BACKGROUND

Diabetes mellitus (DM) is a prevalent disease in older people. DM in older adults has become a major public health problem, affecting an increasing number of individuals worldwide. According to a 2006 national nutrition survey in Japan, the rates of likely DM (HbA1c ≥6.1% or in treatment) were 3.2%, 10.2%, 13.6%, and 18.0% for people in their 40s, 50s, 60s, and 70s or over, respectively. The rates of subclinical DM (HbA1c 5.6–6.1%) were 14.2%, 19.0%, 23.1%, and 24.7% for people in their 40s, 50s, 60s, and 70s or over, respectively [1].

Hearing loss is also highly prevalent in older adult populations [2,3]. Research has shown that presbycusis affects about 30% of people aged 65 and over [4,5], and that about half of the population aged over 75 years has significant hearing loss [6].

A relationship between DM and hearing loss was first proposed in a case report by Jordao in 1857 [7]. Although this potential association has been investigated ever since then [8–13], it has not been as firmly established as the association between DM and its known complications affecting the renal, visual, and peripheral nervous systems. Several factors, such as noise exposure, presbycusis, and syndromic hearing loss, might confound the association between DM and hearing impairment. Although aging is thought to be a key factor in both glucose metabolism and cochlear function, it is difficult to demonstrate the interrelated contribution of DM and aging to hearing impairment.

We aimed to investigate the impact of DM on hearing, and the relationship between this and age, in middle-aged and elderly community-dwelling individuals.

MATERIAL AND METHODS

Subjects

The present study was conducted as part of the comprehensive 'Longitudinal Study of Aging (NILS-LSA)' conducted by the National Institute for Longevity Sciences of the National Center for Geriatrics and Gerontology. The NILS-LSA is a population-based biennial survey of a cohort of approximately 2200 people, which started in November 1997. The subjects of the NILS-LSA were randomly selected from resident registrations, stratified by both age and sex. Details of the methodology used in the NILS-LSA have been reported elsewhere [14]. The study protocol was reviewed by the Ethical Committee of the National Center for Geriatrics and Gerontology, and written informed consent was obtained from all participants.

Data obtained from the 4th wave examination of NILS-LSA were analyzed cross-sectionally in the present study. Participants were 2383 adults aged 40 to 86 years who took part in the NILS-LSA between May 2004 and July 2006. Demographic characteristics, personal history, family history, lifestyle habits, and medical history were obtained from detailed questionnaires filled out before the examination visit. Venous blood was collected early in the morning after at least 12 hours' fasting.

The definition of DM was based on medical history obtained from questionnaires, or defined as a fasting plasma glucose concentration greater than 126 mg/dl and an HbA1c of more than 6.5%, or the taking of medication to lower the blood glucose level. In this way, participants were classified into a DM (+) group and a DM (−) group. Histories of ear disease and occupational noise exposure were obtained from the self-reported questionnaire. Occupational noise was defined in our questionnaires as background noise in a work environment over which the worker could not hold a conversation in a normal voice. Former and current noise exposures were combined. History of ear disease and history of occupational noise exposure were treated as binary variables (presence =1, absence =0).

Those who did not undergo blood testing, had incomplete hearing measurements, or provided invalid questionnaire responses were eliminated from the analysis. Accordingly, 2306 participants with complete data were selected for the present analysis. The subjects were divided into 2 groups for analysis: 40–64 and 65–86 years (Table 1).

Audiometric measurements

Audiometric measurements were examined in a soundproof compartment by laboratory technicians on the same day of the blood draw. Air-conduction pure-tone thresholds at octave intervals from 125 to 8000 Hz were obtained using diagnostic audiometers (AA-73A and AA-78; Rion, Tokyo, Japan). The thresholds over the predetermined output level, according to the Japanese Industrial Standards T 1201 calibration, were treated as that level plus an additional 5 dB; that is to say, over 70 dB at 125 Hz was treated as 75 dB. For analyses of supraliminal levels we used 90 dB at 250 Hz, 105 dB at 500 to 4000 Hz, and 100 dB at 8000 Hz. Pure-tone averages (PTAs) were calculated for the better ear (BE) and the worse ear (WE) in order not to overlook subjects with at least 1 affected ear. The low-frequency PTA was calculated as the average threshold across the 125-, 250- and 500-Hz thresholds. The high-frequency PTA was calculated as the average across the 2000-, 4000- and 8000-Hz thresholds. The mid-frequency PTA was calculated as the average across the 500-, 1000-, 2000- and 4000-Hz thresholds. Hearing impairment was defined as PTAs greater than 25 dB.

Statistical analyses

Statistical analyses were conducted using the Statistical Analysis System (SAS) version 9.13 (SAS Institute, Cary, NC, USA). All values are expressed as mean ± standard error if not specified otherwise. Comparisons of hearing impairment rates between the DM (−) group and DM (+) group by age were performed using the chi-square test. In multivariable analyses, general linear model (GLM) analyses were performed to assess both the individual and the interactive impacts of age and DM on hearing of the BE and WE, based on the mid-frequency PTA. Hearing levels at 7 frequencies were set in the GLM as objective variables. Explanatory variables were age (binary variable; <65 years vs. ≥65 years), DM (binary variable; absence vs. presence), and interaction between age and DM. Moderator variables were sex, history of ear disease, and history of occupational noise exposure.

RESULTS

Table 1 shows the clinicodemographic profile of the subjects by age group and DM status. A total of 2306 participants

Table 1. Clinicodemographic profile of the subjects by DM status and age group.

(mean ± SE)	40–64 years			65–86 years		
	DM (–)	DM (+)	*p*	DM (–)	DM (+)	*p*
N	1349	67		806	84	
Male (%)	50.1	64.2	0.0246	48.4	56.0	NS
Fasting blood glucose (mg/dl)	96.3±0.4	159.7±1.6	<.0001	98.9±0.6	146.2±1.8	<.0001
HbA1c (%)	5.2±0.01	7.4±0.06	<.0001	5.3±0.02	7.2±0.06	<.0001
History of ear disease (%)	41.4	34.3	NS	33.3	33.3	NS
History of occupational noise exposure (%)	19.4	16.4	NS	18.9	25.0	NS

DM – diabetes mellitus.

Table 2. The prevalence of hearing impairment based on the low-frequency, high-frequency and mid-frequency PTA.

Hearing impairment (%)		40–64 years			65–86 years		
		DM (–)	DM (+)	p	DM (–)	DM (+)	p
Better ear	Low-frequency $PTA_{125,250,500}$ >25 dB	5.6	13.4	0.0087	37.0	44.1	NS
	High-frequency $PTA_{2000,4000,8000}$ >25 dB	16.8	44.8	<.0001	75.1	79.8	NS
	Mid-frequency $PTA_{500,1000,2000,4000}$ >25 dB	7.3	13.4	NS	52.0	59.5	NS
Worse ear	Low-frequency $PTA_{125,250,500}$ >25 dB	19.2	31.3	0.0149	60.3	66.7	NS
	High-frequency $PTA_{2000,4000,8000}$ >25 dB	29.0	59.7	<.0001	87.3	88.1	NS
	Mid-frequency $PTA_{500,1000,2000,4000}$ >25 dB	15.7	40.3	<.0001	66.4	75.0	NS

PTA pure tone averages; DM – diabetes mellitus; NS – not significant.

ages 40 through 86 years were analyzed in 4 subject groups: in the younger age bracket (40-64 years), 67 had diabetes and 1349 did not; in the older age-bracket (65–86 years) 84 had diabetes and 806 did not. The prevalence of DM was 4.7% in the younger participants, and 9.4% in the older participants.

Table 2 provides the results from chi-square analysis regarding the prevalence of hearing impairments (based on low-frequency, high-frequency and mid-frequency PTAs) according to age group and DM status. In the younger group, participants with DM had a significantly higher prevalence of hearing impairment than those without DM, for all frequency criteria except mid-frequency in the BE. In contrast, in the older age bracket, no significant differences were observed in the prevalence rates of any defined hearing impairments according to DM status.

The individual and interactive effects of age and DM on the hearing levels at 7 frequencies, from the GLM analysis, are shown in Table 3. The statistically significant main effect of DM was more moderate than that of age, but it was observed from low to high frequencies in both the BE and WE. The direction of each main effect was confirmed for the BE and WE in the lower sections of Table 3, which provide the mean hearing levels in the 4 groups: DM (–) and DM (+) in the younger and the older age-brackets. The main effect of DM was to impair hearing levels at all frequencies except 125 Hz in the BE and 500Hz in the WE. Moreover, the interactive effect of age and DM was statistically significant at 4000 Hz and 8000 Hz in both the BE and WE. The adverse effect of DM on hearing varied according to age.

For the purpose of visual comparison, the interactive effect of age and DM in the BE at 8000 Hz are graphically presented in the Figure 1. The solitary main effect of DM on hearing level was strong in the younger age bracket but less obvious in the older age bracket.

Discussion

We found a statistically significant harmful effect of DM on hearing and noted that this effect varied by age in the high frequencies. The effects of the DM-age interaction were not synergistic at any of the test frequencies; in other words, aging did not intensify the deleterious effects of DM on hearing. The DM-age interaction was additive at below 4000 Hz, but reciprocal at 4000 Hz and 8000 Hz. The impact of DM on hearing at 4000 Hz and 8000 Hz was more severe in the younger than the older participants. Hearing sensitivity at the higher frequencies is particularly vulnerable to ototoxic insults such as aging [4, 6], hazardous noise exposure [14], and ototoxic agents. Accordingly the present results can be explained by the fact that the effect of DM on

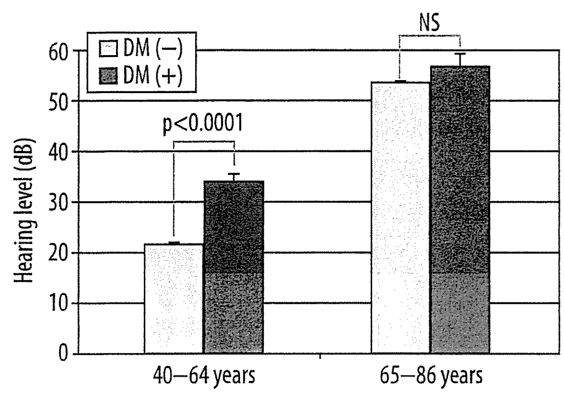
Table 3. Relationship between hearing level, age, and DM status as assessed by general linear model analyses.

		Hearing level at 125 Hz		Hearing level at 250 Hz		Hearing level at 500 Hz		Hearing level at 1000 Hz		Hearing level at 2000 Hz		Hearing level at 4000 Hz		Hearing level at 8000 Hz	
Better ear based on the mid-frequency		**F value**	**p value**	**F value**	**p value**	**F value**	**p value**	**F value**	**p value**	**F value**	**p value**	**F value**	**p value**	**F value**	**p value**
	DM	3.13	NS	4.41	0.0359	6.41	0.0114	6.98	0.0083	5.35	0.0208	11.68	0.0006	18.96	<0.0001
	Age	496.5	<0.0001	445.3	<0.0001	509.1	<0.0001	648.4	<0.0001	907.7	<0.0001	1094	<0.0001	1536	<0.0001
	DM × age	1.49	NS	1.21	NS	1.39	NS	1.04	NS	0.89	NS	5.62	0.0179	8.39	0.0038
		Mean	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**
40–64 years	DM (–)	20.5	19.9–21.1	18.3	17.7–18.9	14.3	13.7–14.9	10.9	10.3–11.6	15.3	14.5–16.0	18.0	17.1–19.0	23.2	22.0–24.3
	DM (+)	22.9	20.7–25.0	20.9	18.6–23.2	17.4	15.1–19.8	14.3	11.7–16.8	18.6	15.7–21.6	25.7	22.0–29.3	34.7	30.3–39.2
65–86 years	DM (–)	29.3	28.6–30.0	26.9	26.2–27.7	23.8	23.1–24.6	22.6	21.8–23.4	30.9	30.0–31.9	39.8	38.7–41.0	54.5	53.1–55.9
	DM (+)	29.8	27.8–31.7	27.8	25.8–29.8	25.0	22.9–27.1	24.1	21.8–26.3	32.4	29.8–35.0	41.4	38.2–44.7	57.1	53.2–61.0
Worse ear based on the mid-frequency		**F value**	**p value**	**F value**	**p value**	**F value**	**p value**	**F value**	**p value**	**F value**	**p value**	**F value**	**p value**	**F value**	**p value**
	DM	6.93	0.0085	9.74	0.0018	3.56	NS	4.26	0.039	9.14	0.0025	11.88	0.0006	16.49	<0.0001
	Age	460.6	<0.0001	408.8	<0.0001	411.9	<0.0001	523.6	<0.0001	753	<0.0001	926.32	<0.0001	1364	<0.0001
	DM × age	0.21	NS	0.18	NS	1.29	NS	1.01	NS	2.47	NS	6.61	0.0102	10.47	0.0012
		Mean	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**
40–64 years	DM (–)	22.8	22.1–23.6	21.1	20.3–22.0	18.4	17.5–19.3	15.6	14.7–16.6	20.4	19.5–21.4	24.2	23.1–25.3	23.2	26.3–28.8
	DM (+)	26.0	23.1–28.9	25.2	21.9–28.4	22.2	18.7–25.8	19.6	16.0–23.3	26.6	22.8–30.3	33.6	29.3–37.9	34.7	35.7–45.5
65–86 years	DM (–)	34.0	33.1–34.9	32.7	31.7–33.8	31.3	30.2–32.4	30.5	29.4–31.7	38.8	37.7–40.0	48.1	46.7–49.4	54.5	59.1–62.2
	DM (+)	36.3	33.7–38.8	35.8	33.0–38.7	32.3	29.2–35.5	32.0	28.7–35.2	40.9	37.6–44.2	49.7	45.9–53.5	57.1	58.1–66.9

Objective variables: Hearing level at respective frequencies; Explanatory variables: DM, age, DM × age; Moderator variables: sex, history of ear disease (presence=1), history of occupational noise-exposure (presence=1).
The degrees of freedom were 1 for all F values. DM – diabetes mellitus; presence vs. absence; age: <65 years vs. ≥65 years;
CI – confidence interval; NS – not significant.

hearing in the higher frequencies might be more emphatic in the younger age bracket because this type of hearing is generally better preserved in younger than in older people.

Regarding the association of diabetes with hearing, Bainbridge et al. reported the risk for hearing loss in people with self-reported DM in a recent study examining a large sample of 5140 non-institutionalized adults in the US National Health and Nutrition Examination Surveys [15]. They found that people with DM were at increased risk for hearing loss. The literature also contains some discussion about the cross-contribution of DM and aging to hearing impairment [9,15–17]. Although Bainbridge et al. mentioned that the relative contribution of DM to hearing impairment might have been stronger among their study group (age 20 to 69 years) than in a previously reported older group, they did not analyze the DM-by-age interaction as it relates to hearing in a straightforward manner. They demonstrated that the prevalence of hearing impairment among people with diagnosed DM statistically exceeded the prevalence among those without DM in all groups except people aged 60 to 69 years. They therefore speculated that hearing of younger people, before the cumulative effects of aging, noise exposure, and other factors have made substantial contributions to hearing impairment, is potentially affected by DM more than in older people. Vaughan et al. tested audiometric measures including ultra-high-frequency range in 342 veterans with DM and 352 without DM. They concluded that patients aged 60 or younger with DM may show early high-frequency hearing loss similar to early presbycusis, while there was less difference in hearing loss between patients with and without DM after age 60 [17]. They found a significant effect of DM in both ears after adjusting for age, but only in the ultra-high-frequency range (10–16 kHz), and the DM-age interaction was significant in the right ear but not in the left at this frequency range. They also demonstrated that differences between patients with and without DM diminished or disappeared at 10, 12.5, 14 and 16 kHz in the right ear as age increased. Vasilyeva et al. prospectively assessed hearing abilities in middle-aged mice with Type 1 DM or Type 2 DM, and found that induction of diabetes in middle-aged CBA/CaJ mice promoted amplification of age-related peripheral hearing loss [18].



The error bars show standard error.

Figure 1. Graphical presentation of the interactive effect of age and DM in BE at 8000 Hz.

The pathophysiological mechanism of hearing impairment in DM has been investigated for years in temporal bone studies using animal models of DM and in human post-mortem cases; however, it has not been completely clarified [19–21]. Some investigators have observed findings of DM-related cochlear microangiopathy, such as vessel wall thickening or atrophy of the stria vascularis, the organ responsible for generating endolymph, which serves as the driving force for hair cell mechanotransduction. However, others have failed to find these changes in DM. Recently, possible biochemical pathways involved in the detrimental effects of DM on sensory end-organs have been advocated [10,22]. The auditory system requires glucose and high-energy utilization for its complex signal processing. The high metabolic demands of the inner ear and the auditory pathway could make them a target of the disease, even before evidence of microvascular complications. This could occur through hyperglycemia, which has effects including oxidative stress, hypoxia and ischemia, activation of the polyol pathway, and increased levels of advanced glycation end products (AGEs), which play an important role in development of atherosclerosis in diabetes.

A recent study provided evidence that various forms of oxidative stress increase in the aging cochlea, while cellular antioxidant defense systems are reduced [23]. The findings mean that, irrespective of the presence of DM, oxidative stress during the aging process leads to dysfunctional degeneration of the cochlear tissue. Another study demonstrated that increased vulnerability of outer hair cells from the base of the cochlea, which responds to higher frequency auditory stimuli compared with those at the apex, was associated with lower levels of the antioxidant glutathione in the basal hair cells [24]. This finding may explain the current result that DM could potentially accelerate early presbycusis, high-frequency sensorineural hearing loss, in the younger age-bracket.

Some limitations of the present study should be mentioned. Although the definition of DM in the present study was based on multiple criteria, medical history and medication taken to lower blood glucose level were obtained by questionnaires. We could not distinguish between type 1 and type 2 DM, and did not take into account severity or duration since DM diagnosis. Additionally, the participants of the NILS-LSA are potentially more health-conscious than average Japanese. Residents selected from resident registrations were invited by mail to an explanatory meeting at which the objectives of NILS-LSA, study design, and detailed procedures of examinations were described. Only those who understood the project and signed a written informed consent form became participants. Employed people would have to get time off to take part in the examination, and those with seriously impaired activities of daily living, rarely attend. Therefore, the present subjects may have been healthier than the subjects in other analyses in the clinical setting.

Despite these possible limitations, however, the present findings that diabetes reduces auditory sensitivity in middle-aged people may indicate potential benefits of early intervention. Yoshikawa et al. has prospectively examined the effect of short-term intervention with lifestyle modification, and has clearly demonstrated that lifestyle modification can significantly reduce circulating AGE levels [25]. Screening for hearing impairment in diabetic patients may be valuable for intervention or prevention, especially in early middle-age.

Conclusions

The present study demonstrated that DM adversely affected hearing in the community-dwelling middle-aged and elderly population. Although the DM-age interaction appeared additive at below 4000 Hz, significant reciprocal effects of this interaction were found at 4000 Hz and 8000 Hz. This suggests that DM could potentially accelerate early presbycusis, high-frequency sensorineural hearing loss. Screening for hearing impairment in patients with DM may provide benefits for prompt intervention or primary prevention, especially in early middle-age.

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Declaration of interest

Nothing declared.

Conflict of interest

None. The funding sources had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Ethical approval

Ethical Committee of the National Center for Geriatrics and Gerontology.

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ORIGINAL ARTICLE

Relationship between number of metabolic syndrome components and dietary factors in middle-aged and elderly Japanese subjects

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Metabolic syndrome (MetS) represents a cluster of risk factors for atherosclerosis and is considered a risk factor for cardiovascular disease. The role of diet in the etiology of MetS is poorly understood, especially among Asian subjects. This cross-sectional study assessed the relationship between diet and the number of MetS components among Japanese men (n=609) and women (n=631). Mean (s.d.) age and body mass index were 57.1 (12.1) years and 22.8 (2.8) kg m^{-2} for men and 55.5 (12.0) years and 22.0 (3.0) kg m^{-2} for women, respectively. Diet was assessed by a 3-day dietary record that included photographs: 16 nutrients, 11 food groups, and energy % of protein and dietary fat were selected as a dietary index. The definition of MetS was based on modified National Cholesterol Education Program, Adult Treatment Panel III criteria, and the number of clustering MetS components was calculated by adding the presence of each five MetS components. A total of 61 men (10.0%) and 46 women (7.3%) were determined to have MetS. After adjusting for age, energy intake, alcohol intake, smoking status and physical activity, a lower intake of vitamin B6 and dietary fiber in men, and lower intake of calcium, milk and dairy products and higher intake of cereal in women were related to the number of MetS components. These results suggest that some dietary factors were related to the number of MetS components among community-dwelling Japanese men and women.
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Keywords: cross-sectional study; dietary record; Japanese; metabolic syndrome

INTRODUCTION

Metabolic syndrome (MetS) represents a cluster of risk factors for atherosclerosis, including visceral obesity, hypertension, dyslipidemia and hyperglycemia; MetS is considered a risk factor for cardiovascular disease.[1] The National Nutrition Survey in Japan, a population-based study among 40- to 74-year-olds, revealed that 24% of men and 12% of women were strongly suspected of having MetS, and 27% of men and 8% of women were suspected of having MetS.[2]

MetS has become a major public health challenge in Japan.[3] The pathophysiology of MetS appears to be largely attributable to insulin resistance with an excessive flux of fatty acids,[1] although this disorder presumably exists as a function of a complex interaction between environmental factors, including diet or physical activity and genetic factors.[4,5]

Although dietary aspects have been linked to individual features of MetS,[6–8] the role of diet in the etiology of this syndrome is poorly understood. Asians have different lifestyle and genetic factors compared with Caucasians,[9,10] but only a few epidemiologic studies examining diet and MetS among Asians have been conducted.[11–13] The aim of this study was to examine the relations between diet and the number of MetS factors among community-dwelling Japanese men and women.

METHODS

Study subjects

Data for this survey were collected as part of the National Institute for Longevity Sciences Longitudinal Study of Aging (NILS-LSA). In this project, the normal aging process has been assessed over time using detailed questionnaires and medical checkups, anthropometrical measurements, physical fitness tests and nutritional examinations. Participants in the NILS-LSA included randomly selected age- and sex-stratified individuals from the pool of residents in the NILS neighborhood areas, Obu City and Higashiura Town of Aichi Prefecture. Details of the NILS-LSA study are reported elsewhere.[14]

Subjects in this study included 1189 men and 1194 women aged 40–86 years who participated in the fourth wave of the NILS-LSA from June 2004 to July 2006. Subjects under non-pharmacological and/or pharmacological treatment for hypertension, hypertriglyceridemia or diabetes were excluded, as were subjects who indicated that they were aware of having these disorders but were not undergoing treatment. There were 334 men and 327 women with hypertension, 241 men and 174 women with hypertriglyceridemia and 104 men and 69 women with diabetes. As some subjects had multiple disorders, a total

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of 489 men and 492 women were excluded from the study. Additionally, subjects who did not fast overnight for venipuncture (11 men and 12 women), those who did not participate or complete the nutrition survey (54 men and 47 women) and those whose energy intake was <1200 kcal per day (2 men and 11 women) or more than 3000 kcal per day (24 men and 1 woman) were also excluded. After these exclusions, 609 men and 631 women remained in the study.

The study protocol was approved by the Committee of Ethics of Human Research of the National Center for Geriatrics and Gerontology. Written informed consent was obtained from all subjects.

Nutritional assessments

Nutritional intakes were assessed by a 3-day dietary record. The dietary record was completed over 3 continuous days (both weekend days and one week-day).[15] Food was weighed separately on a scale (1 kg kitchen scale, Sekisui Jushi, Tokyo, Japan) before being cooked or portion sizes were estimated. Subjects used a disposable camera (27 shots, Fuji Film, Tokyo, Japan) to take photos of meals before and after eating. Dietitians used the photos to complete missing data, and telephoned subjects to resolve any discrepancies or obtain further information when necessary. The averages of the 3-day food and nutrient intakes were calculated according to the fifth edition of the Standard Tables of Foods Composition in Japan and other sources.[15] Alcohol intake in the previous year was assessed by a food frequency questionnaire; trained dieticians interviewed subjects using this questionnaire. According to previous large epidemiological studies,[7,11] we selected 16 nutrients and 11 food groups as a dietary index, along with energy % of protein and dietary fat.

Other measurements

Anthropometric measurements included waist circumference, height and body weight. Waist circumference was measured at the umbilicus[16,17] and body mass index was calculated as weight/height^2 (kg m^{-2}). Blood pressure was measured by an automated sphygmomanometer (BP-203RVII, Omron Colin, Tokyo, Japan) after participants had been comfortably seated for at least 5 min. All venous blood samples were obtained after an overnight fast. The serum was separated promptly, and all lipid analyses were conducted at the clinical laboratory in the health examination center. Serum glucose and triglycerides were measured using enzymatic methods. HDL-cholesterol was measured after dextran sulfate-magnesium precipitation.

Medical history (past and current) and smoking status (yes/no) were collected using questionnaires. Physical activity was assessed by trained interviewers using the Met Score (a multiple of the resting metabolic rate). Participants were interviewed using a semi-quantitative assessment to determine their level of habitual physical activity during leisure time, on the job and sleeping hours,[18] and we calculated the total MetS*minutes score per day (MetS*1000 min per day). For example, walking for pleasure was assigned a 2.5 MetS intensity, and thus the leisure-time physical activity score was 50 MetS*min per day in the case of a 20 min walk every day.[18]

Definition of MetS and components

The definition of MetS was based on modified National Cholesterol Education Program, Adult Treatment Panel III (NCEP-ATP III) criteria.[19] Only the criteria of abdominal obesity was different from that of NCEP-ATP III criteria.[20] For abdominal obesity, we used the International Obesity task Force central obesity criteria for Asia, which defined abdominal obesity as a waist circumference of at least 90 cm for men and at least 80 cm for women.[21]

As stated earlier, study subjects under treatment for hypertension, hypertriglyceridemia and diabetes were excluded before the analyses. Thus, MetS was defined as the presence of three or more of the following five components: (1) abdominal obesity, defined as a waist circumference of at least 90 cm for men and at least 80 cm for women; (2) elevated blood pressure, defined as blood pressure $\geqslant$130/85 mm Hg; (3) hypertriglyceridemia, defined as triglycerides $\geqslant$150 mg per 100 ml ($\geqslant$1.70 mmol l^{-1}); (4) low HDL-cholesterol, defined as HDL-cholesterol <40 mg per 100 ml (<1.0 mmol l^{-1}) in men and <50 mg per 100 ml (<1.3 mmol l^{-1}) in women; and (5) elevated blood glucose levels, defined as fasting blood glucose $\geqslant$100 mg per 100 ml. The number of clustering MetS components was calculated by adding the number of MetS components.

Statistical analyses

All statistical analyses were conducted with Statistical Analysis System, release 9.1.3 (SAS Institute, Cary, NC, USA). Subjects were categorized into four groups according to the number of clustering MetS components (0, 1, 2, 3–5). Values of 3–5 were combined because only a few or no subjects had 4 or 5 MetS components (4 components: 12 men and 5 women; 5 components: 0 men and 2 women). Associations between categorical variables were tested by χ^2 test and 95% confidence interval (CI) was estimated using the PROC FREQ procedure. Comparisons between continuous variables were performed by analysis of variance and trend test. Linear regression models were constructed using the PROC GLM procedure to examine the association between the number of MetS components and dietary indexes, that is, the 11 food groups, 16 nutrients and energy % of protein and dietary fat. Mean nutritional intakes were calculated by the number of MetS components (0, 1, 2, 3–5) after multivariate adjustment for potential confounding factors, which included age, energy intake, alcohol intake, smoking status and physical activity. Additionally, demographic differences between subjects (609 men and 631 women) and those excluded from the study (580 men and 563 women) were analyzed by t-test.

All reported P-values were two-sided, and a P-value <0.05 was considered significant.

RESULTS

Subject characteristics are presented Table 1. Mean (s.d.) age and BMI were 57.1 (12.1) years and 22.8 (2.8) kg m^{-2} for men and 55.5 (12.0) years and 22.0 (3.0) kg m^{-2} for women, respectively. Age and BMI gradually increased with the number of MetS components in both men and in women, whereas mean age of subjects with 2 or 3–5 MetS components was similar in men (59.5 years and 59.5 years, respectively) and women (60.7 and 60.9 years, respectively).

Abdominal obesity, defined as waist circumference $\geqslant$90 cm, was noted in 20.0% of men (95% CI: 16.8–23.2), with a prevalence of 14.4, 41.9 and 70.5% among men with 1, 2 or 3–5 MetS components, respectively. Abdominal obesity, defined as waist circumference $\geqslant$80 cm, was noted in 44.1% of women (95% CI: 40.2–48.0), with a prevalence of 69.7, 84.5 and 97.8% among those with 1, 2 or 3–5 MetS components, respectively. Elevated blood glucose levels were seen in 38.1% of men and 17.9% of women according to the number of MetS components (1, 2 or 3–5) was 49.8, 61.5 and 91.8% in men and 17.1, 41.8 and 73.9% in women, respectively. Hypertriglyceridemia and hypertension were seen in 18.2 and 22.5% of men and 7.5 and 12.8% of women, respectively. Low HDL-C levels occurred in 5.9% of men and 7.0% of women. A total of 61 men (10.0%) and 46 women (7.3%) met the NCEP-ATP III modified criteria for MetS, that is, they had 3–5 MetS components.

In sub-analyses, demographic differences between subjects included in the study (609 men and 631 women) and those excluded from the study (580 men and 563 women) were analyzed. Age, BMI and the other anthropometric variables (for example, blood pressure, waist circumference or fasting glucose levels) were lower among subjects than those excluded (mean (s.d.) age: 56.9 (12.1) vs. 64.8 (11.7) years, mean BMI: 22.5 (2.9) vs. 23.6 (3.2) kg m^{-2}, respectively).

Table 2 shows multivariate adjusted mean food and nutrient intake according to the number of MetS components in men. Among the dietary indexes, daily intakes of vitamin B6 decreased from 1.36 to 1.21 mg, and dietary fiber decreased from 16.2 to 14.5 mg as the number of MetS components increased. Although analysis of covariance did not reach statistical significance, intake of vegetables was lower among men with higher number of MetS components, and decreased from 301.1 to 271.9 g as the number of MetS components increased (ANCOVA P=0.07, trend test P=0.03). In addition, although analysis of covariance or trend tests did not reach statistical

Table 1 Subject characteristics according to the number of metabolic syndrome (MetS) components

		Number of MetS components					
Variable	*All*	*0*	*1*	*2*	*3–5*	P[a]	*Trend* P
Men							
n, %	609 (100%)	222 (36.5%)	209 (34.3%)	117 (19.2%)	61 (10.0%)		
Age (year)	57.1 ± 12.1	55.1 ± 12.5	57.1 ± 11.7	59.5 ± 12.0	59.5 ± 11.0	<0.01	<0.01
Body mass index (kg m^{-2})	22.8 ± 2.8	21.7 ± 2.4	22.5 ± 2.5	24.0 ± 2.7	25.6 ± 2.6	<0.01	<0.01
Alcohol intake (g per day)	14.2 ± 17.3	12.7 ± 16.1	14.6 ± 17.1	15.9 ± 17.8	15.3 ± 21.2	0.38	0.24
Physical activity (MetS*1000 min per day)	2116 ± 302	2107 ± 290	2109 ± 266	2124 ± 334	2159 ± 389	0.65	0.21
Energy intake (kcal/)	2247 ± 335	2247 ± 308	2233 ± 342	2283 ± 337	2227 ± 399	0.59	0.95
Current smoker (*n*, %)	186 (30.5%)	62 (27.9%)	67 (32.1%)	38 (32.5%)	19 (31.2%)	0.76	
Metabolic abnormalities (n, %)							
Waist circumference ⩾90 (cm)	122 (20.0%)	0 (–%)	30 (14.4%)	49 (41.9%)	43 (70.5%)		
Triglyceride ⩾150 (mg per 100 ml)	111 (18.2%)	0 (–%)	24 (11.5%)	44 (37.6%)	43 (70.5%)		
HDL-cholesterol <40 (mg per 100 ml)	36 (5.9%)	0 (–%)	7 (3.4%)	17 (14.5%)	12 (19.7%)		
Blood pressure ⩾130/85 mm Hg	137 (22.5%)	0 (–%)	44 (21.1%)	52 (44.4%)	41 (67.2%)		
Fasting glucose ⩾100 mg per 100 ml	232 (38.1%)	0 (–%)	104 (49.8%)	72 (61.5%)	56 (91.8%)		
Women							
n, %	631 (100%)	272 (43.1%)	210 (33.3%)	103 (16.3%)	46 (7.3%)		
Age (year)	55.5 ± 12.0	51.5 ± 10.9	56.8 ± 12.1	60.7 ± 11.8	60.9 ± 10.9	<0.01	<0.01
Body mass index (kg m^{-2})	22.0 ± 3.0	20.2 ± 1.9	22.7 ± 2.7	23.6 ± 3.0	25.4 ± 3.2	<0.01	<0.01
Alcohol intake (g per day)	3.4 ± 7.6	3.7 ± 7.3	3.2 ± 7.7	2.3 ± 5.3	4.6 ± 12.1	0.27	0.60
Physical activity (MetS*1000 min per day)	2161 ± 160	2187 ± 152	2144 ± 169	2132 ± 131	2143 ± 201	<0.01	0.07
Energy intake (kcal/	1884 ± 288	1884 ± 299	1878 ± 293	1893 ± 275	1895 ± 229	0.97	0.72
Current smoker (*n*, %)	39 (6.2%)	21 (7.7%)	9 (4.3%)	4 (3.9%)	5 (10.9%)	0.17	
Metabolic abnormalities (n, %)							
Waist circumference ⩾80 (cm)	278 (44.1%)	0 (–%)	146 (69.7%)	87 (84.5%)	45 (97.8%)		
Triglyceride ⩾150 (mg per 100 ml)	47 (7.5%)	0 (–%)	6 (2.9%)	21 (20.4%)	20 (43.5%)		
HDL-cholesterol <50 (mg per 100 ml)	44 (7.0%)	0 (–%)	8 (3.8%)	19 (18.5%)	17 (37.0%)		
Blood pressure ⩾130/85 mm Hg	81 (12.8%)	0 (–%)	14 (6.7%)	36 (35.0%)	31 (67.4%)		
Fasting glucose ⩾100 mg per 100 ml	113 (17.9%)	0 (–%)	36 (17.1%)	43 (41.8%)	34 (73.9%)		

Values shown are mean ± s.d.
[a]Statistical significance was determined by analysis of variance or χ^2 test.

significance, higher daily intakes of cholesterol (379.2–404.6 mg) and eggs (52.5–58.2 g) were related to an increased number of MetS components (trend test $P<0.1$).

In women (Table 3), intake of calcium decreased from 609.2 to 549.9 mg daily, and intake of milk and dairy food decreased from 181.2 to 134.9 mg daily as the number of MetS components increased. Cereal intake increased from 382.3 to 418.4 g daily as the number of MetS components increased. Although analysis of covariance and trend test did not reach statistical significance, lower intake of saturated fat was related to an increased number of MetS components, and decreased from 15.7 to 14.8 g daily as MetS components increased (trend test $P<0.1$).

DISCUSSION

Our findings suggest that lower intakes of vitamin B6 and dietary fiber in men, and lower intakes of calcium, milk and dairy products and higher intake of cereal in women are related to the number of MetS components. To our knowledge, this is the first observational study to examine relations between dietary factors and the number of clustering MetS components among Japanese men and women.

In previous epidemiologic studies, dietary fiber, fruits, vegetables and moderate alcohol intake were negatively associated[22–24] and fat and red meat were positively associated[25–27] with MetS in Caucasian or Japanese-Brazilian subjects. Consistent with previous studies,[22,24,28] intake of dietary fiber in men was negatively related to clustering MetS components. Diets rich in dietary fiber are associated with a reduced risk of diabetes and cardiovascular disease. Dietary fiber has a higher satiety value compared with digestible complex carbohydrates and simple sugars because of its bulk and relatively low energy. Fiber may also affect secretion of gut hormones or peptides, such as cholecystokinin or glucagon-like peptid-1, which may act as satiety factors or alter glucose homeostasis.[28,29] Thus, an increased fiber intake may prevent MetS.

Although carbohydrate intake in women did not correlate with the number of MetS components, cereals that mainly consisted of carbohydrates showed a negative effect on the number of MetS components in this study. Carbohydrates are also implicated in changes in blood glucose and insulin concentrations and are known to affect satiety.[30] The beneficial effect of a high carbohydrate diet on glucose tolerance has been reported;[31] however, contradicting reports have also been published.[32–36] Dietary carbohydrate through cereal intake is thought to modulate lipolysis, and a low-carbohydrate diet reduces cardiovascular risk through improvement in hepatic, intravascular and peripheral processing of lipoproteins.[32] Although no positive relation was

Table 2 Energy and multivariate adjusted[a,b] mean food and nutrient intake according to the number of metabolic syndrome (MetS) components in men (n=609)

	Number of MetS components					
Variable	*0*	*1*	*2*	*3–5*	P[c]	*Trend* P
n (%)	222 (36.5%)	209 (34.3%)	117 (19.2%)	61 (10.0%)		
Energy (kcal)	2247±23	2233±23	2283±31	2227±43	0.59	0.95
Nutrients[a]						
Protein (energy %)	3.71±0.03	3.71±0.03	3.71±0.05	3.70±0.06	0.99	0.93
Fat (energy %)	2.71±0.03	2.67±0.04	2.66±0.05	2.79±0.07	0.35	0.36
Carbohydrate (energy %)	13.8±0.1	14.0±0.1	14.0±0.2	13.8±0.2	0.62	0.98
Nutrients[b]						
Protein (g)	82.9±0.7	82.8±0.8	83.5±1.0	82.5±1.4	0.93	0.92
Fat (g)	61.2±0.8	60.3±0.8	60.4±1.1	62.8±1.5	0.46	0.33
Carbohydrate (g)	310.3±2.4	312.7±2.5	312.1±3.3	309.8±4.6	0.89	0.88
Calcium (mg)	619.5±12.4	604.2±12.6	590.1±17.0	588.8±23.5	0.47	0.20
β-Carotene (μg)	3269±118	3274±121	2804±163	3003±225	0.08	0.11
Vitamin E (mg)	9.8±0.2	9.5±0.2	9.1±0.2	9.3±0.3	0.130	0.10
Vitamin B6 (mg)	1.36±0.02	1.35±0.02	1.29±0.03	1.21±0.04	0.006	0.001
Vitamin B12 (μg)	8.8±0.4	8.2±0.4	9.4±0.5	8.0±0.7	0.23	0.70
Folate (μg)	343.6±7.3	352.6±7.5	339.9±10.1	340.4±13.9	0.70	0.65
Vitamin C (mg)	126.4±7.1	127.2±7.2	135.1±9.7	125.1±13.4	0.89	0.93
Saturated fat (g)	16.5±0.3	15.9±0.3	16.0±0.4	16.1±0.5	0.58	0.57
Monounsaturated fat (g)	21.2±0.4	20.8±0.4	20.8±0.5	21.5±0.7	0.66	0.70
Polyunsaturated fat (g)	13.3±0.2	13.4±0.2	13.5±0.3	14.0±0.4	0.55	0.15
Cholesterol (mg)	379.2±8.8	369.0±9.0	396.7±12.2	404.6±16.8	0.15	0.08
Dietary fiber (g)	16.2±0.3	15.9±0.3	14.8±0.4	14.5±0.5	0.002	0.001
Salt (g)	11.8±0.1	12.1±0.1	11.9±0.2	11.6±0.3	0.29	0.28
Foods						
Cereals (g)	512.2±7.5	522.6±7.7	538.3±10.3	512.9±14.2	0.21	0.72
Beans (g)	76.5±4.7	86.9±4.8	86.6±6.4	82.8±8.9	0.41	0.55
Nuts and seeds (g)	6.0±0.6	4.0±0.6	3.9±0.8	5.4±1.2	0.07	0.61
Vegetables (g)	301.1±7.9	304.5±8.1	277.0±10.9	271.9±15.0	0.07	0.03
Fruits (g)	137.1±7.1	130.8±7.3	122.0±9.8	134.3±13.5	0.66	0.72
Fish and shellfish (g)	111.2±3.5	107.1±3.6	109.3±4.9	108.3±6.7	0.88	0.79
Meats (g)	86.2±3.1	89.4±3.2	93.9±4.2	95.0±5.9	0.38	0.13
Eggs (g)	52.5±1.9	53.5±1.9	59.5±2.6	58.2±3.6	0.11	0.07
Milk and dairy food (g)	163.6±8.0	144.3±8.1	140.7±10.9	129.8±15.1	0.12	0.049
Fats and oils (g)	11.3±0.4	11.6±0.4	11.6±0.6	11.6±0.8	0.97	0.77
Confectioneries (g)	45.1±3.3	46.6±3.4	43.2±4.5	46.7±6.3	0.94	0.95

Values shown are mean±s.e.
[a]Adjusted for age, alcohol intake, smoking and physical activity.
[b]Adjusted for age, energy intake, alcohol intake, smoking and physical activity.
[c]Statistical significance was determined by analysis of covariance.

shown between carbohydrate intake and the number of MetS components in this study, recent nutritional reviews indicate that the quantity and type of carbohydrate affect metabolic outcomes.[35] Among cereals, whole grain products that have a lower glycemic index and are richer in fiber and antioxidant vitamins than refined grain products were suggested to improve insulin sensitivity, probably by blunting postprandial glycemic and insulinemic responses.[36] Thus, control of these factors in future studies will be important to determine the most effective dietary approach to prevent metabolic disorders.

In Japan, there has been a significant reduction in the intake of cereals, and rice in particular, in recent decades,[2,37] On the other hand, dietary fat intake is increasing, and consumption of a more Westernized diet is thought to be associated with the evident increase in diabetes mellitus and obesity. In women in this study, saturated fat intake weakly decreased as the number of MetS components increased. Dietary intervention studies show that total fat is not associated with the risk of MetS, although saturated fats increase the risk of MetS, whereas monounsaturated and polyunsaturated fats reduce this risk.[38–40] Our results do not agree with studies that show that saturated fat-rich lipid infusion reduces the insulin sensitivity index more than polyunsaturated fat infusion.[41] Although the reason of this inverse relation was shown in this study is not clear, two possibilities can be considered. First, some intermediate event, such as dietary counseling, could have lead to changes in diet and might have confounded the association between saturated fat intake and metabolic

Table 3 Energy and multivariate adjusted[a,b] mean food and nutrient intake according to the number of metabolic syndrome (MetS) components in women (n=631)

	Number of MetS components					
Variable	*0*	*1*	*2*	*3–5*	P[c]	*Trend* P
n (%)	272 (43.1%)	210 (33.3%)	103 (16.3%)	46 (7.3%)		
Energy (kcal)	1884±18	1878±20	1893±29	1896±43	0.97	0.72
Nutrients[a]						
Protein (energy%)	3.75±0.03	3.84±0.03	3.79±0.05	3.70±0.07	0.15	0.45
Fat (energy%)	2.97±0.03	2.94±0.03	2.93±0.05	2.91±0.07	0.85	0.46
Carbohydrate (energy%)	14.2±0.1	14.2±0.1	14.1±0.2	14.2±0.2	0.97	0.99
Nutrients[b]						
Protein (g)	70.2±0.5	71.9±0.6	71.4±0.9	69.7±1.3	0.16	0.64
Fat (g)	56.4±0.6	55.7±0.7	55.5±0.9	54.7±1.4	0.67	0.28
Carbohydrate (g)	267.4±1.8	266.2±2.0	265.4±2.9	268.2±4.3	0.91	0.93
Calcium (mg)	609.2±11.0	604.8±12.3	556.3±17.9	549.9±26.4	0.024	0.01
β-Carotene (μg)	3358±112	3263±125	2931±181	3508±268	0.18	0.90
Vitamin E (mg)	9.1±0.1	9.0±0.2	9.0±0.2	9.4±0.3	0.70	0.35
Vitamin B6 (mg)	1.13±0.02	1.19±0.02	1.13±0.03	1.15±0.04	0.11	0.98
Vitamin B12 (μg)	6.9±0.3	7.0±0.4	7.4±0.5	6.9±0.8	0.87	0.95
Folate (μg)	333.9±6.8	342.7±7.6	334.2±11.0	360.0±16.3	0.45	0.21
Vitamin C (mg)	121.7±4.2	125.6±4.7	111.0±6.9	131.7±10.1	0.24	0.66
Saturated fat (g)	15.7±0.2	15.5±0.3	15.0±0.4	14.8±0.6	0.23	0.07
Monounsaturated fat (g)	19.1±0.3	19.0±0.3	19.1±0.4	18.8±0.6	0.96	0.74
Polyunsaturated fat (g)	12.1±0.2	12.0±0.2	12.2±0.3	12.2±0.4	0.91	0.67
Cholesterol (mg)	321.1±6.7	339.2±7.4	343.1±10.8	318.7±15.9	0.16	0.95
Dietary fiber (g)	15.2±0.2	15.7±0.3	15.2±0.4	15.5±0.5	0.49	0.82
Salt (g)	10.4±0.1	10.4±0.1	10.6±0.2	10.8±0.3	0.45	0.11
Foods[b]						
Cereals (g)	382.3±5.2	385.8±5.8	400.3±8.4	418.4±12.4	0.03	0.004
Beans (g)	75.4±4.1	80.7±4.6	76.0±6.6	83.1±9.8	0.77	0.58
Nuts and seeds (g)	6.3±0.7	6.9±0.7	6.2±1.1	5.3±1.6	0.81	0.48
Vegetables (g)	285.4±6.5	285.1±7.3	275.2±10.6	322.6±15.6	0.09	0.06
Fruits (g)	152.1±6.7	160.9±7.5	145.3±10.9	131.0±16.1	0.32	0.15
Fish and shellfish (g)	81.9±2.5	89.3±2.8	90.7±4.1	84.2±6.1	0.16	0.69
Meats (g)	65.5±2.0	70.8±2.3	71.1±3.3	66.1±4.9	0.27	0.90
Eggs (g)	48.2±1.6	52.1±1.8	53.1±2.6	50.6±3.9	0.33	0.54
Milk and dairy food (g)	181.2±6.7	177.0±7.4	153.7±10.8	134.9±16.0	0.018	0.003
Fats and oils (g)	11.2±0.3	10.7±0.4	10.6±0.6	10.2±0.8	0.64	0.28
Confectioneries (g)	65.5±2.7	61.6±3.0	60.1±4.4	56.9±6.5	0.52	0.21

Values shown are mean±s.e.
[a]Adjusted for age, alcohol intake, smoking and physical activity.
[b]Adjusted for age, energy intake, alcohol intake, smoking and physical activity.
[c]Statistical significance was determined by analysis of covariance.

risks. We tried to exclude subjects from the analysis who were aware of their potential risks and who may have made dietary changes based on perceived dangers. Second, Japanese subjects consume a relatively large amount of fish containing abundant polyunsaturated fatty acids. The ratio of saturated fat to polyunsaturated fat might be more important than the absolute intake considering the physiologic dietary effect on developing MetS. These factors might have affected our results. Further studies are needed to clarify the role of fat quality in the prevention of MetS.

Calcium, milk and dairy food intake in women decreased with the increase in the number of MetS components. Additionally, although findings were not statistically significant, a similar relation between milk and dairy products and MetS was shown in men (ANCOVA $P=0.12$, trend $P=0.049$). Diets rich in calcium, particularly calcium derived from dairy products, have been shown to be associated with a low prevalence of MetS.[42] The mechanism by which calcium intake can reduce MetS is unclear, but Scholz-Ahrens and Schrezenmeir[42] implied that dietary calcium intake has benefits on traits of MetS, specifically on weight reduction and fat loss. Meijl *et al.*[43] reviewed the physiological effects of three main dairy constituents (calcium, protein and fat) on MetS, and indicated that the effects of calcium might be related to intestinal binding to fatty acids or bile acids or to changes in intracellular calcium metabolism by suppressing calciotropic hormones. In an epidemiologic study, Otsuka *et al.*[44] reported that higher milk consumption was associated with a lower incidence of MetS after 5 years among middle-aged

Japanese male workers, suggesting that calcium derived from dairy products might help prevent MetS.

Vitamin B6 in men was also negatively related to the number of MetS components. Esmaillzadeh *et al.*[45] discussed the favorable effect of whole grain on MetS through the rich content of viscous fiber and showed that intake of whole grains was positively associated not only with dietary fiber (r=0.43) but also with vitamin B6 (r=0.48). Consistent with their study, the results of our study showed favorable effects of dietary fiber and vitamin B6 on the number of MetS components. Hayden and Tyagi[46] reported on the role of water soluble B vitamins, including vitamin B6, in lowering plasma total homocysteine, a risk marker of MetS, through remethylation. Although the precise mechanism of vitamin B6 on MetS is unclear, a favorable association of vitamin B6 to MetS in men may be attributed to a healthier diet that contained rich fiber, milk and dairy products or vegetables.

Although not statistically significant, lower intake of vegetables in men was related to an increased number of MetS components. Higher vegetable intake has been previously reported as a protective factor of MetS or inflammation in women.[7,22] Vegetables rich in dietary fiber are thought to reduce the risk of developing MetS by improving glucose control, and minerals, antioxidants or vitamins contained in vegetables are thought to have a favorable effect on glucose tolerance.[47,48] Our results regarding dietary fiber on MetS may represent the positive effect of vegetable intake.

In men, higher intakes of eggs and cholesterol were related to an increased number of MetS components, although this was not statistically significant (trend $P<0.1$). Excess consumption of eggs should be avoided from the standpoint of preventing hypercholesterolemia among Japanese subjects.[49] Increased dietary cholesterol intake is associated with atherosclerosis.[50] The result of this study may suggest that men with a lower number of MetS components tend to abstain from eating eggs or cholesterol-rich foods. As a result, a dose–response relationship between egg consumption and the number of MetS components was shown in our study.

The lack of other correlations between the number of MetS components and dietary factors, such as fruits, or meats in this study is thought to be due to differences in dietary intake[51] or metabolic responses[9,10] between Caucasian and Japanese subjects.

The relation of diet to the risk of MetS has been examined in many studies, but few have addressed the association with the number of MetS components.[52–54] We considered that the number of MetS components is more closely assessed through the effects of diet, that is, through a dose–response relationship, rather than the prevalence of MetS. In addition, to focus on the dose–response relationship, trend test by general linear model was used, and further *post hoc* analyses were not performed. MetS is a cluster of atherosclerotic cardiovascular disease risk factors[20] but there are some different criteria of MetS in Japan. The ideal threshold for waist circumference used to define abdominal obesity among Japanese men and women is still under discussion.[55] Recently, Kokubo *et al.*[19] reported that the number of MetS components (modified NCEP-ATP III criteria) might be more strongly associated with the incidence of cardiovascular disease than the presence of abdominal obesity (the Japanese criteria) in a general urban Japanese population. We used a modified NCEP-ATP III criteria, that is, a cutoff point of waist circumference that was different from NCEP ATP III (102 cm in men and 88 cm in women, modified: 90 cm in men and 80 cm in women), in this study.[20,21]

Several limitations of this study warrant consideration. First, the cross-sectional nature of the study did not permit the assessment of causality. Subjects under treatment for hypertension, hypertriglyceridemia or diabetes or those aware of morbidities might have modified their food intake, and these subjects were excluded from analysis. However, some plausible relationships between foods or nutrients and MetS have been identified in this study. NILS-LSA, which is a population-based prospective cohort study, followed participants for more than 10 years. Future analyses should examine the associations between the dietary index and MetS.

Second, we used foods and nutrients as an indicator of diet, although these items are consumed in combination, and their complex effects are likely to be interactive or synergistic.[56] Consumption of several foods or food groups might be a more comprehensive variable to assess the impact of diet on disease risk than any single nutrient or food. Third, nutritional intakes were assessed by a 3-day dietary records. The 3-day dietary record is one of the most reliable methods for nutritional assessment; however, it is limited because individual food intake varies greatly from day to day,[15] and it is not clear whether short-term records adequately reflect long-term dietary intake.[57] On the basis of this limitation, we preliminarily decided on 3 continuous days (both weekend days and one weekday) to avoid events or special days such as trips, long vacations or out-of-the-ordinary events and thus minimize food variations. Although the 3-day dietary record is not the best way to assess long-term dietary intake, it can be considered to have a certain level of accuracy that reflects the usual nutrient intakes in this cohort.

Fourth, food consumption and nutrient intake among Japanese have dramatically changed during the past five decades. For example, Westernization of the Japanese diet has lead to decreased consumption of carbohydrates, especially rice, and increased consumption of fat and meat.[2,37] In particular, younger Japanese subjects tend to eat a more Westernized diet.[37] As a result, not only food intake but also the number MetS components might differ among different generations of Japanese subjects. Thus, it may be difficult to detect statistically significant relationships between diet and the number of MetS components in the age group we studied.

In summary, this study showed that some foods and nutritional components are related to the number of MetS components. These results suggest the potential effect of diet on the prevention of MetS among community-dwelling Japanese men and women.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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一般住民における動脈硬化と骨粗鬆症の関連

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一般住民における動脈硬化と骨粗鬆症の関連

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はじめに

骨粗鬆症と動脈硬化の進行は，高齢者の自立を障害してquality of life(QOL)を低下させ，健康寿命に大きく影響する。これら両疾病はともに，加齢に伴い発症・増加する病態である。

骨密度(bone mineral density：BMD)と循環器疾患の関連については，これまでにも多方面からの研究報告が数多くあるが，日本人地域住民男女を対象としての疫学研究はまだ少ない。本研究では，地域在住中高年者を対象に，骨粗鬆症と動脈硬化の関連について横断的に検討を行った。

1　対象と方法

国立長寿医療センター研究所疫学研究所では，老化に関する包括的な疫学調査である「国立長寿医療センター研究所・老化に関する長期縦断疫学研究(NILS-LSA：National Institute for Longevity Sciences-Longitudinal Study of Aging)」を，1997年11月から縦断的(2年ごと)に実施している[1)]。調査対象は，センター周辺(愛知県大府市，知多郡東浦町)の地域住民から，年齢，性別で層化した無作為抽出法で選出された，ベースライン調査時年齢が40～79歳の2,267名である。

本研究では，第1次調査(1997年11月～2000年4月)の参加者のうち，BMD測定および頸動脈超音波検査を受けた女性1,050名(平均年齢±SD：59.0±10.9)，男性1,063名(59.2±10.9)を対象として横断研究を行った。**表1**に対象者特性を示す。

骨粗鬆症の評価は，dual energy X-ray absorptiometry(DXA：Hologic, QDR-4500)で第2～4腰椎と右大腿骨頸部のBMD測定を行い，日本骨代謝学会の「原発性骨粗鬆症の診断基準」[2)]に準じ，BMDが若年成人平均値(young adult mean：YAM)の70～80％を骨量減少，

表1　対象者特性

	男性	女性
対象者数(名)	1,063	1,050
40歳代	274	266
50歳代	267	266
60歳代	255	263
70歳代	267	255
年齢(歳)	59.2±10.9	59.0±10.9
BMI(kg/m^2)	22.9±2.8	22.9±3.3
腰椎BMD(g/cm^2)	1.0±0.2	0.9±0.2
大腿骨頸部BMD(g/cm^2)	0.8±0.1	0.7±0.1
IMT(mm)	0.9±0.5	0.8±0.3

平均値±標準偏差
BMI：body mass index, BMD：bone mineral density, IMT：intima-media thickness

Association between Arteriosclerosis and Osteoporosis in Community Dwelling Population
Marie Takemura：Department of Orthopedics National Center for Geriatrics and Gerontology, *et al.*
Key words：Osteoporosis, Arteriosclerosis, Epidemiology

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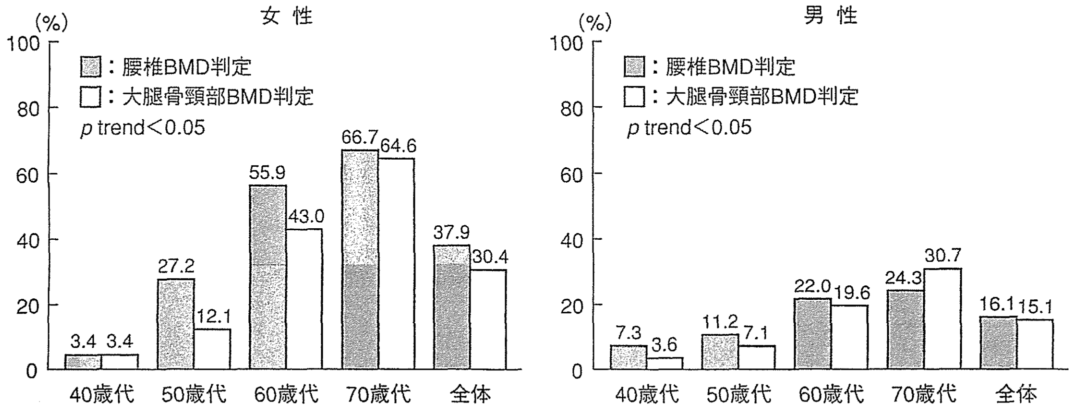

図1　骨粗鬆症/骨量減少の有病率

70%未満を骨粗鬆症と判定した。

また，動脈硬化の評価手段として頸動脈超音波検査(日立メディコ電子走査形超音波断層装置EUB-655，電子リニア形探触子EUP-L3 10MHz)を行った。頸動脈内膜中膜複合体厚(intima-media thickness：IMT)を左右総頸動脈および左右頸動脈分岐部で計測し，その最肥厚部をIMTの代表値とした。IMTが1.1mm以上を異常肥厚とし，動脈硬化ありと判定した。

統計学的検討として，骨粗鬆症および動脈硬化の地域在住中高年者の有病率を性別，年代別に求め，Cochran-Mantel-Haenszel法によるトレンド検定を行った。次に動脈硬化と骨粗鬆症の関連について検討するために，動脈硬化の有無を説明変数とし，年齢およびbody mass index(BMI)を調整した骨粗鬆症有病についての多重ロジスティック回帰分析を性別に行った。解析には，統計プログラムSAS release 9.1.3を使用した。

2　結　果

1）骨粗鬆症/骨量減少の有病率(性別，年代別)

腰椎BMD判定での40歳以上の骨粗鬆症/骨量減少の有病率は，女性37.9%，男性16.1%であった。女性の有病率は加齢で有意に高くなり，特に60歳代以降は急速に高くなった。男性でも，有病率は加齢で有意に高くなった。大腿骨頸部BMD判定でも，女性30.4%，男性15.1%で，男女とも加齢で有意に高くなった(**図1**)。

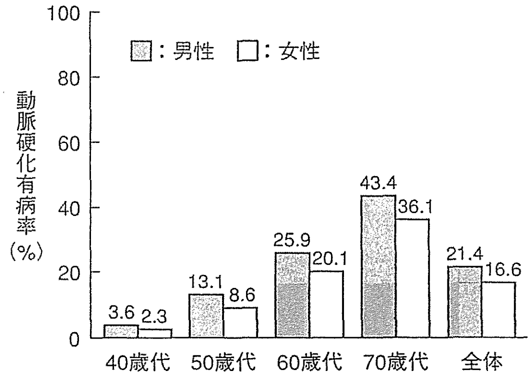

図2　動脈硬化有病率

2）動脈硬化有病率(性別，年代別)

40歳以上の女性の動脈硬化有病率は16.6%，男性は21.4%であった。動脈硬化の有病率は，男女とも加齢で有意に高くなった(**図2**)。

3）動脈硬化と骨粗鬆症との関連

女性で骨粗鬆症診断を腰椎BMDで判定した場合，動脈硬化のある者は，ない者に比べて骨粗鬆症/骨量減少の有病の割合が高かった(オッズ比1.97，95%信頼区間1.03～2.99，p＝0.0014)。また，女性を未閉経群と閉経群に分けて検討したところ，閉経群のみで同様の結果が得られた(1.78，1.19～2.67，p＝0.00052)。一方，大腿骨頸部BMD判定の場合には，いずれも有意な関連は認められなかった。男性での解析では，両部位BMDと動脈硬化のあいだに有意な

表2　多重ロジスティック回帰分析による動脈硬化と骨粗鬆症有病の関連

		オッズ比(95%信頼区間)	p値
腰椎BMD判定の場合	女性全体	1.97(1.03～2.99)	$p=0.0014$
	閉経女性	1.78(1.19～2.67)	$p=0.0052$
	男性全体	0.98(0.63～1.55)	NS
大腿骨頸部BMDの場合	女性全体	0.96(0.63～1.46)	NS
	閉経女性	0.94(0.60～1.43)	NS
	男性全体	0.74(0.27～1.17)	NS

NS：not significant

関連は認められなかった(表2)。

3 考　　察

BMDと心血管系疾患については，低BMDや骨密度減少が，心血管疾患による死亡リスク上昇と関連するという報告や[3,4]，骨粗鬆症の閉経後女性は，年齢や心血管疾患の危険因子を考慮しても，心・血管系イベントの発生リスクが有意に高い[5]など，これまでに多方面からの研究が行われている。日本人を対象とした疫学研究においても，骨粗鬆症や動脈硬化の評価手法はそれぞれの研究で異なるが，BMDと動脈硬化の程度とのあいだに関連を認めたと報告されている[6~9]。本研究では，脳・心血管疾患の予知因子として有用とされるIMT[10]とBMDのデータを用いて，地域住民男女における両疾病間の関連について解析を行った。その結果，骨粗鬆症評価を腰椎BMDで行った場合，女性で動脈硬化のある者は，ない者に比べて骨粗鬆症有病の割合が高くなった。この結果は，これまでの先行研究と矛盾するものではなかった。

女性の骨粗鬆症と心血管疾患は，どちらも閉経後より罹患率が高くなることが臨床的に広く知られている。またエストロゲン受容体は，骨芽細胞や破骨細胞，血管内皮細胞，血管平滑筋細胞に存在することが確認されており，両疾患の進行に共通して関与する因子としてエストロゲンがあげられる。本研究において，女性で両疾病間に有意な関連が認められた要因の一つに，エストロゲンの関与が示唆される。

またエストロゲン以外にも，酸化脂質やビタミンD，副甲状腺ホルモン，オステオカルシン，オステオポンチン，ホモシステイン，アンジオテンシン，マトリックスグラプロテイン，オステオプロテジェリン，一酸化窒素，インターロイキン(IL-6)などは，骨と血管の相互に関与する共通因子として近年検証が進み，いわゆる「骨・血管相関」の機序が解明されつつある。

腰椎は大腿骨頸部に比べ，構成組織として海綿骨の占める割合が高い。エストロゲン減少による骨代謝への影響は，皮質骨よりも海綿骨のほうがより反映されやすいと考えられている。今回の結果において，腰椎と大腿骨に相違を認めた要因の一つとしてエストロゲンの関与が示唆される。

一方，変形性脊椎症では椎体に骨棘形成を認めるが，その割合は，特に男性において加齢に伴い高くなるため，BMDが高く判定されてしまう。また腹部の大動脈石灰化が存在する場合にも，腰椎BMDが過大評価される可能性があり，結果への影響は否定できない。

両疾患の進行には性ホルモン以外にも喫煙，糖尿病，高脂血症など共通の危険因子が存在する。今後，これらの交絡因子を考慮しての検討を要すると考える。

患者のQOL低下を招くおそれのある骨粗鬆症性骨折予防の観点から，動脈硬化の基盤となる高血圧や高脂血症など生活習慣病の日常診療において，骨粗鬆症についても評価や治療の必要性がある。また逆に閉経後女性の骨粗鬆症有病者の日常診療において，脳・心血管疾患発症の基盤となる動脈硬化の存在にも留意すること

が必要と考えられた。

まとめ

地域在住中高年者を対象に，骨粗鬆症と動脈硬化症の有病の関連について横断的解析を行った。女性では年齢とBMIで調整しても，腰椎BMDとIMTとのあいだに有意な関連を認め，骨粗鬆症と動脈硬化進展とのあいだに密接な関連が示唆された。

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疾病予防のための理想的生活

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要 旨

・疾病予防には生活習慣の改善が有用である。現代社会ではメタボリックシンドロームと老年病が大きな問題になっている。
・肥満は多くの疾病の原因ではあるが，75 歳以上の後期高齢者ではむしろ栄養不足が重要となる。メタボリックシンドロームの基準値設定に年齢が考慮されていないのは問題である。ライフステージで生活習慣と疾病予防との関係は異なる。
・さらに摂取エネルギーが少なくても肥満となりやすい遺伝子多型，アルコールの影響が出やすい遺伝子多型，食塩摂取による血圧への影響が大きい遺伝子多型などがみつかっており，生活習慣と疾病との関係には個人差が大きい。
・「国立長寿医療研究センター・老化に関する長期縦断疫学研究(NILS-LSA)」では平成 9 年から 2 年ごとに無作為抽出された地域住民を対象に生活習慣などの背景要因と老化や疾病との関係について調査を行っている。
・個人個人の全ゲノムが容易に解析できるようになれば，特定の個人がどういう疾病にかかりやすいのか，生活をどのようにしたら疾病予防にもっとも効果があるのかを明らかにできるようになるだろう。

はじめに

江戸時代には一般庶民向けの多くの書物が書かれたが，貝原益軒の『養生訓』ほど長期に渡って版を重ね，読み継がれた書物はないだろう。益軒は筑前(福岡県)の黒田藩に 71 歳になるまで藩士として仕えた。その後，84 歳で亡くなるまでに多くの書物を書いている。『養生訓』は益軒が亡くなる 1 年前の 1713 年に執筆された。医師ではなく実際の医療に携わった経験はなかったが，読書家であり，知識が豊富であった。益軒自身が当時としてはきわめて長命であり，また高齢になっても心身ともに健康であった。『養生訓』は書物からの知識だけでなく，自分自身の実際の経験に基づいて書かれており，その内容の多くは現在でも十分に通用する[1)]。

食生活が多くの病気の原因になるという「病は口より入る」，心と病気についての関連を示す「病は気から」は現代でもよく使われる。今では健康を損なう生活習慣の代表である喫煙についても，日本に渡来してからまだそんなに年月が経っていない江戸時代の初期にすでに「たばこは損多し」と喫煙の害を説いている。酒の飲み方についても「酒は半酔に飲め」とほどほどの飲酒を勧めている。

現代での疾病予防としての生活習慣の改善が『養生訓』の時代と大きく違うのは，現代社会が飽食の時代を迎えて，肥満，糖尿病，脂質異常症，高血圧症などのいわゆるメタボリックシンドロー

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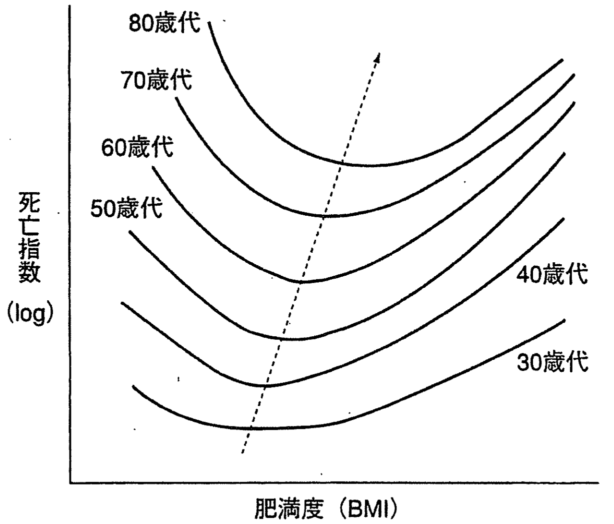

図1　年齢別の肥満度と死亡リスク（模式図）[3]
各年齢の曲線のもっとも低い点が理想的肥満度である。年齢が高くなるとともにこの理想的肥満度が大きくなっていく。

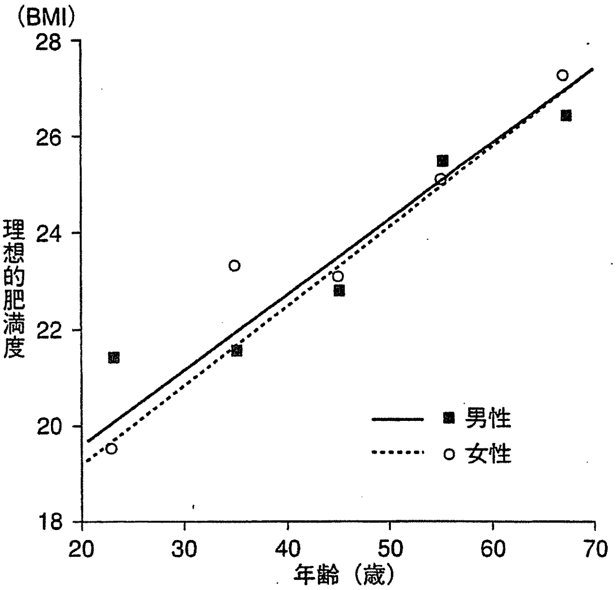

図2　加齢と死亡リスクのもっとも低い肥満度（理想的肥満度）[3]
年齢とともに理想的な肥満度は増加していく。また男女に差はほとんどみられない。

ムが中年期で問題になっていること，高齢者が増加し，認知症や骨粗鬆症などの老年病に罹患する人口が多くなり，その予防としての生活改善が求められていることであろう。

肥満と長寿

肥満の健康への弊害はよく知られている。ラットでは食餌を減らすと寿命が延びる。これは，哺乳類での寿命延長方法として唯一繰り返し証明されているものである。しかし，ヒトでは必ずしも痩せていることが健康や長寿に結びつかない。むしろ高齢者の痩せは予備力の低下を招き，感染症などに対する抵抗力がなくなって，寿命を縮めることになる。

死亡や疾患罹患のリスクを縦軸，肥満度を横軸にとりU字を描く。肥満度の小さい痩せた人は肺炎や結核などの感染症の発病率が高く，肥満度の大きな肥満者は糖尿病や心臓病などの発病率が高くなる。男女別に各年齢でこのようなグラフを作成し，死亡指数のもっとも低い理想的な肥満度を求めてみると，その値は加齢とともに大きくなる（図1，2）。男女で大きな差はなく，年齢とともにほぼ直線的に理想的な肥満度の値が大きくなっていく[2]。身長 170 cm の人では一生を通して 10 年間で約 6 kg の体重増加があると，各年齢での死亡率のもっとも低い肥満度を保つことができる[3]。健康で長生きをするためには，病的に太っている場合は例外として，特に痩せようとせずに年齢とともにむしろ少しずつ太っていくのがよいともいえる。身体の予備能力が低下している高齢者では痩せは危険である。無理な減量は身体にとってむしろ危険である。若い時のダイエットが高齢になってからの骨粗鬆症を招くこともある。

わが国のメタボリックシンドロームの基準値の設定には年齢が考慮されていないことが問題である。肥満が多くの生活習慣病の発症要因となるのは中年期であり，中年期の急激な肥満は危険である。肥満解消のための運動や食事療法が欠かせない。しかし，75 歳以上の後期高齢者ではむしろ低栄養が問題であり，脆弱高齢者を減らして高齢者の寝たきりを予防するためには，栄養改善に心がけるべきであろう。このように，疾病予防のためにはライフステージ別の対応を考えていく必要がある。

ライフステージ別にみた疾病予防

超高齢社会における疾病予防は，高齢に至ってからではなく，基本的には若い頃から健康に関心を持って健康増進に努め，よりよいライフスタイルを守っていくことによって達成される。しかし，人間の身体は年齢によって，あるいは男女で大きく異なる。例えば，女性の身体は閉経前後で劇的に変化する。血清脂質は増加し血圧は高くなり，腹部に脂肪が蓄積するようになる[4]。また，閉経後には骨量が急激に低下する現象がみられることが多い[5]。高齢者の体重減少では骨折のリスクが高くなり[6]，予備力が低下して，死亡率が高くなる[7]。血圧を下げれば記銘力が低下し[8]，コレステロールを下げれば自殺者が増えるという報告もある[9]。性別や年齢，ライフステージで疾病予防のあり方は大きく違うのである。

小児期には，生涯にわたっての健康意識の基礎となるような教育を重点とした疾病予防が重要である。また，小児期にはその後一生にわたって続く塩分や肉類，油脂類への嗜好が形作られる。この時期に，家庭や学校での食育をきちんと行っていかねばならない。

体力がもっとも充実している青年期には，運動の習慣を身につけることが重要である。高齢期の骨塩量は，青年期での最大骨塩量に左右される。この時期に運動やカルシウム摂取で骨塩量を増加させることは，老いてからの骨粗鬆症の予防につながっていく。また，成人病や老年病の基礎になる高血圧症や脂質異常症もこの時期から徐々に始まることが多い。喫煙や飲酒の習慣もほとんどの場合，青年期から始まる。リスクの高い人たちでは，積極的なライフスタイルの改善指導が必要である。

出産を控えた女性は，自分だけでなく次の世代の疾病予防への責任を担っている。妊婦では胎児の健康を考え，授乳婦では母乳への影響を考えねばならない。子供と接する機会のもっとも多い母親は，子供の将来の健康を目指した疾病予防教育の重要な担い手でもある。

中年期には，肥満防止，ストレスへの対処などを行うとともに，家庭と仕事という両面でのライフスタイルの見直しが必要になってくる。また，疾病の早期発見，早期治療という二次予防としての疾病予防もこの時期には重要である。

しかし，高齢期には疾病予防のあり方は大きく異なったものとなる。変化への適応力が低下している高齢者では，環境やライフスタイルの急激な改善は好ましくない。何十年も先のことを考えるのではなく，現在のQOLを高めるような精神的，身体的，社会的支援を行うことが必要である。高齢者の多くはすでに，何らかの慢性疾患に罹患している。高齢者の疾病予防としてはADLの回復，QOLの向上，社会復帰を目指す三次予防を中心に考えるべきであろう。

疾病予防と個人差

疾病の発症には，遺伝的な素因が重要な意味を持つことが多い。疾病の予防指導を効率的に行うためには，遺伝素因，体質の検討が欠かせない。適量の飲酒は，生活習慣病の予防や長寿に有用といわれるが，日本人の場合，アルコール脱水素酵素(ADH)およびアセトアルデヒド脱水素酵素(ALDH)の遺伝子多型により，これらの酵素の活性が低下している人たちがいる。アルコールの代謝に障害があれば，アルコールによる身体への負荷が大きくなる。また，メチレンテトラヒドロ葉酸還元酵素(MTHFR)遺伝子 C677T 多型を持つ人では動脈硬化を引き起こしやすいが，緑黄色野菜を大量に摂ることや葉酸のサプリメントの服用で動脈硬化の進展を予防できることが知られている[10]。

また，日本人には節約遺伝子と呼ばれる遺伝子の変異を持つ人が多い。人類は何十万年と獲物を追って暮らす狩猟生活を送ってきた。安定した食糧供給が得られる農耕や牧畜が行われるようになったのは人類の歴史からするとごく最近のことなのである。人類の歴史は飢餓との戦いであったともいえる。エネルギーの消費を少なくして，脂肪を蓄積できるような遺伝子変異は，生存のために適していた。こうした遺伝子多型としては，peroxisome proliferator-activated receptor γ