Age-related hearing loss, vitamin B-12, and folate in elderly women[1,2]

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ABSTRACT

Background: Hearing impairment is 1 of the 4 most prevalent chronic conditions in the elderly. However, the biological basis of age-related hearing loss is unknown.

Objective: The objective was to test the hypothesis that age-related hearing loss may be associated with poor vitamin B-12 and folate status.

Design: A thorough audiometric assessment was conducted in 55 healthy women aged 60–71 y. Hearing function was determined by the average of pure-tone air conduction thresholds at 0.5, 1, 2, and 4 kHz and was categorized into 2 groups for logistic regression analyses: normal hearing (<20 dB hearing level; $n = 44$) and impaired hearing (≥20 dB hearing level; $n = 11$).

Results: Mean age was the same (65 y) for the normal hearing and impaired hearing groups. Pure-tone averages were inversely correlated with serum vitamin B-12 ($r = -0.58$, $P = 0.0001$) and red cell folate ($r = -0.37$, $P = 0.01$). Women with impaired hearing had 38% lower serum vitamin B-12 (236 compared with 380 pmol/L, respectively, $P = 0.008$) and 31% lower red cell folate (425 compared with 619 nmol/L, respectively, $P = 0.02$) than women with normal hearing. Among participants who did not take supplements containing vitamin B-12 or folate, women with impaired hearing had 48% lower serum vitamin B-12 (156 compared with 302 pmol/L, respectively, $P = 0.0007$) and 43% lower red cell folate (288 compared with 502 nmol/L, respectively, $P = 0.001$) than women with normal hearing.

Conclusion: Poor vitamin B-12 and folate status may be associated with age-related auditory dysfunction. *Am J Clin Nutr* 1999;69:564–71.

KEY WORDS Age-related hearing loss, impaired hearing, hearing impairment, presbycusis, presbyacusis, vitamin B-12, folate, atrophic gastritis, elderly, women, humans

INTRODUCTION

Hearing loss is a major public health problem (1–4). More than 28 million Americans have hearing impairments and this number is expected to increase with the aging of the population (1, 2). Age-related hearing loss is the most prevalent of human auditory disorders (1, 2). Among community-dwelling elderly people, the prevalence of hearing loss is ≈24% in those aged 65–74 y and ≈40% among those ≥75 y of age (3). Along with heart problems, hypertension, and arthritis, hearing impairment is 1 of the 4 leading chronic health conditions experienced by the elderly (1). Despite the high prevalence of hearing impairment, the biological basis of age-related hearing loss is unknown.

Hughes (5) suggested that diet may play a role in the pathogenesis of many auditory disorders. Auditory dysfunction has been associated with deficiencies of several micronutrients in humans (6–9) and young growing animals (10–14). However, we found no studies in humans or experimental animals that specifically examined the role of nutrition in age-related hearing loss.

We propose that age-related hearing loss may be associated with poor micronutrient status. Two of the most common vitamin inadequacies in the elderly are vitamin B-12 and folate (15). In addition, atrophic gastritis affects ≈20–30% of those aged ≥60 y and can lead to the malabsorption of vitamin B-12 (16, 17). Anywhere from 5–15% of the elderly population may be vitamin B-12 deficient (18), and the prevalence of folate deficiency in the elderly has been estimated at 2–20% (19). We suspect that the roles of vitamin B-12 and folate in cellular metabolism, the nervous system, and vascular function (9, 20–22) are important for the auditory system.

The cochlea of the inner ear is where much of the hearing loss in the elderly is believed to occur (23). The cochlea is highly vascularized and is supported by a single artery. High homocysteine concentrations associated with low vitamin B-12 status, low folate status, or both were shown to be a risk factor for cerebral, coronary, and peripheral vascular disease (24). Perhaps high homocysteine concentrations associated with poor vitamin B-12 or folate status also adversely affect blood flow to the cochlea.

Low vitamin B-12 status may also impair myelination of the neurons in the cochlear nerve. Deficiencies of vitamin B-12 and folate or impaired methionine synthase activity results in decreased *S*-adenosylmethionine synthesis, the primary source of methyl

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groups in the nervous system, which may impair methylation reactions in myelin synthesis (25). Alternatively, during vitamin B-12 deficiency, accumulation of methylmalonyl-CoA and propionyl-CoA may result in the synthesis of branched or odd-numbered fatty acids, which may interfere with myelin formation (25).

Only a few investigators have examined the possible associations between poor vitamin B-12 (8, 9, 14, 26–28) or folate (8) status and auditory dysfunction, and little attention has been given to the possible role of these nutrients in age-related hearing loss. Therefore, the objective of this study was to determine whether age-related hearing loss is associated with poor vitamin B-12 status, poor folate status, or both.

SUBJECTS AND METHODS

Subjects

The questionnaires and all procedures were approved by The University of Georgia Institutional Review Board on Human Subjects. Subjects were recruited by advertising in community newspapers and on bulletin boards. Subjects who volunteered and were admitted into the study resided in the community and were physically and cognitively able to comply with the testing procedures (n = 55, aged 60–71 y). All participants were white. Women were studied because we are also exploring the relation of bone health to auditory function (29). Exclusion criteria included a history of diabetes, stroke, ear diseases, noise-induced hearing loss, or unilateral hearing loss, and use of fluorides, bisphosphonates such as Fosamax (Merck & Co Inc, Whitehouse Station, NJ), or calcitonin. Potential participants with conductive hearing loss (air-bone gaps >10 dB) were also excluded. Age-related hearing loss, or presbyacusis, is bilateral sensorineural hearing loss with gradual onset after age 50 y. Age-related hearing loss is a diagnosis that is reached when all other possible etiologies have been ruled out. To identify persons with age-related hearing loss, we excluded anyone who had hearing loss that might have been due to other causes (ear infections, ototoxic medications, genetics, trauma, ear surgery, Meniere disease, or otosclerosis) or who had hearing loss before age 50 y. Questions about these issues were part of the telephone screening and the hearing history questionnaire.

Methods

Blood was collected between 0730 and 1000 after an overnight fast. Complete blood counts and hematologic measures of whole blood, and serum analyses to evaluate liver, kidney, and thyroid function were conducted by a local clinical laboratory (SmithKline-Beecham Clinical Laboratories, Atlanta). Blood samples (n = 48) for the vitamin analyses were frozen at −70°C in cryogenic vials with minimal air space (Nalgene Brand Products, Rochester, NY) until analyzed. Red cells were frozen in 1% ascorbic acid. Serum vitamin B-12, red cell folate, and serum folate were analyzed at the Centers for Disease Control and Prevention in Atlanta (30) with the Quantaphase II B-12/Folate Radioassay (Bio-Rad, Richmond, CA). Seven participants did not provide a sufficient amount of blood to allow measurements of serum vitamin B-12, red cell folate, and serum folate. Serum pepsinogen I was assessed as an indirect index of atrophic gastritis by radioimmunoassay (INCSTAR Corporation, Stillwater, MN).

The participants' histories of chronic health problems and current medications were obtained. While participants were seated, blood pressure was measured 3 times in the right arm during an 8–10-min period with an automated instrument (Critikon Inc, Tampa, FL). Three days of dietary records, including one 24-h recall and 2 d of participant diet records (from 2 weekdays and 1 weekend day), were collected and analyzed using the FOOD-PROCESSOR software (version 6.08; ESHA, Salem, OR). Average daily dietary intakes of vitamin B-12 and folate were determined. The types of vitamin and mineral supplements and the duration and frequency of their use were obtained, and average daily intakes of vitamin B-12 and folate from supplements were calculated. Total average daily intakes of vitamin B-12 and folate were determined by combining the dietary and supplemental intakes.

Auditory exams were conducted at the University of Georgia Speech and Hearing Clinic. Otoscopic examinations of the outer ear and ear canal were conducted to detect excessive ear wax, foreign bodies, or other obvious disorders of the ear canal or ear drum that would prevent a safe and reliable evaluation and to identify obvious disorders that might require a medical referral. Air conduction thresholds at octave intervals from 250 to 8000 Hz and bone conduction thresholds at octave intervals from 500 to 4000 Hz were obtained by using a diagnostic audiometer meeting specifications according to Standard S3.6 of the American National Standards Institute (31) and following standard clinical audiometric procedures. Acoustic immittance, otoacoustic emissions, and speech audiometry tests were also conducted. To categorize hearing function, we used criteria similar to those of the National Health and Nutrition Examination Survey (NHANES; 32) and the Framingham Heart Study (33). Hearing function was assessed as the pure-tone average of the 0.5-, 1-, 2-, and 4-kHz pure-tone air conduction thresholds for the better ear as follows: normal hearing, <20 dB hearing level (n = 38–44) and impaired hearing, ≥20 dB hearing level (n = 10–11). Pure-tone averages were also categorized into 3 groups as follows for some analyses: excellent hearing, <10 dB hearing level (n = 18); good hearing, ≥10 and <20 dB hearing level (n = 20); and impaired hearing, ≥20 dB hearing level (n = 10).

Statistical analysis

In the analyses, $P \leq 0.05$ was considered statistically significant. Because hearing function was not normally distributed, nonparametric statistical analyses were conducted (SAS version 6.10; SAS Institute Inc, Cary, NC; 34). Spearman correlation coefficients were used to assess the relation between pure-tone averages and concentrations of vitamin B-12 and folate in the blood. Wilcoxon scores were used for univariate analyses of the continuous variables (age, blood concentrations, and dietary indexes) and chi-square tests were used to determine the percentage of participants who took a supplement containing vitamin B-12 or folate (multivitamin, multivitamin and mineral, B-complex, or individual supplement containing vitamin B-12 or folate). Chi-square tests were used to determine the percentages of participants that consumed less than the 1989 recommended dietary allowance (RDA; 35) for vitamin B-12 (<2 μg/d) and folate (<180 μg/d) from the diet, from supplements, and from the diet and supplements combined. Chi-square tests were also used to determine the percentages of participants with serum vitamin B-12 concentrations <221 pmol/L (300 pg/mL), 184 pmol/L (250 pg/mL), and 148 pmol/L (200 pg/mL), red cell folate concentrations <294 nmol/L (130 ng/mL), and serum folate concentrations <7.9 nmol/L (3.5 ng/mL). Logistic regression analyses were used to assess the relation between auditory

TABLE 1
Participant characteristics[1]

	Hearing	
	Normal (<20 dB HL) (n = 44)	Impaired (≥20 dB HL) (n = 11)
Age (y)	65 ± 3[2]	65 ± 4
Hearing level (dB)	8.9 ± 4.6 (−2.5–19)[4]	26.8 ± 5.5[3](20–35)
BMI (kg/m^2)	24.7 ± 4.4	25.9 ± 2.8
Serum albumin (g/L)	43 ± 2	42 ± 3
Serum creatinine (μmol/L)	88.4 ± 11.5	87.5 ± 8.0
Blood urea nitrogen (mmol/L)	5.9 ± 1.8	5.6 ± 1.3
Number of chronic health problems	2.3 ± 1.7	2.4 ± 2.0
Number of medications	2.5 ± 1.4	1.8 ± 1.5
Self-reported high blood pressure (%)	30	18
Systolic blood pressure (mm Hg)	122 ± 16	122 ± 14
Diastolic blood pressure (mm Hg)	67 ± 8	67 ± 9

[1] HL, hearing level.
[2] $\bar{x}$ ± SD.
[3] Significantly different from normal hearing group, P = 0.0001.
[4] Range in parentheses.

function and vitamin B-12 or folate nutriture when controlled for age (34). Analyses were conducted in the total sample and in the subset of the sample not taking any of the following supplements: multivitamin, multivitamin and mineral, B-complex, or individual supplement containing vitamin B-12 or folate.

RESULTS

The women who participated were considered healthy; they all lived independently, had normal serum albumin concentrations (>35 g/L), and had an average of 2 chronic health problems (**Table 1**). The most common health problems were arthritis (44%) and high blood pressure (27%). Only a few participants had abnormal blood indexes of liver, kidney, or thyroid function. For blood urea nitrogen, one participant in the normal hearing group had a high concentration (>10.7 mmol/L) of 13.6 mmol/L. For serum aspartate transaminase, one participant in the normal hearing group had a high concentration (>55 U/L) of 76 U/L. For serum alanine transaminase, 2 participants in the normal hearing group had high concentrations (>48 U/L) of 64 and 95 U/L. For triiodothyronine uptake, 2 participants had high values (>35%) of 37% (normal hearing group) and 36% (impaired hearing group). One participant in the normal hearing group had a high total thyroxine concentration (>161 nmol/L) of 243 nmol/L. Four participants had high sedimentation rates (>30 mm/h) of 34 and 37 mm/h (normal hearing group) and 34 and 38 mm/h (impaired hearing group). There were no significant differences between the normal hearing group and the impaired hearing group with regard to age, body mass index (BMI, in kg/m^2), or 110 health-related indexes, with a few exceptions. These indexes included 52 clinical blood measures (such as electrolytes; kidney, liver, and thyroid function tests; lipids; complete blood count; platelet count; and hematologic measures), 25 chronic health problems, and 33 categories of medication. The hearing-impaired women were less likely to use acetaminophen than the women with normal hearing (0% compared with 34%, P < 0.05) and had higher sedimentation rates (20 compared with 12 mm/h, P < 0.05) and serum alkaline phosphatase activities (75 compared with 62 U/L, P < 0.05). However, none of the women had abnormally high alkaline phosphatase activities (>125 U/L).

Hearing function, assessed by averaging the pure tone air conduction thresholds in the better ear at 4 frequencies (0.5, 1, 2, and 4 kHz), was significantly different between the 2 groups of women (P = 0.0001, Table 1). However, the degree of hearing loss in the participants with hearing impairment is considered relatively mild (20–35 dB hearing level).

The relations of auditory function to vitamin B-12 and folate status are shown in **Table 2**. Pure-tone averages were inversely correlated (Spearman's rank-order correlation coefficient) with serum vitamin B-12 (r = −0.58, P = 0.0001), red cell folate (r = −0.37, P = 0.01), and serum folate (r = −0.36, P = 0.01). Compared with participants with normal hearing, participants with impaired hearing had 38% lower mean serum vitamin B-12, 31% lower mean red cell folate, and 25% lower mean serum folate. The associations between pure-tone averages and blood indexes of vitamin B-12 and folate status remained when these nutrient concentrations were dichotomized into values above and below the 15th percentile from NHANES III (36) and when various cutoff values for vitamin B-12, such as <148 pmol/L (<200 pg/mL), <185 pmol/L (<250 pg/mL), and <221 pmol/L (<300 pg/mL) were used (18, 37). These associations were attenuated when age was controlled for, but remained significant for serum vitamin B-12 and red cell folate. When both serum vitamin B-12 and red cell folate were entered into one logistic regression model as continuous variables, they were not significantly associated with pure-tone averages (P = 0.12 and P = 0.26, respectively, when controlled for age). When both serum vitamin B-12 and red cell folate were entered into one logistic regression model as dichotomous variables (with use of NHANES III cutoff values) they were not significantly associated with pure-tone averages (P = 0.36 and P = 0.07, respectively, when controlled for age).

Dietary intakes of vitamin B-12, folate, and energy are also shown in Table 2. Energy intakes were lower in women with impaired hearing than in women with normal hearing. Compared with women with impaired hearing, those with normal hearing were 3 times more likely to meet the RDA (35) for vitamin B-12 (not a significant difference) and 8 times more likely to meet the RDA for folate (P = 0.01; diet plus supplements). Pure-tone averages were more strongly associated with folate intake than with vitamin B-12 intake. Associations between auditory function and

TABLE 2
Nutrition and auditory function in the total sample[1]

	Hearing			
	Normal (<20 dB HL) (n = 38–44)	Impaired (≥20 dB HL) (n = 10–11)	P (unadjusted)[2]	P (adjusted for age)[3]
Serum vitamin B-12 (pmol/L)	380 ± 154[4] [380]	236 ± 150 [206]	0.008	0.02
<148 pmol/L (%)	3	30	0.01	0.03
<185 pmol/L (%)	5	30	0.03	0.05
<221 pmol/L (%)[5]	13	60	0.002	0.01
Red cell folate (nmol/L)	619 ± 223 [638]	425 ± 245 [312]	0.02	0.03
<294 nmol/L (%)[5]	5	40	0.003	0.02
Serum folate (nmol/L)	29.5 ± 14.8 [26.4]	22.0 ± 22.6 [13.5]	0.052	0.25
<7.9 nmol/L (%)[5]	5	30	0.03	0.05
Vitamin B-12 intake				
Diet (μg/d)	4.2 ± 2.3 [3.6]	2.4 ± 1.3 [2.5]	0.02	0.03 (0.05)
<RDA (%)	14	27	0.27	0.25
Supplement (μg/d)	36 ± 156 [0]	6.7 ± 14 [0]	0.39	0.57
<RDA (%)	57	73	0.34	0.26
Total (μg/d)	40 ± 156 [6.3]	9.1 ± 15 [2.5]	0.03	0.48 (0.65)
<RDA (%)	9	27	0.11	0.09
Folate intake				
Diet (μg/d)	332 ± 179 [286]	195 ± 95 [176]	0.01	0.03 (0.05)
<RDA (%)	16	64	0.001	0.01
Supplement (μg/d)	196 ± 261 [0]	122 ± 218 [0]	0.34	0.34
< RDA (%)	57	73	0.34	0.26
Total (μg/d)	528 ± 341 [431]	317 ± 292 [177]	0.02	0.07 (0.12)
<RDA (%)	7	55	0.001	0.01
Energy intake (kJ/d)	8606 ± 1672 [8431]	7472 ± 1414 [7133]	0.04	0.052
Percentage taking supplemental vitamin B-12, folate, or both (%)	43	27	0.34	0.26

[1]HL, hearing level, RDA, recommended dietary allowance (35): 2 μg vitamin B-12/d; 180 μg folate/d.
[2]Wilcoxon statistics for univariate analyses.
[3]Logistic regression analyses; values in parentheses adjusted for energy intake.
[4]$\bar{x}$ ± SD; median in brackets.
[5]Approximately the 15th percentile from the third National Health and Nutrition Examination Survey (36).

vitamin intake were altered after age and energy intake were controlled for, but the associations of auditory function with dietary intake of folate and vitamin B-12 remained significant.

The association of supplement use with auditory function was weak and remained weak when age was controlled for (Table 2). For these analyses, supplements included multivitamins, multivitamins with minerals, B-complex vitamins, vitamin B-12 alone, and folate alone.

Associations between auditory function and vitamin B-12 and folate status were not markedly altered when examined in the subgroup of participants not taking multivitamin or multivitamin and mineral supplements (n = 33; **Table 3**). This subgroup was similar to the total sample in that mean serum vitamin B-12 was 48% lower, mean red cell folate was 43% lower, and mean serum folate was 46% lower in women with impaired hearing than in women with normal hearing. These associations were attenuated when age was controlled for, but they remained significant. Women with hearing impairment consumed significantly less vitamin B-12 and folate than women with normal hearing, and these associations remained significant after age and energy intake were controlled for.

The relations between auditory function and nutritional indexes were also explored when auditory function was categorized into 3 groups in all subjects (n = 48) and in the subgroup of participants not taking supplements containing vitamin B-12 or folate (n = 27; **Table 4**). Auditory function and serum vitamin B-12 had a dose-response relation when compared in women with excellent hearing (<10 dB hearing level), good hearing (≥10 and <20 dB hearing level), and impaired hearing (≥20 dB hearing level). Dose-response relations between auditory function and blood indexes of folate status were observed in all subjects. However, in the subgroup of participants not taking supplements, blood indexes of folate status were lowest in women with impaired hearing compared with the other 2 groups. The associations between auditory function and serum vitamin B-12 and red cell folate remained significant when age was controlled for. Serum pepsinogen I concentrations, shown in **Table 5**, were significantly lower in women with hearing impairment than in women with normal hearing, and the difference remained significant when age was controlled for.

DISCUSSION

Poor auditory function was consistently associated with low concentrations of serum vitamin B-12 and red cell folate in this sample of healthy, independently living older women. These associations remained robust when controlled for age in logistic regression models, when assessed in the subgroup of participants not taking supplements that contained vitamin B-12 or folate, when examined in either 2 or 3 categories of hearing function, and when pure-tone averages were used as continuous variables in correlation analyses. Moreover, the observation that auditory function was not

TABLE 3
Nutrition and auditory function in participants not taking multivitamin or multivitamin and mineral supplements[1]

	Hearing: Normal (<20 dB HL) (n = 20–25)	Hearing: Impaired (≥20 dB HL) (n = 7–8)	P (unadjusted)[2]	P (adjusted for age)[3]
Age (y)	66 ± 3[4]	66 ± 3	0.69	—
Serum vitamin B-12 (pmol/L)	302 ± 85 [274][5]	156 ± 74 [186]	0.0007	0.052
<148 pmol/L (%)	0	43	0.002	—
<185 pmol/L (%)	5	43	0.02	0.04
<221 pmol/L (%)[6]	20	86	0.002	0.01
Red cell folate (nmol/L)	502 ± 156 [493]	288 ± 49 [276]	0.001	0.04
<294 nmol/L (%)[6]	10	57	0.01	0.03
Serum folate (nmol/L)	19.6 ± 8.5 [18.4]	10.5 ± 4.4 [8.8]	0.02	0.02
<7.9 nmol/L (%)[6]	10	43	0.054	0.08
Vitamin B-12 intake				
Diet (μg/d)	4.0 ± 1.8 [4.0]	1.9 ± 1.0 [2.1]	0.01	0.03 (0.04)
< RDA (%)	16	38%	0.20	0.21
Folate intake				
Diet (μg/d)	306 ± 110 [288]	160 ± 63 [157]	0.01	0.01 (0.03)
<RDA (%)	12	75	0.001	0.003
Energy intake (kJ/d)	8562 ± 1564 [8199]	7126 ± 1342 [6952]	0.03	0.05

[1] HL, hearing level; RDA, recommended dietary allowance (35): 2 μg vitamin B-12/d; 180 μg folate/d.
[2] Wilcoxon statistics for univariate analyses.
[3] Logistic regression analyses; values in parentheses adjusted for energy intake.
[4] $\bar{x}$ ± SD.
[5] Median in brackets.
[6] Approximately the 15th percentile from the third National Health and Nutrition Examination Survey (36).

associated with taking a multinutrient supplement suggests that auditory function is specifically related to vitamin B-12 and folate status.

Because our sample size was relatively small and serum vitamin B-12 and red cell folate were highly correlated (r = 0.64, P = 0.001), it was not possible to determine which of these 2 nutrients might be more strongly associated with pure-tone averages. Specifically, logistic regression analysis models that included both serum vitamin B-12 and red cell folate did not clearly identify which of these nutrients was more closely associated with pure-tone averages. Also, the metabolic roles of vitamin B-12 and folate are interrelated and several signs of their deficiencies are similar (22). Low red cell folate concentrations may reflect vitamin B-12 deficiency because during vitamin B-12 deficiency there is inadequate synthesis of tetrahydrofolate, a lack of polyglutamate folate, and leakage of methyltetrahydrofolate-monoglutamate from cells (25).

Auditory function appeared to be more strongly associated with folate intake than with vitamin B-12 intake, perhaps because the absorption of vitamin B-12 may be limited by malabsorption associated with atrophic gastritis, which is common in the elderly (16–18). Only one participant, who was hearing impaired, had a serum pepsinogen I concentration indicative of possible atrophic gastritis (<10 μg/L). However, serum pepsinogen I concentrations were ≈50% lower in women with hearing impairment than in women with normal hearing. Modest decreases in serum pepsinogen I were associated with mild-to-moderate atrophic gastritis established by histologic examination of the fundic gland mucosa (38). However, future studies should include measurement of both serum pepsinogen I and serum pepsinogen II, because the ratio of pepsinogen I to pepsinogen II may provide a more definitive indication of atrophic gastritis (38).

As defined in the exclusion criteria, participants in this study had sensorineural hearing loss. However, the auditory assessment we used cannot absolutely differentiate cochlear hearing loss from auditory (eighth cranial) nerve pathologies. Therefore, the anatomical areas where vitamin B-12 and folate may be influencing hearing function are not known. Most hearing loss in the elderly is peripheral and is associated with cochlear dysfunction (23). Cochlear function is dependent on an adequate vascular supply (39, 40) and normal function of nerve tissue (41). Homocysteine is elevated during deficiencies of vitamin B-12, folate, or both (18, 42), and homocysteine is believed to be a vascular toxin (43, 44) and a neurotoxin (45). Thus, poor vitamin B-12 or folate nutriture might impair the vascular and nervous system of the auditory system through direct or indirect effects, or both, on cellular metabolism, vascular perfusion, and myelin synthesis. Vascular risk factors such as high blood pressure were associated with peripheral hearing loss in large samples of adults, such as the Framingham Heart Study (n = 1662; 21) and the Baltimore Longitudinal Study of Aging (n = 531; 20), but were not associated with hearing loss in our sample. There is also central nervous system involvement in some cases of auditory dysfunction (40). Poor vitamin B-12 and folate status might adversely influence the central nervous system because of the numerous roles that these nutrients play in cellular metabolism, vascular function, and myelin synthesis.

To our knowledge, the potential influence of folate deficiency on auditory function has received little attention (8). Several investigators have examined the association between vitamin B-12 status and auditory function (8, 9, 14, 26–28). However, there is no direct evidence in the literature that age-related hearing loss is associated with vitamin B-12 deficiency. As will be discussed further, most investigators, except for Roman (8), have not conducted valid tests of the type and degree of peripheral hearing loss in their subjects.

TABLE 4
Preliminary study: nutrition and 3 categories of auditory function[1]

	Hearing[2]				
	Excellent (<10 dB HL)	Good (≥10 and <20 dB HL)	Impaired (≥20 dB HL)	*P* (unadjusted)[3]	*P* (adjusted for age)[4]
All subjects[5]					
Serum vitamin B-12 (pmol/L)	456 ± 152 (430)	312 ± 123 (274)	236 ± 150 (206)	0.0005	0.01
Red cell folate (nmol/L)	705 ± 239 (672)	541 ± 179 (548)	425 ± 245 (312)	0.007	0.01
Serum folate (nmol/L)	34.3 ± 13.0 (35.8)	25.2 ± 15.2 (22.7)	22.0 ± 22.6 (13.5)	0.03	0.09
Subjects not taking supplements[6]					
Serum vitamin B-12 (pmol/L)	370 ± 91 (374)	273 ± 66 (263)	156 ± 74 (186)	0.0007	0.002
Red cell folate (nmol/L)	501 ± 137 (474)	502 ± 168 (512)	288 ± 49 (276)	0.004	0.02
Serum folate (nmol/L)	22.3 ± 9.9 (19.1)	18.5 ± 7.9 (17.6)	10.5 ± 4.4 (8.8)	0.04	0.02

[1] HL, hearing level.
[2] $\bar{x}$ ± SD; median in parentheses.
[3] Wilcoxon statistics for univariate analyses.
[4] Logistic regression analyses.
[5] *n* = 18, 20, and 10, respectively, for the 3 groups.
[6] *n* = 6, 14, and 7, respectively, for the 3 groups.

Vitamin B-12 deficiency and auditory dysfunction have been linked primarily in studies of neuropathology (14), tinnitus (8, 9), and abnormal auditory brainstem response (ABR; 26–28).

The influence of vitamin B-12 deficiency on the auditory nerve in rhesus monkeys was examined over a 5-y period (14). Although peripheral hearing thresholds were not monitored, the auditory nerve and other nerves developed active lesions associated with vitamin B-12 deficiency. Shemesh et al (9) examined serum vitamin B-12 in 113 noise-exposed subjects with a mean age of 39 y. Subjects with chronic tinnitus and noise-induced hearing loss were ≈2.6 times more likely to be vitamin B-12–deficient (defined as serum vitamin B-12 ≤250 ng/L) than subjects with normal hearing. Shemesh et al suggested that inadequate vitamin B-12 may be associated with myelin damage in persons with repeated noise exposure. Although the cause of vitamin B-12 deficiency (low intake, malabsorption, or both) was not determined, some subjective improvement in tinnitus was observed in 12 subjects after vitamin B-12 replacement therapy (parenteral, 1 mg/d for 4 mo) (9).

TABLE 5
Serum pepsinogen I concentrations[1]

	Pepsinogen I
	µg/L
Two categories of auditory function	
Normal (<20 dB HL; *n* = 44)	83.0 ± 44.0 (76.9)[2]
Impaired (>20 dB HL; *n* = 11)	44.0 ± 21.5 (44.2)
P (unadjusted)[3]	0.003
P (adjusted for age)[4]	0.01
Three categories of auditory function	
Excellent (<10 dB HL; *n* = 22)	78.7 ± 40.2 (69.1)
Good (≥10 and <20 dB HL; *n* = 22)	87.4 ± 48.0 (87.9)
Impaired (≥ 20 dB HL; *n* = 11)	44.0 ± 21.5 (44.2)
P (unadjusted)[3]	0.01
P (adjusted for age)[4]	0.10

[1] HL, hearing level.
[2] $\bar{x}$ ± SD; median in parentheses.
[3] Wilcoxon statistics for univariate analyses.
[4] Logistic regression analyses.

Processing of sound and speech requires both peripheral and central mechanisms. According to Bess and Humes (46), retrograde degeneration of the first-order auditory neurons and degenerative changes in the brainstem and cortex of older individuals can accompany peripheral hearing impairment of the cochlea. Although we did not assess the auditory brainstem in the present study, relations between ABR and vitamin B-12 deficiency in humans have been examined by others (26–28). The lack of control groups and the small sample sizes (3–10 subjects) make it difficult to reach meaningful conclusions about the role of vitamin B-12 deficiency in ABR. Furthermore, although peripheral hearing loss often leads to abnormal ABR, an abnormal ABR does not necessarily indicate either peripheral hearing loss or a central auditory processing disorder. These studies (26–28) involved examination of a total of 20 subjects, 3 of whom had abnormal ABR (prolonged I–V interpeak latencies). Two of these 3 subjects' I–V latencies were within normal limits when they were retested after repletion with vitamin B-12. Although information about remyelination of the cochlear nerve in the elderly is very limited, Parent (47) states that spontaneous remyelination after an episode of demyelination is the rule rather than the exception in adult peripheral and central pathways.

Vitamin B-12 has also been used in conjunction with other agents, such as clarythromycin, prednisolone, and immunoglobulin G, to treat auditory dysfunction (48, 49). However, a specific rationale for the nutritional component of these treatments was generally not discussed, and the study designs did not allow identification of the unique contribution of vitamin B-12 to changes in auditory function. It is not known whether supplements of vitamin B-12 or folate would improve hearing function or slow the rate of hearing loss in elderly individuals with hearing impairment associated with deficiencies of these nutrients. Cognitive indexes (50) and peripheral and central nervous system symptoms (51) indicating deficiencies of vitamin B-12, folate, or both are sometimes, but not always, improved with repletion.

An epidemic of peripheral neuropathy associated with low intakes of vitamin B-12, folate, thiamine, and sulfur amino acids occurred in Cuba in 1992 and 1993, affecting > 50 000 people (8). Sensorineural deafness characterized by high-frequency hearing loss (4–8 kHz) was generally bilateral and usually symmetrical. Abnormal ABR occurred in 35% of the patients with abnormal audiometry. The investigators reported that treatment of patients with B vitamins produced "rewarding results" but they also noted that "there was minimal return of hearing in response to treatment" (8). Details of the intervention protocol (such as dose and duration) and the postintervention audiologic assessment were not described, and thus, it is difficult to interpret this report.

Our sample size was relatively small and consisted of healthy white women aged 60–71 y with relatively mild hearing loss. Thus, additional studies are needed to determine the roles of vitamin B-12 and folate in auditory dysfunction occurring in men, in adults aged ≥70 y, in other ethnic groups, and in elderly persons with more severe hearing loss. The roles of vitamin B-12 and folate nutriture in both the peripheral and central auditory systems also require investigation.

To our knowledge, this is the first study to show a relation between age-related hearing impairment and vitamin B-12 and folate status. Additional research is needed to confirm our findings and to determine whether, similar to high blood pressure (20, 21), poor vitamin B-12 and folate nutriture might be considered modifiable risk factors for age-related hearing impairment.

REFERENCES

1. Bureau of the Census, US Department of Commerce, Economics and Statistics Administration. Statistical Abstract of the United States, 114th ed. Washington, DC: US Government Printing Office, 1994.
2. US Department of Health and Human Services, National Institutes of Health, National Institute on Deafness and Other Communication Disorders. National Strategic Research Plan. Bethesda, MD: National Institutes of Health, 1993.
3. Jerger J, Chmiel R, Wilson N, Luchi R. Hearing impairment in older adults: new concepts. J Am Geriatr Soc 1995;43:928–35.
4. Public Health Service, National Center for Health Statistics. Healthy People 2000 Review, 1994. Hyattsville, MD: National Center for Health Statistics, 1995:108.
5. Hughes G. Molecular and cellular biology of the inner ear: the next frontier. Am J Otol 1989;10:28–35.
6. Brookes GB. Vitamin D deficiency—a new cause of cochlear deafness. J Laryngol Otol 1983;97:405–20.
7. Sun A-H, Wang Z-M, Xiao S-Z, et al. Idiopathic sudden hearing loss and disturbance of iron metabolism. J Otorhinolaryngol Relat Spec 1992;54:66–70.
8. Roman GC. An epidemic in Cuba of optic neuropathy, sensorineural deafness, peripheral sensory neuropathy and dorsolateral myeloneuropathy. J Neurol Sci 1994;127:11–28.
9. Shemesh Z, Attias J, Ornan M, Shapira N, Shahar A. Vitamin B12 deficiency in patients with chronic-tinnitus and noise-induced hearing loss. Am J Otolaryngol 1993;14:94–9.
10. Sun A-H, Xiao S-H, Li B-S, Li Z-J, Wang T-Y, Zhang Y-S. Iron deficiency and hearing loss. Experimental study in growing rats. J Otorhinolaryngol Relat Spec 1987;49:118–22.
11. Gunther T, Ising H, Joachims Z. Biochemical mechanisms affecting susceptibility to noise-induced hearing loss. Am J Otol 1989;10:36–41.
12. Buckmaster PS, Holliday TA, Bai SC, Rogers QR. Brainstem auditory evoked potential interwave intervals are prolonged in vitamin-B-6-deficient cats. J Nutr 1993;123:20–6.
13. Covell WP. Pathologic changes in the peripheral auditory mechanism due to avitaminosis (A, B complex, C, D, and E). Laryngoscope 1940;2:632–47.
14. Agamanolis DP, Chester EM, Victor M, Kark JA, Hines JD, Harris JW. Neuropathology of experimental vitamin B12 deficiency in monkeys. Neurology 1976;26:905–14.
15. Andres R, Hallfrisch J. Nutrient intake recommendations needed for the older American. J Am Diet Assoc 1989;89:1739–41.
16. Krasinski SD, Russell RM, Samloff IM, et al. Fundic atrophic gastritis in an elderly population: effect on hemoglobin and several serum nutritional indicators. J Am Geriatr Soc 1986;34:800–6.
17. Russell RM. New views on the RDAs for older adults. J Am Diet Assoc 1997;97:515–8.
18. Stabler SP, Lindenbaum J, Allen RH. Vitamin B-12 deficiency in the elderly: current dilemmas. Am J Clin Nutr 1997;66:741–9.
19. Sauberlich HE. Folate status of U.S. population groups. In: Bailey LB, ed. Folate in health and disease. New York: Marcel Dekker, 1995:171–94.
20. Brant LJ, Gordon-Salant S, Pearson JD, et al. Risk factors related to age-associated hearing loss in the speech frequencies. J Am Acad Audiol 1996;7:152–60.
21. Gates GA, Cobb JL, D'Agostino RB, Wolf PA. The relation of hearing in the elderly to the presence of cardiovascular disease and cardiovascular risk factors. Arch Otolaryngol Head Neck Surg 1993;119:156–61.
22. Herbert V, Das KC. Folic acid and vitamin B12. In: Shils ME, Olson JA, Shike M, eds. Modern nutrition in health and disease. 8th ed. Philadelphia: Lea & Febiger, 1994:402–25.
23. Schuknecht HF, Gacek MR. Cochlear pathology in presbycusis. Ann Otol Rhinol Laryngol 1993;102:1–16.
24. Ubbink JB, Vermaak WJH, van der Merwe A, Becker PJ. Vitamin B-12, vitamin B-6, and folate nutritional status in men with hyperhomocysteinemia. Am J Clin Nutr 1993;57:47–53.
25. Savage DG, Lindenbaum J. Folate-cobalamin interactions. In: Bailey LB, ed. Folate in health and disease. New York: Marcel Dekker, 1995:237–86.
26. Krumholz A, Weiss H, Goldstein P, Harris K. Evoked responses in vitamin B12 deficiency. Ann Neurol 1981;9:407–9.
27. Fine E, Hallett M. Neurophysiological study of subacute combined degeneration. J Neurol Sci 1980;45:331–6.
28. Fine E, Soria E, Paroski M, Petryk D, Thomasula L. The neurophysiological profile of vitamin B12 deficiency. Muscle Nerve 1990;13:158–64.
29. Houston DK, Johnson MA, Edmonds J, et al. Age-related hearing loss and vitamin B12, calcium, and bone health in postmenopausal women. FASEB J 1997;11:A237(abstr).
30. Gunter EW, Lewis BL, Koncikowski SM. Laboratory methods used for the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994. Hyattsville, MD: Centers for Disease Control and Prevention, 1996:VII-7-1–VII-7-12.
31. American National Standards. Specifications for audiometers (ANSI S3.6–1996). New York: Acoustical Society of America, 1996.
32. Rowland M. Basic data on hearing levels of adults 25–74 years. United States, 1971–75. Vital Health Stat 11 1980;215. [DHEW publication no. (PHS) 80–1663, 1980.]
33. Moscicki EK, Eikins EF, Baum HM, McNamara PM. Hearing loss in the elderly: an epidemiologic study of the Framingham Heart Study Cohort. Ear Hear 1985;6:184–90.
34. SAS Institute Inc. SAS/STAT user's guide, version 6. 4th ed. Vol 2. Cary, NC: SAS Institute Inc, 1989.
35. National Research Council. Recommended dietary allowances. 10th ed. Washington, DC: National Academy Press, 1989.
36. Wright JD, Bialostosky K, Gunter EW, et al. Blood folate and vitamin B12: United States, 1988–1994. National Center for Health Statistics. Vital Health Stat 11 (in press).

37. Stabler SP. Screening the older population for cobalamin (vitamin B_{12}) deficiency. J Am Geriatr Soc 1995;43:1290–7.
38. Samloff IM, Varis K, Ihamaki T, Siurala M, Rotter JI. Relationships among serum pepsinogen I, serum pepsinogen II, and gastric mucosal histology: a study in relatives of patients with pernicious anemia. Gastroenterology 1982;83:204–9.
39. Gratton MA, Schulte BA. Alterations in microvasculature are associated with atrophy of the stria vascularis in quiet-aged gerbils. Hear Res 1995;82:44–52.
40. Gratton MA, Schmiedt RA, Schulte BA. Age-related decreases in endocochlear potential are associated with vascular abnormalities in the stria vascularis. Hear Res 1996;102:181–90.
41. Willott JF. Aging and the auditory system: anatomy, physiology, and psychophysics. San Diego: Singular Publishing Group, 1991.
42. Selhub J, Jacques PF, Wilson PWF, Rush D, Rosenberg IH. Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. JAMA 1993;270:2693–8.
43. Mancini FP, Di Minno G. Hyperhomocysteinemia and thrombosis: the search for a link. Nutr Metab Cardiovasc Dis 1996;6:168–77.
44. Boushey CJ, Beresford SAA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: probable benefits of increasing folic acid intakes. JAMA 1995;274:1049–57.
45. Bottiglieri T. Folate, vitamin B12, and neuropsychiatric disorders. Nutr Rev 1996;54:382–90.
46. Bess FH, Humes LE. Audiology: the fundamentals. 2nd ed. Baltimore: Williams & Wilkins, 1995:192–4.
47. Parent A. Carpenter's human neuroanatomy. 9th ed. Baltimore: Williams & Wilkins, 1996.
48. Futaki T, Semba T, Kudo Y. Treatment of hydropic patients by immunoglobulin with methyl B12. Am J Otol 1988;9:131–5.
49. Okada T, Kato I, Miho H, et al. Acute sensorineural hearing loss caused by Mycoplasma pneumoniae. Acta Otolaryngol Suppl (Stockh) 1996;522:22–5.
50. Martin DC, Francis J, Protetch J, Huff FJ. Time dependency of cognitive recovery with cobalamin replacement: report of a pilot study. J Am Geriatr Soc 1992;40:168–72.
51. Healton EB, Savage DG, Brust JCM, Garrett TJ, Lindenbaum J. Neurologic aspects of cobalamin deficiency. Medicine (Baltimore) 1991;71:229–45.