 (62.1)	2,317 (66.8)
White	422,367 (63.4)	34,625 (52.1)	1,344 (38.8)
Black/African American	106,464 (16.0)	17,605 (26.5)	1,440 (41.5)
Asian	29,423 (4.4)	2,112 (3.2)	59 (1.7)
51-60 years			
Age Years±SD	55.4±2.9	55.8±2.9	55.7±2.9
Age at Index Years±SD	50.6±4.5	51.3±4.4	51.8±4.3
Female	328,740 (54.0)	53,291 (42.9)	2,411 (42.4)
Male	263,689 (43.3)	68,681 (55.3)	3,196 (56.2)
Hispanic/Latino	45,946 (7.6)	19,007 (15.3)	775 (13.6)
Not Hispanic/Latino	435,652 (71.6)	82,690 (66.5)	4,019 (70.7)
White	425,515 (69.9)	70,879 (57.0)	2,483 (43.7)
Black/African American	88,339 (14.5)	30,975 (24.9)	2,206 (38.8)
Asian	16,428 (2.7)	3,253 (2.6)	93 (1.6)
61-70 years			
Age Years±SD	65.2±2.8	65.4±2.9	65.0±2.8
Age at Index Years±SD	60.2±4.6	60.4±4.6	60.5±4.5
Female	271,625 (50.7)	63,431 (44.0)	2,397 (44.8)
Male	249,225 (46.5)	77,788 (54.0)	2,875 (53.7)
Hispanic/Latino	25,506 (4.8)	17,427 (12.1)	570 (10.7)
Not Hispanic/Latino	396,132 (73.9)	99,681 (69.2)	3,889 (72.7)
White	399,368 (74.5)	87,408 (60.7)	2,666 (49.8)
Black/African American	68,806 (12.8)	32,932 (22.9)	1,837 (34.3)
Asian	8,703 (1.6)	3,450 (2.4)	91 (1.7)
>70 years			
Age Years±SD	79.7±6.5	78.9±6.1	78.1±5.9
Age at Index Years±SD	74.5±7.8	73.5±7.4	73.3±7.2
Female	287,004 (54.2)	75,435 (48.6)	1,887 (48.8)
Male	230,501 (43.5)	76,710 (49.5)	1,876 (48.5)
Hispanic/Latino	17,337 (3.3)	13,061 (8.4)	331 (8.6)
Not Hispanic/Latino	393,512 (74.3)	109,885 (70.9)	2,848 (73.6)
White	411,720 (77.7)	103,340 (66.6)	2,245 (58.0)
Black/African American	53,207 (10.0)	27,168 (17.5)	958 (24.8)
Asian	8,151 (1.5)	4,264 (2.8)	84 (2.2)

Tab. 3. Prevalence rates of comorbidities in diabetic cohorts versus respective non-diabetic cohorts at different decades of age

21-30 Medical Covariates				
Variable	**Cohort**	***n* (%)**	***p*-value Before PSM**	***p*-value After PSM**
Essential Hypertension	Healthy	17,981 (3.4)	-	-
	Low HbA1c	1,621 (20.8)	<0.0001	0.9842
	High HbA1c	157 (23.4)	<0.0001	0.9483
Nicotine Dependence	Healthy	26,598 (5.0)	-	-
	Low HbA1c	643 (8.3)	<0.0001	0.9070
	High HbA1c	95 (14.1)	<0.0001	0.9369
Cannabis Related Disorders	Healthy	17,506 (3.3)	-	-
	Low HbA1c	163 (2.1)	<0.0001	0.6982
	High HbA1c	35 (5.2)	0.0052	0.8034
Cerebral Infarction	Healthy	2,479 (0.5)	-	-
	Low HbA1c	69 (0.9)	<0.0001	0.7939
	High HbA1c	38 (5.7)	<0.0001	0.7145
Atherosclerosis	Healthy	314 (0.1)	-	-
	Low HbA1c	21 (0.3)	<0.0001	0.1696
	High HbA1c	10 (1.5)	<0.0001	1.0000
31-40 Medical Covariates				
Variable	**Cohort**	***n* (%)**	***p*-value Before PSM**	***p*-value After PSM**
Essential Hypertension	Healthy	52,639 (6.9)	-	-
	Low HbA1c	8,749 (32.7)	<0.0001	0.9486
	High HbA1c	615 (33.6)	<0.0001	0.8886
Nicotine Dependence	Healthy	58,002 (7.6)	-	-
	Low HbA1c	3,645 (13.6)	<0.0001	0.8697
	High HbA1c	379 (20.7)	<0.0001	0.8702
Cannabis Related Disorders	Healthy	17,897 (2.3)	-	-
	Low HbA1c	658 (2.5)	0.1775	0.9332
	High HbA1c	70 (3.8)	<0.0001	0.5364
Cerebral Infarction	Healthy	4,943 (0.6)	-	-
	Low HbA1c	334 (1.2)	<0.0001	0.7540
	High HbA1c	90 (4.9)	<0.0001	0.6985
Atherosclerosis	Healthy	745 (0.1)	-	-
	Low HbA1c	94 (0.4)	<0.0001	0.0162
	High HbA1c	10 (0.5)	<0.0001	1.0000
41-50 Medical Covariates				
Variable	**Cohort**	***n* (%)**	***p*-value Before PSM**	***p*-value After PSM**
Essential Hypertension	Healthy	87,693 (13.2)	-	-
	Low HbA1c	29,000 (43.7)	<0.0001	0.9339
	High HbA1c	1,518 (43.8)	<0.0001	0.9614
Nicotine Dependence	Healthy	56,596 (8.5)	-	-
	Low HbA1c	9,674 (14.6)	<0.0001	0.8335
	High HbA1c	696 (20.1)	<0.0001	0.9283
Cannabis Related Disorders	Healthy	10,293 (1.5)	-	-
	Low HbA1c	1,128 (1.7)	0.0023	0.5935
	High HbA1c	117 (3.4)	<0.0001	0.7420
Cerebral Infarction	Healthy	7,276 (1.1)	-	-
	Low HbA1c	1,485 (2.2)	<0.0001	0.5380
	High HbA1c	130 (3.7)	<0.0001	1.0000
Atherosclerosis	Healthy	1,488 (0.2)	-	-
	Low HbA1c	571 (0.9)	<0.0001	0.0160
	High HbA1c	49 (1.4)	<0.0001	0.4601

51-60 Medical Covariates				
Variable	**Cohort**	***n* (%)**	***p*-value Before PSM**	***p*-value After PSM**
Essential Hypertension	Healthy	130,328 (21.4)	-	-
	Low HbA1c	66,145 (53.2)	<0.0001	0.8030
	High HbA1c	3,000 (52.7)	<0.0001	0.9700
Nicotine Dependence	Healthy	58,167 (9.6)	-	-
	Low HbA1c	17,796 (14.3)	<0.0001	0.0032
	High HbA1c	1,195 (21.0)	<0.0001	0.9266
Cannabis Related Disorders	Healthy	7,247 (1.2)	-	-
	Low HbA1c	1,417 (1.1)	0.1287	0.7631
	High HbA1c	154 (2.7)	<0.0001	0.9539
Cerebral Infarction	Healthy	11,333 (1.9)	-	-
	Low HbA1c	4,430 (3.6)	<0.0001	0.6725
	High HbA1c	326 (5.7)	<0.0001	0.9032
Atherosclerosis	Healthy	3,994 (0.7)	-	-
	Low HbA1c	2,405 (1.9)	<0.0001	0.0126
	High HbA1c	165 (2.9)	<0.0001	0.4922
61-70 Medical Covariates				
Variable	**Cohort**	***n* (%)**	***p*-value Before PSM**	***p*-value After PSM**
Essential Hypertension	Healthy	158,240 (29.5)	-	-
	Low HbA1c	85,673 (59.5)	<0.0001	0.5987
	High HbA1c	3,139 (58.7)	<0.0001	0.9218
Nicotine Dependence	Healthy	51,929 (9.7)	-	-
	Low HbA1c	18,153 (12.6)	<0.0001	0.0009
	High HbA1c	1,030 (19.2)	<0.0001	0.9218
Cannabis Related Disorders	Healthy	4,760 (0.9)	-	-
	Low HbA1c	1,156 (0.8)	0.0018	0.7865
	High HbA1c	109 (2.0)	<0.0001	0.2557
Cerebral Infarction	Healthy	15,737 (2.9)	-	-
	Low HbA1c	7,442 (5.2)	<0.0001	0.1493
	High HbA1c	450 (8.4)	<0.0001	0.8890
Atherosclerosis	Healthy	8,640 (1.6)	-	-
	Low HbA1c	8,037 (3.5)	<0.0001	0.5173
	High HbA1c	281 (5.3)	<0.0001	0.8619
≥71 Medical Covariates				
Variable	**Cohort**	***n* (%)**	***p*-value Before PSM**	***p*-value After PSM**
Essential Hypertension	Healthy	209,650 (39.6)	-	-
	Low HbA1c	100,649 (64.9)	<0.0001	0.8681
	High HbA1c	2,614 (67.5)	<0.0001	0.9419
Nicotine Dependence	Healthy	27,876 (5.3)	-	-
	Low HbA1c	10,464 (6.7)	<0.0001	0.0022
	High HbA1c	501 (12.9)	<0.0001	0.8924
Cannabis Related Disorders	Healthy	1,222 (0.2)	-	-
	Low HbA1c	311 (0.2)	0.0274	0.5692
	High HbA1c	31 (0.8)	<0.0001	0.0886
Cerebral Infarction	Healthy	33,120 (6.3)	-	-
	Low HbA1c	11,597 (7.5)	<0.0001	0.2418
	High HbA1c	520 (13.4)	<0.0001	1.0000
Atherosclerosis	Healthy	19,572 (3.7)	-	-
	Low HbA1c	8,886 (5.7)	<0.0001	0.3752
	High HbA1c	337 (8.7)	<0.0001	0.8408

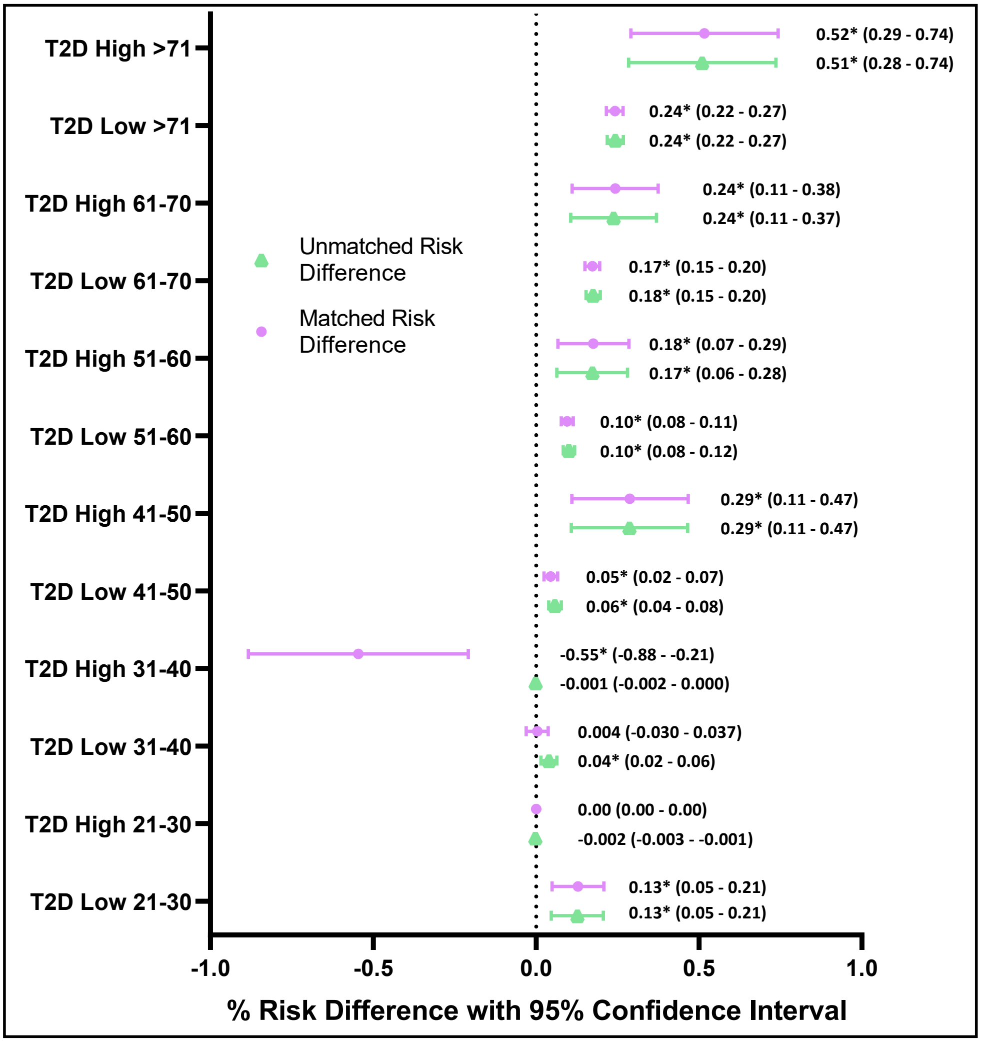

Fig. 2. Forest plot of differences in risk for SNHL of diabetic cohorts vs age-matched controls. At above age 40 years, all diabetic patient cohorts demonstrate significantly greater risk for sensorineural hearing loss than age-matched controls, with older patients having a greater increase in risk than younger patients. Patients with HbA1c ≥14.0% at each decade of age have higher risk than patients with HbA1c 8.0-13.9%.

were 10 (21-30, 0.13%), 11 (31-40, 0.04%), 40 (41-50, 0.06%), 129 (51-60, 0.10%), 259 (61-70, 0.18%), and 387 (≥71, 0.25%). For high HbA1c, these outcomes were 0 (21-30, 0.00%), 0 (31-40, 0.00%), 10 (41-50, 0.29%), 10 (51-60, 0.18%), 13 (61-70, 0.24%), and 20 (≥71, 0.52%). The differences in risk between T2D cohorts and their respective control cohorts are illustrated in Figure 2.

For each T2D cohort ≥41 years old, PSM did not significantly alter the proportion of subjects that developed SNHL [Table 4]. After PSM, all diabetic cohorts ≥41 years old still had significantly greater risk of SNHL ($p \leq 0.0016$ for all comparisons) than their matched controls; a high glycemic index was associated with greater risk of developing SNHL. The 21–30-year-old T2D cohorts with low HbA1c similarly had significantly greater risk of SNHL compared to controls (0.13% vs 0.00%, $p = 0.0016$), whereas the 31-40-year-old low HbA1c cohorts had near-identical risk (0.04% vs 0.04%, $p = 0.8272$). SNHL was not identified in diabetic patients with high HbA1c in the 21-30 (0.00% vs 0.00%, p = N/A) and 31-40 (0.00% vs 0.55%, $p = 0.0015$) age ranges.

DISCUSSION

This population-level study using PSM indicates that there is a significantly greater risk of developing SNHL amongst patients diagnosed with T2D when compared to age-matched patients without diabetes, particularly among individuals aged 41 years and older. These results are consistent with the previous observations of T2D as a risk factor for early-onset SNHL, which highlights the need for routine audiologic assessments for diabetic patients (Bainbridge *et al.* 2010; Baiduc & Helzner, 2019; Shafiepour *et al.* 2022; Al-Rubeaan *et al.* 2021; Hosseini *et al.* 2020; Lin *et al.* 2011; Goman & Lin, 2016; Harner, 1981; Raynor *et al.* 1995; Aladag *et al.* 2009; Kim *et al.* 2017). Additionally, a very high baseline glycemic index correlated with greater SNHL risk within 3.3-5.4 years after diagnosis of diabetes. The increase in risk seen in diabetics over non-diabetics was also larger for patients of more advanced age. These data suggest the possibility of a dose-dependent relationship between glycemic index and risk of SNHL that is exacerbated by older age. However, a similar conclusion could not be drawn for patients 21-30 and 31-40 years old at index, as patients with high HbA1c were comparatively

Tab. 4. Rates of SNHL of diabetic cohorts compared to that of age-matched non-diabetic controls both before and after PSM

Age Group	Trial	Cohorts	Unmatched		Matched	
			n (%)	*p*	n (%)	*p*
21-30	Non-diabetic vs Low HbA1c	Non-diabetic (n=532,654)	10 (0.002)	<0.0001	0 (0.00)	0.0016
		Low HbA1c (n=7,781)	10 (0.13)		10 (0.13)	
	Non-diabetic vs High HbA1c	Non-diabetic (n=532,654)	10 (0.002)	0.9106	0 (0.00)	-
		High HbA1c (n=672)	0 (0.00)		0 (0.00)	
31-40	Non-diabetic vs Low HbA1c	Non-diabetic (n=767,553)	10 (0.001)	<0.0001	10 (0.04)	0.8272
		Low HbA1c (n=26,766)	11 (0.04)		11 (0.04)	
	Non-diabetic vs High HbA1c	Non-diabetic (n=767,553)	10 (0.001)	0.8772	10 (0.55)	0.0015
		High HbA1c (n=1,833)	0 (0.00)		0 (0.00)	
41-50	Non-diabetic vs Low HbA1c	Non-diabetic (n=666,541)	14 (0.002)	<0.0001	10 (0.02)	<0.0001
		Low HbA1c (n=66,437)	40 (0.06)		40 (0.06)	
	Non-diabetic vs High HbA1c	Non-diabetic (n=666,541)	14 (0.002)	<0.0001	0 (0.00)	0.0016
		High HbA1c (n=3,468)	10 (0.29)		10 (0.29)	
51-60	Non-diabetic vs Low HbA1c	Non-diabetic (n=608,434)	20 (0.003)	<0.0001	10 (0.01)	<0.0001
		Low HbA1c (n=124,301)	129 (0.10)		128 (0.10)	
	Non-diabetic vs High HbA1c	Non-diabetic (n=608,434)	20 (0.003)	<0.0001	0 (0.00)	0.0016
		High HbA1c (n=5,688)	10 (0.18)		10 (0.18)	
61-70	Non-diabetic vs Low HbA1c	Non-diabetic (n=535,759)	28 (0.01)	<0.0001	10 (0.01)	<0.0001
		Low HbA1c (n=144,031)	259 (0.18)		255 (0.18)	
	Non-diabetic vs High HbA1c	Non-diabetic (n=535,759)	28 (0.01)	<0.0001	0 (0.00)	0.0003
		High HbA1c (n=5,351)	13 (0.24)		13 (0.24)	
70+	Non-diabetic vs Low HbA1c	Non-diabetic (n=529,773)	35 (0.01)	<0.0001	10 (0.01)	<0.0001
		Low HbA1c (n=155,066)	387 (0.25)		380 (0.25)	
	Non-diabetic vs High HbA1c	Non-diabetic (n=529,773)	35 (0.01)	<0.0001	0 (0.00)	<0.0001
		High HbA1c (n=3,870)	20 (0.52)		20 (0.52)	

few (672 and 1,833, respectively) and therefore yielded no cases of SNHL; this age group requires further investigation. Due to the projected rise in T2D in younger generations in the United States within the next four decades, it will be essential to emphasize the importance of effective glycemic control to prevent future SNHL (Tönnies, 2023).

Although there is still no general consensus regarding the pathological mechanism behind diabetic ototoxicity, most current theories attribute injury of inner ear structures to either microvascular damage-induced ischemia or direct oxidative damage mediated by hyperglycemia (Nakae & Tachibana, 1986; Fukushima *et al.* 2005; Raynor *et al.* 1995; Smith *et al.* 1995). It has also been reported that patients with hypertension may also be at greater risk of developing hearing loss, resulting from either the ototoxic effects of certain medications, such as loop diuretics, or ischemia of the highly-sensitive cochlear apex secondary to microvascular occlusion, that mirrors the theories pertaining to diabetic otopathology (Nawaz *et al.* 2021; Agarwal *et al.* 2013; Friedland *et al.* 2009; Carrasco *et al.* 1990). Prior to PSM, all diabetic cohorts in this study were found to have a significantly greater prevalence of essential hypertension ($p < 0.0001$), and nearly all had higher rates of stroke, atherosclerosis, and smoking history ($p \leq 0.0274$) compared to non-diabetic controls. These findings raise the possibility that the increased SNHL risk amongst T2D patients is secondary to diabetes-associated cardiovascular disease, rather than a direct effect of hyperglycemia. This explanation would also align with theories suggesting an ischemic inner ear pathology underlying diabetes-associated SNHL but would require further study for confirmation.

There are several limitations to this study. As the TriNetX database builds patient cohorts using ICD-10 billing codes, it could only query for diagnosis of T2D and certain documented HbA1c values (i.e., highest, most recent). Therefore, patients with undetected T2D were likely erroneously categorized as non-diabetic, and the information regarding long-term blood glucose management and average HbA1c ranges could not be properly obtained. Similarly, the lack of audiometric data and the reliance on diagnostic codes by TriNetX leads to the possibility that patients with clinically relevant hearing loss may be incorrectly categorized as having no SNHL in the EHR. The very high cutoff of 14.0% also resulted in smaller high HbA1c cohort populations, which limited analysis of SNHL outcomes in patients age ≤40 years, and possibly led to outcomes with 1-9 patients being erroneously reported as 10 by TriNetX. Future studies may benefit from further evaluation of hearing loss risk in young diabetic patients particularly, as well as from identifying hearing loss in patients using audiometric testing and implementing additional HbA1c stratifications.

CONCLUSION

Based on population-level data obtained from the TriNetX US Collaborative Network, this study finds a significant increase in the risk of developing SNHL in patients diagnosed with T2D compared to non-diabetic patients of matched age. This trend was not clearly observed in patients forty years or younger, which may represent a cutoff to begin clinical screenings. The results of this study endorse the need for hearing loss evaluations in diabetic care, especially in the aging population. The risk of developing SNHL is also greater in patients with a higher HbA1c, suggesting a positive correlation with blood glucose level. Further investigation is required, however, to determine if hyperglycemia is directly responsible for inner ear pathology, or secondarily via generalized cardiovascular disease. Future studies should include audiometric testing to evaluate severity of hearing loss and should place emphasis on investigating SNHL risk in diabetic populations forty years old or younger. Research to elucidate the role of blood glucose in the pathogenesis of diabetes-associated SNHL is also needed.

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