Table 1
Primer sequence, annealing temperature, PCR product size, restriction endonuclease, and digestion pattern for the MTHFR C677T, A1298C, and A1793G polymorphisms

Position	Exon	Sequence 5′–3′	Annealing temperature (°C)	Size (bp)	Nuclease	Digestion pattern (bp)
C677T	Ex4-F	AGTCCCTGTGGTCTCTTCATC	58	387	Gain of *Hin*fI site	152/235
	Ex4-R	GGAGATCTGGGAAGAACTCAG				
A1298C	Ex7-MF	AGATGTGGGGGGAGGAGCTGACCAGTGC*AG	62	175	Gain of *Fnu*4HI site	28/147
	Ex7-MR	GCCCCA**CAGCCTGGCCTA**CAGCT				
A1793G	Ex11-F	TTGGAGAGCCCTGTTAATCTTG	58	390	Loss of *Bsr*BI site	125/264
	Ex11-R	AGAGACACGAAGGAGAGTGGAG				

* Mismatch position (A–C) for creation of an artificial *Fnu*4HI site.
** Mismatch positions (both of C–A) for abolishment of *Fnu*4HI sites.

After informed consent was given, blood leukocyte DNA was isolated using the standard phenol–chloroform method. We generated the three primer sets according to a genomic sequence in the NCBI database (GenBank accession No: AF257484). Table 1 depicts each of the primer sequences, the annealing temperature, the PCR product length, the restriction enzymes for PCR-restriction fragment length polymorphism (RFLP) analysis, and the digestion pattern. "Hot start" PCR reactions for each primer set were performed using a supplied kit (TaKaRa, Japan) in standard PCR reaction conditions. The amplified PCR products for each primer set were subjected to RFLP analysis by agarose electrophoresis. ApoE genotypes were determined by a standard *Hha*I RFLP analysis [6,7].

The Hardy–Weinberg equilibrium was confirmed for both populations. The allele frequencies and the number of positive individuals having at least one polymorphism or haplotype were compared using the chi-square test. The possible effects of each haplotype on LOAD were determined using logistic regression analysis with age, sex, and the presence of at least one ApoE ε4 allele as covariates. We also stratified the data sets into two types of subjects: subjects possessing at least one ApoE ε4 allele and subjects without an ApoE ε4 allele. Odds ratios (ORs) were calculated with exact 95% confidence intervals (CIs). *P* values and significance considerations are two-sided and subject to a significance level of 5%. Analyses were performed with the SPSS statistical package (Japanese version 11).

3. Results

A total of 307 Japanese subjects from a western region of Japan were enrolled, including 129 individuals with a clinical diagnosis of LOAD and 178 cognitively normal controls (CTLs). The mean age at onset of patients with LOAD was 74.4 years (65–85, S.D. = 5.4), and 76.0% were women. The corresponding values of the CTL group were 74.4 (65–85, S.D. = 4.5), and 73.0% were women.

Concurrences of the genotype distributions of C677T with A1298C indicated complete linkage disequilibrium between the polymorphisms at nucleotide 677 and nucleotide 1298, as previously reported [10,22]. Correspondingly, we did not detect the combinations of 677CT and 1793AA, 677TT and 1793AA, or 677TT and 1793AG, indicating complete linkage disequilibrium between all of these polymorphisms. Nor did we detect combinations of 1298AA and 1793AG, 1298AA and 1793AA, or 1298AC and 1793AA, indicating that the 1793A polymorphism is a concomitant allele to the 1298A allele. Thus, the 1298A and 1793A allele are always in the *cis* configuration. From these results, we divided the regional haplotypes of the MTHFR gene into four haplotypes, which we named Haplotype A (wild type 677C-1298A-1793G), Haplotype B (677T-1298A-1793G), Haplotype C (677C-1298C-1793G), and Haplotype D (677C-1298C-1793A) (Fig. 1); this results in eight diplotypes (genotypes). Further data analysis was performed using these haplotypes. The diplotype distributions between AD and CTL did not statistically differ because of a small number of cases for each diplotype (Table 2). Logistic regression analysis adjusted by age, gender, and the presence of at least one ApoE ε4 allele demonstrated a significant protective effect of Haplotype C (OR = 0.426; 95% CI = 0.220–0.827; $P = 0.012$, presence of at least one Haplotype C versus absence of Haplotype C), whereas the presence

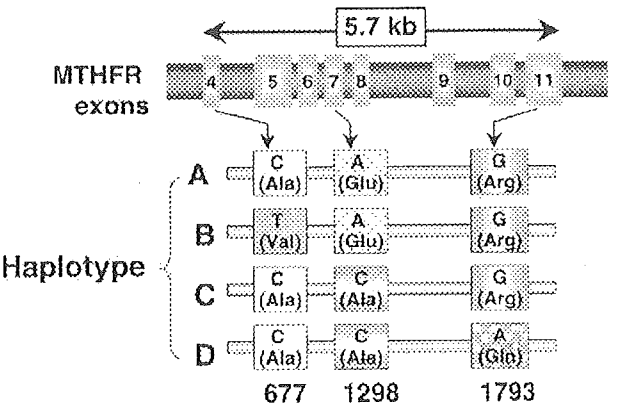

Fig. 1. A schematic representation of the estimated regional haplotypes of the MTHFR gene.

Table 2
Diplotype distribution and haplotype frequency for exon 4 to exon 11 of the MTHFR gene

	Diplotype distribution (%)									
	AA	AB	AC	AD	BB	BC	BD	CC	CD	DD
AD	25 (19.4)	49 (38.0)	5 (3.9)	9 (7.0)	17 (13.2)	6 (4.7)	10 (7.8)	3 (2.3)	3 (2.3)	2 (1.6)
CTL	31 (17.4)	49 (27.5)	17 (9.6)	10 (5.6)	25 (14.0)	18 (10.1)	18 (10.1)	3 (1.7)	6 (3.4)	1 (0.6)

Table 3
Logistic regression analysis of at least one of each haplotype adjusted by age, gender, and at last one ApoE ε4 allele

	d.f.	Odds ratio	95.0% CI	*P* value
Haplotype B	1	0.921	0.553–1.532	0.750
Haplotype C	1	0.426	0.220–0.827	0.012*
Haplotype D	1	1.023	0.549–1.906	0.943

* Statistically significant.

Table 4
Logistic regression analysis classified by ApoE ε4 status of at least of one each haplotype adjusted by age and gender

	d.f.	Odds ratio	95.0% CI	*P* value
Haplotype B				
ε4 (−)	1	1.180	0.638–2.183	0.598
ε4 (+)	1	0.502	0.176–1.427	0.196
Haplotype C				
ε4 (−)	1	0.293	0.115–0.744	0.010*
ε4 (+)	1	0.592	0.198–1.771	0.349
Haplotype D				
ε4 (−)	1	0.885	0.416–1.884	0.752
ε4 (+)	1	0.977	0.299–3.190	0.969

* Statistically significant.

Haplotype B and Haplotype D conferred no significant advantage (OR = 0.921; 95% CI = 0.553–1.532; $P = 0.750$, presence of at least one Haplotype B versus absence of Haplotype B, and OR = 1.023; 95% CI = 0.549–1.906; $P = 0.943$, presence of at least one Haplotype D versus absence of Haplotype D) (Table 3). Expectedly, the estimated risk of AD in the presence of ApoE ε4 was highly significant (OR = 5.318; 95% CI = 3.153–8.972; $P < 0.001$, presence of at least one ApoE ε4 allele versus absence of ApoE ε4 allele). Subsequent analysis stratified according to the ApoE ε4 status revealed that the protective effect of Haplotype C of the MTHFR gene against LOAD was more prominent in the group lacking the ApoE ε4 allele (OR = 0.293; 95% CI = 0.115–0.744; $P = 0.010$, presence of at least one Haplotype C versus absence of Haplotype C) (Table 4).

4. Discussion

In the present study, we used regional haplotypes to assess the association between polymorphisms (C677T, A1298C, and A1793G) in the gene encoding the MTHFR enzyme and susceptibility to LOAD. We evaluated complete linkage disequilibrium between the 677C and 1298A alleles in our samples as previous reported results [10,22]. Importantly, we found that the 1793G allele always appeared in *trans* with 677T and in *cis* with 1298C. Therefore, we allocated the regional haplotypes of the MTHFR gene into four haplotypes (Fig. 1).

We found that presence of at least one Haplotype C was significantly protective against LOAD (Table 3). Furthermore, the protective effect of Haplotype C was more predominant in ApoE ε4-negative individuals as compared to ApoE ε4-positive individuals (Table 4).

The marked impact of the MTHFR 677T allele in reducing enzyme activity and thermolability and increasing plasma Hcy levels has been well characterized. Although the influence of the 1298C allele (equivalent to Haplotype C) on MTHFR enzyme thermolability has been shown to be negligible, the effects on reducing the enzyme activity in vitro are controversial in independent studies [23,24]. The effects of the 1298C-1793A haplotype (Haplotype D) on the metabolism or activity of MTHFR enzyme have also yet to be discovered.

Biological studies have demonstrated the allele-specific antioxidant potential of ApoE (ε2 > ε3 > ε4) [4,11]. In addition, recent studies using ApoE-deficient transgenic mice have proposed that folate, a major regulatory factor for MTHFR activity and levels of the non-protein Hcy, quenches oxidative damage [20,21]. Therefore, MTHFR dismetabolism and/or inappropriate folate intake may impair the capacity against oxidative stress. We found the enhanced protective effect of Haplotype C of the MTHFR gene in ApoE ε4 lacking individuals, indicating that Haplotype C may have synergic beneficial effects with the negativity of ApoE ε4 against oxidative stress.

In conclusion, we propose that the extended genotypes and haplotypes of the MTHFR gene have important implications for the pathogenesis of LOAD. A negative correlation between the 1298C allele and plasma Hcy levels and an inverse association between Vitamin B-12 status and plasma Hcy have been reported for the 1298C allele [1,10]. In addition, it has been reported that allele or haplotype construction of the MTHFR gene differs according to ethnicity [18] and the polymorphisms of the MTHFR gene have implications for human fertility and dietary folate consumption [16,17]. However, because Haplotype C of the MTHFR gene is a genetic factor that provides protection

against the development of LOAD in the Japanese population, we suggest further analysis of samples from different ethnicities or communities to avoid type 1 (false positive) error. Studies to clarify the effects of the estimated haplotypes on MTHFR metabolism will also be required.

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Genetic Analysis of Familial Alzheimer's Disease in a Japanese Population

Yosuke Wakutani[a], *Yoshiki Adachi*[a], *Kenji Wada-Isoe*[a], *Kaoru Yamagata*[a], *Katsuya Urakami*[b], *Kenji Nakashima*[a]

Departments of [a]Neurology, Institute of Neurological Sciences, and [b]Biological Regulation, School of Health Science, Faculty of Medicine, Tottori University, Yonago, Japan

Alzheimer's disease (AD) is one of the most common neurodegenerative disorders in the elderly population. The pathological hallmarks (amyloid plaque, neurofibrillary tangle and neuronal cell loss) have been well characterized. The causal genes for early-onset familial Alzheimer's disease (FAD) are the presenilin 1 (PS-1) gene on chromosome 14 [1], the presenilin 2 (PS-2) gene on chromosome 1 [2] and the amyloid precursor protein (APP) gene on chromosome 21 [3]. In addition, apolipoprotein E (APOE) allele 4 ($\varepsilon 4$), located on chromosome 19, is a well-established genetic risk factor for sporadic AD [4]. Among these genes, mutations in PS-1 seem to be the most common genetic factor underlying the development of early-onset FAD. To date, over 100 missense mutations for PS-1, 8 mutations for PS-2 and 16 mutations for APP are cited in an online database (AD mutation database; http://molgen-www.uia.ac.be/ADMutations/). Several PS-1 mutations and only an APP mutation (V717I) were previously described in the Japanese population (table 1) [2, 5–19]. Eighteen missense mutations in the PS-1 gene were reported in the Japanese familial AD (FAD) pedigrees. No pathogenic mutation of the PS-2 gene has been identified in the Japanese population. In this chapter, we report the results of our most recent studies of these three genes in FAD and sporadic AD patients in a Japanese population.

Subjects and Methods

Patient Samples

Twenty-two Japanese patients were selected from 5 early-onset (<65 years old) FAD patients (mean age of onset: 58.2 years), 7 late-onset (>65 years old) FAD patients

Table 1. APP, PS-1 and PS-2 gene mutations in Japanese FAD and sporadic AD

	Exon	Mutation	Reference
PS-1	5	V96F	5
		E123K	6
	6	H163R[1]	5, 7, 8, 9
	7	E184D	10
		G209R	11
		I213T	5
		G217D	12
		F237I[2]	13
	8	A260V	2, 14
		S266G	15
	8	R269H	9
		E273A	9
		E280A	8
		A285V	2
	9	S290C	16
	11	G384A	9
		N405S	17
	12	A431V	18
APP	17	V717I	19

[1]This mutation was reported in early-onset FAD and early-onset sporadic AD.

[2]This mutation was reported in early-onset FAD with spastic paraparesis.

(mean age of onset: 70.3 years old), and 10 early-onset sporadic AD patients (mean age of onset: 55.4 years). All patients fulfilled the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorder Association (NINCDS-ADRDA) criteria for probable and possible AD [20]. These diagnoses were assisted by MRI or CT imaging studies. We defined patients as having FAD if at least 2 members were affected in a family and the difference in age of onset was less than 20 years. Genomic DNA was extracted from peripheral leukocytes using the standard phenol-chloroform method and subjected to PCR amplifications.

Primers and PCR Amplification

Intronic primers were generated to amplify exons 16, 17 and 18 of the APP gene, exons 3–12 of the PS-1 and PS-2 genes. The primer sequences are provided in table 2. In brief, 50–100 ng DNA was amplified using PCR in each 15 μl reaction mixture using 1 mmol of specific primers and 0.8 units of Taq DNA polymerase (TaKaRa, Tokyo, Japan) in supplied 1 × PCR buffer for 35 cycles of 30 s at 94°C for denaturing, 30 s at 58°C for annealing, and 40 s at 72°C for extension.

Table 2. PCR primers (5′→3′)

APP		Size, bp
APP Ex16-F	TAGAAAGAAGTTTTGGGTAGGCTTT	260
APP Ex16-R	AGAGTTAATAGGTCATTTGGCAAGACA	
APP Ex17-F	AATGAAATTCTTCTAATTGCGTTT	258
APP Ex17-R	TTCTCTCATAGTCTTAATTCCCACTT	
APP Ex18-F	TTACTGCTTCTCCATGTTCACC	249
APP Ex18-R	TTCTATAAATGGACACCGATGG	
PS-1		
PS1Ex-3F	TCTTTCCCTTTTCAGAACCTCA	222
PS1-Ex3R	CAGAGGTGAGGGGAGATGATAA	
PS1-Ex4F	TCATAGTGACGGGTCTGTTGTT	423
PS1-Ex4R	CTTCAAGGTGATGATGACATGC	
PS1-Ex5F	TTCTGTGTTGGAGGTGGTAATG	287
PS1-Ex5R	CTGTGACAAGAATACCCAACCA	
PS1-Ex6F	AGTCTGGGCGACAAAGTGAG	237
PS1-Ex6R	TGATAGCTACACAGCACAAAGG	
PS1-Ex7F	GTTTGGGAGCCATCACATTATT	373
PS1-Ex7R	AGATGAGGAAAGAAAACACTCCA	
PS1-Ex8F	CCTTCGTTAATTCCTCCCTACC	248
PS1-Ex8R	CATGTGCTTCAGTTCCGATAAA	
PS1-Ex9F	GGAGAAATGATGGCTTGTTGTT	266
PS1-Ex9R	GGAGTCTATGACCAAAGAAAGACG	
PS1-Ex10F	CAATGACAGCTAGTTACTGTTTCCA	346
PS1-Ex10R	TTCATTTTATTCTCAAAAAGGTTGA	
PS1-Ex11F	ATTCATTGTGGGGTTGAGTAGG	294
PS1-Ex11R	GAACTGCCTTAAAGGGACTGTG	
PS1-Ex12F	CTTGTGATTGAGTTTTGCCTGA	294
PS1-Ex12R	TGTCCTCCCCAGATTTTGTTAT	

PS-2		Size, bp
PS2-Ex3F	GTCTCACAGGAAAGTGGAACAAG	284
PS2-Ex3R	GAATGTCTGGTTTTCATCTGTAAGG	
PS2-Ex4F	TGGAAAGCAACATTCAAACTTC	456
PS2-Ex4R	TTCTTCATCCCTGCTCTTTACC	
PS2-Ex5F	TAGCAGGTCCAGAATCACTCAAG	318
PS2-Ex5R	GTTTTTCTAAAGGCGGCTGTTT	
PS2-Ex6F	GCTTGGGTATCAGTCTCAGGAT	258
PS2-Ex6R	GAGCTCGATGGTCATCTTTCC	
PS2-Ex7F	GAATGGTGGTAAACTGCTAGGC	407
PS2-Ex7R	CTCTGCAGAAAGGGATGCAAG	
PS2-Ex8F	GCTACAGGGCAGGCTCTTCT	206
PS2-Ex8R	ACCCCGAGTCAGGCAGAG	
PS2-Ex9F	GCTTTCTGGGACGCAGACT	311
PS2-Ex9R	TGGTTTTCAACGGACCTTTC	
PS2-Ex10F	ACCCCTTCTTGGAGCTTTGT	282
PS2-Ex10R	GAGCCTCCACCCTCTGTCTC	
PS2-Ex11F	GGGCCAGAGTTTCTCTTCTTTT	281
PS2-Ex11R	CCCTAGGGATCCTGAGACCTG	
PS2-Ex12F	CCCAGGGACTAGACCATGACT	290
PS2-Ex12R	AACTGCATCCAATGAAAATTCC	

Table 3. Identified mutation and polymorphism

	Exon (PCR region)	Polymorphism	Amino acid	NCBI SNP cluster ID
APP	Exon 16	2032 G/A	D678N	–
	Exon 18	IVS17-10 T/C	intron	–
PS-2	Exon 3	69 T/C	A23A	rs11405
		129 C/T	N43N	rs6759
	Exon 4	IVS3-42 G/A	intron	rs1295644[1]
		IVS3-29 T/C	intron	rs1295643
		260 T/C	H87H	rs1046240[1]
	Exon 5	IVS5+30 G/C	intron	rs2236910
	Exon 8	861 C/T	P287P	–
	Exon 9	IVS8-24 G/A	intron	rs2802267
	Exon 11	IVS11+24 G/A	intron	rs2855562

[1]These are linked polymorphisms in our samples.

Single-Strand Conformation Polymorphism Analysis and Sequence Analysis

PCR products of AD samples for screening were subjected to single-strand conformation polymorphism (SSCP) analysis. One microliter of PCR product was denatured in formamide-containing buffer at 95°C for 8 min, quickly chilled on ice, and electrophoresed on a 12% polyacrylamide gel with 10% glycerol at 4°C for 24 h at 200 V. DNA bands were visualized using silver staining. The mobility-shifted band was directly cut from the gel using a freshly prepared razor blade. The eluted band was re-amplified under identical PCR conditions for 45 cycles. The purified PCR product derived from the extra band was subjected to direct sequencing using a Big Dye cycle sequence kit (Amersham Bioscience Japan, Tokyo, Japan) and the ALF automated luminescent sequencer (Applied Biosystems Japan, Tokyo, Japan). APOE genotyping was carried out according to standard procedures [22].

Results

In PCR-SSCP analysis, 2 extra conformers in the APP gene (exon 16, exon 18), none in the PS-1 gene and 9 in the PS-2 gene were observed. Table 3 shows the identified mutation and polymorphisms identified by sequence analysis. No missense mutations in the PS-1 and PS-2 gene were detected in any samples. Except for the IVS17-10 T/C polymorphism of the APP gene and the 861 C/T (P287P) polymorphism of the PS-2 gene, the identified polymorphisms were previously reported in the NCBI SNP database (the APP gene; http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId = 35, the PS-1 gene; http://www.ncbi.nlm.

nih.gov/SNP/snp_ref.cgi?locusId = 5663 and the PS-2 gene; http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId = 5664). We identified an entirely novel APP gene mutation (2032 G/A D678N [APP770 numbering]) in an early-onset FAD pedigree containing 3 affected members with a mean age of onset of 59.7 years and APOE genotype ε3/ε3.

Discussion

In the present study, we systematically conducted mutation screening of the PS-1, PS-2 and APP genes in samples from patients diagnosed with varied forms of AD. No pathogenic mutations of the PS-1 or PS-2 genes were identified. In the APP gene, we identified a novel mutation (D678N) in an early-onset FAD pedigree. This mutation is equivalent to an amino acid substitution of Asp at position 7 of amyloid-β (Aβ) (Asp7-Aβ) with Asn (Asn7-Aβ). We hypothesize that Asn7-Aβ derived from the D678N mutant APP has altered fibrillogenic and/or catabolic properties that increase accumulation of protein and/or the neurotoxic potential of Aβ, eventually leading to AD. In vitro studies will be necessary to characterize the pathogenic impact of the D678 mutation on fibrillogenesis and/or secretase activity.

We identified 2 novel SNPs in the APP gene and 9 SNPs (including 1 novel SNP) in the PS-2 gene. The IVS17-10 T/C polymorphism of the APP gene, identified from an EOSAD patient (age of onset: 59 years), is close to a splicing acceptor site and may raise a possibility to influence splicing efficiency. The genetic case-control study of this polymorphism is currently under way. While 861 C/T (P287P) polymorphism of the PS-2 gene was found in an FAD pedigree of variable age of onset (age 63–75), we have not obtained sufficient segregation data regarding this mutation. Furthermore, since 861 C/T (P287P) is a silent polymorphism, it is unclear whether this polymorphism (or a linked mutation) of the PS-2 gene contributes to the development of this FAD pedigree.

Genetic linkage studies have demonstrated multiple susceptible loci for FAD [22–26]. Additional studies are required to identify as many candidate genes as possible to elucidate the pathomechanisms of AD and improve our strategies for treatment and prevention of AD.

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Yosuke Wakutani
Department of Neurology, Institute of Neurological Sciences
Faculty of Medicine, Tottori University
Nishimachi 36–1, Yonago, Tottori 683–8504 (Japan)
Tel. +81 859 34 8034, Fax +81 859 34 8083, E-Mail ywaku@grape.med.tottori-u.ac.jp

Population-Based Door-to-Door Survey of Migraine in Japan: The Daisen Study

Takao Takeshima, MD, PhD; Kumiko Ishizaki, MD, PhD; Yoko Fukuhara, MD, PhD; Tamami Ijiri, MD; Masayoshi Kusumi, MD, PhD; Yosuke Wakutani, MD, PhD; Masatada Mori, MD, PhD; Mika Kawashima, MD, PhD; Hisanori Kowa, MD, PhD; Yoshiki Adachi, MD, PhD; Katsuya Urakami, MD, PhD; Kenji Nakashima, MD, PhD

Objectives.—To determine prevalence and characteristics of migraine in Japan, and to investigate use of medical care and whether food preference is associated with risk of migraine.

Methods.—Structured questionnaires were given to all adult residents (N = 5758; 2681 men and 3077 women) in Daisen, a rural community in western Japan. Second questionnaires, specific to headache, were given to 1628 residents with headache. A telephone survey was also carried out. Statistical Packages for the Social Sciences analyzed the data.

Results.—The 1-year prevalence of migraine was 2.3% (migraine with aura, 0.4% and without aura, 1.9%) in men and 9.1% (migraine with aura, 1.0% and migraine without aura, 8.1%) in women. Overall prevalence of migraine in Daisen was 6.0% (95% confidence interval [CI], 5.4% to 6.6%). Women observed a 5.9-fold higher risk of migraine than men (odds ratio, 5.9; 95% CI, 4.5 to 8.0; $P < .0001$, after age adjustment, by logistic analysis). Fatigue and loss of vigor were predominant premonitory symptoms of migraine. Fatigue, mental stress, and lack of sleep were the main headache triggers. Over a 3-month period, 20.3% of migraineurs experienced time or days off work due to headache. Only 7.3% of those with migraine with aura and 5.3% of those with migraine without aura had consulted a physician, and of those with migraine, 61.0% with aura and 71.8% without aura had never visited a medical doctor for their headache.

Consumption of alcohol and cigarette smoking did not influence the risk for migraine or tension-type headache, after age and gender adjustment (logistic analysis).

Migraineurs consume significantly more fatty/oily foods, coffee, and tea than nonheadache subjects of the same community. Migraineurs consume significantly fewer fish than nonheadache residents.

Conclusions.—Only a few Japanese migraineurs receive benefits of medical services and recent advances of headache medicine. Public education concerning headaches is one of the most urgent issues in Japan.

Key words: epidemiology, foods, medical care, migraine, prevalence of migraine, tension-type headache

Abbreviations: MWA migraine with aura, MWOA migraine without aura, ETTH episodic tension-type headache, CTTH chronic tension-type headache, TTH tension-type headache

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From the Department of Neurology, Institute of Neurological Sciences, Tottori University Faculty of Medicine, Yonago, Japan. Dr. Urakami is now with the Section of Environment and Health Science, Department of Biological Regulation, School of Health Science, Tottori University Faculty of Medicine.

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Address all correspondence to Dr. Takao Takeshima, Department of Neurology, Institute of Neurological Sciences, Tottori University Faculty of Medicine, 36-1 Nishimachi, Yonago 683-8504, Japan.

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Migraine is common and features of the disorder are well documented; however, detailed features of Japanese migraineurs remain to be studied and prevalence waits to be confirmed. In the late 1980s, a preliminary study of migraine prevalence in 2 areas of western Japan was carried out. A prevalence of 1.9% on Sanin Island and 3.5% in Daisen was reported.[1,2] These prevalences were lower than those of migraine reported from Western countries.[3,4] In 1997, Sakai and Igarashi surveyed Japan nationwide by telephone interview and reported a migraine prevalence of 8.4%.[5] In the present study, a detailed, population-based, door-to door survey was conducted in Daisen. The major objectives of this study were: (1) to clarify migraine prevalence based on the diagnostic criteria of the International Headache Society (IHS), (2) to reveal features of migraine in a community-based survey in Japan, and (3) to investigate the use of medical care of Japanese with headache. In addition, we also surveyed food preference and its possible association with headaches.

SUBJECTS AND METHODS

Daisen is a rural community in Tottori prefecture, western Japan. Total population was 7135 in 1999; there were 5758 residents aged 20 years or older (2681 men and 3077 women). Major industries were agriculture, dairy farming, and tourism.

An initial survey was performed as part of the health care program of Daisen. Under the cooperation of local public health nurses, questionnaires were delivered to all residents who were 20 years of age or older. The questionnaires requested information regarding occupation, general health perception, sleep condition, physical and mental symptoms, current health problems, past history of illness, smoking and drinking habits, physical conditions, food preference, presence of headache, limb weakness and numbness, visual ability, speech ability, and dizziness.

The headache section of the questionnaire included areas of headache experience within the previous year, except for that attributed to common cold or hangover; severity; characteristics; site of headache; mean duration; frequency; aura; premonitory symptoms; associated symptoms (nausea, vomiting, photophobia, phonophobia, sore shoulder, dizziness, vertigo, eye congestion, lacrimation, floating sensation); and use of medical care. Subjects were encouraged to include details of their headaches. The initial survey was carried out in September of 1999.

Of the 5758 eligible subjects, 4795 (83.4%) completed the questionnaire. Forty-nine subjects responded anonymously. Of the 4795 responders, 2148 were men and 2617 were women. Thirty subjects did not clarify their gender, and 46 did not state their age. Of 4795 responders, 1628 subjects had some headache. The second questionnaire, directed specifically to headache, requested detailed characteristics of their headache, time or days off work or housework, age at onset, use of headache remedies, family history, headache triggers, pattern of medical care use, reasons for not seeking medical care for headache, and headache-specific quality-of-life questionnaires developed by the authors. Public health nurses and neurologists (authors) delivered the second questionnaire to the 1628 residents with headache; it was completed by 1264 (77.6%).

Headache type was diagnosed according to the criteria of the International Headache Society (IHS).[6] Headache categories used in this analysis were: migraine with aura (MWA), migraine without aura (MWOA), episodic tension-type headache (ETTH), chronic tension-type headache (CTTH), and other headaches. All answers to the questionnaires were reviewed by the authors, not only yes or no or multiple-choice answers, but also free comments were reviewed to determine headache type.

Characteristics of headaches were unclear in 57 subjects based on the questionnaire answers. Telephone interviews proved successful in 52 of these subjects. It was suspected that 5 subjects had cluster headaches; however, we did not identify anyone with cluster headache.

Some subjects stated that they always used remedies, and that the headaches would disappear within 4 hours. Others indicated that they always slept to alleviate the headaches. Thus, they did not know how long headaches continued without medication or with unsuccessful medication. Therefore, we included them in the migraine group, as long as other features were compatible with migraine. Subjects who had both migraine and ETTH were categorized into the migraine

group. Some subjects who had headaches compatible with ETTH and occasionally experienced different headache(s) with nausea, but did not fulfill IHS criteria for migraine, were categorized into the ETTH group.

Finally, all data from the questionnaires and telephone surveys were recorded in a Microsoft Access database. The prevalence of each type of headache was calculated. The distributions and frequency of itemized data were analyzed. Using a statistical package (Statistical Package for the Social Sciences, version 11J, SPSS Japan, Tokyo), logistic analysis was carried out. To estimate risk, we calculated the odds ratio (OR) and 95% confidence interval (CI). The significance limit was set at $P = .05$. P values are stated as the actual number. For logistic analysis, cases with data defects were omitted, and the eligible numbers of cases in each analysis were stated in each Table. The results of questions about limb weakness, numbness, visual ability, and speech ability (initial survey) and results of the quality-of-life questionnaires (second survey) were excluded from this report. Analysis of quality-of-life data will be reported elsewhere.

RESULTS

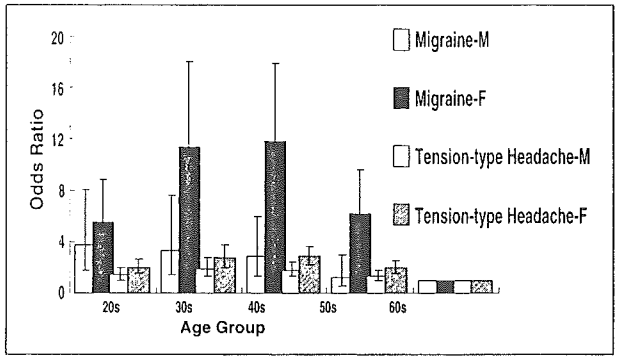
One-Year Prevalence of Migraine.—Prevalence of migraine was 2.3% (with aura, 0.4% and without aura, 1.9%) in men and 9.1% (with aura, 1.0% and without aura, 8.1%) in women. Overall prevalence of migraine was 6.0% in Daisen. The 95% CI of migraine prevalence was 5.4% to 6.6%. The prevalence of each headache category in each age group is shown in Table 1.

The prevalence of migraine was significantly high in young and middle-aged women. Daisen has many elderly people as shown in the census column of Table 1. The adjusted prevalence of migraine with respect to the national census of Japan in 1995 was 7.3% (men, 2.7% and women, 11.4%).

Table 1.—One-Year Prevalence of Headache in Daisen, Japan (1999)*

Gender	Age Group, y	Migraine With Aura	Migraine Without Aura	Episodic Tension-type Headache	Chronic Tension-type Headache	Other	Census of Diasen, 1999
Male	2–29	2 (0.5)	13 (3.5)	51 (13.9)	4 (1.1)	0 (0.0)	368
	3–39	2 (0.7)	8 (2.8)	55 (19.2)	3 (1.0)	2 (0.7)	287
	4–49	2 (0.4)	14 (2.7)	97 (18.4)	5 (0.9)	1 (0.2)	527
	5–59	1 (0.2)	7 (1.3)	77 (14.1)	7 (1.3)	4 (0.7)	547
	6–69	3 (0.7)	3 (0.7)	63 (14.8)	8 (1.9)	3 (0.7)	425
	70+	1 (0.2)	6 (1.2)	47 (9.1)	12 (2.3)	5 (1.0)	516
	Unstated	–	–	3	–	–	
	Total	11 (0.4)	51 (1.9)	393 (14.7)	39 (1.5)	15 (0.6)	2670
	95% CI	0.2–0.7	1.4–2.4	13.4–16.1	1.0–1.9	0.3–0.9	
Female	2–29	3 (0.8)	36 (9.1)	106 (26.8)	6 (1.5)	0 (0.0)	396
	3–39	8 (2.5)	48 (15.1)	89 (28.1)	15 (4.7)	0 (0.0)	317
	4–49	4 (0.8)	86 (17.6)	157 (32.2)	10 (2.0)	0 (0.0)	488
	5–59	5 (1.0)	51 (10.4)	130 (26.6)	9 (1.8)	2 (0.4)	489
	6–69	8 (1.6)	19 (3.7)	105 (20.3)	22 (4.3)	12 (2.3)	516
	70+	2 (0.2)	8 (0.9)	138 (16.0)	20 (2.3)	21 (2.4)	864
	Unstated	–	1	2	–	–	
	Total	30 (1.0)	249 (8.1)	727 (23.7)	82 (2.7)	35 (1.1)	3070
	95% CI	0.6–1.3	7.2–9.1	22.2–25.2	2.1–3.2	0.8–1.5	
Unstated	70+	–	–	–	1	–	
	Unstated	–	1	5	–	1	
	Total	–	1	5	1	1	
Total		41 (0.7)	301 (5.2)	1125 (19.6)	122 (2.1)	51 (0.9)	5740
95% CI		0.5–0.9	4.7–5.8	18.6–20.6	1.8–2.5	0.7–1.1	

*Values are numbers (percentages).



Relative risk of migraine and age. Odds ratios of migraine and tension-type headache were analyzed by logistic analysis in both genders. Graph bars indicate 95% confidence intervals. The 30s and 40s age groups are predominant for female migraineurs. M indicates male; F, female.

Women showed a 5.9-fold higher risk for migraine than men (OR, 5.9; 95% CI, 4.5 to 8.0; $P < .0001$, after age adjustment, by logistic analysis). Age and risk of headache was analyzed by the logistic analysis method in both genders (Figure).

Clinical Features of Migraine and Tension-type Headache.—Clinical features were analyzed and are shown in Table 2. As defined in IHS criteria, subjects with migraine tended to have moderate to severe headaches, and subjects with tension-type headache (TTH) had mild to moderate headaches. Some subjects, who indicated a headache duration of less than 4 hours, used medications immediately after onset or slept (or both) to alleviate headache. These are the reasons why half of the migraineurs had headaches of less than 4 hours' duration. Expression of headache character varied. *Gang-gang* and *zuki-zuki* are Japanese onomatopoeia, indicating moderate to severe throbbing headaches. Approximately half of migraineurs had bilateral headache. Aura/premonitory and associated symptoms are summarized in Table 3. Family history was positive in 42.3% of migraineurs, and 30.8% had first-degree relatives with headache. The prevalence of a positive family history in ETTH was 23.5% (14.2% in first-degree relatives) and 29.5% in CTTH (16.8% in first-degree relatives).

Headache triggers are summarized in Table 4. Fatigue, mental stress, and lack of sleep were the major triggers. Only a few subjects listed wine and chocolate as triggers.

General Health Perception and Impact of Headaches.—Twenty point three percent of migraineurs and 10.4% of those with TTH had experienced time or days off work due to headaches within the previous 3 months (Table 5). Mean loss of workdays was 3.5 days per 3 months. General health perception was significantly worse in both migraineurs and subjects with TTH than in nonheadache subjects. Half of migraineurs had sleep disturbance (Table 6).

Use of Medical Care by Migraineurs.—Sixty-one percent of subjects with MWA and 71.8% of those with MWOA had never visited a physician for their headaches. Only 7.3% of those with MWA and 5.3% of those with MWOA continuously consulted a doctor (Table 7). The major reason why they did not consult a physician was that they thought their headache would improve spontaneously shortly after standing. Forty-six point nine percent of residents with MWA and 27.1% of residents with MWOA always used a headache remedy for attacks, and the majority used only over-the-counter (OTC) medicine (Table 7). Among those who consulted a doctor, 57% of subjects with MWA and 58% of subjects with MWOA visited a primary physician at the initial visit, and the other 43% of subjects with MWA and 42% of subjects with MWOA visited a hospital in the Daisen area. About 50% of migraineurs (with and without aura) visited internists; 28%, neurologists; 17%, neurosurgeons; and 6% visited other specialties (orthopedia-trics, pain clinic, etc).

Alcohol, Cigarette Smoking, and Food Preference.—The simple rate of an habitual drinker was significantly higher in female migraineurs (17.0%; men, 54.7%) and women with TTH (17.9%; men, 59.0%) than in controls (11.4%; men, 59.7%; chi-square test); however, the significance disappeared after age adjustment. Finally, consumption of alcohol and cigarette smoking did not influence the risk for migraine or TTH after age and gender adjustment (logistic analysis).

Food preference and risk of migraine and TTH were analyzed by logistic analysis after age and gender adjustment (Table 8). Migraineurs consumed significantly more fatty/oily foods, coffee, and tea than nonheadache subjects in the same community.

Table 2.—Clinical Features of Migraine and Tension-type Headache*

Feature	Migraine With Aura (n = 41)	Migraine Without Aura (n = 301)	Episodic Tension-type Headache (n = 1125)	Chronic Tension-type Headache (n = 122)
Severity				
Mild	15.0	34.4	84.8	71.8
Moderate	55.0	40.8	14.6	23.1
Severe	30.0	24.8	0.6	5.1
Duration, mean				
<1 h	19.5	26.0	41.6	29.2
1–4 h	36.6	25.7	34.1	25.0
4–24 h	26.8	34.7	19.2	8.3
24–72 h	9.8	7.0	2.7	7.5
3–7 days	2.4	2.0	1.6	0.8
>7 days/daily/near daily	4.9	4.7	0.8	29.2
Frequency				
Several times/year	31.7	39.0	49.7	0.0
1 or 2/month	24.4	33.6	31.3	0.0
3 or 4/month	12.2	13.7	8.9	0.0
1 or 2/week	22.0	7.2	10.1	14.0
3 or 4/week	4.9	2.1	0.0	26.9
Daily/near daily	4.9	4.5	0.0	59.1
Characteristics				
Throbbing/pulsating	41.5	44.9	13.1	18.9
Gang-gang	34.1	30.9	13.8	18.0
Zuki-zuki	39.0	44.5	39.5	37.7
Feeling of heaviness	34.1	26.9	32.8	45.1
Tightness/pressing	12.2	12.6	3.4	7.4
Pricking	7.3	4.3	1.8	3.3
Tickling/smarting	9.8	3.0	2.6	2.5
Hammer blow	2.4	1.3	0.4	0.0
Site of pain				
Unilateral	39.0	39.9	29.0	27.0
Bilateral	48.8	48.8	32.6	43.4
Whole head	22.0	15.6	5.7	19.7
Frontal	26.8	12.3	5.0	8.2
Temple/temporal	24.4	27.6	11.5	23.8
Parietal	9.8	6.0	2.3	4.9
Occipital	41.5	38.2	30.9	41.0
Eyeache	14.6	6.6	2.0	4.1
Periorbital	26.8	23.9	14.3	19.7
Deep orbital	7.3	6.6	2.2	3.3

*Values are percentages. n indicates the number of valid answers in each headache category. Characteristics and site data include multiple answers (sums beyond 100%).

Migraineurs consumed significantly fewer fish than nonheadache residents.

COMMENTS

We have carried out some epidemiological studies of various neurological disorders in Daisen.[7-10] Since residents and local governments are cooperative with our studies, we were able to achieve a high recovery rate of questionnaires and to obtain reliable data for this study. This is the first detailed, population-based, door-to-door survey of migraine in Japan. The prevalence of migraine was 2.3% in men and 9.1% in women. Overall prevalence of migraine in Daisen was 6.0%. When this survey is regarded as a partial sample of the larger Japanese population, CI can be calculated as 5.4% to 6.6%.

In our preliminary survey in the late 1980s, the prevalence of chronic headaches in Daisen was 12.2%.

Table 3.—Aura/Premonitory and Associated Symptoms of Headaches*

Symptom	Migraine With Aura (n = 41)	Migraine Without Aura (n = 272)	Episodic Tension-type Headache (n = 951)	Chronic Tension-type Headache (n = 107)
Aura/Premonitory				
Scintillating scotoma	90.2	0.0	0.0	0.0
Visual disturbance	22.0	1.5	2.8	4.7
Extremity numbness	7.3	1.1	1.4	1.9
Extremity weakness	2.4	0.0	0.0	0.0
Loss of vigor	31.7	11.4	5.2	6.5
Fatigue	41.5	35.3	24.5	27.1
Others	0.0	4.0	2.0	0.0
Associated				
Nausea	61.0	63.8	6.0	9.8
Vomiting	36.6	24.6	0.5	0.8
Photophobia	43.9	17.9	2.8	5.7
Phonophobia	24.4	17.9	2.0	8.2
Eye congestion	14.6	4.7	3.7	10.7
Lacrimation	14.6	3.0	2.1	7.4
Sore shoulder	65.9	50.5	44.6	59.0
Dizziness/vertigo	46.3	22.9	12.3	23.0
Floating sensation	14.6	6.0	3.0	4.9

*Values are percentages. n indicates the number of valid answers in each headache category.

and the prevalence of migraine was 3.5%.[2] Although the diagnosis was based on IHS criteria, the sensitivities of questionnaires used in the previous studies required improvement. Validated questionnaires were used in this study. In addition to an increasing number of migraineurs relating to change of life-styles or environment (or both), the improvement of study methods, including questionnaires and diagnostic procedures.

Table 4.—Headache Triggers*

Trigger	Migraine With Aura (n = 31)	Migraine Without Aura (n = 213)	Episodic Tension-type Headache (n = 412)	Chronic Tension-type Headache (n = 71)
Fatigue	64.5	61.0	47.1	50.7
Mental stress	35.5	30.5	20.1	28.2
Lack of sleep	51.6	45.1	32.0	36.6
Excess sleep	3.2	8.9	5.6	1.4
Change of weather	22.6	20.7	11.4	12.7
Menses	12.9	20.7	11.2	11.3
Release from mental pressure	3.2	3.3	1.9	2.8
Fast/hunger	0.0	0.9	1.2	1.4
Using PC	12.9	6.6	4.9	5.6
Bright light	3.2	4.2	1.2	2.8
Wine	0.0	1.4	1.9	0.0
Chocolate	0.0	0.0	0.7	0.0
Ice cream	0.0	1.4	2.2	0.0
Smoking	3.2	3.3	1.7	2.8
Others	16.1	23.5	14.8	16.9

*Values are percentages. n indicates the number of valid answers in each headache category.

Table 5.—Impact of Headache on Daily Life and Work*

Area of Impact†	Migraine With Aura	Migraine Without Aura	Episodic Tension-type Headache	Chronic Tension-type Headache
Time or days off work				
Yes	25.8	19.5	9.3	16.4
Days, mean (SD), No.	1.8 (0.8)	3.8 (4.8)	2.1 (1.6)	1.6 (0.5)
No	74.2	80.5	90.7	83.6
Unable to do housework				
Yes	27.3	28.0	9.5	8.8
Days, mean (SD), No.	2.0 (1.1)	2.8 (4.4)	2.2 (2.0)	1.5 (0.5)
No	72.7	72.0	90.5	91.2

*Values are percentages unless otherwise indicated.
†Within the previous 3 months.

was one of the reasons why the prevalence of migraine doubled within 10 years. Sakai and Igarashi reported a prevalence of migraine of 8.4% (3.6% in men, 12.9% in women) in Japan based on their nationwide telephone survey.[5] Since Daisen has predominantly elderly people, 6.0% of crude prevalence of migraine appears to be in accordance with previous findings. Actually, the adjusted prevalence to the national census of Japan in 1995 was 7.3%.

Prevalence of migraine was reported to be 3.0% in China,[11] 3.0% in Ethiopia,[12] 9.0% in Malaysia,[13] 9.1% in Taiwan,[14] 12.1% in France,[15] 13.0% in the United States,[4] 13.2% in Sweden,[16] 27.5% in Germany,[17] and 29.1% in Thailand.[18] Prevalence of migraine in Daisen was slightly lower than previous findings from the United States or from European countries. Stewart et al reported variation in migraine prevalence by race; ie, prevalence of migraine in Asian Americans was

Table 6.—Impact of Headache on General Health Perception and Sleep

	Health Perception			Sleep	
	Good	Fair	Poor	Good	Poor
Nonheadache (n = 3045),%	24.0	66.6	9.4	79.8	20.2
Migraine with aura (n = 40),%	2.5	77.5	20.0	46.3	53.7
Odds ratio	1.0	16.7	57.6	1.0	4.2
95% confidence interval		2.3–123.5	6.7–492.3		2.3–7.8
P		.006	.0002		<.0001
Migraine without aura (n = 300),%	14.0	76.0	10.0	56.4	43.6
Odds ratio	1.0	3.2	6.6	1.0	2.7
95% confidence interval		2.2–4.6	3.8–11.5		2.1–3.5
P		<.0001	<.0001		<.0001
Episodic tension-type headache (n = 1115),%	13.5	75.1	11.5	66.0	34.0
Odds ratio	1.0	2.5	4.0	1.0	1.9
95% confidence interval		2.1–3.1	3.0–5.5		1.6–2.2
P		<.0001	<.0001		<.0001
Chronic tension-type headache (n = 121),%	11.6	60.3	28.1	65.5	34.5
Odds ratio	1.0	2.2	8.8	1.0	2.1
95% confidence interval		1.2–4.0	4.3–17.7		1.4–3.1
P		.009	<.0001		.0002

Table 7.—Behavior and Pattern of Use of Medical Care for Headaches*

	Migraine With Aura	Migraine Without Aura	Episodic Tension-type Headache	Chronic Tension-type Headache
Consult physician				
No. of residents	41	301	1125	122
Never	61.0	71.8	89.3	68.9
Once	9.8	7.0	3.7	3.3
Couple times	22.0	15.9	4.7	15.6
Consult continuously	7.3	5.3	2.2	12.3
Never consult physician				
No. of residents	14	123	286	39
Too busy	14.3	16.3	14.7	7.7
Headache not severe enough	35.7	29.3	49.7	43.6
Will improve spontaneously after standing	57.1	56.9	51.4	53.8
Headache not serious enough	7.1	15.4	14.3	20.5
OTC medication is effective	21.4	53.7	32.9	41.0
Physician will not help	7.1	0.8	1.4	2.6
Do not know where to go	0.0	2.4	1.7	2.6
No difference between prescribed drug versus OTC	7.1	5.7	4.2	12.8
Other reasons	21.4	8.9	5.6	10.3
Do not consult continuously				
No. of residents	13	69	95	23
Too busy	7.7	15.9	8.4	13.0
Headache not severe enough	38.5	30.4	45.3	43.5
Will improve spontaneously after standing	30.8	27.5	38.9	39.1
Headache not serious enough	7.7	8.7	3.2	4.3
OTC medication is effective	23.1	30.4	25.3	17.4
Headache will not threaten life	7.7	8.7	3.2	4.3
Physician will not help	7.7	4.3	2.1	13.0
Do not know where to go	0.0	5.8	2.1	13.0
No difference between prescribed drug versus OTC	7.7	11.6	3.2	4.3
Physician did not help	0.0	8.7	3.2	13.0
Other reasons	15.4	14.5	12.6	21.7
Use of headache remedy				
No. of residents	32	214	414	78
Always	46.9	27.1	19.3	32.1
Occasionally	37.5	51.4	42.8	41.0
Never	15.6	21.5	37.9	26.9
Remedies	33.3	22.7	27.8	35.7
Prescription	50.0	61.0	61.5	39.3
OTC	16.7	16.3	10.7	25.0
Both	33.3	22.7	27.8	35.7

*Values are percentages. OTC indicates over-the-counter.

9.2% in women and 4.1% in men, while in Caucasians it was 20.4% in women and 8.6% in men.[19] The difference of migraine prevalence among communities might be caused from differences in diagnostic accuracy and methods of subject samplings, or from differences in genetic and environmental factors. The migraine prevalence of Asian Americans is quite similar to our present results.

The predominance of females is significant in the present results as in previous studies that implicated pathophysiological relations to hormonal activity. The female to male ratio of prevalence of MWA was 0.7/0.4 = 1.75 and of MWOA, 8.1/1.9 = 4.2. Female predominance of migraine was more pronounced in MWOA than in MWA, in accord with earlier observations.[5,20] As shown in the Figure, migraine

Table 8.—Food Preference and Migraine, Adjusted by Age and Gender

	Migraine (n = 340)			Tension-type Headache (n = 1226)		
	Odds Ratio	95% CI	*P*	Odds Ratio	95% CI	*P*
Breakfast						
Daily	1.1	0.7–1.7	.79	0.9	0.7–1.2	.42
Couple times/week	1.0	0.6–2.0	.90	1.0	0.7–1.5	.86
Rare/never	1.0			1.0		
Green-yellow vegetable						
Everyday	0.8	0.6–1.1	.14	0.8	0.7–0.92	.003
Every other day	0.9	0.7–1.2	.57	0.8	0.7–0.97	.02
Occasionally/never	1.0			1.0		
Fruits						
Everyday	1.0	0.8–1.3	.97	0.7	0.6–0.9	.0001
Every other day	1.1	0.8–1.4	.70	0.8	0.7–1.0	.02
Occasionally/never	1.0			1.0		
Fresh vegetable						
Everyday	1.1	0.7–1.6	.67	0.8	0.7–1.0	.09
Every other day	1.0	0.8–1.3	.86	0.9	0.8–1.1	.28
Occasionally/never	1.0			1.0		
Eggs						
Everyday	1.0	0.7–1.3	.83	0.8	0.7–1.0	.053
Every other day	0.9	0.6–1.2	.37	0.8	0.7–1.0	.03
Occasionally/never	1.0			1.0		
Fish						
Everyday	0.7	0.5–1.0	.04	0.8	0.7–1.0	.02
Every other day	1.0	0.7–1.3	.90	0.9	0.7–1.0	.14
Occasionally/never	1.0			1.0		
Meat						
Everyday	1.1	0.8–1.4	.56	1.0	0.8–1.2	.98
Every other day	1.0	0.8–1.5	.78	1.0	0.9–1.2	.75
Occasionally/never	1.0			1.0		
Milk						
Everyday	1.1	0.5–1.3	.55	0.8	0.7–0.9	.01
Every other day	1.1	0.5–1.5	.66	0.9	0.7–1.0	.12
Occasionally/never	1.0			1.0		
Soybeans and related foods (Tofu and Nattou)						
Everyday	0.8	1.2–2.3	.39	0.8	0.6–1.1	.10
Every other day	0.9	1.0–1.8	.63	0.8	0.6–1.1	.10
Occasionally/never	1.0			1.0		
Oil/fat						
Everyday	1.7	0.6–1.2	.002	1.1	0.9–1.3	.32
Every other day	1.3	0.8–1.4	.10	1.0	0.8–1.2	.96
Occasionally/never	1.0			1.0		
Seaweed						
Everyday	0.9	0.5–1.2	.38	0.9	0.7–1.0	.10
Every other day	1.1	0.7–1.1	.56	0.9	0.7–1.0	.08
Occasionally/never	1.0			1.0		
Potatoes						
Everyday	0.7	1.7–3.5	.18	0.7	0.5–0.9	.01
Every other day	0.9	1.0–2.7	.35	0.8	0.7–1.0	.02
Occasionally/never	1.0			1.0		
Coffee/tea						
Everyday	2.4	0.6–1.9	<.0001	1.1	0.9–1.3	.32
Every other day	1.6	0.8–2.2	.08	1.0	0.8–1.3	.89
Occasionally/never	1.0			1.0		
Night meal						
Everyday	1.0	0.6–1.9	.90	0.9	0.7–1.3	.70
Every other day	1.3	0.8–2.2	.27	1.1	0.8–1.5	.55
Occasionally/never	1.0			1.0		

was predominant in the 30s and 40s age groups in women.

Approximately 5% of migraineurs and 59% of residents with CTTH in Daisen complained of daily or near-daily headache (Table 2). Although it is not listed in the IHS classification system, "chronic daily headache (CDH)" is one of the most important issues. Chronic daily headache consists of transformed migraine, CTTH, new daily persistent headache (NDPH), and hemicrania continua (HC).[21,22] There was no case of NDPH or HC in this survey. Although all subjects categorized to the CTTH group fulfilled the diagnostic criteria of CTTH, some of them may also fulfill the diagnostic criteria for transformed migraine.

Clinical Features of Migraine and Tension-type Headache.—Eighty-five percent of residents with MWA and 65.6% of residents with MWOA stated that their headaches were greater than moderate, which suggested the headaches inhibited daily activities. Approximately half of migraineurs stated that their mean headache duration was less than 4 hours. Duration of headache in Japanese migraineurs may tend to be shorter than that of Caucasians. Sakai and Igarashi reported the prevalence of migraine by the exact IHS criteria was 6.0%, and the prevalence of modified-criteria migraine (less than 4 hours' duration or less than 5 times occurrence of attack) was 2.4%, with an overall prevalence of 8.4%.[5] In a study in Taiwan, the prevalence of migraine was 9.1% when modified criteria for shorter headache duration was included.[14]

In this study, 31.7% of subjects with MWA and 39.0% of subjects with MWOA had only a few attacks per year. The expression of *zuki-zuki* is a Japanese onomatopoeia, indicating moderate to severe throbbing pain. Approximately 40% of subjects with TTH expressed their headache characteristics using *zuki-zuki*. Approximately half of migraineurs had bilateral headaches. Nausea was the most common associated symptom. These features are compatible with earlier findings from Western countries.

Six percent of subjects with ETTH experienced headaches with nausea. These subjects had both IHS-defined ETTH and other headaches with nausea that did not fulfill IHS-defined migraine. These subjects may develop migraine in the future.

Fatigue, mental stress, and lack of sleep were the major triggers in migraineurs. Twenty percent of migraineurs stated menses and change of weather as possible triggers.

Migraine Is One of the Major Health Problems in Japan.—Only 20.3% of migraineurs and 10.4% of subjects with TTH had experienced time or days off work due to headaches. In addition, 27.3% of migraineurs could not do their housework. Health perception was significantly poorer in migraineurs and those with TTH than in nonheadache subjects. Although migraine burdened residents, more than two thirds never consulted a physician for headache. Sakai and Igarashi reported 2.7% of migraineurs visited a physician regularly, and 12.2% visited occasionally.[5] This was confirmed by our door-to-door survey in Daisen, and it emphasized that migraine is one of the major health problems in Japan. Patient education concerning headache syndromes including migraine is necessary in Japan.

Food Preference and Risk of Migraine.—The odds ratio of coffee and tea consumption was significantly higher in migraineurs. Caffeine is widely used and supplemented to headache remedies because caffeine is believed to have some beneficial effects in acute headache treatment. In contrast, chronic use of excess caffeine can cause caffeinism or chronic headaches.[23] Thus, the present results may indicate 2 possibilities: either coffee and tea (probably caffeine) increase the risk of migraine, or in contrast, migraineurs know and use the potential benefits of coffee and tea for protecting or stopping headache attacks. Based on our clinical experience, we tend to support the latter possibility; however, this must remain speculative. Grant reported that the most common foods causing migraine were wheat (78%), oranges (65%), eggs (45%), tea and coffee (40% each), chocolate and milk (37% each), beef (35%), and corn, cane sugar, and yeast (33% each), and when an average of 10 common foods were avoided, there was a dramatic decrease in the number of headaches per month—85% of patients becoming headache-free.[24] In contrast, Medina and Diamond reported that diet appeared to be relatively unimportant in migraine attacks.[25] The present findings suggested that food with a high fat content increased the risk of migraine, and daily fish intake