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DIETARY ANTIOXIDANT INTAKE IS ASSOCIATED WITH THE PREVALENCE BUT NOT INCIDENCE OF AGE-RELATED HEARING LOSS

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Abstract: *Objectives:* Diet is one of the few modifiable risk factors for age-related hearing loss. We aimed to examine the link between dietary and supplement intakes of antioxidants, and both the prevalence and 5-year incidence of measured hearing loss. *Design:* Cross-sectional and 5-year longitudinal analyses. Setting: Blue Mountains, Sydney, Australia. *Participants:* 2,956 Blue Mountains Hearing Study participants aged 50+ at baseline, examined during 1997-9 to 2002-4. *Measurements:* Age-related hearing loss was measured and defined as the pure-tone average of frequencies 0.5, 1.0, 2.0 and 4.0 kHz >25 dB HL. Dietary data were collected in a semi-quantitative food frequency questionnaire, and intakes of -carotene; -carotene; -cryptoxanthin; lutein and zeaxanthin; lycopene; vitamins A, C and E; iron and zinc were calculated. *Results:* After adjusting for age, sex, smoking, education, occupational noise exposure, family history of hearing loss, history of diagnosed diabetes and stroke, each standard deviation (SD) increase in dietary vitamin E intake was associated with a 14% reduced likelihood of prevalent hearing loss, odds ratio, OR, 0.86 (95% confidence interval, CI, 0.78-0.98). Those in the highest quintile of dietary vitamin A intake had a 47% reduced risk of having moderate or greater hearing loss (>40 dB HL) compared to those in the lowest quintile of intake, multivariable-adjusted OR 0.53 (CI 0.30-0.92), P for trend = 0.04. However, dietary antioxidant intake was not associated with the 5-year incidence of hearing loss. *Conclusions:* Dietary vitamin A and vitamin E intake were significantly associated with the prevalence of hearing loss. However, dietary antioxidant intake did not increase the risk of incident hearing loss. Further large, prospective studies are warranted to assess these relationships in older adults.

Key words: Age-related hearing loss, antioxidant, vitamin A, vitamin E, Blue Mountains Eye Study, Blue Mountains Hearing Study.

Introduction

Age-related hearing loss (presbycusis) is the leading cause of hearing loss in the world, creating a significant burden not only for persons with this condition, but also for people who communicate with them (1). Hence, the identification of risk factors and development of preventive strategies is important to reduce the impact and burden of age-related hearing loss on the global aging population. Aside from biological degeneration resulting from the aging process itself, genetic risk factors, exposure to noise or toxic substances, and the occurrence of certain diseases may predispose individuals to age-related hearing loss (2). The greatly improved knowledge regarding the etiology, symptoms and epidemiology of age-related hearing loss has not been matched by our ability to successfully alleviate its detrimental consequences (3).

It has been hypothesized that aged animals have a reduction in blood supply to the cochlea (4). It is this generalized hypoperfusion that leads to the generation of reactive oxygen metabolites (ROM), which may cause cochlear damage (1, 5). Several animal studies have demonstrated the otoprotective effects of free radical scavengers and the antioxidant properties of vitamins C and E, and beta carotene have been shown to protect from inner ear damage caused by aging, noise exposure, acoustic trauma, aminoglycosides, and cisplatin (3, 5, 6). In a 16-week human trial, daily vitamin C supplementation (600 mg/d) in 23 individuals with age-related hearing loss resulted in an average of 3.8 dB audiometric threshold improvement in hearing sensitivity ($p < 0.01$) (3). In contrast, a recent prospective study of 3559 cases of hearing loss showed that higher intake of vitamin C, E and beta carotene did not reduce the risk of hearing loss in men aged 40-74 years (5). However, this study included only self-reported hearing loss data and did not objectively measure hearing loss by audiometric testing. Further, the authors did not have information on noise exposure, which is a potential confounder for hearing loss.

Due to the lack of longitudinal data on the association between dietary antioxidants and age-related hearing loss, we used a large representative cohort of adults aged 50+ years to examine the link between dietary and supplement intakes of antioxidants, and both the prevalence and 5-year incidence of hearing loss. Our findings could have important implications in a public health sense, as dietary intake represents a modifiable factor that could prevent or delay hearing loss (5).

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Subjects and methods

Study population

The Blue Mountains Hearing Study (BMHS) is a population-based survey of age-related hearing loss conducted during the years 1997-2004 among participants of the Blue Mountains Eye Study (BMES) cohort (7). During 1992-4, 3,654 participants 49 years or older were examined (82.4% participation; BMES-1). Surviving baseline participants were invited to attend 5-year follow-up examinations (1997-9, BMES-2), at which 2334 (75.1% of survivors) and an additional 1174 newly eligible residents were examined i.e. those who had moved into the study area or study age group. At the 10 year follow-up (2002-4, BMES-3), 1952 participants (75.6% of survivors) were re-examined, respectively. Hearing was measured at BMES-2 and BMES-3 i.e. in BMES-2, 2956 participants aged 50+ yrs had audiometric testing performed and of those 1309 were followed up at BMES-3 and also had audiometric testing performed on them at this follow-up.

Dietary data

Dietary data were collected using a 145-item self-administered food frequency questionnaire (FFQ), modified for Australian diet and vernacular from an early Willett FFQ (8), and included reference portion sizes. Participants used a 9-category frequency scale to indicate the usual frequency of consuming individual food items during the past year. The electronic version of the Australian Tables of Food Composition 1990 (9) was used to calculate the intake of most nutrients. β-carotene intake was estimated using the Australian Tables of Food Composition 1990. This database represented the most up-to-date nutrient composition information based on laboratory analyses of Australian food produced available at that time. However, only one carotenoid, -carotene, was included in the database. The United States Department of Agriculture Carotenoid Food composition database (10) was used to estimate the intakes of other carotenoids, including -carotene, β-cryptoxanthin, combined lutein and zeaxanthin, and lycopene.

Assessment of confounders

Information on potential confounders was collected at baseline. At face-to-face interviews with trained interviewers, a comprehensive medical history that included information about hearing, demographic factors, socio-economic characteristics and lifestyle factors, was obtained from all participants. Presence of physician-diagnosed stroke was also assessed. Diabetes was defined either by history or from fasting blood glucose ≥7.0 mmol/L.

Audiological examination

Pure-tone audiometry at both visits was performed by audiologists in sound-treated booths, using standard TDH-39 earphones and Madsen OB822 audiometers (Madsen Electronics, Copenhagen, Denmark), calibrated regularly to Australian standards. Audiometric thresholds for air-conduction stimuli were established for frequencies at 0.25, 0.5, 1, 2, 4, 6 and 8 kHz for each ear individually. We determined hearing impairment as the pure-tone average of audiometric hearing thresholds at 0.5,1, 2, and 4 Hz (PTA0.5-4KHz), defining any hearing loss as PTA0.5-4KHz >25 dB HL, mild hearing loss as PTA0.5-4KHz >25-40 dB HL; moderate or greater hearing loss as PTA0.5-4KHz >40 in the better of the two ears (11). This defined hearing loss as bilateral.

A person was considered at risk for incident bilateral hearing loss during the 5-year period when hearing loss was observed only at the 5-year follow-up examination among participants without hearing loss in the better ear at baseline. In this instance, hearing status changed from no hearing loss at baseline (defined by PTA0.5-4KHz in the better ear of ≤25 dB HL) to bilateral hearing loss (defined as a PTA0.5-4KHz >25 dB HL in the better ear) at the follow-up examination.

Statistical analysis

SAS statistical software (SAS Institute, Cary NC) version 9.1 was used for analyses including t-tests, Chi-square tests and logistic regression. The authors examined the association of baseline dietary antioxidant intake and the prevalence and 5-year incidence of age-related hearing loss. The study factors included α-carotene; β-carotene; β-cryptoxanthin: combined lutein and zeaxanthin; lycopene; vitamins A (retinol equivalents), C, and E; and iron and zinc as cofactors for antioxidant enzymes. Dietary intakes were energy-adjusted using the residual method described by Willett and Stampfer (12). Total intake (from diet and supplements) was calculated for β-carotene, retinol equivalents, iron, zinc and vitamins C and E by adding the energy-adjusted dietary intake and crude supplement intake.

Antioxidant intakes were analyzed as continuous variables (per standard deviation, SD) and as quintiles. The lowest quintile was the reference group. The association between antioxidant intakes and hearing loss was examined in logistic regression models, adjusting first for age and sex, and then further adjusting for confounders that were found to be significantly associated with the prevalence (i.e. education, smoking, previous history of diagnosed stroke and diabetes, family history of hearing loss and exposure to noise at work), and incidence (i.e. family history of hearing loss and exposure to noise at work) of hearing loss in our older cohort. We additionally adjusted for serum folate in both prevalence and incidence of hearing loss analyses, because of reported associations between folate and hearing loss (13). The results of the logistic regression analyses are expressed as adjusted odds ratios (OR) with 95% confidence intervals (CI).

Combination of nutrients studies were also studied based on previously published reports of animal models that have shown that vitamins A, C and E act in synergy with magnesium to protect hearing function (6). The median intake of vitamins A, C and E, and zinc, based on the total sample was used as the cut-off value. The higher intake group was defined as

participants with an above median intake of each of the 4 nutrients, and the low-intake group had a below median intake of each of the nutrients. Participants in these groups were considered the referent group.

Results

The prevalence of hearing loss was assessed during the baseline hearing study i.e. in BMES-2. Of the 2956 that had audiometric testing performed on them at BMES-2, 2443 also had complete dietary data and hence, were included for cross-sectional analyses. After adjusting for age and sex, each SD increase in dietary vitamin E intake was associated with 14% reduced likelihood of prevalent hearing loss, OR 0.86 (CI 0.77-0.96). This association persisted after multivariable adjustment, OR 0.88 (CI 0.78-0.98). Table 1 shows the association between antioxidants from the diet (in quintiles) and prevalence of any hearing loss (>25 dB HL). We did not observe any significant associations between either of the dietary antioxidants and any level of hearing loss (Table 1). We did not observe any significant associations with mild hearing loss (data not shown). However, when we examined the association with moderate or greater hearing loss (>40 dB HL), those in the highest quintile of dietary vitamin A intake had a 47% reduced odds of having hearing loss compared to those in the lowest quintile of intake, multivariable-adjusted OR 0.53 (CI 0.30-0.92), with a significant trend observed across the quintiles (P for trend = 0.04). However, moderate or greater hearing loss was not significantly associated with the dietary intake of other antioxidants (data not shown). Significant associations, however, were not observed for total antioxidant intake (diet and supplements) and prevalence of hearing loss (data not shown).

Five-year incidence of hearing loss included participants examined at BMES-2 who also had hearing data and who were then subsequently followed-up at BMES-3 and had audiometric testing performed on them (n=1309). Of these, 798 participants also had complete dietary data available, and so were included for incidence analyses. Table 2 shows the association between quintiles of dietary antioxidant intake and 5-year incidence of hearing loss. Increasing dietary antioxidant intakes from diet alone did not predict incident hearing loss. Similarly, no significant associations with the incidence of hearing loss were observed when the nutrients were analysed as continuous variables (data not shown). Further, no significant relationship between total antioxidant intake (from diet and supplements combined) and incident hearing loss was observed.

The median total intakes for total vitamin A, vitamin C, vitamin E and zinc were 1703 g, 200 mg, 8.4 mg and 11.9 mg, respectively. After stratifying the cohort into persons with above-median and below-median intakes for all 4 of these nutrients, with reference to those with intakes in between, no significant associations were found between either the higher or lower intake groups and prevalence or incidence of hearing loss (data not shown). These results remained similar after analyzing the combined intake of these 4 nutrients from diet alone. Based on previously published human studies (14-16) we analyzed biologically plausible interactions between dietary antioxidants and the prevalence or incidence hearing loss. After multivariable adjustment, we observed no significant interaction between zinc and: vitamin A (p = 0.37), and vitamin C (p = 0.10) on the prevalence of hearing loss. However, we observed a significant interaction between vitamins C and E leading (p = 0.02), after multivariable adjustment. Hence, we conducted stratified analyses and found that those subjects in highest quintile (5th quintile) of vitamin E intake but lowest quintile of vitamin C intake had a significantly lower prevalence of hearing loss (p=0.03), after multivariable adjustment, compared to subjects in the lowest quintile of both vitamin C and E intakes.

Table 1

Association between dietary antioxidant intake and prevalence of hearing loss (>25 dB HL), presented as odds ratio (OR) and 95% confidence intervals (CI)

Nutrient (quintile)	Age-related hearing loss, OR (95% CI)		
	No. of cases/ No. at risk	Age-sex adjusted	Multivariate adjusted*
Vitamin A, retinol equivalents, g			
1 ≤1190.9	163/488	1.0 (reference)	1.0 (reference)
2 1190.9-1539.8	148/489	0.87 (0.64, 1.18)	0.99 (0.72, 1.38)
3 1539.9-1874.9	158/489	1.04 (0.76, 1.42)	1.14 (0.82, 1.58)
4 1875.3-2380.2	164/489	1.00 (0.74, 1.37)	1.12 (0.81, 1.56)
5 ≥2380.5	150/488	0.93 (0.68, 1.27)	0.98 (0.71, 1.37)
P value for trend		0.86	0.94
Vitamin C, mg			
1 ≤113.40	160/488	1.0 (reference)	1.0 (reference)
2 113.6-147.8	156/489	0.90 (0.66, 1.23)	0.90 (0.65, 1.24)
3 147.9-183.3	161/489	0.97 (0.74, 1.32)	1.01 (0.73, 1.39)
4 183.3-234.1	167/489	1.04 (0.77, 1.42)	1.06 (0.77, 1.46)
5 ≥234.1	139/488	0.82 (0.60, 1.12)	0.84 (0.60, 1.17)
P value for trend		0.21	0.29
Vitamin E, mg			
1 ≤5.66	174/488	1.0 (reference)	1.0 (reference)
2 5.67-7.06	163/489	1.07 (0.79, 1.45)	1.00 (0.73, 1.37)
3 7.07-8.19	154/489	1.03 (0.75, 1.39)	0.92 (0.67, 1.27)
4 8.19-9.93	132/489	0.96 (0.71, 1.32)	0.96 (0.69, 1.33)
5 ≥9.95	160/488	1.13 (0.83, 1.54)	1.12 (0.81, 1.53)
P value for trend		0.39	0.30
β-carotene, g			
1 ≤3971.4	147/488	1.0 (reference)	1.0 (reference)
2 3972.4-5820.1	154/489	1.16 (0.85, 1.59)	1.24 (0.90, 1.73)
3 5822.5-7404.0	174/489	1.39 (1.02, 1.90)	1.55 (1.12, 2.16)
4 7406.8-9970.3	150/489	0.98 (0.72, 1.34)	1.02 (0.73, 1.42)
5 ≥9971.6	158/488	1.07 (0.78, 1.47)	1.17 (0.84, 1.64)
P value for trend		0.83	0.85
Zinc, mg			
1 ≤9.99	169/488	1.0 (reference)	1.0 (reference)
2 9.99-11.13	134/489	0.94 (0.69, 1.29)	0.95 (0.69, 1.31)
3 11.13-12.02	150/489	1.03 (0.75, 1.40)	1.09 (0.79, 1.50)
4 12.02-13.27	145/489	0.93 (0.68, 1.27)	0.95 (0.69, 1.32)
5 ≥13.28	169/488	1.16 (0.86, 1.58)	1.12 (0.81, 1.55)
P value for trend		0.86	0.46

*Adjusted for age, sex, education, current smoking, history of diagnosed stroke and diabetes, family history of hearing loss and exposure to noise at work.

Table 2
Association between dietary antioxidant intake and 5-year incidence of hearing loss (>25 dB HL) presented as odds ratio (OR) and 95% confidence intervals (CI)

Nutrient (quintile)	Age-related hearing loss, OR (95% CI)		
	No. of cases/ No. at risk	Age-sex adjusted	Multivariate adjusted*
Vitamin A, retinol equivalents, g			
1 ≤1218.9	30/166	1.0 (reference)	1.0 (reference)
2 1224.2-1573.9	31/164	0.72 (0.39, 1.34)	0.77 (0.41, 1.45)
3 1575.0-1874.9	29/148	1.06 (0.58, 1.91)	1.10 (0.60, 2.00)
4 1875.5-2362.2	25/162	0.81 (0.44, 1.48)	0.85 (0.46, 1.58)
5 ≥2371.3	26/158	0.84 (0.46, 1.54)	0.85 (0.46, 1.56)
P value for trend		0.73	0.69
Vitamin C, mg			
1 ≤116.78	27/155	1.0 (reference)	1.0 (reference)
2 116.85-149.86	29/160	1.03 (0.56, 1.88)	1.10 (0.59, 2.02)
3 149.86-185.63	30/164	0.88 (0.47, 1.64)	0.95 (0.51, 1.78)
4 185.76-237.08	29/164	0.63 (0.33, 1.20)	0.66 (0.34, 1.26)
5 ≥237.49	26/155	0.92 (0.50, 1.69)	0.91 (0.49, 1.69)
P value for trend		0.93	0.75
Vitamin E, mg			
1 ≤5.56	33/151	1.0 (reference)	1.0 (reference)
2 5.58-6.95	30/157	0.73 (0.40, 1.33)	0.72 (0.39, 1.33)
3 6.95-8.09	19/169	0.78 (0.43, 1.44)	0.81 (0.44, 1.50)
4 8.09-9.85	25/153	0.88 (0.48, 1.60)	0.93 (0.51, 1.69)
5 ≥9.86	34/168	0.94 (0.53, 1.69)	0.94 (0.52, 1.69)
P value for trend		0.63	0.70
β-carotene, g			
1 ≤4114.1	29/165	1.0 (reference)	1.0 (reference)
2 41167.0-5921.7	27/159	0.96 (0.52, 1.77)	0.91 (0.49, 1.70)
3 5922.6-7528.9	30/153	1.12 (0.61, 2.07)	1.19 (0.64, 2.20)
4 7546.4-9991.2	29/164	0.86 (0.47, 1.59)	0.88 (0.48, 1.63)
5 ≥9992.7	26/157	1.12 (0.60, 2.06)	1.13 (0.61, 2.10)
P value for trend		0.82	0.73
Zinc, mg			
1 ≤10.04	25/144	1.0 (reference)	1.0 (reference)
2 10.05-11.18	37/173	1.71 (0.94, 3.10)	1.73 (0.95, 3.15)
3 11.19-12.08	22/162	0.53 (0.26, 1.06)	0.51 (0.25, 1.02)
4 12.08-13.34	23/156	0.98 (0.52, 1.85)	0.97 (0.51, 1.85)
5 ≥13.34	34/163	1.20 (0.64, 2.24)	1.16 (0.62, 2.17)
P value for trend		0.95	0.96

*Adjusted for age, sex, family history of hearing loss and exposure to noise at work.

Discussion

Dietary factors have been suspected to play a pivotal, yet poorly defined role in age-related hearing loss (1). In the current report, we present data from the first population-based study to assess the link between dietary intake of antioxidants and both the prevalence and incidence of measured age-related hearing loss in both men and women. Higher intakes of vitamin A and E were inversely associated with the prevalence of hearing loss. Overall, there was no temporal link between dietary antioxidant intake and the incidence of hearing loss in an older population.

Reactive oxygen metabolites may cause cochlear damage (5). It has been hypothesised that dietary incorporation of antioxidants might benefit aging individuals in preserving auditory cells, such as the spiral ganglion and the cells of the stria vascularis, and thus, could reduce the hearing loss associated with age (17). Our cross-sectional findings supported this hypothesis, specifically; higher dietary vitamin E intakes were associated with a reduced likelihood of hearing loss. Vitamin E, present in lipids in cells (18), is a donor antioxidant that reacts with and reduces peroxyl radicals and hence, inhibits the propagation cycle of lipid peroxidation (6, 19). Given the free radical scavenging properties of vitamin E it is not surprising that it has been shown to reduce inner ear damage in an animal model (1). Additionally, vitamin E has been used to tread idiopathic sudden hearing loss, with acceptable results (3, 20). Moreover, this protective influence of vitamin E on hearing function was observed among older adults with low vitamin C intake.

As the concentration of vitamin A (retinol equivalents) in the inner ear has been observed to be high (21, 22), the association between vitamin A and the prevention of hearing loss has been investigated. In our cohort, we observed that participants in the highest quintile of vitamin A intake compared with the remaining population were 47% less likely to have moderate or greater hearing loss (>40 dB HL). This is biologically plausible, given that vitamin A is known to scavenge singlet oxygen, and as singlet oxygen contributes to the formation of lipid hydroperoxides, the removal of singlet oxygen prevents lipid peroxidation (6, 19). Our findings are in agreement with an animal study showing that retinoic acid (an active metabolite of retinol) prevented noise-induced hearing loss (23). These data also concur with a recent cross-sectional Japanese study of 762 adults aged 65 years or older (21). In this study, Michikawa et al. showed that serum levels of retinoic acid were inversely related to the prevalence of hearing impairment.

In contrast, we were not able to show that combined intakes of antioxidants reduced the prevalence of hearing loss. These results conflict with a recent animal study which demonstrated that treatment with a combination of antioxidants (i.e. vitamins A, C, and E) was clearly more effective than any single category of agents, in reliably reducing noise-induced hearing loss or sensory cell death (6). We cannot rule out the possibility that the level of antioxidant intake in our population may not have been high, and a significant association could have been observed with a combination of high doses of antioxidants.

Dietary antioxidants individually or in combination did not predict the 5-year incidence of hearing loss in our cohort. These findings correspond with a prospective U.S. study of 26,273 men aged 40 to 74 years at baseline (5). The authors showed that higher intake of vitamins C, E and β-carotene did not reduce the risk of incident hearing loss in men. We need to highlight that the negative results in both these studies are only indicative of the relationship between specific antioxidant intake in the ranges consumed and hearing loss (5). Further large prospective studies are warranted to confirm our findings.

Key strengths of our study include its representative community-based sample with relatively high participation, minimizing selection bias, the use of a validated food questionnaire to collect dietary information, and detailed questionnaires that permitted careful assessment of potential confounding variables. Further, we used standardized,

audiometric testing to measure hearing sensitivity. Additionally, study participants were unaware of the study question and our dietary data were collected before detection of the 5-year incidence of hearing loss, reducing indication bias arising from behavioural change after the hearing loss was diagnosed. However, there are some study limitations to consider. First, dietary assessment by FFQ in which respondents have to estimate typical intake frequencies of food items and their portion sizes, can potentially introduce measurement error and bias. We cannot rule this possibility out, but overall the validity of antioxidant categories compared to weighted food records was moderately good (24, 25). Further, the likelihood of recall bias operating in a longitudinal study is limited (26). Second, relatively small numbers of incident cases of hearing loss at follow-up may have limited our study power in order to detect a significant temporal association with dietary antioxidant intake. Third, the duration of follow-up is short and the mean age of the cohort is relatively old, hence, most of the influences resulting from dietary antioxidants may have already been exerted, resulting in the significant associations observed with prevalent hearing loss, but not influencing the incidence of hearing loss.

In conclusion, we show that higher vitamin A and E intakes are associated with a reduced prevalence of age-related hearing loss. However, longitudinal data did not demonstrate any association between dietary antioxidant intake and hearing loss in our cohort of older adults, most probably because of insufficient study power. Future prospective studies with larger numbers and longer follow-up will be useful to establish whether antioxidants are potential, modifiable factors that could reduce the incidence of age-related hearing loss. There is also a need for high quality randomised controlled trials of long duration to determine whether auditory benefits are derived from treatment with antioxidants.

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