

A Prospective Study of Caffeine Intake and Risk of Incident Tinnitus



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ABSTRACT

BACKGROUND: Caffeine is a commonly consumed substance that has been thought to play a role in the development of tinnitus, but prospective data are lacking. We prospectively evaluated the association between caffeine intake and self-reported tinnitus in a female cohort.

METHODS: Participants were 65,085 women in the Nurses' Health Study II, aged 30 to 44 years and without tinnitus at baseline in 1991, who completed questionnaires about lifestyle and medical history every 2 years and food frequency questionnaires every 4 years. Information on self-reported tinnitus and date of onset was obtained from the 2009 questionnaire, with cases defined as those reporting experiencing symptoms "a few days/week" or "daily." Multivariable adjusted hazard ratios were calculated using Cox proportional hazards regression models.

RESULTS: At baseline, the mean age of the cohort was 36.3 years and the mean caffeine intake was 242.3 mg/d. After 18 years of follow-up, 5289 incident cases of tinnitus were reported. There was a significant inverse association between caffeine intake and the incidence of tinnitus. Compared with women with caffeine intake less than 150 mg/d (150 mg corresponds to ~ one 8-ounce cup of coffee), the multivariable adjusted hazard ratios were 0.85 (95% confidence interval, 0.76-0.95) for those who consumed 450 to 599 mg/d and 0.79 (0.68-0.91) for those who consumed 600 mg/d or more.

CONCLUSIONS: In this prospective study, higher caffeine intake was associated with a lower risk of incident tinnitus in women.

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KEYWORDS: Caffeine; Epidemiology; Tinnitus

Tinnitus is a highly prevalent condition estimated to affect 50 million Americans, severely disabling 3 million.^{1,2} In the majority of cases, the precise pathophysiology underlying tinnitus remains unknown, and in the absence of a reversible underlying condition, treatment is generally not highly effective.^{3,4} Preventing the development of the condition

may prove to be the best way to reduce its burden on the individual and society. Although some risk factors such as hearing loss and trauma are well established, evidence for other risk factors is scarce.

Caffeine is the most commonly used psychoactive substance, frequently consumed in coffee.⁵ More than 50% of Americans drink coffee, and the per capita intake is 2 cups per day.⁶ Although caffeine has been implicated in the development of tinnitus,^{7,8} evidence to support caffeine as a risk factor or exacerbating factor for tinnitus is lacking in the medical literature. However, caffeine cessation or reduction in intake to reduce tinnitus symptoms has been recommended by national primary care and specialty organizations.^{9,10} Of note, a recent randomized controlled crossover trial failed to demonstrate an improvement in tinnitus symptoms with cessation of caffeine intake.¹¹

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With the high prevalence of caffeine intake and tinnitus, prospective evaluation of this relation is important. Therefore, we prospectively examined the association between caffeine intake and the risk of incident tinnitus in 65,085 women in the Nurses' Health Study II.

METHODS

Study Population

The Nurses' Health Study II cohort began in 1989 with questionnaires completed by 116,430 female registered nurses aged 25 to 42 years. Questionnaires have been mailed on a biennial basis to update the exposure information and the incidence of a wide variety of medical conditions. The follow-up rate for this cohort exceeds 90% of eligible person-time.

We excluded individuals if they reported onset of tinnitus before 1991 (the first year that caffeine intake was assessed) or if they had a history of cancer (excluding nonmelanoma skin cancer). Participants were eligible to contribute person-time to the study as of their 30th birthday, which is the youngest age for which we were able to estimate the onset of tinnitus.

Assessment of Caffeine Intake

Caffeine intake was assessed using detailed, extensively validated semiquantitative food frequency questionnaires that inquired about the average intake of more than 130 foods and beverages over the preceding year in 1991 and at 4-year intervals thereafter.¹²⁻¹⁴

The relevant beverages on the questionnaire included low-calorie cola (eg, Diet Coke or Diet Pepsi with caffeine), regular cola (eg, Coke, Pepsi, or other cola beverages with sugar), tea with caffeine, tea without caffeine, coffee with caffeine, and decaffeinated coffee. In 2003 and 2007, a question about the intake of dairy coffee drinks—hot or cold (eg, cappuccino) also was included. The relevant foods included candy bars (eg, Snickers, Milky Way, Reeses), dark chocolate (eg, Hershey's Dark or Dove Dark), milk chocolate—bar or pack (eg, Hershey's, M&M's), and brownies. The response options for specified serving sizes were never or less than once per month; 1 to 3 per month; 1 per week; 2 to 4 per week; 5 to 6 per week; 1 per day; 2 to 3 per day; 4 to 5 per day; and 6 or more per day.

Total caffeine intake was calculated using US Department of Agriculture food composition sources. For example, the caffeine content of the specific items was considered to be 137 mg per cup of coffee, 47 mg per cup of tea, 46 mg per can or bottle of cola beverage, and 7 mg per serving of chocolate candy.¹⁵ This method of determining caffeine intake was shown to be valid in prior studies.¹²⁻¹⁴

Ascertainment of Tinnitus

Participants were asked on the 2009 questionnaire "In the past 12 months, have you had ringing, roaring, or buzzing in your ears?" The response categories were never, once per week or less, a few days per week, or daily. To determine the date of onset, participants were asked "At what age did this first begin?" (<30, 30-39, 40-49, 50-59, and ≥60 years). Onset of tinnitus was defined to be the midpoint of an age interval (eg, 35 years for the age category of onset of 30-39 years). We defined a case as a participant who reported tinnitus occurring a few days per week or daily.

Assessment of Covariates

Data on body mass index (BMI) and intake of tobacco were collected on each questionnaire. On the 2009 questionnaire, each participant was asked if he/she had a hearing problem and the age when a change was first noticed. Data on other health conditions were ascertained on each questionnaire. Conditions of interest included diabetes, hypertension, multiple sclerosis, and depression, because these have been associated with tinnitus.^{2,7,16,17} Data regarding use of medications proposed to be associated with tinnitus were obtained from the biennial questionnaires (analgesics [acetaminophen, aspirin, ibuprofen, other nonsteroidal anti-inflammatory drugs, and cyclooxygenase-2 inhibitors], thiazide diuretics, furosemide, and selective serotonin reuptake inhibitors/other antidepressants). The Crown Crisp Questionnaire, used to assess phobic anxiety, was administered in 1993 and 2005 and was used to adjust for phobic anxiety based on score categories.^{18,19}

Statistical Methods

The time of observation was between 1991 and 2009. Participants who did not return a questionnaire for one time period and who remained eligible contributed person-time for later time intervals. Participants were censored after the onset of tinnitus or diagnosis of cancer.

Cox proportional hazards regression models were used to estimate multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) on the basis of categories of cumulative average caffeine intake (in 150 mg/d increments, which is ~1 cup of coffee). We used the Anderson-Gill data structure and stratified by age and calendar year. Information on caffeine intake on each subsequent questionnaire was used to update the cumulative average caffeine intake up to that point. Covariates considered in multivariable-adjusted models included age (continuous), hearing loss, smoking status (current, past, or never), comorbid conditions (diabetes, hypertension, multiple sclerosis, and depression), medications used at least 1 day per week (analgesics, diuretics, and antidepressants),

CLINICAL SIGNIFICANCE

- In women, the incidence rate of tinnitus increases with age and reaches a value greater than 1 per 100 per year in the sixth decade of life.
- Higher caffeine intake is associated with a lower risk of incident tinnitus in women.

BMI, and smoking status. We used stratified models to examine whether the relation between caffeine intake and incident tinnitus varied by age (<50 or ≥50 years) and self-reported hearing loss. We also evaluated the association between decaffeinated coffee and incident tinnitus, after excluding those who consumed caffeinated coffee, to explore whether any observed relations were due to coffee (the major source of caffeine in this cohort) or caffeine.

Covariate information was updated at the beginning of each time period using the most recently available responses. Participants with missing covariate data were assigned to a missing category for that specific time period.

Level of significance (α) for 2-tailed *P* values was <.05. We used SAS version 9.3 for UNIX statistical software package (SAS Institute Inc, Cary, NC).

RESULTS

There were 65,085 women included in the analysis. The baseline characteristics of the cohort according to category of caffeine intake are shown in **Table 1**. At baseline, the mean age of the cohort was 36.3 years, the mean BMI was 24.5 kg/m², and the mean caffeine intake was 242.3 mg/d. Comorbidities present at baseline included hearing problems (prevalence = 3.3%), history of depression

(13.7%), diabetes (0.8%), hypertension (6.1%), and multiple sclerosis (0.3%). With increasing caffeine intake, there were higher percentages of participants who reported smoking, depression, aspirin use, and ibuprofen use. The incidence rate of tinnitus increased substantially with age, ranging from 104 per 100,000 person-years for those aged <40 years to 1273 per 100,000 person-years for those aged ≥50 years (**Table 2**).

The age and multivariable-adjusted HRs of the association between caffeine intake and incident tinnitus are shown in **Table 3**. After adjusting for age, there was a significant inverse association between caffeine intake and the incidence of tinnitus at higher levels of caffeine intake (HR, 0.89; 95% CI, 0.80-0.99 for 450-599 mg/d and HR, 0.83; 95% CI, 0.73-0.95 for ≥600 mg/d, *P* for trend <.001). After adjusting for other potential confounders, a slightly greater inverse association was observed between caffeine intake and tinnitus at higher levels of caffeine intake: HR, 0.85 (95% CI, 0.76-0.95) for 450 to 599 mg/d and HR 0.79 (95% CI, 0.68-0.91) for ≥600 mg/d (*P* for trend <.001). The association between caffeine intake and tinnitus did not vary by age (*P* for interaction, .5) or hearing loss (*P* for interaction, .8).

To exclude further the possibility that tinnitus onset might have led to decreased caffeine consumption, we

Table 1 Baseline Characteristics of Women in 1991 by Category of Caffeine Intake

	Energy-Adjusted Caffeine Intake, mg/d				
	0-149 (n = 29,037)	150-299 (n = 13,049)	300-449 (n = 13,188)	450-599 (n = 4453)	600+ (n = 5358)
Age, y*	35.7 (4.7)	36.2 (4.7)	37.0 (4.3)	37.1 (4.4)	37.7 (4.2)
BMI, kg/m ²	24.4 (5.3)	24.7 (5.4)	24.2 (4.8)	24.6 (5.1)	24.7 (4.9)
Smoking Status					
Never, %	77.8	68.0	55.0	52.5	39.5
Past, %	16.9	22.3	30.8	27.6	27.4
Current, %	5.2	9.5	14.0	19.7	33.0
Hearing problem, %	3.3	3.1	3.5	3.6	3.4
History of hypertension, %	5.9	6.6	5.6	6.4	6.4
History of diabetes, %	0.7	0.9	0.6	0.8	1.1
History of depression, 2003, %	12.9	13.7	14.2	14.8	16.0
History of multiple sclerosis, %	0.3	0.4	0.3	0.4	0.4
Thiazide diuretic use, %	1.6	1.8	1.7	1.9	1.8
Furosemide use, 1989, %	0.4	0.4	0.3	0.5	0.7
Aspirin use, %	3.6	4.8	4.5	5.0	6.2
Ibuprofen use, %	7.3	10.4	10.1	10.6	12.2
Acetaminophen use, %	6.7	8.2	7.6	8.2	8.1
COX-2 inhibitors use, 2001, %	8.6	9.4	9.3	10.3	10.6
SSRI use, 1997, %	7.2	7.9	8.3	9.0	9.1
Other antidepressant use, 1993, %	9.0	10.0	9.5	10.9	11.6
Anxiety Crown-Crisp Score					
≤2, %	58.1	56.1	56.2	55.7	53.2
≥3, %	31.8	32.7	32.2	32.1	35.3

The values in the table reflect responses from 1991 unless otherwise indicated. Use of medication refers to use at least 1 day per week. Values are means (standard deviation) or percentages and are standardized to the age distribution of the study population.

BMI = body mass index; COX = cyclooxygenase; SSRI = selective serotonin reuptake inhibitor.

*The value is not age adjusted.

Table 2 Age-Specific Tinnitus Incidence Rates

Age (y)	Person-y	Cases	Incidence Rate per 100,000 Person-y
<40	348,676	361	104
40-49	545,612	2286	419
≥50	207,464	2642	1273
Total	1,101,753*	5289	475

*Total differs slightly because of rounding.

compared caffeine intake in participants before and after the time they indicated they developed tinnitus, but we found no differences. For example, between 1991 and 1999, there was no significant change in caffeine consumption category among participants who indicated their onset of tinnitus was between 1995 and 1999 ($P = .53$ using Bowker's test of symmetry). We also examined changes in mean caffeine intake over time among those who did and did not develop tinnitus to account for potential temporal trends. There was a similar slight decrease in total caffeine consumption between 1991 and 1999 among those who did develop tinnitus (19.1 mg, 95% CI, 8.5-29.7) and those who did not develop tinnitus during follow-up (14.3 mg, 95% CI, 12.7-15.9). The decreased consumption over time was not significantly different between groups.

There was no association between decaffeinated coffee intake and incident tinnitus. Compared with those who drank decaffeinated coffee less than once per month, the multivariable adjusted HR for tinnitus was 1.00 (95% CI, 0.89-1.13) for those who drank 2 to 3 cups per day and 0.85 (95% CI, 0.62-1.16) for those who drank 4 or more cups per day (P for trend = .9).

DISCUSSION

Main Findings

In this large, prospective study among women, we observed an inverse association between caffeine intake and incident tinnitus. The majority (~70%) of caffeine intake in these

individuals was from coffee consumption. We did not find an association between decaffeinated coffee intake and incident tinnitus. This suggests it is caffeine rather than another component of coffee that was associated with a decreased incidence of tinnitus.

Comparison with Other Studies

A recent randomized controlled crossover trial failed to demonstrate an improvement in tinnitus symptoms with cessation of caffeine intake while demonstrating harm in the way of withdrawal symptoms among participants.¹¹ The investigation included men and women with a mean age of 59.2 years. A mean difference in tinnitus severity score of 0.04 (95% CI, 1.99-1.93) was observed between patients during caffeine-consuming and caffeine-abstaining states. Our study examined the risk of incident tinnitus, whereas the aforementioned study¹¹ evaluated the effect of caffeine on existing tinnitus. On the basis of the results of these studies, there is not persuasive evidence that reducing caffeine intake would be beneficial with respect to tinnitus. We are not aware of other prospective studies evaluating the association between caffeine and incident tinnitus.

The precise pathophysiology underlying subjective tinnitus remains unknown. Purported mechanisms include hyperactivity of the ascending auditory pathways or a reduced suppressive influence of the central nervous system.²⁰ Caffeine is a central nervous system stimulant, and this biologic action may have led to the idea that it may play a role in the development of tinnitus. Noting a paucity of evidence for such an association, Bagueley et al²¹ suggested that if such an association exists, the stimulatory effect of caffeine may lead to increased detection of tinnitus through increased arousal or anxiety.

In addition to general stimulatory effects of caffeine on the central nervous system, caffeine has been shown to have a direct effect on the inner ear in both in vitro and animal studies. Caffeine is thought to result in shortening of outer hair cells, and this effect may be mediated through the release of calcium from ryanodine receptors.²² At this time, it is unclear whether this pathway is involved in the

Table 3 Age and Multivariable-Adjusted Hazard Ratios for the Association Between Caffeine Intake and Incident Tinnitus

Caffeine Intake in mg/d	No. of Cases	Person-y	Age-adjusted HR (95% CI)	Multivariate Model* HR (95% CI)
0-149	2268	470,228	1.00 (referent)	1.00 (referent)
150-299	1394	274,909	0.96 (0.89-1.02)	0.94 (0.88-1.00)
300-449	1029	214,588	0.93 (0.87-1.01)	0.91 (0.84-0.98)
450-599	364	80,433	0.89 (0.80-0.99)	0.85 (0.76-0.95)
≥600	234	61,595	0.83 (0.73-0.95)	0.79 (0.68-0.91)
			$P_{\text{trend}} < .001$	$P_{\text{trend}} < .001$

CI = confidence interval; HR = hazard ratio.

*Covariates in model included caffeine, age, hearing loss, medications, medical conditions, phobic anxiety, BMI, and smoking status. Medications included acetaminophen, aspirin, ibuprofen, other nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, thiazide diuretics, furosemide, and selective serotonin reuptake inhibitors/other antidepressants. Medical conditions included diabetes mellitus, hypertension, multiple sclerosis, and depression.

development or protection from tinnitus, and therefore this may be a topic for future investigation.

Study Limitations

The presence of tinnitus was established on the basis of self-report; however, there is no diagnostic test for tinnitus, so it is not possible to validate a self-report of tinnitus. Hearing loss also was self-reported, so there was likely some misclassification of this covariate. There does remain the possibility of misclassification due to recall with respect to the date of onset of tinnitus. Furthermore, the questionnaire does not distinguish between subjective and objective tinnitus, but the majority of cases of tinnitus are subjective. Finally, our cohort was composed of women who were predominantly Caucasian. Because there are no previous studies that have examined the association between caffeine and incidence tinnitus in men, it is unknown whether the findings apply to men or other racial groups.

CONCLUSIONS

In this prospective study, higher caffeine intake was associated with a reduced risk of tinnitus. At present, the mechanism underlying this association remains unknown. Given that our investigation evaluated the incidence of tinnitus and not the effect of caffeine among participants with existing tinnitus, we are unable to make a recommendation as to whether the addition of caffeine would improve symptoms.

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