



Type 2 diabetes and the risk of incident hearing loss

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Abstract

Aims/hypothesis Type 2 diabetes mellitus has been implicated as a risk factor for hearing loss, with possible mechanisms including microvascular disease, acoustic neuropathy or oxidative stress. A few small studies have examined the longitudinal association between type 2 diabetes and hearing loss, but larger studies are needed. Our objective was to examine whether type 2 diabetes (including diabetes duration) is associated with incident hearing loss in two prospective cohorts: Nurses' Health Studies (NHS) I and II.

Methods We conducted a longitudinal study of 139,909 women to examine the relationship between type 2 diabetes and the risk of self-reported incident hearing loss. A physician-diagnosis of diabetes was ascertained from biennial questionnaires. The primary outcome was hearing loss reported as moderate or worse in severity (categorised as a 'moderate or severe' hearing problem, or 'moderate hearing trouble or deaf') on questionnaires administered in 2012 in NHS I and 2009 or 2013 in NHS II. Cox proportional hazards regression was used to adjust for potential confounders.

Results During >2.4 million person-years of follow-up, 664 cases of moderate or worse hearing loss were reported among those with type 2 diabetes and 10,022 cases among those without type 2 diabetes. Compared with women who did not have type 2 diabetes, those with type 2 diabetes were at higher risk for incident moderate or worse hearing loss (pooled multivariable-adjusted HR 1.16 [95% CI 1.07, 1.27]). Participants who had type 2 diabetes for ≥ 8 years had a higher risk of moderate or worse hearing loss compared with those without type 2 diabetes (pooled multivariable-adjusted HR 1.24 [95% CI 1.10, 1.40]).

Conclusions/interpretation In this large longitudinal study, type 2 diabetes was associated with a modestly higher risk of moderate or worse hearing loss. Furthermore, longer duration diabetes was associated with a higher risk of moderate or worse hearing loss.

Keywords Hearing loss · Longitudinal · Nurses' Health Study · Type 2 diabetes

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Abbreviations

AMED Alternate Mediterranean diet
FPG Fasting plasma glucose
NHS Nurses' Health Study

Introduction

The association between type 2 diabetes and hearing loss is controversial. Most available data are cross-sectional, where hearing loss may have preceded the onset of type 2 diabetes. Longitudinal studies are limited by sample size [1, 2] or short duration of follow-up [3]. Cruickshanks et al found that a high level of HbA_{1c}, but not the diagnosis of diabetes itself, was associated with a higher risk of incident hearing loss [2]. A Korean cohort study found a 36% higher risk for incident hearing loss among those with diabetes [3]. Findings from the few studies investigating the association between the duration of type 2 diabetes and hearing loss have been inconsistent.

Research in context

What is already known about this subject?

- Several studies have reported type 2 diabetes as an independent factor associated with hearing loss, while others found no significant relationship between these two conditions
- Most of the available data on this subject are cross-sectional

What is the key question?

- Is type 2 diabetes independently associated with a higher risk of incident hearing loss?

What are the new findings?

- Type 2 diabetes is independently associated with a higher risk of multivariable-adjusted incident hearing loss
- Longer duration of type 2 diabetes (≥ 8 years) is associated with a higher risk of moderate or worse hearing loss

How might this impact on clinical practice in the foreseeable future?

- These findings suggest that preventing type 2 diabetes could potentially reduce the burden of hearing loss

Because prospective data are limited, we examined the relationship between type 2 diabetes and incident hearing loss in the Nurses' Health Studies (NHS) I and II ($n = 139,909$). We also assessed whether longer duration of disease was associated with a higher risk of hearing loss.

Methods

Study participants NHS I and NHS II are prospective cohort studies where participants have been followed with biennial questionnaires, eliciting information on diet, lifestyle and various health outcomes, with a follow-up of $>90\%$ of the eligible person-time.

We limited the analysis to those women who provided information on their hearing on the 2012 (NHS I), 2009 and/or 2013 (both NHS II) questionnaires. We excluded women who reported a hearing problem that started before baseline in the NHS I (1984) and NHS II (1995) and women who reported a history of cancer other than non-melanoma skin cancer.

The NHS I/II were approved by the Institutional Review Board. The Institutional Review Board allows for the return of questionnaires as implied consent.

Ascertainment of type 2 diabetes Women who reported a physician-diagnosis of diabetes on baseline or biennial questionnaires were sent supplementary questionnaires to categorise reported causes: type 1 diabetes, type 2 diabetes (possible, probable, definite/confirmed), gestational diabetes, impaired glucose tolerance and secondary diabetes. The confirmation of diabetes in NHS I and NHS II has been described in detail [4, 5]. We included only women who had a confirmed or probable diagnosis of type 2 diabetes.

A confirmed diagnosis of type 2 diabetes was defined as: (1) an elevated fasting plasma glucose (FPG) concentration and at least one classic symptom related to diabetes; (2) at least two elevated plasma glucose measurements on different occasions, in the absence of symptoms; or (3) treatment with blood glucose-lowering medications. A probable diagnosis of type 2 diabetes was defined as self-reported diabetes, along with one of the following: (1) elevated plasma glucose measured on one occasion but no symptoms or drug therapy; or (2) classic symptoms and glycosuria. In both cohorts, information on type 2 diabetes was updated every 2 years.

Ascertainment of diabetes duration In NHS I and NHS II, we excluded individuals with prevalent diabetes before 1976 ($n = 288$) and before 1989 ($n = 499$), respectively. We included women with incident type 2 diabetes diagnosed between 1976 and 1984 in NHS I.

Ascertainment of hearing loss The primary outcome was self-reported moderate or worse hearing loss. In NHS I, information was obtained from the 2012 long-form questionnaire in which participants were asked, 'Do you have a hearing problem?' (response options: none, mild, moderate, severe), and if so, at what age a change in hearing was first noticed. In NHS II, information was obtained from the 2009 and 2013 questionnaires. In the 2009 long-form questionnaire, participants were asked, 'Do you have a hearing problem?' (response options: no, mild, moderate, severe), and 'At what age did you first notice a change in your hearing?' In the 2013 main questionnaire, participants were asked, 'Which best describes your hearing?' (response options: excellent, good, a little hearing trouble, moderate hearing trouble, deaf), and 'Have you noticed a change in your hearing?' If the response to the latter

was ‘Yes’, participants were asked, ‘At what age did you first notice a change in your hearing?’

A priori, we chose to examine the incidence of self-reported moderate or worse hearing loss to minimise misclassification. In a validation study of self-reported hearing loss, compared with audiometrically measured hearing loss, the sensitivity of a single question to detect moderate or worse hearing loss (classified by audiometry as better ear-pure tone average [(PTA)_{0.5,1,2,4 kHz}] >40 dB) among women aged less than 70 years was 95%, and the specificity was 65% [6]. As a secondary outcome, we also assessed the incidence of mild hearing loss.

Ascertainment of covariates Covariate data were obtained and updated from biennial questionnaires. In this analysis, we considered the following covariates: age; race; tinnitus; BMI; waist circumference; alcohol consumption (g/day); physical activity (quintiles of metabolic equivalents of task [METs]/week); smoking (never, past, current smoker); hypertension; frequent use of non-steroidal anti-inflammatory drug (NSAIDs), aspirin and paracetamol (also known as acetaminophen); and alternate Mediterranean diet (AMED) scores (a healthy dietary pattern inversely associated with hearing loss) [7].

Statistical analysis Analyses were performed prospectively, with person-time allocated according to exposure status (type 2 diabetes) at the start of each follow-up period. Participants were censored at the reported onset of hearing loss or new cancer diagnosis.

We used Cox proportional hazards regression analysis to estimate the HR of moderate or worse hearing loss. Women who reported a history of impaired FPG, gestational diabetes or secondary diabetes contributed follow-up time as non-diabetic participants and re-entered the analysis if they subsequently developed confirmed or probable type 2 diabetes. Women who reported mild hearing loss on the 2009 NHS II questionnaire were excluded but re-entered the analysis if they subsequently reported moderate or worse hearing loss in the 2013 questionnaire. We investigated the risk of moderate or

worse hearing loss and mild hearing loss in each cohort, and then pooled the multivariable-adjusted HRs. We then examined the association between hearing loss and duration of type 2 diabetes.

We used backward selection, with type 2 diabetes and covariates as time-dependent variables, and a *p* value threshold of <0.10 for retaining covariates. For consistency, we retained the following covariates in all models: age, AMED score, waist circumference, BMI, physical activity, hypertension, tinnitus, paracetamol use, ibuprofen use and race. We tested for collinearity between age and duration of type 2 diabetes in each cohort; Spearman’s correlation coefficients were <0.2 when tested at multiple time points. SAS software, version 9.4 (Cary, NC, USA) was used for all analyses.

Results

There were 936 participants with type 2 diabetes at baseline and 7009 women who developed type 2 diabetes during follow-up. During 2,418,720 person-years of follow-up, 664 incident cases of moderate or worse hearing loss developed among women with type 2 diabetes and 10,022 cases in those without type 2 diabetes (Table 1). The pooled multivariable-adjusted HR for moderate or worse hearing loss in those with type 2 diabetes was 1.16 (95% CI 1.07, 1.27) compared with individuals without diabetes.

There was a higher risk of moderate or worse hearing loss in those participants who had type 2 diabetes for 8 or more years compared with those without type 2 diabetes (pooled multivariable-adjusted HR 1.24 [95% CI 1.10, 1.40; Table 2).

There was no statistically significant interaction with age or BMI (data not shown).

Baseline characteristics of participants are shown in ESM Table 1. In a secondary analysis, type 2 diabetes was associated with a slightly higher risk of mild hearing loss (multivariable-adjusted HR 1.08 [95% CI 1.01, 1.14]) compared with no type 2 diabetes (ESM Table 2). The cohort-specific results for the relationship between duration of diabetes and the risk of moderate or worse hearing loss are shown in ESM Table 3.

Table 1 Age-adjusted and multivariable-adjusted HRs for moderate or worse hearing loss among women in NHS I/II with type 2 diabetes

Variable	NHS I		NHS II		Pooled results for NHS I and NHS II	
	No type 2 diabetes	Type 2 diabetes	No type 2 diabetes	Type 2 diabetes	No type 2 diabetes	Type 2 diabetes
Participants (<i>n</i>)	7703	550	2319	114	10,022	664
Person-years	1,293,748	54,952	1,041,912	28,108	2,335,660	83,060
Age-adjusted HR (95% CI)	1.00 (ref)	1.20 (1.10, 1.31)	1.00 (ref)	1.42 (1.17, 1.72)	1.00 (ref)	1.28 (1.09, 1.50)
Multivariable-adjusted HR (95% CI) ^a	1.00 (ref)	1.15 (1.05, 1.26)	1.00 (ref)	1.24 (1.02, 1.52)	1.00 (ref)	1.16 (1.07, 1.27)

Exposure: type 2 diabetes; outcome: moderate or worse hearing loss

^a Covariates: AMED score, waist circumference, BMI, physical activity, hypertension, tinnitus, paracetamol use, ibuprofen use and race

Ref, reference

Table 2 Pooled age-adjusted and multivariable-adjusted HRs for risk of moderate or worse hearing loss based on duration of type 2 diabetes among women in the NHS I/II

Variable	No type 2 diabetes	0 to <4 years duration	4 to <8 years duration	≥8 years duration
Participants (<i>n</i>)	10,022	192	150	322
Person-years	2,335,660	30,659	21,474	30,927
Age-adjusted HR (95% CI)	1.00 (ref)	1.14 (0.99, 1.33)	1.36 (0.81, 2.28)	1.31 (1.17, 1.47)
Pooled multivariable-adjusted HR (95% CI) ^a	1.00 (ref)	1.08 (0.93, 1.26)	1.23 (0.83, 1.82)	1.24 (1.10, 1.40)

Exposure: duration of type 2 diabetes in years; outcome: moderate or worse hearing loss

^a Covariates: AMED score, waist circumference, BMI, physical activity, hypertension, tinnitus, paracetamol use, ibuprofen use and race

Discussion

Among 139,909 women in NHS I and NHS II, we found a modest, independently significant higher risk of self-reported moderate or worse hearing loss in those with type 2 diabetes compared with individuals without the disease. We also found a higher risk in those who had type 2 diabetes for 8 or more years.

Our pooled multivariable-adjusted HR for hearing loss among those with type 2 diabetes as compared with those without type 2 diabetes was lower than previously reported [2, 3]; however, other studies tended not to finely adjust for potentially important confounders, such as BMI. In our analysis, BMI and age were the strongest confounders. Higher BMI and waist circumference have been previously shown to be risk factors for incident hearing loss [2, 8], and type 2 diabetes and obesity may induce hearing loss through similar mechanisms, including oxidative stress [9, 10]. The finding of an increased risk of hearing loss with type 2 diabetes independent of BMI suggests there may be other pathways contributing to diabetes-related hearing loss. Autopsies of individuals with diabetes showed atrophy of the spiral ganglion and demyelination of the auditory nerve [11].

In all Cox proportional hazards models, we carefully and finely adjusted for age (updated with every biennial questionnaire) to avoid confounding by age. When including BMI and age as quadratic covariates in the pooled multivariable-adjusted model for moderate or worse hearing loss, the HR was unchanged.

Studies assessing diabetes disease duration and hearing loss have yielded inconsistent results. One study reported an OR of 2.08 [95% CI 1.10, 3.94] for hearing loss with diabetes duration ≥10 years compared with an OR of 1.41 [95% CI 0.96, 2.06] for diabetes duration <10 years [1], while another found no significant association between hearing loss and diabetes duration [12]. We found that having type 2 diabetes for ≥8 years was associated with a higher risk of moderate or worse hearing loss compared with individuals without diabetes.

This is the largest prospective study to examine the risk of incident hearing loss in relation to type 2 diabetes. The information obtained from NHS I and NHS II is highly reliable and follow-up rates are high. Validation studies within the Nurses'

Studies have demonstrated the reliability of self-reported diabetes [5]. However, we did not have enough information to assess the association between glycaemic control or impaired glucose tolerance with hearing loss. Although hearing loss was based on self-report, self-reported hearing loss has been found to be a reliable indicator of hearing loss [13–15] and the sensitivity of a single question to detect moderate or worse hearing loss has been shown to be high among women [6]. The hearing loss-related questions in the 2013 NHS II questionnaire were slightly different from the 2009 questionnaire; however, there are other published studies from NHS II that combined the responses from the 2009 and 2013 questionnaires and found a positive association between certain risk factors and hearing loss [7, 16]. Due to the observational design, residual confounding cannot be excluded.

Based on the findings from this large longitudinal study, type 2 diabetes is associated with a modestly higher risk of hearing loss and, with regards to diabetes duration, having diabetes for 8 or more years is associated with a higher risk. These findings may have important public health implications and suggest that preventing type 2 diabetes could potentially reduce the burden of hearing loss.

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Data availability The datasets generated and/or analysed during the current study are not publicly available due to preserving participant confidentiality, but are available from the corresponding author on reasonable request.

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