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ORIGINAL ARTICLE

Risk factors associated with cognitive decline in the elderly with type 2 diabetes: Pooled logistic analysis of a 6-year observation in the Japanese elderly diabetes intervention trial

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Aim: Considerable attention has been paid to the association between type 2 diabetes mellitus (T2DM) and cognitive dysfunction in the elderly. T2DM is often comorbid with several other metabolic disturbances, including hypertension and dyslipidemia. These comorbid diseases might be associated with cognitive impairment. Many clinical indices should be included as variables for the association with cognitive decline. In the current study, we tried to identify the associated factors with cognitive decline during a 6-year period in elderly T2DM considering the changes in the clinical indices during the follow-up period.

Methods: The subjects in the present study were 63 Japanese Elderly Interventional Trial participants who were administered the Mini-Mental State Examination at baseline, at the third year, and at the end of the 6-year follow-up period. We applied the pooled logistic analysis method to consider the changes in clinical indices during the observation period and tried to identify the factors associated with cognitive decline during the 6 years in elderly type 2 diabetics using repeated measured data for glycated hemoglobin A1c, blood pressure and serum lipids.

Results: In the current study, low high-density lipoprotein-cholesterol and higher diastolic blood pressure were significantly associated with cognitive decline by pooled logistic analysis in the 6-year observation of older diabetic subjects. Higher glycated hemoglobin A1c had a tendency toward association with cognitive decline.

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Conclusion: The results suggest that comprehensive management of diabetes, including dyslipidemia and hypertension, might contribute to the prevention of declines in cognitive function in older diabetic patients. **Geriatr Gerontol Int 2012; 12 (Suppl. 1): 110–116.**

Keywords: diastolic blood pressure, glycated hemoglobin A1c, high-density lipoprotein cholesterol, Mini-Mental State Examination.

Introduction

Considerable attention has been paid to the association between type 2 diabetes mellitus (T2DM) and cognitive dysfunction in the elderly. Numerous cross-sectional studies have investigated neuropsychological functioning in non-demented patients with T2DM.[1,2] Systematic reviews of the literature show a cognitive profile of mild to moderate decrements in cognitive functioning in patients with T2DM.[3,4]

Higher glycemic levels measured by glycated hemoglobin A1c (HbA1c) were associated with lower scores in a wide range of cognitive assessments in the The Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) study.[5] That study, however, only analyzed the data cross-sectionally. Several longitudinal studies have examined the risk of cognitive decline associated with type 2 diabetes.[6–8] However, these studies have not examined the effects of the status of blood glucose, blood pressure and serum lipid profiles. T2DM is often complicated with several other metabolic disturbances, including hypertension and dyslipidemia.[9] These comorbid diseases might be associated with cognitive impairment. Indeed, a longitudinal study has shown that the comorbidity of hypertension with T2DM exacerbates cognitive decline.[10] Many clinical indices should therefore be included as variables for the association with cognitive decline.

In the current study, we applied the pooled logistic analysis method to consider changes in the clinical indices during the follow-up period and to identify the associated factors with cognitive decline during a 6-year period in elderly T2DM.

Methods

Participants

The subjects were 63 Japanese Elderly Interventional Trial (J-EDIT)[11] participants who were administered the Mini-Mental State Examination (MMSE) at baseline, at the third year, and at the end of the 6-year follow-up period. The study protocol was approved by the ethical committees at all of the enrolled institutions, and written informed consent was obtained from each patient.

Functional assessment

The MMSE was administered to most patients on registration.[12] The second and third assessments were carried out at the third year and the end of the 6-year observation period. The MMSE is a global test of orientation, attention, calculation, language and recall with a score of 0–30.

Depressive mood was assessed by a short version of the Geriatric Depression Scale (GDS-15).[13]

Assessment of diabetes mellitus, complications and comorbidities

The diagnosis and patient data regarding DM, blood examinations and complications were obtained from the clinical charts.[14] After overnight fasting, blood samples were taken by venipuncture to assess serum levels of glucose, HbA1c, total cholesterol, triglycerides and high-density lipoprotein cholesterol (HDL-C). The value for HbA1c (%) is estimated as an National Glycohemoglobin Standardization Program equivalent value (%) calculated by the formula HbA1c (%) = HbA1c (Japan Diabetes Society)(%) + 0.4%.[15] Diabetic nephropathy was assessed according to the mean urinary albumin-to-urinary creatinine ratio (ACR) and was classified as no nephropathy (ACR < 30 μg/mg creatinine) or the existence of nephropathy (ACR30 μg/mg creatinine). Diabetic retinopathy was assessed by a fundoscopic examination carried out through dilated pupils by experienced ophthalmologists, and was classified into two categories: mild (no retinopathy or intraretinal hemorrhages and hard exudates), or serious (soft exudates, intraretinalmicrovascular abnormalities, venous calibre abnormalities, venous beading, neovascularization of the disc or other areas in the retina, preretinal fibrous tissue proliferation, preretinal or vitreous hemorrhage and/or retinal detachment). Diabetic neuropathy was defined as either a loss of the Achilles tendon reflex without neuropathic symptoms including paresthesia, or the presence of neuropathic symptoms.

Statistical analysis

A 5-point or greater decline in MMSE compared with baseline was defined as a significant cognitive decline at

the 3- and 6-year examinations.[16] Descriptive statistics for baseline characteristics in patients with and without cognitive decline were compared by χ^2-tests or *t*-tests. Profiles of HbA1c, blood pressure and serum lipid, which were measured at baseline, 3 years and 6 years after follow up, were summarized for the with and without cognitive decline groups.

We used pooled logistic regression models[17,18] to identify the factors associated with cognitive decline within a relatively short period, using repeated measured data for HbA1c, blood pressure and serum lipids. Briefly, we first divided each individual's observation into two separate 3-year long intervals according to the MMSE examination schedule: from baseline to the end of the second year, and from the start of the third to the end of the sixth year. We treated each interval as a short-term follow-up study, where only cognitive decline-free individuals could enter the subsequent "study" and then pooled the repeated observations to model the probability of developing cognitive decline in each 3-year interval. This pooling repeated-observation method is the extension of person-time analyses in epidemiology, which allows information from individuals who remain at risk during the first interval to be updated by measurements at the 3rd-year examination in the second interval. Two observations per individuals contributed to the analyses if they were free of cognitive decline in the first interval, otherwise one observation contributed. Although our companion study[19] found that the existence of diabetic nephropathy at baseline predicted cognitive decline during the 6 years, we didn't include it in this pooled logistic analysis as a result of the small sample, so that we could focus on the predictive power of following repeated measured covariates: HbA1c, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), HDL-C and triglycerides (TG). These covariate values included in the analyses were averaged over the baseline, first and second years in the first interval, and averaged over the fourth to sixth years in the second. Three models were made, and all models were adjusted for age, sex and GDS-15. Because the association of a depressive mood with cognitive dysfunction has been reported,[20,21] the GDS-15 score was included in the adjusting values. Because the underlying risk of developing cognitive decline might be different in the first and second intervals, the interval effect was included in all models. Confidence intervals (CI) for odds ratios (OR) were calculated for generalized estimating equation (GEE) type robust standard errors. All analyses were carried out with SAS software (version 9.1.3; SAS Institute, Cary, NC, USA).

Results

Nine subjects had cognitive decline during the observational period. Table 1 summarizes the baseline characteristics of the patients with or without declines of 5 points or greater for the MMSE scores. Patients with cognitive decline were older and had higher SBP and TG, lower HDL-C, and more nephropathy and neuropathy.

The values at baseline, the third year and the sixth year are shown in Table 2. HbA1c and TG were continuously higher, and HDL-C was lower in the group of

Table 1 Baseline characteristics

	All ($n = 63$)	Cognitive decline ($n = 9$)	Non-cognitive decline ($n = 54$)	*P*-value
Sex (male)*	28 (44.4)	3 (33.3)	25 (46.3)	0.469
Age at baseline†	72.4 (5.1)	76.6 (5.1)	71.7 (4.8)	0.007
HbA1c (%)†	7.8 (0.5)	7.8 (0.4)	7.9 (0.5)	0.674
TC (mg/dL)†	213.1 (33.9)	228.2 (53.5)	210.6 (29.5)	0.151
TG (mg/dL)†	131.2 (80.0)	187.3 (90.3)	121.9 (75.0)	0.022
HDL-C (mg/dL)†	60.8 (17.0)	48.6 (13.3)	62.9 (16.8)	0.018
LDL-C (mg/dL)†	126.6 (29.0)	142.2 (38.9)	124 (26.6)	0.082
SBP (mmHg)†	138.7 (13.7)	142.9 (13.2)	138 (13.7)	0.328
DBP (mmHg)†	74.6 (8.6)	75.8 (4.3)	74.4 (9.1)	0.669
BMI (kg/m^2)†	22.9 (2.8)	23.7 (3.5)	22.8 (2.7)	0.415
Nephropathy (presence)*	12 (19.4)	3 (33.3)	9 (17.0)	0.251
Retinopathy (presence)*	28 (57.1)	4 (50.0)	24 (58.5)	0.655
Neuropathy (presence)*	49 (83.1)	6 (100.0)	43 (81.1)	0.243
Smoking at baseline*	5 (9.1)	1 (12.5)	4 (8.5)	0.717

*n (%). †Mean (SD). *P*-values were calculated by χ^2-test for dichotomous variables and by *t*-test for continuous variables. BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

Table 2 Changes of clinical indices

	Cognitive decline (n = 9)	Non-cognitive decline (n = 54)	All (n = 63)
HbA1c			
Baseline	7.8 (0.4)	7.9 (0.5)	7.8 (0.5)
3 years	7.9 (0.9)	7.7 (0.8)	7.7 (0.8)
6 years	7.6 (1.1)	7.4 (0.9)	7.4 (1.0)
TC			
Baseline	228.2 (53.5)	210.6 (29.5)	213.1 (33.9)
3 years	190.9 (24.2)	200.1 (30.2)	198.8 (29.4)
6 years	183.6 (24.2)	179.2 (32.6)	179.7 (31.7)
HDL-C			
Baseline	48.6 (13.3)	62.9 (16.8)	60.8 (17.0)
3 years	45.1 (10.6)	56.8 (14.1)	55.1 (14.2)
6 years	51.8 (4.6)	56.6 (13.6)	56.1 (13.0)
LDL-C			
Baseline	142.2 (38.9)	124 (26.6)	126.6 (29.0)
3 years	114.3 (23.7)	119.7 (26.9)	118.9 (26.3)
6 years	106.6 (19.0)	103.8 (26.2)	104.1 (25.3)
TG			
Baseline	187.3 (90.3)	121.9 (75.0)	131.2 (80.0)
3 years	155.7 (58.9)	120.3 (62.4)	125.5 (62.7)
6 years	123.5 (36.3)	94.7 (43.3)	97.9 (43.2)
SBP			
Baseline	142.9 (13.2)	138 (13.7)	138.7 (13.7)
3 years	136.5 (7.7)	133 (16.9)	133.5 (16.0)
6 years	128 (14.8)	131.8 (14.2)	131.3 (14.2)
DBP			
Baseline	75.8 (4.3)	74.4 (9.1)	74.6 (8.6)
3 years	73.6 (12.6)	69.9 (8.5)	70.4 (9.1)
6 years	67.7 (6.1)	68.5 (10.5)	68.4 (10.1)

DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

Table 3 Results of multiple pooled logistic regression analysis

	Model 1			Model 2			Model 3		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
HbA1c	2.14	0.91–5.02	0.08	1.96	0.74–5.17	0.18	1.85	0.70–4.88	0.22
HDL-C	0.32	0.13–0.79	0.01	0.31	0.11–0.90	0.03	0.29	0.12–0.73	<0.01
SBP	1.55	0.84–2.87	0.16				1.16	0.40–3.41	0.78
DBP				5.28	1.79–15.62	<0.01	4.64	1.17–18.35	0.03
TC							1.13	0.69–1.84	0.63
TG							1.00	0.88–1.14	0.96

DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

cognitive decline. The TC and both SBP and DBP decreased in both groups during the observational period.

We presented the results of three pooled logistic regression models to determine the predictors of cognitive decline (Table 3). All three models were adjusted for age, sex and GDS-15. Model 1 included HbA1c, HDL-C and SBP. Model 2 included HbA1c, HDL-C and DBP. Model 3 included HbA1c, HDL-C, SBP, DBP, TC and TG. In each model, lower HDL-C (per

10 mg/dL increase for HDL-C: OR = 0.32 [95% CI = 0.13–0.79] in Model 1 to 0.29 [95% CI = 0.12–0.73] in Model 3) and higher DBP (per 10 mmHg increase for DBP: $R = 5.28$ [95% CI = 1.79–15.62] in Model 2 and 4.64 [95% CI = 1.17–18.35] in Model 3) were significantly associated with more than 5-point declines in MMSE during the 3-year period in each interval. The results in Model 1 through Model 3 suggest that higher HbA1c also tends to be associated with cognitive decline (per 1% increase for HbA1c: OR = 2.14, [95% CI = 0.91–5.01] in Model 1; OR = 1.85, [95% CI = 0.70–4.88] in Model 3).

Discussion

In the current study, lower HDL-C and higher DBP were significantly associated with cognitive decline by pooled logistic analysis during the 3 to 6-year follow-up period in older type 2 diabetic patients. Higher HbA1c had a tendency toward an association with cognitive decline.

Our previous study that analyzed the association between the clinical indices collected at baseline in the J-EDIT study and cognitive decline[19] showed that baseline HDL-C was a significant predictor of cognitive decline during the 6-year period, and systolic, but not diastolic BP, was associated with cognitive decline. The factors associated with cognitive decline were similar to the present study. We found no association of TG, HDL-C, BP or HbA1c with lower MMSE score in the cross-sectional analysis in the baseline data of the J-EDIT.[21] Comprehensive treatment in metabolic disturbance in T2DM might have impacts over a longer time frame.

Several observational studies have found that low HDL-C is significantly associated with greater cognitive decline.[22–24] HDL-C contains apolipoprotein E (APOE). One of the four isoforms, the APOE-ε4, is a well-known risk factor for Alzheimer's disease,[25] and multiple findings show that the association between APOE-ε4 and decreased levels of HDL-C increase the susceptibility to Alzheimer's disease.[26,27] Furthermore, low HDL-C and the APOE-ε4 genotype are both associated with an increased incidence of atherosclerosis, a significant contributor to cerebral hypoperfusion,[28] and stroke.[29,30] In the current study, the APOE genotypes were not determined. The relationship among APOE genotypes, low HDL-C and cognitive decline should be further investigated. Ward *et al.* have reported that decreased levels of HDL-C are associated with cognitive declines and gray matter reductions.[31] Quantitative brain imaging analysis might be warranted to elucidate the underlying mechanism of decreased levels of HDL-C in patients with cognitive decline.

The mechanism of the association between higher diastolic hypertension and cognitive decline remains unclear. Impaired cognitive function in T2DM patients is associated with small vessel disease in the brain.[32] DBP levels accelerate white matter lesions[33] and hippocampal atrophy.[34] It can be hypothesized that higher DBP affects cognitive functions by the accelerations in small arterioles in the brain. Indeed, higher DBP has been found to be associated with cognitive impairment in two cross-sectional studies. However, the DBP in the current study was lower than in these two studies,[35,36] at baseline lower than 80 mmHg and at follow up lower than 70 mmHg. These values were lower than the recommended BP in clinical guidelines for diabetics.[37] Several studies have shown that lower diastolic blood pressure (lower than 70 mmHg) might be associated with a risk for dementia[38,39] or white matter lesions and brain atrophy.[40,41] The target blood pressure for antihypertensive therapy in older diabetics should therefore be set very carefully.

As shown in Table 2, HbA1c was continuously higher during the 6 years in the group with cognitive decline. In Model 1 in Table 3, a statistical model including HbA1c, HDL-C, SBP is presented, with higher HbA1c being statistically associated with cognitive decline. In the analysis of the association between the clinical indices and cognitive decline in the same cohort, we did not find that HbA1c at baseline was a significant factor.[19] A recent report from the Atherosclerosis Risk in Communities Study also did not find a significant association between HbA1c at baseline and cognitive decline after a 6-year observation.[42] In the current analysis, however, HbA1c during the 6 years was significantly associated with cognitive decline. The finding in the current study further implies the importance of glycemic control for the preservation of cognitive function in older diabetes patients. In our own analysis that analyzed the indices at baseline, we did not find the association between HbA1c at baseline and cognitive decline.[19] A single HbA1c value might not be indicative of long-term glycemic control. Therefore, it would not necessarily be linked to changes in the central nervous system and secondary effects on cognitive performance. Repeated assessments of HbA1c are needed to increase the precision of the measurement and to thereby elucidate the effects of glycemic control on cognitive performance.

The limitations of the current study are as follows. First, the study was observational. The cause and effect was not clear in the nature of the research design. Second, the number of subjects with cognitive decline was small. A future study carried out at a larger scale would be warranted.

In conclusion, the results of the current study suggested that comprehensive management of diabetes, including dyslipidemia and hypertension, might contribute to the prevention of declines in cognitive function in older diabetic patients.

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Conflict of interest

There is no conflict of interest. The J-EDIT Study Group has not cleared any potential conflicts.

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ORIGINAL ARTICLE

Risk factors associated with cognitive decline in the elderly with type 2 diabetes: Baseline data analysis of the Japanese elderly diabetes intervention trial

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Aim: Recent evidence has shown that type 2 diabetes mellitus (T2DM) in the elderly is a risk factor for cognitive dysfunction or dementia. However, the precise mechanisms have not yet been elucidated. In the current study, we attempted to elucidate the association of clinical indices and diabetic complications at baseline with cognitive declines after 6-year follow up in type 2 diabetic elderly.

Methods: The subjects were 261 participants who were administered the Mini-Mental State Examination (MMSE) at baseline and after 6 years, at the end of the observation period. The cognitive decline was determined as a 5-point or greater decline in MMSE scores during the observation period. Logistic regression analysis to find the factors associated with cognitive decline, adjusted for age and sex, were carried out, and factors with *P*-values of less than 0.2 were included in four models of multiple logistic regression analysis.

Results: We found that the existence of diabetic nephropathy, higher systolic blood pressure and higher serum triglycerides (or lower high-density lipoprotein cholesterol) at baseline were significantly associated with cognitive declines after 6 years in Japanese elderly diabetics in all four models.

Conclusion: The comorbidity of diabetic nephropathy, hypertension and hypertriglyceridemia at baseline were associated with more than 5-point declines in MMSE. Elucidation of the underlying mechanisms of this association is warranted. **Geriatr Gerontol Int 2012; 12 (Suppl. 1): 103–109.**

Keywords: diabetic nephropathy, high-density lipoprotein cholesterol, Mini-Mental State Examination, systolic blood pressure, triglycerides.

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Introduction

Recent evidence has shown that type 2 diabetes mellitus (T2DM) in the elderly is a risk factor for cognitive dysfunction or dementia.[1] However, the precise mechanisms underlying T2DM-related cognitive dysfunction or the development of dementia have not yet been elucidated.

Higher blood glucose itself is a risk for cognitive impairment. A large-scale follow-up study in type 1 DM, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study, showed that higher glycated hemoglobin A1c (HbA1c) levels are associated with cognitive decline.[2] Data from a relatively short-term intervention study also suggest that the status of glycemic control might ameliorate cognitive performance.[3,4]

DM is a disease involving the impairment of glycemic metabolism, but it is also a complex metabolic disorder and is often comorbid with several other metabolic disturbances, including hypertension and dyslipidemia,[5] which themselves are vascular risk factors. These disturbances have been reported to be associated with cognitive dysfunction in diabetics.[6] Some studies have shown an association between blood pressure and the prevalence of dementia.[7,8] Dyslipidemia has also been reported to be associated with cognitive dysfunction.[9,10]

Furthermore, diabetes is associated with microvascular complications (retinopathy, nephropathy, neuropathy), and these are also reportedly associated with cognitive dysfunction.[11–14]

Although, as aforementioned, several factors have been hypothesized to contribute to diabetes-related cognitive dysfunction, to our knowledge there have been few studies in which the cognitive declines in elderly diabetics were prospectively observed.

In the current study, we attempted to elucidate the association of vascular risk factors and complications at baseline with cognitive declines after a 5-year follow up in diabetic elderly.

Methods

Participants

The subjects were 261 Japanese Elderly Interventional Trial (J-EDIT)[15] participants who were administered the Mini-Mental State Examination (MMSE) at baseline and at the end of the 6-year observation period. The study protocol was approved by the ethical committees at all of the enrolled institutions, and written informed consent was obtained from each patient.

Functional assessment

The MMSE was administered to most patients on registration.[16] The second assessment was carried out at the end of the 6-year observation period. The MMSE is a global test of orientation, attention, calculation, language and recall with a score of 0–30.

Depressive mood was assessed by a short version of the Geriatric Depression Scale (GDS-15).[17]

Assessment of diabetes mellitus, complications and comorbidities

The diagnosis and patient data regarding DM, blood examinations and complications were obtained from the clinical charts.[18] After overnight fasting, blood samples were taken by venipuncture to assess serum levels of glucose, HbA1c, total cholesterol, triglycerides and high-density lipoprotein cholesterol (HDL-C). The value for HbA1c (%) is estimated as a National Glycohemoglobin Standardization Program equivalent value (%) calculated by the formula HbA1c (%) = HbA1c (Japan Diabetes Society) (%) + 0.4%.[19] Diabetic nephropathy was assessed according to the mean urinary albumin-to-creatinine ratio (ACR) and was classified as no nephropathy (ACR < 30 μg/mg) or the existence of nephropathy (microalbuminemia: 30 ACR < 300 μg/mg or more advanced). Diabetic retinopathy was assessed by fundoscopic examination carried out through dilated pupils by experienced ophthalmologists, and was classified into two categories: mild (no retinopathy or intraretinal hemorrhages and hard exudates), or serious (soft exudates, intraretinal microvascular abnormalities, venous calibre abnormalities, venous beading, neovascularization of the disc or other areas in the retina, preretinal fibrous tissue proliferation, preretinal or vitreous hemorrhage and/or retinal detachment). Diabetic neuropathy was defined as either the loss of the Achilles tendon reflex without neuropathic symptoms including paresthesia, or the presence of neuropathic symptoms.

Statistical analysis

A 5-point or greater decline in MMSE during the 6 years was defined as a significant cognitive decline.[20] Descriptive statistics for baseline-characteristics in patients with and without cognitive decline were compared by χ^2-tests or *t*-tests. Logistic regression analyses were carried out to find the factors associated with cognitive decline over the 6-year period. For the first of the analyses, logistic regression models for baseline variables were separately fitted, all of which included age at baseline, sex and GDS-15 scores, and items with the *P*-value of <20% were used for the next analyses. We then specified several combinations of the items used and fitted multiple logistic regression models corresponding to them, in which a *P*-value of <5% was considered to be statistically significant. All analyses were carried out with SAS software (version 9.1.3; SAS Institute, Cary, NC, USA).

Results

Table 1 summarizes the baseline characteristics of the patients with or without declines of 5 points or greater MMSE scores. There were no significant differences in terms of the medication profile. Previous clinical incidence of stroke was recorded in three patients out of 23 in the cognitive decline group and 19 patients out of 238 in the cognitively preserved group. MMSE at baseline also showed no difference between the groups. Patients with cognitive decline were significantly older, and had higher systolic blood pressure (SBP), triglycerides (TG), lower HDL-C and serum albumin, and more nephropathy, retinopathy and neuropathy.

A total of 20 patients had stroke during the observation in the group without cognitive decline (238 in total), whereas three out of 23 patients with cognitive decline did so ($P = 0.453$ by χ^2-test).

To find the factors associated with more than 5-point declines in MMSE over the 6-year period, logistic regression models adjusted by age, sex and GDS-15 scores were fitted separately for baseline variables listed in Table 1.

The factors associated with MMSE declines ($P < 0.02$) were SBP, TG, HDL-C and the existence of diabetic nephropathy, retinopathy and neuropathy (Table 2).

We constructed four multiple logistic regression models to determine the predictors of cognitive decline,

Table 1 Baseline characteristics by Mini-Mental State Examination decline status (subjects without information on diabetes complications were excluded)

	All subjects ($n = 261$)	5-point decline in MMSE		P-value‡
		Yes ($n = 23$)	No ($n = 238$)	
Sex (male)*	111 (42.5)	10 (43.5)	101 (42.4)	0.923
Age at baseline† (years)	70.6 (4.3)	72.8 (5.4)	70.4 (4.1)	0.010
MMSE	28.6 (2.1)	28.0 (2.0)	28.6 (2.1)	0.218
HbA1c (%)†	8.0 (0.8)	8.0 (0.7)	8.1 (0.8)	0.734
TC (mg/dL)†	202.4 (32.1)	207.8 (44.7)	201.9 (30.7)	0.402
TG (mg/dL)†	127.4 (70.0)	161.3 (84.2)	124.1 (67.7)	0.015
HDL (mg/dL)†	57.1 (17.1)	50 (11.9)	57.7 (17.4)	0.039
LDL (mg/dL)†	120.7 (29.3)	125.5 (37.3)	120.3 (28.5)	0.415
Albumin (mg/dL)†	4.2 (0.3)	4.1 (0.4)	4.3 (0.3)	0.032
Hypertension (presence)*	179 (68.6)	19 (82.6)	160 (67.2)	0.129
SBP (mmHg)†	134.9 (14.9)	144 (21.4)	134 (13.9)	0.002
DBP (mmHg)†	74.5 (9.3)	75.0 (9.5)	74.5 (9.3)	0.826
Weight circumference (cm)†	82.7 (10.0)	85.7 (10.5)	82.5 (9.9)	0.157
BMI (kg/m^2)†	23.6 (3.5)	23.7 (3.0)	23.6 (3.5)	0.839
Nephropathy (presence)*	33 (12.6)	8 (34.8)	25 (10.5)	<.001
Retinopathy (presence)*	110 (42.1)	15 (65.2)	95 (39.9)	0.019
Neuropathy (presence)*	170 (65.1)	20 (87.0)	150 (63.0)	0.021
Stroke history (presence)*	22 (8.4)	3 (13.0)	19 (8.0)	0.404
IHD history (presence)*	33 (12.6)	3 (13.0)	30 (12.6)	0.952
Smoking at baseline*	42 (16.9)	5 (23.8)	37 (16.3)	0.380
Current drinker at baseline*	148 (56.7)	13 (56.5)	135 (56.7)	0.985
Ex-drinker at baseline*	80 (30.7)	6 (26.1)	74 (31.1)	0.619
Insulin use (presence)*	78 (29.9)	11 (47.8)	67 (28.2)	0.049
Hypoglycemia (presence)*	75 (28.7)	10 (43.5)	65 (27.3)	0.102
Received antihypertensive drug at baseline*	139 (53.3)	13 (56.5)	126 (52.9)	0.742
Received antihyperlipidemic drug at baseline*	108 (41.4)	9 (39.1)	99 (41.6)	0.819
Received ACE inhibitor at baseline*	49 (18.8)	6 (26.1)	43 (18.1)	0.347
Received statin drug at baseline*	13 (5.0)	2 (8.7)	11 (4.6)	0.391
Received fibrate drug at baseline*	7 (2.7)	1 (4.3)	6 (2.5)	0.605
Received ACE inhibitor or ARB at any timing*	157 (60.2)	18 (78.3)	139 (58.4)	0.063
Received statin drug at any timing*	154 (59)	13 (56.5)	141 (59.2)	0.800

n (%). †Mean (SD). ‡P-values are based on χ^2-test for binary data (symbol) and t-test for continuous data (symbol†). ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; HDL, high density lipoprotein cholesterol; IHD, ischemic heart disease; LDL, low density lipoprotein cholesterol; MMSE, Mini-Mental State Examination; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

Table 2 Results of logistic regression analysis adjusted by age and sex

	Odds ratio (95% CI)	*P*-value
BMI (kg/m2)	0.96 (0.82–1.13)	0.638
Waist circumference (cm)	1.03 (0.97,1.08)	0.338
SBP (per 10 mmHg)	1.43 (1.06,1.92)	0.019
DBP (per 10 mmHg)	1.11 (0.67,1.81)	0.691
Hypertension	1.92 (0.62,5.95)	0.260
Insulin use	1.25 (0.49,3.19)	0.634
FBS (mg/dL)	1.00 (0.99,1.01)	0.704
HbA1c (%)	1.03 (0.62,1.72)	0.901
TC (per 10 mg/dL)	1.07 (0.95,1.22)	0.267
TG (per 10 mg/dL)	1.07 (1.01,1.12)	0.013
HDL-C (per 10 mg/dL)	0.66 (0.47,0.93)	0.018
Albumin (g/dL)	0.61 (0.2,1.88)	0.391
Retinopathy	2.02 (0.81,5.07)	0.133
Nephropathy	2.37 (0.82,6.91)	0.113
Neuropathy	4.38 (0.98,19.58)	0.053
Stroke	1.10 (0.29,4.18)	0.889
IHD	0.53 (0.11,2.46)	0.418
Hypoglycemia	1.79 (0.71,4.49)	0.217
Smoker	1.87 (0.56,6.24)	0.310
Current Drinker	1.03 (0.32,3.31)	0.965
Ex-Drinker	2.14 (0.52,8.77)	0.290

BMI, body mass index; DBP, diastolic blood pressure; FBS, fasting blood glucose; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IHD, ischemic heart disease; LDL, low density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

adjusting MMSE decline-associated factors simultaneously (Table 3). As a result of the possible colinearity between TG and HDL-C, either of these two factors was used in the model. All four models were adjusted for age, sex and GDS-15. Model 1 included SBP, TG and the existence of nephropathy. Model 2 included the existence of retinopathy instead of nephropathy. Model 3 included the existence of neuropathy instead of nephropathy or retinopathy. Model 4 included SBP, TG and the existence of nephropathy, retinopathy and neuropathy. Table 3 shows the results of multiple logistic regression analyses. In each model, SBP, TG and the existence of diabetic nephropathy were significantly associated with more than 5-point declines in MMSE during the 6-year period. The adoption of HDL-C instead of TG into the multiple logistic regression analyses showed similar results.

Discussion

In the current study, we found that the existence of diabetic nephropathy, higher systolic blood pressure and higher serum TG or HDL-C at baseline are significantly associated with cognitive decline over a 6-year period in Japanese elderly diabetics.

The mechanism of the association between diabetic nephropathy and cognitive decline remains to be elucidated. Several observational studies reported that nephropathy or microalbuminuria was a risk factor for cognitive decline.[21,22] Microalbuminuria has been reported to be a risk factor for cerebral small vessel disease (lacunae and white matter lesions),[23] and cerebral small vessel disease is one of the major causes of cognitive impairment.[24,25] In diabetic patients, diabetic nephropathy, endothelial dysfunction and inflammation are reportedly mutually interrelated;[26] and these factors might affect cognition. Inflammation[27,28] and endothelial dysfunction[29,30] are both reportedly associated with cognitive dysfunction. Our previous study, which analyzed the association between clinical indices and baseline MMSE scores, showed that the existence of diabetic nephropathy was associated with lower baseline MMSE scores in this same cohort.[31]

Hypertension was also associated with cognitive declines in the current study. Several studies have shown that the combination of hypertension and diabetes exacerbates the cognitive function.[32,33] The underlying mechanism of the association between hypertension and cognitive impairment in diabetics might include cerebrovascular diseases and vascular dysfunction. It has been known that hypertension facilitates vascular occlusion and compromises cerebral infarction,[34–37] including small silent ones. Cerebrovascular alterations precede the cognitive declines.[38]

Table 3 Results of multiple logistic regression analysis

	Model 1 Odds ratio (95% CI)	*P*-value	Model 2 Odds ratio (95% CI)	*P*-value	Model 3 Odds ratio (95% CI)	*P*-value	Model 4 Odds ratio (95% CI)	*P*-value
TG (per 10 mg increase)	1.07 (1.01–1.14)	0.018	1.06 (1.00–1.13)	0.045	1.07 (1.00–1.13)	0.036	1.07 (1.01–1.14)	0.029
or								
HDL-C (per 10 mg increase)	0.67 (0.45–0.98)	0.038	0.68 (0.47–1.00)	0.052	0.70 (0.48–1.01)	0.055	0.71 (0.49–1.03)	0.072
(TG)	1.46 (1.04–2.05)	0.030	1.47 (1.05–2.06)	0.024	1.52 (1.08–2.13)	0.016	1.44 (1.02–2.04)	0.037
SBP (per 10 mmHg increase)								
(HDL)	1.42 (1.0–2.0)	0.048	0.70 (0.48–1.01)	0.055	1.47 (1.04–2.08)	0.031	1.41 (1.00–1.99)	0.053
(TG)	4.48 (1.28–15.67)	0.019	–	–	–	–	3.72 (1.02–13.65)	0.047
Existence of nephropathy								
(HDL-C)	4.06 (1.17–14.05)	0.027					3.22 (0.89–11.59)	0.074
(TG)	–	–	2.76 (0.95–8.01)	0.063	–	–	2.09 (0.68–6.38)	0.196
Existence of retinopathy								
(HDL-C)			2.78 (0.96–8.08)	0.060			2.08 (0.68–6.33)	0.198
(TG)	–	–	–	–	4.42 (0.95–20.62)	0.058	4.09 (0.86–19.45)	0.077
Existence of neuropathy								
(HDL-C)					4.24 (0.92–19.68)	0.065	3.68 (0.79–17.19)	0.098

All four models were adjusted with age, sex and Geriatric Depression Scale-15. Model 1 included systolic blood pressure (SBP), triglyceride (TG) or high-density lipoprotein (HDL), and the existence of nephropathy. Model 2 included the existence of retinopathy instead of nephropathy. Model 3 included the existence of neuropathy instead of nephropathy or retinopathy. Model 4 included SBP, TG, and the existence of nephropathy, retinopathy and neuropathy.
Upper lines in each column show the results of the models including TG, and lower lines show the results of the models including HDL.

Hypertension also alters the structure of cerebral blood vessels and disrupts intricate vasoregulatory mechanisms that assure blood supply to the brain,[39] and the dysfunction of the blood vessels might fail to supply adequate blood supply to the working neurons.

We found that hypertriglycemia at baseline is associated with cognitive decline. Several studies have focused on hypertriglyceridemia and its relationship to dementia.[40–42] Whether moderate hypertriglyceridemia is an independent risk factor for cardiovascular disease remains a source of debate, but a meta-analysis of thousands of patients followed up for >10 years has shown that a triglyceride elevation of 1 mmol/L increases the risk of cardiovascular disease independently of HDL-C.[43]

Lower HDL-C was also associated with cognitive decline in the current study, although it seemed slightly weaker than that of TG. Several studies reported the association of low HDL-C and cognitive impairment or dementia.[44–46]

Micro or small vessel impairments not necessarily accompanied with neurological symptoms might underlie the association between higher TG or lower HDL-C levels and the cognitive declines found in the current study, although the precise mechanism should be elucidated.

Neither fasting blood glucose nor HbA1c were associated with cognitive declines in the current study. Factors other than blood glucose control, including factors found in the current study, might have a larger impact on cognitive function in diabetics. The participants involved in the J-EDIT had relatively worse control of blood glucose, though this control improved significantly during the follow-up period. The changes in glucose control might have affected the results.

Several medications, including statins[47] and renin-angiotensin inhibitors,[48] are reportedly associated with cognitive protection. No significant difference, however, was found in terms of the medication at baseline between the groups with or without cognitive decline.

In summary, we have analyzed the factors associated with greater declines in cognitive function, based on MMSE scores, over a 6-year period. The comorbidity of diabetic nephropathy, hypertension and hypertriglyceridemia at baseline were associated with more than 5-point declines in MMSE. Elucidation of the underlying mechanisms of this association is warranted.

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Conflict of interest

There is no conflict of interest. The J-EDIT Study Group has not cleared any potential conflicts.

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ORIGINAL ARTICLE

Dietary pattern and mortality in Japanese elderly patients with type 2 diabetes mellitus: Does a vegetable- and fish-rich diet improve mortality? An explanatory study

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Aim: To assess the effect of dietary patterns on all deaths and diabetes-related deaths in the Japanese Elderly Diabetes Intervention Trial (J-EDIT).

Methods: We investigated relationships between that of overall mortality and dietary pattern, and diabetes-related deaths and dietary pattern as observed among 912 registered cases of the J-EDIT study, which is a prospective follow-up study of elderly Japanese type 2 diabetic patients.

Results: Factor analysis with the factor number 3 led to deriving three dietary patterns (healthy type, snack type and greasy type). The relationship between these patterns and overall mortality or diabetes-related death was investigated. Although not statistically significant, there was a lower tendency of overall mortality and diabetes-related deaths for the healthy type dietary pattern. When the tendencies of overall mortality were analyzed for "young-old," who are younger than 75 years-of age, and "old-old" of over 75 years-of-age, the mortality rate for the greasy type and healthy type dietary patterns were nearly the same and higher than the snack type dietary pattern in young-old. In contrast, in old-old, a higher mortality rate was reported for the greasy type dietary pattern and a lower mortality rate was reported for the healthy type dietary pattern. The hazard ratio by Cox regression analysis for greasy type to healthy type in old-old was 3.03 ($P = 0.04$, CI 1.07–8.57). Furthermore, in old-old, as vegetable consumption increased, the lower the tendency for

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overall mortality, and the more fish that was consumed, the overall mortality significantly decreased ($P = 0.020$) in the tertile.

Conclusions: The greasy type dietary pattern with an increased amount of sugar, fat and meat led to poor life prognosis for elderly Japanese type 2 diabetic patients. The healthy type dietary pattern rich in vegetable and fish, which is similar to the Mediterranean diet and Dietary Approach to Stop Hypertension diet, was suggested to improve life prognosis.
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Keywords: dietary pattern, elderly type 2 diabetes mellitus, mortality, sugar- fat- and meat-rich diet, vegetable- and fish-rich diet.

Introduction

The relationship between diet and health is an ancient interest, and nutritional epidemiology is one of the important branches of epidemiology.[1] In the study of circulatory disease since World War II, "associations between food and disease" has become one of the major research topics, yielding important study results such as the over consumption of salt and saturated fatty acids being risk factors for arteriosclerosis.[2–4]

According to the Vital Statistics Survey, and the National Health and Nutrition Survey by the Japanese Ministry of Health, Labor and Welfare, the disease frequency patterns of modern Japanese are becoming similar to that of Europe and the USA, with the Westernization of diet characterized by increased meat and fat consumption. Studies on Japanese immigrants who moved to the USA and other countries showed that in the younger generations, their dietary and disease patterns resemble that of the general population in the country they live in, as observed in second generation Japanese and, to a greater degree, in the third generation.[5]

The recent research has focused more on dietary patterns to investigate the relationship between disease and diet, rather than the individual food, such as meat and fat or nutrient factors. We have seen favorable results of these approaches, such as the "Mediterranean diet" and "Dietary Approach to Stop Hypertension (DASH) diet," that were reportedly effective in reducing atherosclerosis.[6–11]

Based on these background findings, we have planned an explanatory study on the relationship between dietary pattern and mortality with the cases registered in a randomized comparative study of elderly diabetes patients and healthy life expectancy, the Japanese Elderly Diabetes Intervention Trial (J-EDIT.) We would like to caution that we present this study as an explanatory study based on 1000 participants from J-EDIT; as the majority of reports statistically investigated the effectiveness of dietary pattern had subject populations of tens of thousands to hundreds of thousands, and it was unknown how strongly we were able to hypothetically confirm the results.

Methods

Participants and follow up

The data at study registration and for the events from the subgroup of 912 cases with valid responses to the nutritional survey in J-EDIT were analyzed as the subjects.

The study design and the details of J-EDIT are described in the article by Araki *et al.*[12] in the present issue of the journal, and the details of the questionnaire for the nutritional survey are described in the article by Yoshimura *et al.*[13] and Kamada *et al.*[14] Following is a brief outline of the study: J-EDIT studied elderly type 2 diabetes patients, randomizing them to standard therapy or intensive therapy. It was a prospective randomized controlled trial that followed the patients for 6 years. A total of 39 facilities throughout Japan participated, and 1173 patients were registered from March 2001 to February 2002.

After the sixth year of follow up, the drop-out rate was 8.9%,[12] but considering that the participants are elderly, the follow-up rate is excellent (death is treated as a cut-off in the calculation for the drop-out rate).

Data on diet

For the 912 patients that submitted consent at the start of survey, the nutritional survey was carried out using a questionnaire for the frequency of food intake developed by Yukio Yoshimura *et al.* of Shikoku University.[13] Various data were obtained; however, for the present study, we focused on the data for the amount of food intake that classified the food into 16 classes adjusted for the energy contents (see Table 1).

Clinical measurements and end-points

At the time of patient registration, information such as health history, anthropometric measurements (body

Table 1 Factor analysis of Food Frequency Questionnaire Based On Food Groups data

	Factor pattern		
	Factor1	Factor2	Factor3
Grains	−0.01381	−0.62273	−0.20002
Nuts	−0.00282	0.26514	−0.32125
Potato	0.06179	0.43822	−0.20527
Sugar	0.02085	0.55776	0.04851
Cake	−0.65543	0.46833	−0.09534
Fat	−0.09459	0.21467	0.45972
Beans	0.38596	−0.04934	−0.35434
Fruit	0.00396	0.4124	−0.30199
Vegetables	0.67618	0.2742	0.0019
Other vegetables	0.66522	0.32309	0.03519
Seaweed	0.54044	0.16768	−0.07672
Seasoning	−0.36263	0.18651	−0.16649
Fish	0.40058	−0.04679	−0.3489
Meat	0.11449	−0.0528	0.72903
Egg	0.02962	−0.09866	0.31668
Milk	−0.00566	−0.21447	0.21014

Rotation method: Promax (power = 3). Factor 1 vegetables, other vegetables, seaweed, fish: "healthy". Factor 2 sugar, cake, potato, fruit, less grain: "snack". Factor 3 meat, fat: "greasy".

height, bodyweight, waist and hip circumferences) and blood biochemical examination were obtained. End-points were death as a result of myocardial infarction, cardiac sudden death, cerebrovascular disorders, renal failure, hypoglycemia or hypoglycemia, unexpected accident, malignant neoplasm, pneumonia and other causes. For analysis, we created two groups as follows, which were treated as composite endpoints: (i) all deaths – included nine kinds of all fatal events; and (ii) diabetes-related deaths – out of nine fatal events, five kinds including myocardial infarction, cardiac sudden deaths, cerebrovascular disorders, renal failure and deaths caused by hypoglycemia or hyperglycemia were selected. For analyzing diabetes-related deaths, four kinds of deaths other than diabetes-related deaths (unexpected accident, malignant neoplasm, pneumonia an other causes) were treated as cut-offs.

Statistical analysis

For the nutritional data, the overall tendency was studied by principal component analysis. Based on this result, oblique factor analysis (Promax rotation) with the factor number of three was carried out. From the results of factor analysis, three dietary patterns were extracted, and the background data for each dietary pattern were described. Also, Cox regression analysis including several adjustment factors was carried out.

All analysis was carried out using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

The detailed report on nutrition as a whole is reported in the present issue of the journal by Yoshimura *et al.* and Kamada *et al.*[13,14] In these reports, using the data of food intake that classified food into 16 classes, multivariable analysis was carried out, and from the dietary pattern obtained, the relationship to mortality was studied. Although the study design for the J-EDIT was a randomized control study by two groups, in which elderly diabetes patients were randomly allocated to standard therapy or intensive therapy,[12] there was no significant difference in the distribution of dietary patterns in the two groups (data not shown); therefore, we combined the two groups and analyzed them as a single cohort in the present.

Dietary patterns

First, the principal component analysis was carried out (data not shown). The cumulative contribution ratio was approximately 33% up to the third eigenvector, and 54% up to the sixth eigenvector. For the first eigenvector, there was a great contribution from green and yellow vegetables, other vegetables and mushrooms, seaweeds, fish, and beans. For the second eigenvector, the contribution from sugars, fats and meats was great. The third eigenvector was fruits, nuts, sweets (confectionaries), seasonings and articles for tastes. It was difficult to extract clear characteristics for the fourth eigenvector or greater.

From these results, we classified the dietary patterns into three groups, and carried out the factor analysis of three factors. Table 1 shows the results of the Promax rotation.

We interpreted these results suggest that group one is subjects who consume a large amount of green and yellow vegetables, other vegetables and mushrooms, seaweeds, fish, and beans; thus we determined the group as the fish and vegetable type. The third group was interpreted as the meat-diet type, consuming a large amount of meats and fats. The second group was notable for the intake of sweets, potatoes and fruits, with a large amount of fish and meat consumption and a low amount of grain; thus we determined that group as the snack and side-order type. We called the first group the "healthy type," the second group "snack type" and the third group "greasy type" based on their characteristics. The numbers of subjects in each group were: 328 in healthy type, 268 in snack type and 316 in greasy type.

Background data of each dietary pattern group

The backgrounds of the subjects by the dietary pattern are shown in Table 2. The age distribution was very similar in all dietary patterns. Bodyweight and body mass index (BMI) were slightly higher in the snack group; however, the difference was not clinically meaningful. No major difference was observed in glycated hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG) levels among the three groups; however, the rate of receiving insulin therapy and no medication was low in the snack group, and a large percentage of patients reported taking oral antihyperglycemic drugs. No significant difference in other items was found in the three groups.

The frequencies of the history of ischemic heart disease were all within 15–17% and there was no difference in the three groups. The history of cerebrovascular disease in the greasy type group was 15%, and compared with that of 10% in the healthy group and 12% in the snack group, it was high a value; however, there was no significant difference between the groups.

Table 2 Baseline characteristics for the three dietary groups

	Healthy ($n = 328$)	Snack ($n = 268$)	Greasy ($n = 316$)	*P*-value*1
Male/female	144/184	112/156	160/156	
Age (SD)	71.7 (468)	71.8 (4.72)	71.9 (4.66)	
	Mean (SD)	Mean (SD)	Mean (SD)	
Height	155.1 (8.0)	155.2 (8.5)	156.4 (9.0)	0.09
Weight	56.8 (9.6)	58.9 (10.1)	58.4 (10.3)	0.027*2
BMI	23.6 (3.2)	24.4 (3.5)	23.6 (3.4)	0.02*3
Waist	82.7 (10.2)	84.6 (9.8)	84.3 (10.3)	0.06
Hip	93.6 (8.1)	94.1 (7.8)	93.9 (7.9)	0.69
HbA1c	8.0 (0.8)	8.1 (0.9)	8.1 (1.0)	0.66
FPG	166.3 (48.5)	166.4 (50.4)	169.4 (51.9)	0.71
T-chol	202.5 (34.3)	202.1 (35.7)	203.4 (36.0)	0.90
TG	124.3 (70.8)	137.0 (75.0)	140.1 (114.5)	0.06
HDL-chol	57.1 (18.9)	56.0 (19.2)	55.9 (16.6)	0.67
LDL-chol	121.8 (29.1)	118.6 (32.8)	120.5 (31.5)	0.47
SBP	137.8 (15.7)	135.2 (16.0)	136.2 (15.9)	0.14
DBP	74.8 (9.7)	74.6 (10.0)	75.2 (10.0)	0.78
Alb	4.2 (0.4)	4.2 (0.3)	4.2 (0.3)	0.08
Serum Cr	0.8 (0.2)	0.9 (0.6)	0.8 (0.3)	0.06
Urine A/C	198.2 (586.1)	215.1 (558.7)	209.3 (581.7)	0.94
eGFR	66.3 (17.0)	65.4 (21.7)	66.2 (18.9)	0.82
Past history, *n* (%)				
Ischemic heart disease	51 (15.6)	41 (15.3)	55 (17.4)	0.74
Cerebrovascular disease	34 (10.4)	33 (12.3)	49 (15.5)	0.14
Mode of therapy for diabetes mellitus, *n* (%)				
No medication	39 (11.9)	21 (7.8)	30 (9.5)	0.027*4
Oral antihyperglycemic drug	189 (57.6)	185 (69.0)	184 (58.2)	
Insulin	100 (30.5)	62 (23.1)	102 (32.3)	
Medication for dyslipidemia	117 (36.1)	119 (44.6)	124 (39.4)	0.11
Medication for hypertension	189 (58.3)	152 (57.4)	175 (55.7)	0.79
Smoking, *n* (%)				
Current	48 (15.5)	36 (14.3)	49 (16.4)	0.50
Former	85 (27.4)	75 (29.9)	99 (33.1)	
Never	177 (57.1)	140 (55.8)	151 (50.5)	

*1*P*-value for general association between the row and column variables. *2*P*-value of *t*-test 0.101 (healthy *vs* snack), 0.051 (healthy *vs* greasy). *3*P*-value of *t*-test 0.016 (healthy *vs* snack), 0.966 (healthy *vs* greasy). *4*P*-value of χ^2-test 0.015 (healthy *vs* snack), 0.595 (healthy *vs* greasy). Alb, albumin; BMI, body mass index; Cr, creatinine; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin A1c; HDL-chol, high-density lipoprotein cholesterol; LDL-chol, low-density lipoprotein cholesterol; SBP, systolic blood pressure; T-chol, total cholesterol; TG, triglyceride.

Table 3 Diet pattern and all death events

Group	MI	Sudden death	CVD	Renal failure	Hyper-, hypo-glycemia	Accident	Malignant neoplasm	Pneumonia	Others	Total
Healthy	3	4	1	0	0	0	9	3	3	**23**
Snack	4	1	1	1	1	0	5	0	3	**16**
Greasy	3	5	3	0	0	0	11	1	5	**28**
Total	10	10	5	1	1	0	25	4	11	**67**

CI, coronary intervention; CVD, cerebrovascular disease; HF, heart failure; MI, myocardial infarction.

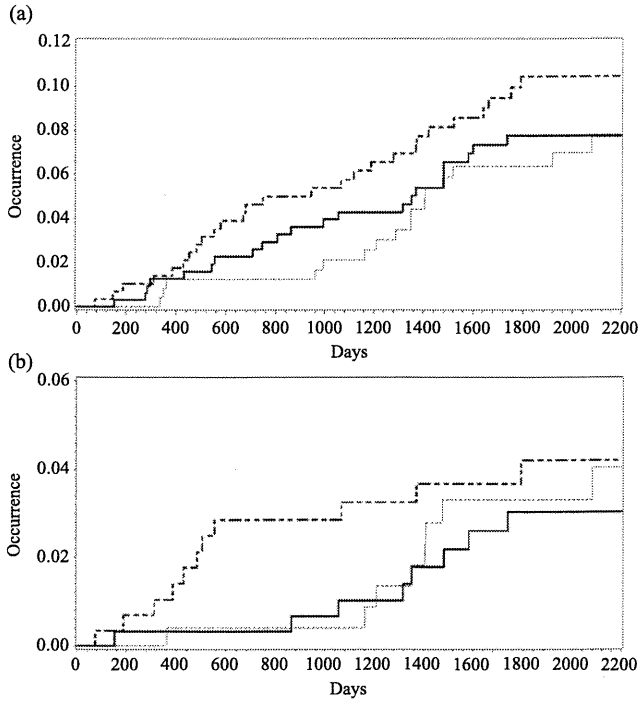

Figure 1 Kaplan–Meier curves for dietary pattern and the events that occurred. a) Overall mortality. b) Diabetes-related deaths.

Dietary patterns and events

The numbers of fatal events for each dietary pattern are shown in Table 3. No clear difference was observed in types of fatal events and the number occurred.

Survival analysis

Figure 1 shows the Kaplan–Meier curve of overall mortality and diabetes-related deaths. Both overall mortality and diabetes-related deaths were not significantly different between the groups ($P = 0.35$ for overall mortality and $P = 0.35$ for diabetes-related deaths, log–rank test for three groups), although the results show that there was a tendency of more deaths reported in the greasy type group, and less in the healthy or snack type groups.

Cox regression analysis of overall mortality and diabetes-related deaths, adjusted for several factors, were carried out. The only factors that showed significance were age and sex for overall mortality and age for diabetes-related deaths, and despite the large hazard ratio in dietary pattern and death between the greasy type and healthy type, there was no significant relationship (Table 4).

Young-old versus old-old

As suggested from the results of Cox regression analyses, age is a significant factor for both overall mortality and diabetes-related deaths. In order to lessen the effect of age, we investigated the relationship between diet and overall mortality or diabetes-related deaths by dividing the subjects into younger than 75 years-of-age (young-old) or 75 years-of-age or older (old-old) at the time of registration.

Figure 2 shows the relationship between overall mortality and dietary pattern by Kaplan–Meier curve. Among the young-old, the mortality rate for greasy type and healthy type were nearly equal, and higher than snack type; however, among the old-old, higher numbers of all cause deaths occurred in greasy type, and healthy types showed notable tendencies of a lower mortality rate. The results of the log–rank test did not identify the significant difference between the mortality rates of young-old in the three groups ($P = 0.62$); however, the mortality was lower compared with other types in the healthy type of old-old, and the difference was significant ($P = 0.05$). According to the Cox regression analyses of old-old, the hazard ratio of greasy type to healthy was 3.03 ($P = 0.04$, CI 1.07–8.57). Although there is no statistical difference, diabetes-related deaths also showed similar results that the healthy type had lower mortality (data not shown).

Vegetable, fish intake and events

The characteristic of healthy type is the high intake of vegetables and relatively high intake of fish. Therefore, we classified these two items (with adjustment for

Table 4 Cox regression

Variables	Hazard ratio	All death CI	*P*-value	Hazard ratio	DM-related death CI	*P*-value
Age (for 1 age)	1.10	(1.04–1.15)	<0.001	1.13	(1.04–1.22)	<0.001
Sex (female/male)	0.50	(0.30–0.83)	<0.001	0.49	(0.22–1.08)	0.08
HbA1c (for 1%)	1.04	(0.80–1.35)	0.79	1.21	(0.88–1.68)	0.24
SBP (1 mmHg)	1.01	(0.99–1.02)	0.50	1.00	(0.98–1.02)	0.93
Past History (Ischemic Heart Disease) with/without	0.94	(0.49–1.80)	0.84	1.25	(0.50–3.12)	0.63
Past History (Cerebrovascular Disease) with/without	1.25	(0.65–2.39)	0.51	2.04	(0.85–4.87)	0.11
Snack group / Healthy group	0.95	(0.50–1.81)	0.88	1.26	(0.47–3.38)	0.64
Greasy group / Healthy group	1.31	(0.75–2.31)	0.35	1.40	(0.56–3.51)	0.47

HbA1c, glycated hemoglobin A1c; SBP, systolic blood pressure

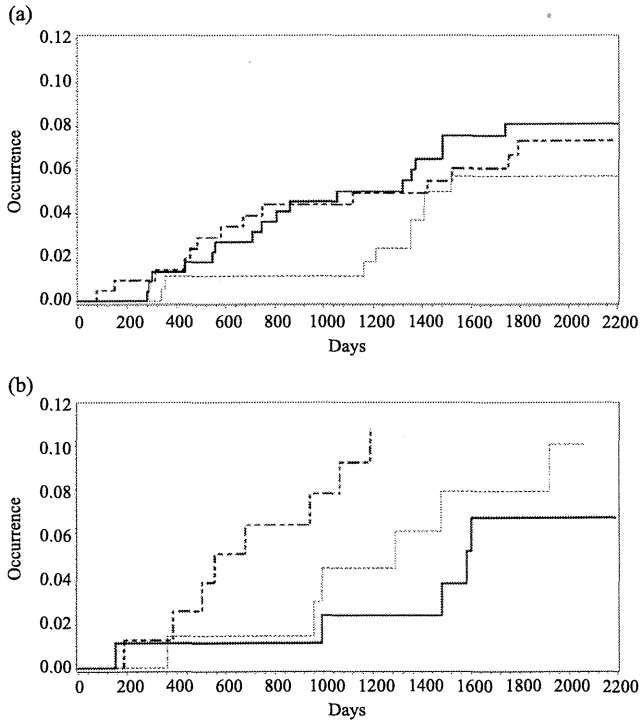

Figure 2 Kaplan–Meier curve for dietary pattern and overall mortality. a) Young-old (65 years-of-age or older to less than 75 years-of-age) b) Old-old (75 years-of-age or older, $n = 258$). The mortality rate for the healthy type dietary pattern in old-old was significantly low ($P = 0.05$) compared with other groups.

energy) into tertile, and investigated the relationship to overall mortality separately for young-old and old-old. In the tertiles for vegetable intake, no clear tendency was observed in young-old; however, in the old-old, we observed the tendency of lower mortality rate in the group with the larger amount of vegetable intake ($P = 0.24$, log–rank test for three groups. Fig. 3a,b, Table 5).

Also for the tertiles for fish intake, we did not observe a notable tendency, but there was a significant difference between the groups in old-old ($P = 0.020$, log–rank test), showing that higher intake reduced mortality. By Cox regression analysis using the same adjustment factors as the previous section, the hazard rate of the medium intake group to low intake group was 0.35 ($P = 0.035$), and 0.43 for the high intake group ($P = 0.12$, Fig. 3c,d, Table 5).

Discussion

The relationship between diet and disease has been discussed since ancient times, but the relationship between particular dietary patterns, such as the Mediterranean diet or DASH diet, and various diseases, such as arteriosclerosis and cancers, and the relationship to life prognosis have become the focus of active discussion from the beginning of the year 2000. These dietary patterns that have been said to be "good for health" have much in common with the diet of the healthy type we observed from the present diet survey.

The characteristics of the Mediterranean diet is a high intake of vegetables, beans, fruits, nuts, grains and olive oil, and a relatively high intake of fish, low to medium intake of dairy products, and low intake of meats.[7] The foods that compose the DASH diet are also similar in general, and in brief, the program encourages adequate intake of vegetable, fruits and low-fat dairy products, and reduced intake of meats and sugars.[15,16] The diet of the healthy type observed as the results of this analysis was characterized by the high intake of vegetables and seaweeds, and the relatively high intake of fish and beans, but the intake of meats, fats and sugars remained low. In contrast, the greasy type was characterized by the high intake of meats and fats. Despite the large difference in ethnicities and the geographies where the Mediterranean diet and DASH diet were born, it is of particular interest that very similar dietary patterns were observed.