higher activity of the triglyceride-free fatty acid cycle could explain the increased REE observed in men with upper-body obesity [Tataranni et al., 1994]. In the present study, as shown in Table 4, WHR tended to be higher in the middle-aged ($r=0.117$, $p=0.07$) and elderly men ($r=0.123$, $p=0.06$) with higher REE, which is likely to support the above reports.

However, WHR is no more than the ratio of the waist circumference to the hip. That is, it is unclear as to what a higher WHR means, larger waist circumference or relatively smaller hip. More recently, several studies have demonstrated that the waist circumference itself was also positively associated with the prevalence of CHD risk factors [Rexrode et al., 1998; Onat et al., 1999; Gray et al., 2000]. Thus, it is interesting to examine the relationships between the waist circumference and REE. The results of this study indicate, however, that no significant correlations exist between the waist circumference and REE in any of the study groups, which suggests that not all the subjects with larger waist circumferences have higher REE.

Ravussin et al. [1988] observed that initial energy expenditure negatively correlated with the rate of change in body weight over a two-year follow-up period. In the United States, obesity is more prevalent in African-Americans than in Caucasians. Several investigators have studied the relationship between obesity and REE using African-Americans and Caucasians [Albu et al., 1997; Carpenter et al., 1998; Forman et al., 1998; Foster et al., 1997]. They found that African-Americans had a lower REE than Caucasians, and that it may be related to the differences observed in the prevalence of obesity between African-Americans and Caucasians. In Pima Indians, it was revealed that people with lower REE due to a familial (genetic) factor had a higher prevalence of obesity [Bogardus et al., 1986]. These findings may indicate that lower REE leads to an increase in body weight. The results of this study indicate that the hip was significantly and negatively associated with REE in the elderly men, suggesting that adipose tissue would be likely to be accumulated in the hip of the subjects with lower REE.

As shown in Table 4, although IFA significantly and negatively correlated with REE in the elderly men, no associations were observed between SFA and REE in any of the groups. Armellini et al. [1992] reported that no difference was observed in IFA between the highest and lowest quartiles of REE adjusted for age and FFM. Leenen et al. [1992] examined this without adjusting for FFM or FM and found that an increase in IFA was positively correlated with a higher level of REE in women but not in men. Our observations are inconsistent with these two findings because they did not adjust REE for age, FFM or FM.

In this study, significant associations between REE and hip circumference or IFA were observed only in the elderly men. Several reasons for the results should be mentioned. Physical activity energy expenditure is the most variable component of total energy expenditure in free-living individuals [Goran and Poehlman, 1992] and decreases with age [Crespo et al., 1996]. Correlations between REE and hip circumference or IFA may be diminished by relatively larger variances of physical activity energy expenditure in the middle-aged subjects compared to the elderly. Although lower correlation coefficients of women between REE and IFA may be partially explained by smaller variances of those compared with men, detailed causes of the differences could not be well explained in the current data.

In conclusion, our data show that REE is affected by age, but not diminished by the natural menopausal transition in Japanese middle-aged women. Lower REE may be closely related to greater hip and IFA in elderly men.

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Prevalence of Self-perceived Auditory Problems and their Relation to Audiometric Thresholds in a Middle-aged to Elderly Population

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Objectives—Hearing loss has been identified as one of the most frequent conditions affecting the elderly population. The purpose of this study was to provide estimates of the prevalence of self-perceived hearing problems in a middle-aged to elderly general population and to make a comparison among generations and between genders regarding the relationship between audiometric measurements and hearing problems.

Material and Methods—The study was conducted using a population-based sample of 2150 adults, aged 40–79 years, who participated in the Longitudinal Study of Aging conducted by the National Institute for Longevity Sciences between 1997 and 2000. A questionnaire on hearing problems was administered and pure-tone audiometry was conducted.

Results—A third of subjects in their 40s and half of the subjects aged > 60 years were aware of having difficulty hearing. The audiometric thresholds in both the better and worse ears were associated with self-perceived hearing difficulty in all age groups. Statistically significant age and gender differences were observed in each respondent group. The older group tended to underestimate their hearing difficulty in comparison with the younger group, and males tended to underestimate their hearing difficulty more than females.

Conclusion—These results may contribute to the development of an intervention strategy for auditory rehabilitation for the middle-aged and elderly populations. *Key words: adult, hearing, population-based study, pure-tone threshold, questionnaire*

INTRODUCTION

In the abridged life tables for Japan published in 2000, life expectancy at birth was 77.64 years for men and 84.62 years for women (1), the highest levels in the world. In a society characterized by such longevity, it is necessary to address quality-of-life problems related to aging in an attempt to raise the potential for activity in the elderly population.

Auditory function is very important for obtaining communication information and in maintaining social aspects of life. It is a well-known fact that hearing threshold deteriorates with increasing age (2), and hearing loss has been identified as one of the most frequent conditions affecting the elderly. The prevalence of hearing loss has been reported in previous studies focusing on the elderly, and previous results from selected relevant studies are summarized in Table I. The prevalence statistics on hearing loss show variations as a result of the use of diverse audiometric criteria and groups of subjects with different age distributions (3–7). The prevalence of self-reported hearing problems was also investigated in different age populations (3, 5, 8, 9). However, the ways in which the prevalence of self-perceived hearing problems in the elderly differs from those in the middle-aged, and how the relationship between self-reported hearing and audiometric thresholds differs between these generations, have seldom been investigated.

It is necessary to ascertain the actual auditory state in the early stages of aging before discussing how to cope with hearing problems in the elderly. The purpose of this study was to provide estimates of the prevalence of self-perceived hearing problems in the middle-aged to elderly general population and to make a comparison among generations and between genders regarding the relationship between audiometric measurement and hearing problems.

MATERIAL AND METHODS

Study population

The general protocol of the study has been reported in detail elsewhere (10, 11). In summary, the study population consisted of subjects from the Longitudinal Study of Aging (NILS-LSA) conducted by the National Institute for Longevity Sciences, a study of a cohort of 2267 subjects with a 2-year follow-up. For the purposes of this report, the first-wave study of NILS-LSA, conducted between November 1997 and April 2000, was used. Individuals from the target age population in resident registrations of Ohbu-city (population 70,000) and Higashiura-town (population 40,000) were randomly selected for participation in cooperation with the local governments, and the group was then stratified by both age and gender. This research area is located in the central part of Japan

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Table I. *The prevalence of hearing loss and self-reported hearing problems reported in previous studies*

Prevalence of hearing loss defined by audiometric hearing thresholds:

Study	References	Year	Subjects	Definition of hearing loss	Prevalence of hearing loss (%)
Framingham cohort (USA)	(3)	1990	1662 participants aged 63–95 years	0.5, 1 and 2 kHz >25 dB	29
				0.5, 1, 2 and 3 kHz >25 dB	42
Epidemiology of Hearing Loss Study (USA)	(4)	1998	3556 participants aged 48–92 years	0.5, 1, 2 and 4 kHz >25 dB	45.9
Blue Mountains Hearing Study (Australia)	(5)	2001	2015 participants aged 55–100 years	0.5, 1, 2 and 4 kHz >25 dB	39.4
National Study of Hearing (UK)	(6, 7)	1989	2662 participants aged 17–80 years	0.5, 1, 2 and 4 kHz ≥25 dB	16.1
		1995		0.5, 1, 2 and 4 kHz ≥25 dB	26.1

Prevalence of self-reported hearing problems:

Study	References	Year	Subjects	Question used in this study	Prevalence of self-reported problems (%)
Framingham cohort (USA)	(3)	1990	1662 participants aged 63–95 years	Do you have a hearing problem now?	50 (men); 35 (women)
Blue Mountains Hearing Study (Australia)	(5)	2001	1931 participants aged 55–100 years	Do you feel you have a hearing loss?	55.9
Valby Project (Denmark)	(8)	1997	2915 residents aged ≥80 years	Do you have hearing problems?	33–66
	(9)	1997			

adjoining Nagoya City, has a population of >2 million and in terms of its characteristics is somewhere between an urban and a rural area. Selected residents were invited by mail to an explanatory meeting at which the objectives of the NILS-LSA, the study design and the detailed examination procedures were described. Only those who understood the project and signed a written informed consent form were allowed to participate. The Ethical Committee of Chubu National Hospital reviewed all the study procedures. The age at baseline was 40–79 years, and the number of subjects in each decade of age (40s, 50s, 60s, 70s) was intended to be the same, enabling us to disregard the age distribution of the background population. In the present study, of the 2267 participants, ≈2150 subjects with analyzable responses were investigated. Participants with incomplete audiograms or inconsistent responses to questionnaires due to misreading and/or errors during the compilation of materials were eliminated from the analysis. The age and gender distributions of the subjects are shown in Table II.

Procedures

Participants completed a series of questionnaires prior to the examination visit. The questionnaires consisted of >130 question items designed to elicit demographic characteristics, personal history, family history, lifestyle habits and information on the presence of various medical problems. When many blanks were found on a questionnaire, examiners attempted to supplement the data by conducting a short interview at the time of the examination visit.

The questions concerning ears and hearing are indicated in Table III. The responses to 9/14 of the questions in Table III are discussed in this study. Regarding Q1, "Do you feel you have hearing loss?", respondents who answered "Yes" or "Occasionally" went on to answer Q1-1 to Q1-5. Respondents who answered "No" skipped to Q2.

Table II. *Number of subjects by gender and age group*

Age group (years)	Males	Females	Total
40–49	284	254	538
50–59	275	264	539
60–69	279	265	544
70–79	266	263	529
Total	1104	1046	2150

Table III. *The questions concerning ears and hearing*

Q1. Do you feel you have hearing loss?
1. Yes 2. Occasionally 3. Never

If you answered "Yes" or "Occasionally", please continue, otherwise go to Q2.
Q1-1. Do you feel that any difficulty with your hearing restricts activities of your life?
1. Yes 2. Occasionally 3. Never
Q1-2. Do you feel that any difficulty with your hearing causes you loss of self-confidence?
1. Yes 2. Occasionally 3. Never
Q1-3. Do you experience difficulty understanding the speech of others though you can hear speech sounds?
1. Yes 2. Occasionally 3. Never
Q1-4. Can you follow a television newscast at the most comfortable volume?
1. Yes, I can follow almost all of what is being said 2. Can't follow occasionally 3. Can't follow more often than half the time
Q1-5. Can you follow a conversation among four or five people in a quiet room?
1. Yes, I can follow almost all of what is being said 2. Can't follow occasionally 3. Can't follow more often than half the time
Q2. Have you ever been determined to have a hearing impairment based on a hearing test (e.g. in a medical check-up or at an ENT clinic)?
1. Yes 2. No 3. Never had a hearing test
Q3. Do you use a hearing aid?
1. Often 2. Occasionally 3. No, I don't use it eventhough I have it 4. I don't have a hearing aid.
Q4. Are you aware of tinnitus?
1. Yes, always 2. Occasionally 3. No
Q5. Have you ever suffered from any ear disease?
1. Yes 2. No 3. Don't know

If you answered "Yes", please continue, otherwise go to Q6.
Q5-1. Have you ever had ear surgery?
1. Yes (Right/Left/Both) 2. No 3. Don't know
Q5-2. If you know the name of your ear disease, please mark or fill in the blank.
1. Otitis media (Right/Left/Both) 2. Otitis externa (Right/Left/Both) 3. Sudden deafness (Right/Left/Both) 4. Ménière's disease 5. Others ( )
Q6. Have you ever worked in an environment in which there was background noise over which you could not hold a conversation in a normal voice?
1. Yes, at present 2. In the past, not now 3. Never
Q7. Do you use a headphone in daily life?
1. Yes, after 2. Occasionally 3. Rarely 4. Never

Air conduction pure-tone thresholds at octave intervals from 500 to 8000 Hz for the right and left ears were obtained using a test method recommended by the Japan Audiological Society (12), using a diagnostic audiometer (AA-73A; Rion, Tokyo) calibrated according to Japanese Industrial Standards T 1201. The thresholds over the maximum output level of this audiometer were treated as a level plus an additional 5 dB, i.e. 105 dB at 500–4000 Hz and 100 dB at 8000 Hz. Bone conduction was measured if air conduction thresholds at any of the frequencies 500, 1000, 2000 or 4000 Hz were >25 dB hearing level.

For the purpose of determining the association between subjective and measured hearing, the thresholds for both the better and worse ears were analyzed, in order not to overlook subjects with only one affected ear. For each subject, the ears were classified as either the better (BE) or worse ear (WE), depending on a pure-tone average (PTA) of the thresholds at 500, 1000, 2000 and 4000 Hz.

Statistical analysis

Data were processed and analyzed using SAS version 6.12 software (13). Age differences in the distribution of responses to questions were determined using Cochran–Mantel–Haenszel statistics. Differences among groups in terms of responses to questions and age differences in pure-tone thresholds were tested using Tukey–Kramer's multiple comparison method, and trends in pure-tone thresholds by age were also examined (GLM procedure). Gender differences with regard to pure-tone thresholds were determined using a t-test. The criterion for significance was set at $p < 0.05$ for all results.

RESULTS

Table IV shows, by age group and gender, the distribution of respondents for the questions regarding hearing problems. By combining respondents who answered "Occasionally" to Q1 with those who

answered "Yes", the proportions of male respondents were 34%, 41%, 53% and 60% for subjects in their 40s, 50s, 60s and 70s, respectively. The proportions of female respondents were 40%, 46%, 45% and 52% for subjects in their 40s, 50s, 60s and 70s, respectively. There was a statistically significant higher prevalence of self-perceived hearing loss in older subjects of both genders.

The number of respondents who answered "Yes" or "Occasionally" to Q1 was 998, and all of these respondents were then asked to advance to Q1-1 to Q1-5. Because four of these respondents answered only three or four of these five questions, further analysis of prevalence was conducted using the remaining 994 respondents. By combining the respondents who answered "Occasionally" to Q1-1 with those who answered "Yes", roughly one-sixth of respondents in their 40s and one-third of those in their 70s felt that their living activities were restricted due to hearing impairment, as shown in Table IV. The prevalence of respondents to Q1-2 who felt a loss of self-confidence due to hearing impairment was similar to that of respondents to Q1-1. Meanwhile, $>80\%$ of respondents to Q1-3 in all age groups and of both genders reported having difficulty understanding the speech of others although they could detect the sounds of speech. The percentage of respondents to Q1-5 who found it difficult to follow a conversation among four or five people in a quiet room was relatively higher than that of respondents to Q1-4 who found it difficult to follow television newscasts. The prevalence of hearing problems, according to the answers to each of Q1-1 to Q1-5, was significantly higher in the older age group, for both genders.

Notably, 2.8% of all subjects (6.1% of those respondents who had hearing difficulty) had hearing aids. However, one-third of those who reported having a hearing aid reported not using the device effectively.

The relationship between self-perceived hearing difficulty and audiometric thresholds is indicated in Table V. A change with increasing age, focusing on the same self-perceived hearing group, was displayed by the thresholds of both the BE and the WE. Significantly greater deterioration of thresholds was observed in descending order of age groups for both genders in terms of the threshold of either ear at all frequencies and in all respondent groups. In each age group, statistically significant elevation of thresholds among the three respondent groups was observed in the order "No", "Occasionally" and "Yes", except for thresholds at 500 and 2000 Hz in females in their 40s regarding the BE. With regard to the thresholds of the WE, statistically significant differences were observed among the three respondent groups in all age groups and for both genders at all frequencies. Statistically significant gender differences were observed in all age groups in all respondent groups.

DISCUSSION

The International Classification of Functioning, Disability and Health (ICF) of the World Health Organisation provides an instructive description for eliciting and recording information on the functioning and disability of an individual and is used for the evaluation of impairments of body functions (14). In the ICF, impairments are described as problems in body function constituting significant deviation or loss, activity limitations as difficulties an individual may have in executing activities and participation restrictions as problems an individual may have participating in life situations, which may necessitate environmental barriers or facilitators. In the present study, pure-tone thresholds were used to assess hearing impairment, and Q1-3 to Q1-5 were used to assess the extent of activity limitation.

Based on the results of Q1 and Q1-1 to Q1-5, the percentage of subjects with self-perceived hearing difficulty was considerable, not only in the elderly group but also in the middle-aged group. Half of the subjects aged >60 years and one-third of subjects in their 40s were aware of hearing loss, and $>80\%$ of those with reported hearing loss, regardless of age and sex, perceived themselves to have difficulty understanding speech. Based on the results of Q1-1 and Q1-2, approximately one out of three subjects with self-perceived hearing loss in their 70s and one out of six subjects with self-perceived hearing loss in their 40s felt that they had a hearing handicap. In contrast, the rate of owning a hearing aid was only 2.8% among all subjects, which corresponded to 6.1% of the respondents with self-perceived hearing loss. This finding seems incompatible with the number of subjects with reported hearing difficulty (998/2150; 46%). The existence of a latent demand for intervention in hearing problems was presumed. It has been shown that rehabilitative intervention, including hearing aid provision and counseling, can reduce hearing handicap (15–17). The necessity to initiate intervention for minimally hearing-impaired adults when they first begin to notice difficulty was also emphasized in a previous study (18).

With regard to the prevalence of hearing loss, definitions of hearing loss assessed by PTA in the current literature vary according to which ear (i.e. better, worse, right, left or both) is used for classifying the individual and which frequencies are included in the PTA to determine the better/worse ear (3–7). Furthermore, a large intersubject variability was observed in terms of self-perceived handicap of

Table IV. *Distribution of respondents to the questions about hearing problems by age group and gender*

Response	Males												Females												Total		
	40–49 years			50–59 years			60–69 years			70–79 years			40–49 years			50–59 years			60–69 years			70–79 years					
	N	%	95% CI	*N*	%	95% CI	*N*	%	95% CI	*N*	%	95% CI	*N*	%	95% CI	*N*	%	95% CI	*N*	%	95% CI	*N*	%	95% CI	*N*	%	95% CI
Q1. Do you feel you have hearing loss?																											
Yes	15	5	2.7–7.9	36	13	9.1–17.1	51	18	13.7–22.8	72	27	21.7–32.4	15	6	3.0–8.8	21	8	4.7–11.2	30	11	7.5–15.1	51	20	14.6–24.2	291	13	12.1–15.0
Occasionally	82	29	23.6–34.1	76	28	22.4–32.9	98	35	29.5–40.7	89	33	27.8–39.1	86	34	28.0–39.7	101	38	32.4–44.1	90	34	28.3–39.7	85	32	26.7–38.0	707	33	30.9–34.9
No	187	66	60.3–71.4	163	59	53.5–65.1	130	47	40.7–52.4	105	40	33.6–45.3	153	60	54.2–66.3	142	54	47.8–59.8	145	55	48.7–60.7	127	48	42.2–54.3	1152	54	51.5–55.7
Total	284	100		275	100		279	100		266	100		254	100		264	100		265	100		263	100		2150	100	
Q1-1. Do you feel that any difficulty with your hearing restricts activities of your life?																											
Yes	4	4	0.2–8.1	1	1	0–2.61	10	7	2.7–10.7	22	14	8.4–19.1	0	0	–	2	1	0–3.9	3	3	0–5.4	11	8	3.5–12.8	53	5	3.9–6.7
Occasionally	3	13	6.6–20.2	26	23	15.4–31.0	33	22	15.5–28.8	42	26	19.4–33.1	15	15	7.9–21.8	13	11	5.2–16.1	25	21	13.8–28.6	30	22	15.2–29.2	197	20	17.3–22.3
No	80	83	74.9–90.0	85	76	68.0–83.8	106	71	63.9–78.4	96	60	52.4–67.6	86	85	78.2–92.1	107	88	81.9–93.5	90	76	68.6–83.9	94	70	61.9–77.4	744	75	72.2–77.5
Total	97	100		112	100		149	100		150	100		101	100		122	100		118	100		135	100		994	100	
Q1-2. Do you feel that any difficulty with your hearing causes you loss of self-confidence?																											
Yes	2	2	0–4.9	1	1	0–2.6	7	5	1.3–8.1	13	8	3.9–12.4	0	0	–	1	1	0–2.4	2	2	0–4.0	7	5	1.4–8.9	33	3	2.2–4.4
Occasionally	8	8	2.8–13.7	16	14	7.8–20.8	23	15	9.6–21.2	43	27	20.0–33.7	18	18	10.4–25.3	10	8	3.3–13.1	21	18	10.9–24.7	30	22	15.2–29.2	169	17	14.7–19.3
No	87	90	83.6–95.7	95	85	78.2–91.5	119	80	73.4–86.3	104	65	57.6–72.4	83	82	74.7–89.6	111	91	85.9–96.1	95	80	73.4–87.7	98	73	65.1–80.1	792	80	77.2–82.2
Total	97	100		112	100		149	100		160	100		101	100		122	100		118	100		135	100		994	100	
Q1-3. Do you experience difficulty understanding the speech of others though you can hear speech sounds?																											
Yes	9	9	3.5–15.1	20	18	10.8–25.0	35	23	16.7–30.3	50	31	24.1–38.4	11	11	4.8–17.0	11	9	3.9–14.1	19	16	9.5–22.7	32	24	16.5–30.9	187	19	16.4–21.2
Occasionally	70	72	63.2–81.1	72	64	55.4–73.2	95	64	56.0–71.5	93	58	50.5–65.8	75	74	65.7–82.8	88	72	64.2–80.1	76	64	55.8–73.0	85	63	54.8–71.1	654	66	62.8–68.7
No	18	19	10.8–26.3	20	18	10.8–25.0	19	13	7.4–18.1	17	11	5.9–15.4	15	15	7.9–21.8	23	19	11.9–25.8	23	20	12.3–26.6	18	13	7.6–19.1	153	15	13.1–17.6
Total	97	100		112	100		149	100		160	100		101	100		122	100		118	100		135	100		994	100	
Q1-4. Can you follow a television newscast at the most comfortable volume?																											
Can't follow more often than half the time	0	0	–	2	2	0–4.2	3	2	0–4.3	6	4	0.8–6.7	0	0	–	0	0	–	2	2	0–4.0	6	4	1.0–7.9	19	2	1.1–2.8
Can't follow occasionally	11	11	5.0–17.7	18	16	9.3–22.9	35	23	16.7–30.3	51	32	24.7–39.1	9	9	3.4–14.5	13	11	5.2–16.1	20	17	10.2–23.7	32	24	16.5–30.9	189	19	16.6–21.5
Yes, almost all of what is being said	86	89	82.3–95.0	92	82	75.0–89.2	111	75	67.5–81.5	103	64	57.0–71.8	92	91	85.5–96.6	109	89	83.9–94.8	96	81	74.3–88.4	97	72	64.3–79.4	786	79	76.5–81.6
Total	97	100		112	100		149	100		160	100		101	100		122	100		118	100		135	100		994	100	
Q1-5. Can you follow a conversation among 4 or 5 people in a quiet room?																											
Can't follow more often than half the time	1	1	0–3.0	1	1	0–2.6	6	4	0.9–7.2	9	6	2.1–9.2	0	0	–	0	0	–	3	2	0–5.4	7	5	1.4–8.9	27	3	1.1–2.8
Can't follow occasionally	26	27	18.0–35.6	37	33	24.3–41.7	61	41	33.0–48.8	79	49	41.6–57.1	27	27	18.1–35.4	33	27	19.2–34.9	47	40	31.0–48.7	58	43	34.6–51.3	368	37	16.6–21.5
Yes, almost all of which is being said	70	72	63.2–81.1	74	66	57.3–74.8	82	55	47.0–63.0	72	45	37.3–52.7	74	73	64.6–81.9	89	73	65.1–80.8	68	58	48.7–66.5	70	52	43.4–60.3	599	60	76.5–81.6
Total	97	100		112	100		149	100		160	100		101	100		122	100		118	100		135	100		994	100	

Table V. *Mean air conduction pure-tone thresholds (dB HL), standard error (SE) and 95% CI for the BE and the WE by age group and gender for the three respondent groups to Q1*

			500 Hz			1000 Hz			2000 Hz			4000 Hz			8000 Hz		
Ear	Gender	Age (years)	Mean	SE	95% CI	Mean	SE	95% CI	Mean	SE	95% CI	Mean	SE	95% CI	Mean	SE	95% CI
Yes, I feel I have hearing loss																	
BE	Male	40–49	13	1.7	9–16	13	2.1	8–17	23	4.5	13–33	32	6.6	18–46	37	7.0	22–52
		50–59	18	2.8	12–24	19	3.2	12–25	25	3.4	18–32	39	3.8	32–47	45	4.2	36–53
		60–69	22	2.1	18–26	27	2.2	22–31	38	2.1	33–42	52	2.2	48–57	62	2.3	58–67
		70–79	29	1.8	26–33	36	1.9	32–40	45	2.0	41–49	60	1.6	57–63	72	1.7	69–76
BE	Female	40–49	11	2.2	7–16	8	1.5	5–12	10	1.9	6–14	12	3.0	5–18	26	5.5	15–38
		50–59	17	2.5	12–22	15	3.2	9–22	19	2.9	13–25	19	3.6	12–27	36	4.1	27–45
		60–69	24	2.7	18–29	20	2.8	14–26	27	3.3	21–34	31	3.6	23–38	48	4.0	40–56
		70–79	29	2.3	24–33	31	2.5	26–36	39	2.3	35–44	48	2.2	44–53	67	2.9	62–73
I occasionally feel I have hearing loss																	
BE	Male	40–49	12	0.8	10–13	10	0.7	8–11	12	1.2	10–14	19	1.8	15–22	25	1.8	22–29
		50–59	13	0.9	11–14	12	1.1	10–14	16	1.1	14–18	31	2.0	27–35	33	1.9	30–37
		60–69	14	0.8	12–16	14	0.9	12–16	21	1.3	19–24	34	1.9	30–38	44	2.1	40–48
		70–79	20	1.0	18–22	20	1.2	18–23	31	1.6	28–34	48	1.7	45–52	67	1.7	63–70
BE	Female	40–49	11	0.8	10–13	7	0.9	5–9	9	0.8	8–11	9	0.8	7–11	18	1.4	16–21
		50–59	13	0.7	12–15	8	0.7	6–9	12	0.9	10–14	15	1.2	13–18	28	1.5	25–30
		60–69	16	0.9	14–18	13	0.9	11–15	19	1.1	17–21	23	1.6	20–26	40	2.0	36–44
		70–79	20	1.2	17–22	19	1.3	17–22	24	1.4	22–27	33	1.8	30–37	58	2.0	54–62
No, I do not feel I have hearing loss																	
BE	Male	40–49	9	0.4	8–10	7	0.4	6–7	9	0.5	8–10	13	0.8	11–14	19	0.9	18–21
		50–59	10	0.5	9–11	9	0.5	7–10	12	0.6	11–13	19	1.0	17–21	27	1.1	25–29
		60–69	13	0.6	11–14	11	0.7	10–13	17	0.9	15–19	29	1.5	26–32	40	1.5	37–43
		70–79	15	0.8	13–17	15	0.9	14–17	23	1.2	20–25	38	1.8	34–41	53	1.8	50–57
BE	Female	40–49	9	0.5	8–10	4	0.4	4–5	8	0.5	7–9	6	0.5	5–7	16	0.9	14–18
		50–59	11	0.6	9–12	7	0.5	6–9	11	0.6	10–12	10	0.7	9–12	23	1.2	20–25
		60–69	14	0.7	13–15	12	0.7	10–13	17	0.8	15–18	19	1.0	17–21	36	1.4	33–39
		70–79	18	0.8	17–20	14	0.9	13–16	20	1.0	18–21	25	1.2	22–27	51	1.7	47–54
Yes, I feel I have hearing loss																	
WE	Male	40–49	29	6.4	15–43	30	7.5	14–46	36	7.5	20–52	53	7.1	37–68	52	7.7	35–68
		50–59	33	4.7	23–43	34	4.7	25–44	39	4.8	29–48	53	4.1	45–62	58	4.5	49–67
		60–69	33	3.5	26–40	40	3.3	33–46	51	3.0	45–57	65	2.6	59–70	71	2.6	66–76
		70–79	40	2.6	35–45	47	2.3	42–51	57	2.0	53–61	68	1.7	65–72	79	1.7	76–82
WE	Female	40–49	24	6.7	10–38	23	7.0	8–38	24	5.5	12–36	25	6.2	12–39	36	7.6	20–53
		50–59	27	4.6	17–37	24	5.0	13–34	28	5.1	17–38	31	5.4	20–43	47	6.0	35–60
		60–69	34	4.4	25–43	33	4.4	24–42	39	4.3	31–48	44	4.2	35–52	62	4.4	52–71
		70–79	47	3.2	40–53	47	3.0	41–53	53	2.8	48–59	61	2.9	56–67	79	2.3	74–84
I occasionally feel I have hearing loss																	
WE	Male	40–49	16	1.4	13–18	14	1.3	11–17	17	1.4	14–20	26	1.9	22–30	29	2.0	25–33
		50–59	16	1.0	14–18	16	1.1	14–19	23	1.4	20–26	38	2.0	34–42	40	2.3	36–45

Table V (*Continued*)

Ear	Gender	Age (years)	500 Hz			1000 Hz			2000 Hz			4000 Hz			8000 Hz		
			Mean	SE	95% CI	Mean	SE	95% CI	Mean	SE	95% CI	Mean	SE	95% CI	Mean	SE	95% CI
		60–69	19	1.3	16–21	19	1.4	17–22	27	1.5	24–30	41	1.9	37–45	51	2.1	47–56
		70–79	26	1.6	23–29	28	1.8	24–32	39	1.7	36–43	55	1.9	51–59	71	1.8	67–74
WE	Female	40–49	15	1.1	13–17	10	1.0	8–12	14	0.9	12–15	13	1.0	11–15	20	1.4	17–23
		50–59	16	1.2	14–19	12	1.0	10–14	18	1.1	15–20	21	1.5	19–24	33	1.7	30–36
		60–69	23	1.8	19–27	21	1.8	17–24	27	1.8	23–30	31	2.0	27–35	46	2.3	41–51
		70–79	25	1.4	22–28	25	1.6	21–28	32	1.7	28–35	43	2.0	39–46	62	1.9	58–65
No, I do not feel I have hearing loss																	
WE	Male	40–49	12	0.5	11–13	9	0.5	8–10	13	0.6	12–14	18	0.9	16–20	21	1.0	19–23
		50–59	14	0.7	12–15	12	0.7	11–14	17	0.8	15–19	25	1.2	23–28	32	1.4	29–35
		60–69	16	0.8	15–18	15	0.9	13–16	22	1.1	20–24	36	1.5	33–39	46	1.8	42–49
		70–79	18	1.0	16–20	20	1.2	18–23	19	1.5	26–32	45	1.7	41–48	58	1.6	55–61
WE	Female	40–49	11	0.5	10–13	7	0.5	6–8	12	0.6	11–13	11	0.7	9–12	18	1.0	16–20
		50–59	13	0.7	12–15	10	0.6	9–12	15	0.7	13–16	15	0.8	13–17	26	1.3	23–29
		60–69	19	0.8	17–21	15	0.8	14–17	20	0.9	18–22	24	1.3	21–26	40	1.5	37–43
		70–79	22	1.0	20–24	19	1.0	17–21	25	1.1	23–27	34	4.1	26–42	55	1.8	52–59

patients with unilateral or mild hearing loss (18). These results mean that some subjects with unilateral or mild hearing loss reported "no handicap" while others with similarly unilateral or mild hearing loss reported "significant handicap". Consequently, the pure-tone thresholds for both the BE and the WE were adopted for the present analysis in order to reflect the real condition of respondents with at least one affected ear.

A significant relationship was found between self-perceived hearing difficulty and pure-tone thresholds in all age groups. In the present study, the single question "Do you feel you have hearing loss?" performed reasonably in terms of stratification of subjects by hearing level. In a previous study, this question was regarded to be sufficiently sensitive and specific to provide a reasonable estimate of the prevalence of hearing loss (5).

The other result obtained using this question in the present study was that the correspondence of the pure-tone thresholds to self-reported hearing loss differed significantly among age groups and between genders. When Q1 was answered, no special listening condition was presented and no additional limitation such as "Compared to other people of your age" was given. Interestingly, the hearing thresholds changed with increasing age in the same self-perceived hearing group. It might be said that, if the hearing thresholds were equivalent, (i) the older group underestimated their hearing difficulty compared to the younger group and (ii) the males underestimated their hearing difficulty compared to the females. As a result, we found the inversion that the thresholds in subjects in their 70s without self-reported hearing difficulty were significantly worse than those of subjects in their 40s with self-reported hearing difficulty. In terms of performance-based tests, it is known that the elderly have poorer speech identification abilities for a given hearing threshold level (19, 20). For self-reported measures of functioning, younger subjects with hearing loss reported more handicapping effects of sensitivity loss than elderly subjects with hearing loss (21, 22). Old age can have opposite effects on performance-based tests and self-reported measures. Several explanations for this discrepancy have been proposed. One is that elderly persons who prefer staying at home, avoiding difficult communication situations and social interaction have fewer demands for oral communication (23). Alternatively, hearing loss is compensated for or becomes accustomed to, both consciously and unconsciously, when the loss develops gradually (24). On the other hand, underestimation of self-handicap in elderly people with hearing loss can prevent them from receiving auditory rehabilitation. The reluctance to wear a

hearing aid exacerbates a sense of isolation from family and society. Additionally, many problems arise when fitting the elderly with hearing aids. Many fear technology, have difficulty operating an electronic device, lack manual dexterity, are reluctant to accept having a handicap and have low motivation to use the device (24).

It has been suggested that early rehabilitative intervention in a pre-retirement working class population of people aged 50–65 years would be more effective (25). When there is no significant difference in hearing level between those who are aware of their own hearing problems and those who are unaware or in denial, the former are more likely to accept auditory rehabilitative intervention. It was demonstrated in the present study that the prevalence of self-perceived hearing problems in the middle-aged was considerable. Newman et al. (18) found that three-quarters of subjects with unilaterally normal hearing and mild hearing losses reported some degree of communication and psychosocial problems. The existence of a potential demand for early intervention may thus be suggested.

In the current study, the prevalence of self-perceived hearing difficulty was demonstrated from a population-based survey administered in Japan. These auditory problems were related to audiometric thresholds. The older group tended to underestimate their hearing difficulty in comparison with the younger group, and males showed a greater tendency than females to underestimate their hearing difficulty. Our results may contribute to the development of an intervention strategy for auditory rehabilitation for the middle-aged and elderly populations.

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ELSEVIER

Age-related Change in Contrast Sensitivity Among Japanese Adults

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Purpose: To evaluate the age-related change in contrast sensitivity seen in a middle-aged to elderly Japanese population.

Methods: Contrast sensitivity and visual acuity were measured in subjects aged 40 to 79 years randomly recruited from a community in Aichi prefecture near Nagoya, Japan. Contrast sensitivity tests were performed using the Vistech contrast sensitivity test chart (VCTS 6500). The results were statistically analyzed relative to age.

Results: A statistically significant decrease in contrast sensitivity was seen with advancing age at each spatial frequency (Cochran-Mantel-Haenszel: $P < .001$). This trend was detected even when the subjects were limited to only those having a corrected visual acuity of 1.0 or better (Cochran-Mantel-Haenszel: $P < .001$). Overall, 9.4% of the eyes with good visual acuity had poor contrast sensitivity at a high spatial frequency, while in the 70–79-year-old group, the percentage with poor contrast sensitivity reached 21.1%.

Conclusions: The age-related decrease in contrast sensitivity was confirmed at all frequencies in our population, even when adjusted for visual acuity. Our results suggest that contrast sensitivity tests, especially at high frequencies, assess aspects of visual function that cannot be determined in the elderly population from visual acuity tests alone. **Jpn J Ophthalmol 2003;47:299–303** © 2003 Japanese Ophthalmological Society

Key Words: Adult, aging, contrast sensitivity, population-based study.

Introduction

Traditionally, visual acuity is a measure of the eye's ability to resolve small, high-contrast targets. However, by measuring only visual acuity, we can miss many visual problems because the objects in our daily life have various levels of contrast and a diverse range of sizes. It has been suggested that assessing contrast sensitivity would provide additional information about vision quality,[1] and that contrast sensitivity screening for ophthalmic disease in the elderly is more efficient than testing for visual acuity alone.[2]

Despite these advantages, the use of contrast sensitivity testing has not become prevalent. One reason may be that visual acuity testing is a basic and simple method for assessing visual function. In fact, it is well known that the results of visual acuity tests are strongly associated with contrast sensitivity and other visual function tests. Therefore, many clinical and epidemiological studies have tested only for visual acuity to assess visual function.

Although it is widely accepted that contrast sensitivity decreases with age, the accurate distribution of contrast sensitivity values according to age has not been established. This study investigated the effect of aging on visual contrast sensitivity in a large, middle-aged to elderly population, when adjustment was made for visual acuity, and demonstrates an age-related distribution pattern seen with contrast sensitivity values.

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Materials and Methods

The National Institute for Longevity Sciences-Longitudinal Study of Aging (NILS-LSA), started in 1997, is a

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population-based prospective cohort study of aging.[3] Using the NILS-LSA data, we studied the association between age and the contrast sensitivity of vision in community-dwelling participants aged 40 to 79 years randomly recruited from regions close to NILS in Aichi prefecture, near Nagoya, Japan. The study protocol was approved by the Committee on the Ethics of Human Research of National Chubu Hospital and NILS, with written informed consent obtained from each subject.

In the present study, we analyzed the baseline data of NILS-LSA obtained from March 1997 to April 2000. During this period, 2267 people (1136 men and 1131 women) participated in the NILS-LSA. Eyes with a previous history of cataract surgery and those without contrast sensitivity data were excluded. Therefore, data from 4344 eyes were included in the present study.

Distant visual acuity was measured for each eye initially by presenting correction at 5 meters. If the participant was unable to read the target at the 1.0 equivalent line, best-corrected visual acuity testing was performed following optimal refraction. Contrast sensitivity was measured for each eye using the Vistech contrast sensitivity test chart (VCTS 6500; Vistech Consultants, Dayton, OH, USA) at 3 meters, making any necessary correction for distance vision. The Vistech chart consists of 45 circular targets arranged in five rows and nine columns. Each target contains a sine-wave contrast grating, and each row has a different spatial frequency (1.5 cycles per degree [cpd], 3 cpd, 6 cpd, 12 cpd, and 18 cpd) with the contrast decreasing across the columns. The gratings are either vertical or tilted ±15° from vertical. At each spatial frequency the final reliable contrast value was adopted as the contrast sensitivity for each participant. Over the VCTS 6500 chart, the illumination was standardized with the illumination meter supplied with the Vistech test (390 lux at center). In the present study, the contrast sensitivity was counted as zero when it was impossible to identify the highest contrast target for each frequency.

For analysis, the participants were divided into four age groups: 40–49, 50–59, 60–69, and 70–79 years. We used theCochran-Mantel-Haenszel chi-square tests to assess the relationship between contrast sensitivity and age at each frequency. Data were analyzed using the Statistical Analysis System release 6.12. A probability value of $<.05$ was considered statistically significant.

Results

A statistically significant decrease in contrast sensitivity was detected with advancing age at each spatial frequency (Cochran-Mantel-Haenszel: $P < .001$) (Table 1). A portion of all the eyes (21.0%) had zero contrast sensitivity at the highest frequency (18 cpd), and 42.8% of the eyes from the oldest age group (70–79 years) were unable to identify the highest contrast target at 18 cpd.

Table 2 shows the distribution of contrast sensitivity for eyes that had a corrected visual acuity of 1.0 or better. It was also shown that the oldest age group had lower contrast sensitivities at each frequency (Cochran-Mantel-Haenszel: $P < .001$). Despite having good visual acuity, 9.4% of all eyes had zero contrast sensitivity at the highest frequency (18 cpd). In the 70–79 year age group, 21.1% of the eyes had a zero value at 18 cpd.

Discussion

Our report on the distribution of visual contrast sensitivity within a large Japanese population confirmed the generally accepted trend for contrast sensitivity to decrease with advancing age. Interestingly, this trend was detected even when data were limited to subjects having a corrected visual acuity of 1.0 or better. In the 70–79 year age group, particularly, 21.1% of the subjects with good visual acuity had zero contrast sensitivity at 18 cpd.

It is known that certain visual problems, such as cataracts and glaucoma, may affect the eye's contrast sensitivity, with cataracts being the most common cause of decreased contrast sensitivity in middle-aged and elderly populations. Rouhiainen et al.[4] have reported that a significant association between contrast sensitivity and lens opacification was seen at high spatial frequencies in cortical opacities and at low and medium frequencies in posterior subcapsular opacities; when adjusted for age and visual acuity, however, nuclear opacification did not impair contrast sensitivity. Therefore, it seems likely that cataracts (cortical or posterior subcapsular) should be primarily responsible for the trend of decreased contrast sensitivity with age in our subjects with good visual acuity.

There are some limitations in the present study. The reliability of Vistech VCTS 6500 has been reported to be uncertain,[5] and we have not had the opportunity to examine this question within the population of the present study. However, there are some advantages in using the Vistech chart for testing large populations, in that testing requires only a few minutes and, therefore, is not taxing for cognitively impaired or elderly participants. In addition, the large number of subjects in the NILS-LSA contributes to the general applicability of our results.

It has been widely accepted that a corrected visual acuity of 1.0 or better is considered normal. In the present study, therefore, good visual acuity was defined as a corrected visual acuity of 1.0 or better regardless of

Table 1. Distribution (Percentile) of Contrast Sensitivity in all Eyes

Frequency*	Contrast Sensitivity									Value of Chi-square(df = 1)†
1.5 (cpd)	0	3	7	12	20	35	70	120	170	
40–49 (y) (n = 1128)	0 (0.0)	12 (0.2)	0 (0.0)	3 (0.3)	204 (18.1)	664 (58.9)	228 (20.2)	21 (1.9)	6 (0.5)	
50–59 (y) (n = 1123)	2 (0.2)	1 (0.1)	0 (0.0)	6 (0.5)	276 (24.6)	643 (57.3)	184 (16.4)	9 (0.8)	2 (0.2)	266.4
60–69 (y) (n = 1102)	3 (0.3)	3 (0.3)	2 (0.2)	13 (1.2)	397 (36.0)	557 (50.5)	114 (10.3)	13 (1.2)	0 (0.0)	$p < .001$
70–79 (y) (n = 991)	7 (0.7)	12 (1.2)	6 (0.6)	45 (4.5)	474 (47.8)	377 (38.0)	67 (6.8)	3 (0.3)	0 (0.0)	
Total (n = 4344)	12 (0.3)	18 (0.4)	8 (0.2)	67 (1.5)	1351 (31.1)	2241 (51.6)	593 (13.7)	46 (1.1)	8 (0.2)	
3 (cpd)	0	4	9	15	24	44	85	170	220	
40–49 (y) (n = 1128)	1 (0.1)	0 (0.0)	1 (0.1)	2 (0.2)	20 (1.8)	323 (28.6)	649 (57.5)	126 (11.2)	6 (0.5)	
50–59 (y) (n = 1123)	2 (0.2)	1 (0.1)	1 (0.1)	5 (0.5)	40 (3.6)	393 (35.0)	592 (52.7)	88 (7.8)	1 (0.1)	299.7
60–69 (y) (n = 1102)	3 (0.3)	1 (0.1)	2 (0.2)	6 (0.5)	64 (5.8)	500 (45.4)	445 (40.4)	77 (7.0)	4 (0.4)	$p < .001$
70–79 (y) (n = 991)	9 (0.9)	9 (0.9)	9 (0.9)	23 (2.3)	123 (12.4)	521 (52.6)	268 (27.0)	25 (2.5)	4 (0.4)	
Total (n = 4344)	15 (0.4)	11 (0.3)	13 (0.3)	36 (0.8)	247 (5.7)	1737 (40.0)	1954 (45.0)	316 (7.3)	15 (0.4)	
6 (cpd)	0	5	11	21	45	70	125	185	260	
40–49 (y) (n = 1128)	1 (0.1)	4 (0.4)	7 (0.6)	58 (5.1)	305 (27.0)	265 (23.5)	403 (35.7)	77 (6.8)	8 (0.7)	
50–59 (y) (n = 1123)	2 (0.2)	1 (0.1)	18 (1.6)	78 (7.0)	341 (30.4)	264 (23.5)	335 (29.8)	78 (7.0)	6 (0.5)	526.4
60–69 (y) (n = 1102)	3 (0.3)	5 (0.5)	59 (5.4)	134 (12.2)	432 (39.2)	199 (18.1)	219 (19.9)	47 (4.3)	4 (0.4)	$p < .001$
70–79 (y) (n = 991)	24 (2.4)	30 (3.0)	96 (9.7)	216 (21.8)	425 (42.9)	119 (12.0)	71 (7.2)	9 (0.9)	1 (0.1)	
Total (n = 4344)	30 (0.7)	40 (0.9)	180 (4.1)	486 (11.2)	1503 (34.6)	847 (19.5)	1028 (23.7)	211 (4.9)	19 (0.4)	
12 (cpd)	0	5	8	15	32	55	88	125	170	
40–49 (y) (n = 1128)	8 (0.7)	15 (1.3)	100 (8.9)	182 (16.1)	243 (21.5)	232 (20.6)	278 (24.7)	64 (5.7)	6 (0.5)	
50–59 (y) (n = 1123)	13 (1.2)	28 (2.5)	110 (9.8)	199 (17.7)	223 (19.9)	203 (18.1)	298 (26.5)	44 (3.9)	5 (0.5)	593.3
60–69 (y) (n = 1102)	36 (3.3)	45 (4.1)	192 (17.4)	267 (24.2)	242 (22.0)	158 (14.3)	135 (12.3)	27 (2.5)	0 (0.0)	$p < .001$
70–79 (y) (n = 991)	129 (13.0)	101 (10.2)	274 (27.7)	227 (22.9)	159 (16.0)	66 (6.7)	29 (2.9)	5 (0.5)	1 (0.1)	
Total (n = 4344)	186 (4.3)	189 (4.4)	676 (15.6)	875 (20.1)	867 (20.0)	659 (15.2)	740 (17.0)	140 (3.2)	12 (0.3)	
18(cpd)	0	4	7	10	15	26	40	65	90	
40–49 (y) (n = 1128)	112 (9.9)	75 (6.7)	76 (6.7)	249 (22.1)	269 (23.9)	213 (18.9)	117 (10.4)	17 (1.5)	0 (0.0)	
50–59 (y) (n = 1123)	129 (11.5)	81 (7.2)	90 (8.0)	237 (21.1)	248 (22.1)	206 (18.3)	124 (11.0)	8 (0.7)	0 (0.0)	526.6
60–69 (y) (n = 1102)	245 (22.2)	139 (12.6)	102 (9.3)	263 (23.9)	188 (17.1)	110 (10.0)	48 (4.4)	7 (0.6)	0 (0.0)	$p < .001$
70–79 (y) (n = 991)	424 (42.8)	183 (18.5)	96 (9.7)	169 (17.1)	77 (7.8)	31 (3.1)	9 (0.9)	2 (0.2)	0 (0.0)	
Total (n = 4344)	910 (21.0)	478 (11.0)	364 (8.4)	918 (21.1)	782 (18.0)	560 (12.9)	298 (6.9)	34 (0.8)	0 (0.0)	

*cpd: cycles per degree.

†Relationship between contrast sensitivity and age was assessed using Cochran-Mantel-Haenszel Statistics for 4 by 9 table at each frequency.

Table 2. Distribution (Percentile) of Contrast Sensitivity in the Eyes with Good Visual Acuity (≥1.0)

Frequency*	Contrast Sensitivity									Value of Chi-square(df = 1)*†
1.5 (cpd)	0	3	7	12	20	35	70	120	170	
40–49 (y) (n = 1011)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	172 (17.0)	604 (59.7)	210 (20.8)	19 (1.9)	6 (0.6)	
50–59 (y) (n = 904)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	195 (21.6)	534 (59.1)	165 (18.3)	8 (0.9)	2 (0.2)	67.1
60–69 (y) (n = 668)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)	195 (29.2)	377 (56.4)	81 (12.1)	12 (1.8)	0 (0.0)	$p < .001$
70–79 (y) (n = 370)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)	134 (36.2)	192 (51.9)	40 (10.8)	1 (0.3)	0 (0.0)	
Total (n = 2953)	0 (0.0)	1 (0.0)	1 (0.0)	4 (0.1)	696 (23.6)	1707 (57.8)	496 (16.8)	40 (1.4)	8 (0.3)	
3 (cpd)	0	4	9	15	24	44	85	170	220	
40–49 (y) (n = 1011)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	12 (1.2)	273 (27.0)	599 (59.3)	120 (11.9)	6 (0.6)	
50–59 (y) (n = 904)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.2)	19 (2.1)	288 (31.9)	512 (56.6)	81 (9.0)	1 (0.1)	65.0
60–69 (y) (n = 668)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.3)	13 (2.0)	269 (40.3)	315 (47.2)	64 (9.6)	4 (0.6)	$p < .001$
70–79 (y) (n = 370)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (3.2)	189 (51.1)	154 (41.6)	14 (3.8)	1 (0.3)	
Total (n = 2953)	0 (0.0)	0 (0.0)	2 (0.1)	5 (0.2)	56 (1.9)	1019 (34.5)	1580 (53.5)	279 (9.5)	12 (0.4)	
6 (cpd)	0	5	11	21	45	70	125	185	260	
40–49 (y) (n = 1011)	0 (0.0)	2 (0.2)	3 (0.3)	33 (3.3)	256 (25.3)	247 (24.4)	388 (38.4)	74 (7.3)	8 (0.8)	
50–59 (y) (n = 904)	0 (0.0)	0 (0.0)	6 (0.7)	34 (3.8)	248 (27.4)	230 (25.4)	308 (34.1)	72 (8.0)	6 (0.7)	122.7
60–69 (y) (n = 668)	0 (0.0)	1 (0.2)	10 (1.5)	46 (6.9)	234 (35.0)	146 (21.9)	182 (27.3)	45 (6.7)	4 (0.6)	$p < .001$
70–79 (y) (n = 370)	0 (0.0)	0 (0.0)	6 (1.6)	39 (10.5)	197 (53.2)	70 (18.9)	51 (13.8)	6 (1.6)	1 (0.3)	
Total (n = 2953)	0 (0.0)	3 (0.1)	25 (0.9)	152 (5.2)	935 (31.7)	693 (23.5)	929 (31.5)	197 (6.7)	19 (0.6)	
12 (cpd)	0	5	8	15	32	55	88	125	170	
40–49 (y) (n = 1011)	1 (0.1)	7 (0.7)	67 (6.6)	152 (15.0)	221 (21.9)	222 (22.0)	271 (26.8)	64 (6.3)	6 (0.6)	
50–59 (y) (n = 904)	3 (0.3)	9 (1.0)	64 (7.1)	130 (14.4)	186 (20.6)	182 (20.1)	283 (31.3)	42 (4.7)	5 (0.6)	159.5
60–69 (y) (n = 668)	6 (0.9)	9 (1.4)	67 (10.0)	143 (21.4)	174 (26.1)	127 (19.0)	117 (17.5)	25 (3.7)	0 (0.0)	$p < .001$
70–79 (y) (n = 370)	2 (0.5)	15 (4.1)	89 (24.1)	88 (23.8)	98 (26.5)	46 (12.4)	26 (7.0)	5 (1.4)	1 (0.3)	
Total (n = 2953)	12 (0.4)	40 (1.4)	287 (9.7)	513 (17.4)	679 (23.0)	577 (19.5)	697 (23.6)	136 (4.6)	12 (0.4)	
18 (cpd)	0	4	7	10	15	26	40	65	90	
40–49 (y) (n = 1011)	69 (6.8)	58 (5.7)	63 (6.2)	228 (22.6)	254 (25.1)	206 (20.4)	116 (11.5)	17 (1.7)	0 (0.0)	
50–59 (y) (n = 904)	58 (6.4)	53 (5.9)	61 (6.8)	191 (21.1)	218 (24.1)	197 (21.8)	118 (13.1)	8 (0.9)	0 (0.0)	132.9
60–69 (y) (n = 668)	73 (10.9)	70 (10.5)	64 (9.6)	163 (24.4)	151 (22.6)	97 (14.5)	43 (6.4)	7 (1.1)	0 (0.0)	$p < .001$
70–79 (y) (n = 370)	78 (21.1)	59 (16.0)	49 (13.2)	95 (25.7)	52 (14.1)	27 (7.3)	8 (2.2)	2 (0.5)	0 (0.0)	
Total (n = 2953)	278 (9.4)	240 (8.1)	237 (8.0)	677 (22.9)	675 (22.9)	527 (17.9)	285 (9.7)	34 (1.2)	0 (0.0)	

*cpd: cycles per degree.

†Relationship between contrast sensitivity and age was assessed using Cochran-Mantel-Haenszel Statistics for 4 by 9 table at each frequency.

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age group. However, it seems likely that there was some difference in distribution of visual acuity among age groups even in the subjects with good visual acuity, because some subjects with visual acuity of 1.0 or better should have various degrees of cataract. In the NILS-LSA, the distribution of visual acuity of 1.0 or better and the estimation of cataract were not well investigated. It is possible that this also affected our results.

The traditional test for visual acuity examines only high contrast, high frequency sensitivity, using high contrast black on white letters. Testing only for visual acuity when assessing visual function may be inadequate because objects in daily life vary in levels of contrast and range of size under various lighting conditions. In particular, within the middle-aged to elderly population, pathological problems, such as presbyopia and decreasing transparency of media, will degrade their visual condition. Contrast sensitivity measures two variables, size and contrast, while visual acuity measures only size; therefore, contrast sensitivity tests provide additional information about vision.

Our report on the distribution of contrast sensitivity in a middle-aged to elderly population demonstrates that there is an age-related decrease in contrast sensitivity at all frequencies. It was also shown that 9.4% of the eyes having good visual acuity (1.0 or better) had poor contrast sensitivity at a high frequency, especially in the 70–79 year group where 21.1% of eyes had poor contrast sensitivity. In addition, our results showed that the distribution of contrast sensitivity at the higher frequencies was wider than that at the lower frequencies. Therefore, our results suggest that contrast sensitivity tests can assess different aspects of visual function that visual acuity tests alone do not address, especially at high frequencies. We believe that contrast sensitivity should also be measured when assessing the visual function of middle-aged or elderly populations for a complete assessment of visual quality.

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MTHFR Gene Polymorphism as a Risk Factor for Silent Brain Infarcts and White Matter Lesions in the Japanese General Population

The NILS-LSA Study

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Background and Purpose—Silent brain infarcts (SBI) and white matter lesions are relatively common neuroimaging findings, especially in the elderly population. The genetic background for SBI and white matter lesions in a large Japanese general population was investigated.

Methods—Subjects were recruited from participants in the National Institute for Longevity Sciences, Longitudinal Study of Aging. Genotyping of methylenetetrahydrofolate reductase (MTHFR) C677T gene mutation and brain MRI examination were performed in 1721 subjects free of any history of stroke. SBI and white matter lesions were diagnosed from MRI findings.

Results—Of 1721 MRI examinations, SBI was observed in 178 (10.3%). The prevalence of SBI and white matter lesions increased with age. The prevalence of SBI was significantly higher in subjects with the MTHFR TT genotype compared with the TC+CC genotype (14.6% versus 9.5%; 42 of 288 versus 136 of 1433; χ^2=6.71; P=0.010). The stage of white matter lesions was not significantly different. In subjects ≥60 years of age (n=849), the prevalence of SBI was significantly higher in TT than TC+CC (27.7% versus 16.6%; 36 of 130 versus 119 of 719; χ^2=9.16; P=0.002). The prevalence of moderately advanced white matter lesions was also significantly higher in TT than TC+CC (60.7% versus 49.0%; 79 of 130 versus 352 of 719; χ^2=9.16; P=0.002). After correction for other risk factors, the MTHFR TT genotype was independently associated with SBI (odds ratio [OR], 1.72; 95% CI, 1.10 to 2.68; P=0.018) and moderately advanced white matter lesions (OR, 1.58; 95% CI, 1.07 to 2.33; P=0.02).

Conclusions—These findings indicate that the MTHFR TT genotype is an independent risk factor for SBI and white matter lesions in the general Japanese population, especially in elderly subjects. **(*Stroke*. 2003;34:1130-1135.)**

Key Words: amine oxidoreductases ■ brain infarction ■ elderly ■ polymorphism ■ white matter

Silent brain infarcts (SBI) and white matter lesions, which are often incidentally identified during CT or MRI scanning in asymptomatic individuals, are relatively common neuroimaging findings, especially in the elderly population.[1-3] However, the presence of SBI and white matter lesions has been identified as an independent risk factor for the development of future symptomatic stroke[4,5] and dementia.[6] Accordingly, the underlying mechanisms have been the focus of much research.[1-3,7,8] Population-based studies have been performed to identify risk factors for SBI.[2,3] It has been demonstrated that classic risk factors such as hypertension and smoking are involved in the development of SBI.[1-3,7,8] The genetic predisposition to SBI has also been studied.[9,10] However, a population-based study to identify a candidate gene for SBI has not been performed.

Methylenetetrahydrofolate reductase (MTHFR) catalyzes the irreversible conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which serves as a methyl donor in the reaction converting homocysteine (Hcy) to methionine.[11,12] An increased plasma Hcy level has consistently been shown to be an independent risk factor for atherosclerotic disorders in several meta-analyses.[11-13] On the other hand, a common mutation of MTHFR, which results in a mild increase in the plasma level of Hcy, has not been reported as a consistent risk factor for atherothrombotic disorders, including stroke.[11,12,14] Although there could be several possible mechanisms underlying the discrepancy, the sampling of cases and controls might account for part of the discrepancy.

Two studies have evaluated the association between MTHFR gene C677T mutations and SBI.[9,10] Both studies

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failed to demonstrate significant associations. One evaluated subjects undergoing medical checkup.[9] To evaluate the genetic predisposition to SBI, community-based sampling of subjects would be less biased in the selection of cases and controls and would eliminate regional differences. Another study evaluated community-dwelling elderly subjects[10]; however, the number of subjects was too small to reach a conclusion. The National Institute for Longevity Sciences, Longitudinal Study of Aging (NILS-LSA) is a comprehensive study on aging in the Japanese general population.[15] In this standardized cohort with >1700 subjects, we investigated the association between MTHFR C677T mutations and the prevalence of SBI. All participants underwent brain MRI examination and were genotyped for the MTHFR C677T mutation.

Methods

Subject Selection

All participants were independent residents in Obu and Higashiura in the Aichi prefecture in central Japan. Residents 40 to 79 years of age were randomly selected from the resident register in cooperation with the local government. They were stratified by both age and sex. Randomly selected men and women were invited by mail to attend an explanatory meeting. At that meeting, the procedures for each examination and the follow-up schedule were fully explained. Written, informed consent to the entire procedure was obtained from each participant. Participants in the present study were recruited from subjects examined in 1997 to 1999. In total, 1758 subjects completed the entire procedure. Among them, 1721 subjects, 876 men and 845 women, free of any history of stroke, including transient ischemic attack, were evaluated in the present study. The ethics committee of the Chubu National Hospital approved all procedures of the NILS-LSA.

Research Area

The residential area of the present study is in the south of Nagoya. It is a commuter town and an industrial area for the Toyota group but still has many orchards and farms; thus, it has both urban and rural characteristics. This research area is in the center of Japan, and the climate is average for Japan. We examined a representative sample of the area's population via a national postal questionnaire of prefecture-stratified random samples of 3000 households from all prefectures in Japan and showed that the lifestyle of this area was the most typical of all areas in Japan.[15]

Risk Factor Evaluation

Details of physical examinations were published elsewhere.[15] In brief, lifestyle, medical history, and prescribed drugs were examined by questionnaires. Anthropometric and blood pressure measurements were performed by a physician. Venous blood was collected early in the morning after at least a 12-hour fast for measurement of serum lipids and plasma glucose. Blood pressure was measured twice at ≥5-minute intervals in subjects in the sitting position by doctors using a standard sphygmomanometer. The mean of 2 determinations was obtained for each participant. As risk factors for stroke, hypertension, glucose intolerance, hyperlipidemia, and smoking status were evaluated. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, and/or the use of an antihypertensive drug. Glucose intolerance was defined as fasting plasma glucose ≥110 mg/dL, HbA1c ≥5.8%, and/or the use of medication for lowering blood glucose. Hyperlipidemia was defined as serum total cholesterol ≥230 mg/dL, serum triglycerides ≥170 mg/dL, and/or the use of a lipid-lowering drug.

Brain MRI Examination

Brain MRI imaging was performed in all participants in the present study with a 1.5-T scanner (Toshiba Visart) at the NILS. The head position was oriented in the scanner and stabilized during the scanning procedure by use of a head support. To establish slice orientation, the first scanning sequence consisted of a T1-weighted sagittal series (repetition time [TR], 500 ms; echo time [TE], 15 ms; matrix, 256×256) centered in the midline to define the orbitomeatal line. The second series of T1-weighted axial images (TR, 500 ms; TE, 15 ms; thickness, 8 mm; gap, 1.5 mm; matrix, 256×256) and T2-weighted axial images (TR, 4000 ms; TE, 120 ms; thickness, 8 mm; gap, 1.5 mm; matrix, 320×320) were oriented parallel to the orbitomeatal line. Fourteen slices were taken at each examination.

An infarct was defined as a lesion ≥0.3 cm in diameter shown as a low-signal-intensity area on T1-weighted images that was also visible as a hyperintense lesion on T2-weighted images.[16,17] Small lesions (<1.5 cm) were diagnosed as lacunae. White matter lesions, depicted on T2-weighted images, were classified into 5 grades: grade 0, no abnormality; grade 1, minimal periventricular signal hyperintensities in the form of caps confined exclusively to the anterior horns; grade 2, hyperintensities in both the anterior and posterior horns of the lateral ventricles, periventricular unifocal patches, or rims lining the ventricles; grade 3, multiple periventricular hyperintense punctuate lesions reaching early confluence in the periventricular region; and grade 4, diffuse lesions.[16,17] A neurologist (F.M.) blinded to the clinical status of the subjects interpreted all MRI series.

MTHFR Genotype Analysis

Genomic DNA was extracted from peripheral blood lymphocytes by the standard procedure. MTHFR C677T mutation was determined by allele-specific primer–polymerase chain reaction (ASP-PCR) method. The single nucleotide polymorphism region of the gene was amplified by PCR with 2 ASPs (C-specific primer, 5′-GAAGGTGTCTGCGGGAXCC-3′; T-specific primer, 5′-GAGAAGGTGTCTGCGGGAXTC-3′) and a biotin-labeled common antisense primer (5′-biotin-GAATGTGTCAGCCTCAAAGAAA-3′). Amplified allele-specific DNA products were used for colorimetric genotyping. For MTHFR genotyping, 2 types of wells conjugated with the allele-specific C-type probe (5′-TCTGCGGGAXCCGATTTCAT-3′) or T-type probe (5′-TCTGCGGGAXTCGATTTCAT-3′) were prepared. The amplified DNA product was denatured with NaOH and added to each well. Then, it was hybridized at 37°C for 30 minutes with hybridization buffer containing formamide. After the wells were washed thoroughly, alkaline phosphatase–conjugated streptavidin was added to each well, and the plate was incubated at 37°C for 15 minutes. After the wells were washed, 0.8 mmol/L WST-1[2-(4-iodophenyl)-3-(4-nitrophenyl)-5-(2,4-di- sulfophenyl)-2H-tetrazolium, monosodium salt] and 0.4 mmol/L BCIP (5-bromo-4-chloro-3-indolyl phosphate p-toluidine salt), a substrate for alkaline phosphatase, was added, and colorimetry was performed. The genotypes were identified by the absorbance signal ratio between C type–specific and T type–specific wells. The validity of the ASP-PCR method was confirmed with genotyped DNA samples obtained by the standard method reported by Frosst et al.[18] KOD polymerase derived from Thermococcus kodakaraensis KOD1 was used.[19] The fidelity of our method is 3.4 times higher than that with *Taq* DNA polymerase. The mutation rate with this method is 0.35%.[19]

Statistical Analysis

All values are expressed as mean±SD if not specified. The associations between SBI and white matter lesions and MTHFR genotype were analyzed by χ^2 test. Logistic regression analysis was used to explore the independence of the effect of the MTHFR TT genotype on the prevalence of SBI and the presence of white matter lesions. All statistical analyses were performed with SAS software (SAS Institute Inc). A value of $P<0.05$ was considered statistically significant.

TABLE 1. Background Characteristics of Subjects With Silent Brain Infarcts and Moderate White Matter Lesions

	Silent Brain Infarcts		White Matter Lesions	
	(−)	(+)	Grades 0–1	Grades 2–4
n	1543	178	1225	496
Male, %	50	64†	51	52
Age, y	58±11	69±8‡	55±10	68±8‡
BMI, kg/m²	22.9±3.0	23.2±3.3	23.0±3.0	22.8±4.1
SBP, mm Hg	123±19	134±19‡	122±19	130±21‡
DBP, mm Hg	75±11	80±11‡	75±11	78±12‡
T-Chol, mg/dL	220±35	220±34	219±35	222±36
HDL-Chol, mg/dL	62±15	59±17*	62±16	61±15
Triglyceride, mg/dL	122±87	126±60	123±93	122±61
Blood glucose, mg/dL	103±21	108±23*	103±21	105±22
Hypertension, %	31	66‡	27	51‡
Hyperlipidemia, %	48	52	46	54*
Glucose intolerance, %	21	35‡	21	28*
Current smoker, %	23	24	24	21

MTHFR indicates methylenetetrahydrofolate reductase; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; T-Chol, total cholesterol; HDL-Chol, high density lipoprotein cholesterol.

Values are mean±SD. *$P<0.05$, †$P<0.001$, ‡$P<0.0001$ versus corresponding controls [silent brain infarcts (−) and white matter lesions 0–1].

Results

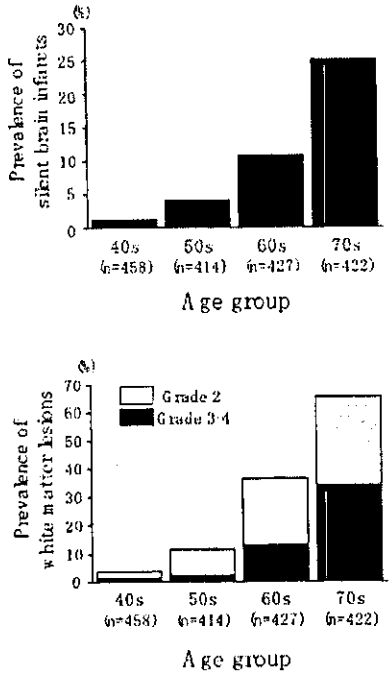
Background Characteristics of Participants and Prevalence of SBI

Table 1 summarizes the backgrounds of all participants subdivided by the presence of SBI and moderately advanced white matter lesions. The presence of SBI and white matter lesions was associated with advanced age, hypertension, and glucose intolerance. The prevalence of SBI and white matter lesions significantly increased with age (the Figure). In subjects ≥60 years of age, SBI was observed in 18.3% (155 of 849).

MTHFR Gene Mutation and SBI and White Matter Lesions

The breakdown of the total 1721 subjects by MTHFR C677T gene mutation was as follows: CC genotype, 623; CT genotype, 810; and TT genotype, 288. The distribution of MTHFR genotypes was consistent with published reports on Japanese subjects[18–20] and was in agreement with the Hardy-Weinberg proportion ($P=0.80$).

The prevalence of SBI and the grade of white matter lesions are shown in Table 2. The prevalence of SBI was significantly higher in subjects with the MTHFR TT genotype compared with C carriers (CT+CC). However, there was no significant association between MTHFR genotype and grade of white matter lesions. Because SBI and white matter lesions were prevalent only after the age of 60 years, the associations between MTHFR genotype and prevalence of SBI and white matter lesions were evaluated in subjects ≥60 years of age. In this population, the MTHFR genotype



Age-dependent increases in prevalence of SBI and white matter lesions. Prevalence of both types of lesion increased with age.

was significantly associated with the presence of SBI and white matter lesions (Table 3).

To further investigate whether the MTHFR genotype is associated with SBI independently of other known risk factors, logistic regression analysis for SBI was performed with 3 models including the following risk factors: hypertension, hyperlipidemia, glucose intolerance, smoking, and

TABLE 2. Prevalence of Silent Brain Infarcts and White Matter Lesions in 3 MTHFR Genotypes in Total Subjects

MTHFR (n)	CC (623)	CT (810)	TT (288)	CC+CT (1433)	Total (1721)
No SBI	568	729	246	1297	1543
SBI	55	81	42	136	178
		$\chi^2=7.23$		$\chi^2=6.71$*	
		$P=0.027$		$P=0.010$	
Lacunae	51	68	37	119	156
		$\chi^2=6.21$		$\chi^2=6.17$*	
		$P=0.045$		$P=0.013$	
White matter lesions					
Grades 0–1	455	571	199	1026	1225
Grade 2	93	143	51	236	287
Grades 3–4	75	96	38	171	209
		$\chi^2=2.65$		$\chi^2=0.75$*	
		$P=0.62$		$P=0.69$	
Grades 2–4	168	239	89	407	496
		$\chi^2=1.84$		$\chi^2=0.73$*	
		$P=0.40$		$P=0.39$	

SBI indicates silent brain infarct.

*Comparison with MTHFR TT genotype.

TABLE 3. Prevalence of Silent Brain Infarcts and White Matter Lesions in 3 MTHFR Genotypes in Subjects Aged 60 or Over

MTHFR (n)	CC (304)	CT (415)	TT (130)	CC+CT (719)	Total (849)
No SBI	257	343	94	600	694
SBI	47	72	36	119	155
		χ^2=9.58		χ^2=9.16*	
		P=0.008		P=0.002	
Lacunae	44	63	32	107	139
		χ^2=8.08		χ^2=8.10*	
		P=0.018		P=0.004	
White matter lesions					
Grades 0–1	155	212	51	367	418
Grade 2	78	114	42	192	234
Grades 3–4	71	89	37	160	197
		χ^2=6.69		χ^2=6.20*	
		P=0.153		P=0.045	
Grades 2–4	149	203	79	352	431
		χ^2=6.15		χ^2=6.15*	
		P=0.046		P=0.013	

SBI indicates silent brain infarct.
*Comparison with MTHFR TT genotype.

MTHFR genotype in subjects ≥60 years of age (Table 4). It revealed that the MTHFR TT genotype was independently associated with SBI, asymptomatic lacunar infarctions, and white matter lesions of grade 2 or higher.

Discussion

Meta-analyses have revealed a consistent association between the plasma level of Hcy and atherosclerotic disorders.[11,13] Boushey et al[13] reported that the odds ratio (OR) for coronary arterial disease with a 5-μmol/L Hcy increment was 1.6 (95% CI, 1.4 to 1.7) for men and 1.8 (95% CI, 1.3 to 1.9) for women in their meta-analysis. Recently, it has also been reported that a high Hcy level was significantly associated with SBI and white matter lesions.[10,20] Although MTHFR C677T mutation is a major cause of mild hyperhomocysteinemia, Brattstrom et al[14] showed in their meta-analysis that the mutation did not increase cardiovascular risk in their 5869 controls and 6644 cases. They suggested that the modest increase in plasma concentration of Hcy found in patients with cardiovascular disease is an epiphenomenon, a consequence of the effects of the well-established standard risk factors for vascular disease and renal function, and that it is not directly causal. However, Ueland et al[11] further extended the interpretation of the findings of meta-analysis. Because the estimated relative risk for atherosclerotic disorders associated with a modest increase in plasma Hcy (2.6 μg/mL) by MTHFR TT mutation is 1.10 to 1.15, it is expected that a larger population would be necessary to prove a significant association with the MTHFR TT genotype.[11] These findings indicate that the genetic association between MTHFR TT genotype and atherosclerotic disorders is not conclusive.

The association between the MTHFR gene mutation and SBI has been studied in the Japanese population.[9,10] Those studies reported a lack of association between MTHFR and SBI. In a study by Notsu et al,[9] SBI patients were recruited from consecutive patients who underwent brain MRI examination for a health screening examination. Accordingly, these subjects were neither randomly selected nor community-based samples. One of the concerns in the recruitment of participants in medical checkups is that the possibility that some could have subtle symptoms prompting them to have a medical checkup, including brain MRI, cannot be excluded. To evaluate the genetic predisposition to SBI, community-based sampling of subjects would be less biased in the selection of cases and controls and would eliminate regional differences. Another study reported by Matsui et al[10] was a community-based study. Although they did not find a positive association, the number (38 cases) was too small to reach a conclusion. To respond to these concerns, large, population-based, random sampling is advisable. NILS-LSA is a community-based random sample study in central Japan. Our preliminary study indicated that the area is representative of the total Japanese population. Region-dependent differences in folic acid[21] could also be eliminated. All participants underwent brain MRI, and genotyping was performed. The advantage of a community-dwelling study is minimal bias in the selection of cases and controls. On the other hand, a disadvantage is that the number of cases of concern is small,

TABLE 4. Odds Ratio for Presence of Silent Brain Infarcts, Lacunar Lesions, and White Matter Lesions in Subjects Aged 60 or Over

	Model I		Model II		Model III	
	OR	CI	OR	CI	OR	CI
SBI	1.93	1.25–2.97	1.82	1.18–2.82	1.72	1.10–2.68
	P=0.0028		P=0.0073		P=0.018	
Lacunae	1.91	1.22–3.00	1.81	1.15–2.86	1.71	1.08–2.73
	P=0.0049		P=0.011		P=0.024	
White matter lesions						
Grades 2–4	1.62	1.10–2.37	1.63	1.11–2.39	1.58	1.07–2.33
	P=0.013		P=0.013		P=0.02	

OR indicates odds ratio; CI, 95% confidence interval; SBI, silent brain infarct. Model I, no correction for other risk factors; model II, correction for sex, smoking, hyperlipidemia, and glucose intolerance; model III, correction for sex, smoking, hyperlipidemia, glucose intolerance, and hypertension.