who provided valid responses formed the study cohort. We excluded 6,333 individuals who did not provide written consent for review of their Long-term Care Insurance (LTCI) information, 1,979 persons who had already been certified as having a disability by the LTCI at the time of the baseline survey, five persons who had died or moved during the period of the baseline survey, and 514 persons who left blank more than 24 of the 39 food items on the food frequency questionnaire (FFQ). Thus, 14,260 responses were analyzed for the purpose of this study.

During the 5-year period covered by the study, only 121 individuals were lost to follow-up because they moved away from the study area, without developing any functional disability; thus, the follow-up rate was 99.2%. From 62,755 person-years, incident functional disability was determined in 2,360 persons, and the number of all-cause deaths without incident functional disability was 842.

Dietary Assessment

We asked about the average frequency of consumption of each food using a 39-item FFQ, for which we had previously conducted a validation study in the same region (the precinct of Ohsaki Public Health Center, Miyagi) (22). In brief, 113 participants (55 men and 58 women) provided four 3-day diet records within a 1-year period and subsequently responded to the FFQ. The method used for calculating food and nutrient intake from the FFQ was developed in this study. Based on these data, we calculated the volume of consumption of individual foods according to the FFQ. For estimation of energy and protein intake from the food consumption volume based on the FFQ, we used a food composition table that corresponded to the items listed in the questionnaire. This food composition table was developed by using the Standard Tables of Food Composition published by the Science and Technology Agency of Japan (22).

Dietary Pattern Derivation

To derive dietary patterns, we used two methods: (i) factor analysis (principal component analysis) and (ii) confirmatory factor analysis.

The factor analysis was conducted by using the daily consumption (weight in grams) of 39 food items from the FFQ. If the reported frequency was blank, we assumed that the item was never consumed. We used the PROC FACTOR procedure in SAS version 9.3 to obtain a three-factor score. To achieve a simpler structure with greater interpretability, the factors were rotated by an orthogonal transformation (varimax rotation function in SAS). This allowed three major dietary patterns to be identified. We named them (i) the Japanese pattern, (ii) the animal food pattern, and (iii) the high dairy pattern. For each pattern and each participant, we calculated a factor score by summing the consumption of each food item weighted by its factor loading.

In order to strengthen our dietary pattern analysis, we further used confirmatory factor analysis, which is characterized by hypothesis-oriented approach. Recently, confirmatory factor analysis has been used increasingly as a major analytical method in dietary pattern research, such as studies of the Mediterranean diet (23–25). We identified nine food items that formed the Japanese Diet Index Score: rice, miso soup, seaweeds, pickles, green and yellow vegetables (green vegetables, carrot, pumpkin, tomato), fish (raw fish, fish boiled with soy, roast fish, boiled fish paste, dried fish), green tea, beef and pork (beef, pork, ham, sausage), and coffee. In a previous study based on the dietary record method, these items had been reported to have higher absolute factor scores for the traditional Japanese pattern (26). Another study has also reported that these items are characteristic of the traditional Japanese diet (27). For each of the seven positive components (rice, miso soup, seaweeds, pickles, green and yellow vegetables, fish, and green tea), participants received 1 point if their intake was more than or equal to the sex-specific median. For each of the two negative components (beef and pork, and coffee), participants received 1 point if their intake was below the sex-specific median. Thus, the Japanese Diet Index Score ranged from 0 to 9, with higher scores indicating greater dietary conformity.

Covariate

Body mass index was calculated as the self-reported body weight (kg) divided by the square of the self-reported body height (m).

The K6 was used as an indicator of psychological distress (19,20). Respondents were asked about their mental status over the last month by using six questions. Total point scores ranged from 0 to 24. As the optimal cutoff point for mental illness in the validation study, we classified individuals with scores of ≥13 as having psychological distress (20).

The Kihon Checklist was developed to predict functional decline in community-dwelling elderly individuals. With regard to the motor function score in the Kihon Checklist, respondents were asked about their current motor function status by using five binary questions yielding total point scores ranging from 0 to 5. As the optimal cutoff point for functional decline suggested in the validation study, we classified individuals with scores of <3 as having better motor function (21).

LTCI System in Japan

In this study, we defined incident functional disability as certification for LTCI in Japan, which uses a nationally uniform standard of functional disability. LTCI is a mandatory form of social insurance to assist daily activity in the frail elderly individuals (28–32). Everyone aged ≥40 years pays premiums, and everyone aged ≥65 years is eligible for formal caregiving services. When a person applies to the municipal government for benefits, a care manager visits his or her home and assesses the degree of functional disability using a questionnaire developed by the Ministry of Health, Labor, and Welfare. Then, the municipal government calculates the standardized scores for physical and mental functions on the basis of the questionnaire and assesses whether the applicant is eligible for LTCI benefits (certification). There are a total of 74 items in the questionnaire, and these are classified into six dimensions: motor function (13 items), activity of daily living (12 items), cognitive function (9 items), mental and behavioral disorders (15 items), adaptation to social life (6 items), and use of medical procedures (12 items). If a person is judged to be thus eligible, the Municipal Certification Committee decides on one of seven levels of support, ranging from Support Level 1, Support Level 2, and Care Level 1 to Care Level 5. In brief, LTCI certification levels are defined as follows. Support Level 1: "limited in instrumental activities of daily living but independent in basic activities of daily living (ADLs)"; Care Level 2: "requiring assistance in at least one basic ADL task"; Care Level 5: "requiring care in all ADL tasks". A community-based study has shown that levels of LTCI certification are well correlated with ability to perform activities of daily living, and with Mini-Mental State Examination scores (33). LTCI certification has already been used as a measure of incident functional disability in the elderly individuals (34–36).

Follow-up and Case Details

Incident functional disability was set as our endpoint, which was defined as LTCI certification. The primary outcome was LTCI certification (Support Level 1 or higher), in which deaths without LTCI certification were treated as censored. In the subanalysis, we set the criteria of disability toward a more severe level, that is, Care Level 2 (requiring assistance with one basic activities of daily living task) or higher.

We obtained a data set that included information on the date of LTCI certification, death, or emigration from Ohsaki City Government based on an agreement about the secondary use of data. With regard to LTCI certification, information on care level was also provided. All data were transferred from the Ohsaki City Government under the agreement related to Epidemiologic Research and Privacy Protection yearly each December.

Ethical Issues

We considered the return of completed questionnaires to imply consent to participate in the study involving the baseline survey data and subsequent follow-up of death and emigration. We also confirmed information regarding LTCI certification status after obtaining written consent along with the questionnaires returned from the participants at the time of the baseline survey. The Ethics Committee of Tohoku University Graduate School of Medicine (Sendai, Japan) reviewed and approved the study protocol.

Statistical Analysis

We counted the person-years of follow-up for each participant from December 16, 2006 until the date of incident functional disability, date of emigration from Ohsaki City, date of death, or the end of the study period (November 30, 2011), whichever occurred first.

We used the multiple adjusted Cox proportional hazard model to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for incident functional disability according to quartiles of the dietary pattern score. Dummy variables were created for the quartiles of each dietary pattern score, and the lowest quartile of a dietary pattern score was used as a reference category. Multivariate models were adjusted for the following variables. Model 1 was sex and age adjusted. To examine whether the association between the dietary patterns and functional disability was attributable to a healthy physical status or other lifestyle factors, Model 2 was further adjusted for history of stroke, myocardial infarction, hypertension (individuals with self-measured systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg were also defined as hypertensive), arthritis, osteoporosis and fracture, education level, smoking status, alcohol consumption, body mass index, psychological distress score, time spent walking per day, and motor function score. Model 3 was fully adjusted and included energy and protein intake (category of sex-specific tertile).

All data were analyzed using SAS version 9.3 (SAS Inc., Cary, NC). All statistical tests described here were two sided, and differences at $p < .05$ were accepted as significant.

Results

Among 14,260 participants, the proportion of men was 44.8%, mean (*SD*) age was 73.9 (6.0) years, and mean (*SD*) body mass index was 23.6 (3.4). The number of participants for whom data on the FFQ were any missing was 7,352 (the distribution of missing shows in Supplementary Figure 1).

Table 1 shows factor loadings, which are equivalent to simple correlations between the food items and dietary patterns. A positive loading indicates that a food item is positively associated with the dietary pattern, and a negative loading indicates an inverse association with the dietary pattern. That is, food items highly loaded within a dietary pattern are highly correlated with each other.

The Japanese pattern was loaded heavily on fish, vegetables, mushrooms, potato, seaweeds, pickles, soybean and fruits, whereas the animal food pattern was loaded heavily on various animal-derived foods (beef, pork, ham, sausage, chicken, liver, eggs, and butter). The high dairy pattern was heavily loaded on dairy products (yoghurt, cheeses, and butter), margarine, and

Table 1. Factor-Loading Matrix for the Major Dietary Pattern Identified by Factor Analysis (n = 14,260)*

	Japanese Pattern	Animal Food Pattern	High Dairy Pattern
Rice	0.01	0.31	−0.39
Miso soup	0.06	0.04	−0.07
Beef	−0.09	0.47	0.08
Pork (excluding ham, sausage)	0.15	0.56	0.01
Ham, sausage	0.05	0.49	0.25
Chicken	0.15	0.56	0.00
Liver	−0.06	0.42	0.15
Egg	0.25	0.33	0.04
Milk	0.19	0.01	0.26
Yoghurt	0.21	−0.09	0.47
Cheeses	−0.02	0.28	0.46
Butter	−0.07	0.39	0.45
Margarine	−0.07	0.23	0.49
Deep fried dishes, tempura	0.15	0.47	0.04
Fried vegatable	0.40	0.32	0.02
Raw fish, fish boiled with soy, roast fish	0.44	0.26	−0.11
Boiled fish paste	0.29	0.38	0.15
Dried fish	0.33	0.30	0.05
Green vegetables	0.66	0.10	0.08
Carrot, pumpkin	0.65	−0.03	0.23
Tomato	0.44	−0.12	0.37
Cabbage, lettuce	0.60	0.17	0.16
Chinese cabbage	0.64	0.15	−0.05
Wild plant	0.19	0.22	0.16
Mushrooms (shiitake, enokitake)	0.43	0.27	0.04
Potato	0.65	0.07	0.12
Seaweeds	0.63	0.02	0.19
Pickles (radish, Chinese cabbage)	0.41	0.04	−0.06
Food boiled with soy	0.23	0.23	0.32
Boiled beans	0.22	0.11	0.37
Soybean (tofu, fermented soybeans)	0.56	0.11	−0.04
Orange	0.54	−0.12	0.34
Other fruits	0.54	−0.13	0.39
Fresh juice	0.13	0.13	0.37
Confectioneries	0.26	0.16	0.17
Green tea	0.28	0.02	0.04
Black tea	0.03	0.09	0.37
Coffee	0.05	0.13	0.18
Chinese tea	0.01	0.04	0.25
Variance explained (%)	12.8	7.1	6.3

*Absolute values <−0.3 or >0.3 are underlined.

black tea, and negatively loaded on rice. These three dietary patterns explained 26.1% of the variance.

Table 2 compares the characteristics of participants according to the quartiles of each dietary pattern score. Participants with a higher Japanese pattern score were less likely to be male, to be current smokers and drinkers, and to suffer from psychological distress. Additionally, participants with a higher Japanese pattern score were more likely to have ≥19 years of education, to walk ≥1 h/d, and to have greater intake of energy and protein. Conversely, participants with a higher animal food pattern score were more likely to be male, to be current smokers and drinkers. Additionally, participants with a higher animal food pattern score were more likely to walk ≥1 h/d, to have better motor function, and to have greater intake of energy and protein, and were less likely to suffer from psychological distress and to have ≥19 years of education. Participants with a high dairy pattern score tended to be female, and were similar to those with a higher Japanese dietary pattern score except for psychological distress, time spent walking, and intake of energy and protein.

The association between the dietary patterns and functional disability, along with HRs and associated 95% CIs, are shown in Table 3. We found that a higher Japanese pattern score was inversely associated with the incident risk of functional disability (p trend <.001 in Model 3). This inverse association did not differ between the sexes (p = .057 for interaction with sex; data not shown). On the other hand, the animal food pattern and the high dairy pattern were not significantly associated with functional disability in any of the models.

Even when we set stricter criteria for disability (basic activities of daily living impairment), the results for the

Table 2. Baseline Characteristics According to Dietary Pattern Score Quartiles (n = 14,260)

Characteristics	Dietary Pattern Score Quartiles			
	1 (Low)	2	3	4 (High)
Age (y), mean (*SD*)				
Japanese pattern	74.0 (6.3)	73.7 (5.9)	73.6 (5.8)	74.3 (5.8)
Animal food pattern	74.0 (6.2)	73.9 (6.0)	73.7 (5.8)	74.0 (5.9)
High dairy pattern	74.3 (5.9)	74.2 (6.1)	73.7 (5.9)	73.4 (5.9)
Men (%)				
Japanese pattern	56.8	49.1	39.1	34.5
Animal food pattern	19.9	36.8	52.6	70.1
High dairy pattern	67.8	45.3	34.6	31.7
Education until age ≥19 y (%)				
Japanese pattern	21.6	25.8	29.2	31.7
Animal food pattern	30.3	26.6	25.5	26.1
High dairy pattern	16.2	23.4	30.0	38.7
Current smoker (%)				
Japanese pattern	20.3	15.1	10.3	7.4
Animal food pattern	6.9	11.6	15.2	19.4
High dairy pattern	21.5	12.5	10.1	9.0
Current drinker (%)				
Japanese pattern	43.2	41.2	36.1	30.2
Animal food pattern	23.4	33.4	41.1	52.2
High dairy pattern	49.6	36.2	32.9	31.9
Body mass index (kg/m^2), mean (*SD*)				
Japanese pattern	23.6 (3.5)	23.5 (3.4)	23.6 (3.3)	23.7 (3.2)
Animal food pattern	23.6 (3.4)	23.6 (3.5)	23.6 (3.2)	23.5 (3.2)
High dairy pattern	23.6 (3.3)	23.6 (3.4)	23.6 (3.4)	23.6 (3.4)
Psychological distress (%)*				
Japanese pattern	7.3	4.7	4.1	3.1
Animal food pattern	6.3	4.4	4.2	4.2
High dairy pattern	4.3	5.5	4.7	4.5
Time spent walking ≥1 h/d (%)				
Japanese pattern	24.6	24.7	28.1	31.9
Animal food pattern	23.1	26.0	28.1	32.2
High dairy pattern	31.5	26.7	26.7	24.5
Better motor function (%)†				
Japanese pattern	75.8	77.8	78.6	78.4
Animal food pattern	73.3	76.4	78.7	82.2
High dairy pattern	77.7	76.1	77.3	79.5
Energy (kcal), mean (*SD*)‡				
Japanese pattern	1,214 (395)	1,384 (366)	1,484 (365)	1,614 (374)
Animal food pattern	1,188 (301)	1,336 (322)	1,493 (344)	1,735 (409)
High dairy pattern	1,573 (436)	1,390 (393)	1,367 (379)	1,428 (368)
Protein (g), mean (*SD*)				
Japanese pattern	40.8 (12.1)	50.2 (11.3)	56.4 (11.5)	63.6 (12.2)
Animal food pattern	44.1 (11.7)	49.1 (11.7)	55.2 (11.3)	65.6 (13.1)
High dairy pattern	55.4 (14.1)	50.7 (14.6)	51.8 (14.1)	55.8 (14.1)

*Kessler six-item psychological distress scale ≥13.
†Motor function score in Kihon Checklist <3.
‡Except energy intake from alcohol drinking.

Japanese pattern score did not change. In Model 3, the multivariate HRs (95% CI) for the successive categories of the Japanese pattern score were: 1 (reference), 0.87 (0.73–1.03), 0.71 (0.59–0.86), and 0.74 (0.61–0.90) (p trend <.001; data not shown). To examine possible reverse causality, we reanalyzed the association after excluding 900 participants who experienced incident functional disability in the first 2 years of follow-up, but the results did not change substantially in Model 3 (p trend <.001; data not shown). Additionally, when we excluded participants who had any history of disease that might have affected dietary habit (stroke, myocardial infarction, diabetes, arthritis, osteoporosis, fracture, cancer, kidney disease, and hepatic disease), the results did not change substantially in Model 3 (p trend = .007; data not shown). The Japanese pattern score was also inversely associated with all-cause mortality (p trend = .028 in Model 3; data not shown).

Table 4 shows the results of incident functional disability according to the quartiles of the Japanese Diet Index Score. In this analysis, we included 514 persons who left

Table 3. Association Between Dietary Pattern Scores and Incident Functional Disability (n = 14,260)

	Dietary Pattern Score Quartiles				
	1 (Low)	2	3	4 (High)	p trend
Japanese pattern					
Number of event	711	591	522	536	
Person-years	15,159	15,649	15,948	15,999	
Model 1*	1.00 (reference)†	0.83 (0.75–0.93)	0.72 (0.64–0.81)	0.65 (0.58–0.72)	<.001
Model 2‡	1.00 (reference)	0.90 (0.80–1.00)	0.80 (0.71–0.89)	0.75 (0.67–0.84)	<.001
Model 3§	1.00 (reference)	0.91 (0.82–1.02)	0.82 (0.73–0.92)	0.77 (0.68–0.88)	<.001
Animal food pattern					
Number of event	616	620	557	567	
Person-years	15,601	15,730	15,767	15,657	
Model 1*	1.00 (reference)	1.04 (0.93–1.16)	0.97 (0.86–1.09)	1.00 (0.88–1.13)	.697
Model 2‡	1.00 (reference)	1.08 (0.96–1.21)	1.03 (0.91–1.16)	1.09 (0.96–1.23)	.313
Model 3 §	1.00 (reference)	1.10 (0.98–1.23)	1.07 (0.95–1.21)	1.16 (1.02–1.31)	.053
High dairy pattern					
Number of event	615	611	558	576	
Person-years	15,502	15,618	15,905	15,730	
Model 1*	1.00 (reference)	0.96 (0.85–1.07)	0.89 (0.79–1.00)	0.98 (0.87–1.10)	.465
Model 2‡	1.00 (reference)	0.99 (0.89–1.11)	0.95 (0.84–1.07)	1.10 (0.98–1.24)	.217
Model 3§	1.00 (reference)	0.99 (0.88–1.11)	0.95 (0.84–1.07)	1.11 (0.99–1.26)	.158

*Adjusted for age (65–69, 70–74, 75–79, 80–84, and ≥85 y) and sex.
†HR (95% CI).
‡Adjusted for model 1 + history of disease (stroke, myocardial infarction, hypertension, arthritis, osteoporosis, fracture [yes, no]), educational level (age when last graduation of school <16, 16–18, ≥19 y, missing), smoking (never, former, current, missing), alcohol drinking (never, former, current, missing), body mass index (in kg/m^2: <18.5, 18.5–24.9, ≥25.0, missing), psychological distress score (<13, ≥13, missing), time spent walking (<30 min/d, 30 min to 1 h/d, ≥1 h/d, missing), and motor function score (<3, ≥3, missing).
§Adjusted for model 2 + tertile categories of energy intake and protein intake (sex-specific tertile, missing).

Table 4. Confirmatory Factor Analysis: Association Between Japanese Diet Index Score and Incident Functional Disability (n = 10,148)

	Japanese Diet Index Score (quartiles)*				
	1 (Low)	2	3	4 (High)	p trend
Index score	<4	4	5	≥6	
Number of event	374	333	374	481	
Person-years	9,793	9,293	10,661	15,261	
Model 1†	1.00 (reference)‡	0.88 (0.76–1.02)	0.82 (0.71–0.94)	0.72 (0.63–0.83)	<.001
Model 2§	1.00 (reference)	0.92 (0.79–1.07)	0.87 (0.76–1.01)	0.77 (0.67–0.88)	<.001
Model 3‖	1.00 (reference)	0.94 (0.81–1.09)	0.90 (0.77–1.05)	0.79 (0.68–0.92)	.002

*Index score was constituted by nine food items that reported to have higher absolute factor scores for the traditional Japanese pattern. For each of the seven positive components (rice, miso soup, seaweeds, pickles, green and yellow vegetables, fish, and green tea), participants received 1 point if their intake was more than or equal to the sex-specific median. For each of the two negative components (beef and pork and coffee), participants received 1 point if their intake was below the sex-specific median.
†Adjusted for age (65–69, 70–74, 75–79, 80–84, and ≥85 y) and sex.
‡HR (95% CI).
§Adjusted for model 1 + history of disease (stroke, myocardial infarction, hypertension, arthritis, osteoporosis, fracture [yes, no]), educational level (age when last graduation of school <16, 16–18, ≥19 y, missing), smoking (never, former, current, missing), alcohol drinking (never, former, current, missing), body mass index (in kg/m^2: <18.5, 18.5–24.9, ≥25.0, missing), psychological distress score (<13, ≥13, missing), time spent walking (<30 min/d, 30 min to 1 h/d, ≥1 h/d, missing), and motor function score (<3, ≥3, missing).
‖Adjusted for model 2 + tertile categories of energy intake and protein intake (sex-specific tertile, missing).

blank more than 24 items on the FFQ and then excluded 4,626 persons for whom data on items of the Japanese Diet Index Score were missing (10,148 persons were included in the analysis). We found a significant inverse association between the Japanese Diet Index Score and functional disability (p trend = .002 in Model 3).

Discussion

In this population-based cohort study, we identified three dietary patterns derived by factor analysis among the Japanese population: the Japanese pattern, animal food pattern, and high dairy pattern, which were consistent with our previous study using the same FFQ, except for the third pattern because in the present study the volume of alcohol consumption was not available (6). The Japanese pattern was associated with a decreased risk of incident functional disability. No apparent association was observed for either the animal food pattern or the high dairy pattern. To our knowledge, this is the first study to have proved the association between the Japanese dietary pattern and incident risk of functional disability.

Our study had a number of strengths: (i) it was a large population-based cohort study of 14,260 persons; (ii) it had a follow-up rate of almost 100%; (iii) many confounding factors were taken into account.

We also considered the effects of reverse causality. Even after excluding individuals who experienced incident functional disability in the first 2 years of follow-up, the strong inverse association between the Japanese pattern and functional disability persisted. The earlier findings suggest that the present results are unlikely to be explained by reverse causality.

This inverse association between the Japanese pattern and functional disability was consistent with previous studies of the Mediterranean diet and Healthy Eating Index (11–16). The Japanese pattern has some characteristics in common with the Mediterranean diet, for instance, high intake of vegetables, fruits, legumes, and fish, and low intake of meat and dairy products (4,37). Thus, the mechanism of this association might be similar to that reported in the previous studies of the Mediterranean diet. On the other hand, the Healthy Eating Index pattern in three previous studies may not be fully consistent with Japanese pattern because meat, but not fish, was recommended in the Healthy Eating Index. Furthermore, vegetables, fruits, and legumes are common components of the above three patterns. Previous studies have reported that a plant-based diet reduces cardiovascular risk, type 2 diabetes, and bone loss (37–42). Although a diet consisting only of plant-based foods may lack certain nutrients (42), a dietary pattern including an abundant amount of these plant-based items may decrease the risk of functional disability.

On the other hand, the Japanese pattern is reported to differ from the Mediterranean diet in that energy intake is lower (43). The Japanese pattern score was positively correlated with energy intake (Table 2), but the results did not change substantially even when energy intake and body mass index were added in the multivariate model. The inverse association seems difficult to explain in terms of energy intake alone, and micronutritional components might have a role. Because the Japanese pattern included a variety of foods that explained 12.8% of the overall variance, this pattern may contain various micronutritional components and have a good nutrient balance.

In the present study, we used two different dietary pattern derivation methods to strengthen the reliability of our results. When we repeated the analysis by using confirmatory factor analysis, higher conformity with the Japanese Diet Index Score was also associated with a decreased risk of incident functional disability. Because these factors in the Japanese Diet Index Score were based on nationwide validity studies of dietary pattern, the Japanese Diet Index Score may represent the most common diet items in Japanese population. However, the Japanese diet also varies in several aspects according to region. For example, residents of Okinawa, who are known for their longer average life expectancy, often eat the traditional Okinawan diet that includes unique food items such as bitter melon, mugwort, and turmeric (44).

Additionally, in the analysis using each item from the Japanese Diet Index Score as an exposure variable (dichotomous variable by sex-specific median), a significant inverse association was observed for items other than fish and vegetables (data not shown). These results suggested that traditional Japanese foods were also associated with a decreased risk of incident functional disability. Previous studies have also examined the health impact of individual Japanese foods and their nutritional components, including soybeans (as well as miso soup), seaweed, and green tea (45–49).

This study had several limitations. First, we did not investigate the causes of functional disability in participants who received LTCI certification. Thus, the mechanism responsible for reduction of functional disability by intake of a Japanese diet remained unidentified. Second, not all potential confounding factors were considered, as we used only indirect measures of physical and cognitive function for adjustment. Third, because not all candidates applied for LTCI certification, this study may not have been completely free from detection bias. The degree of this bias remains to be verified.

In conclusion, the findings of this cohort study indicate that higher conformity with the Japanese dietary pattern is significantly associated with a lower risk of incident functional disability. This result suggests that the Japanese dietary pattern contributes to extended healthy life expectancy.

Supplementary Material

Supplementary material can be found at: http://biomedgerontology.oxfordjournals.org/

Funding

This work was supported by Health Sciences Research grants (nos. H24-Choju-Ippan-005 and H23-Junkankitou [Seisyu]-Ippan-005) from the Ministry of Health, Labour and Welfare of Japan.

Acknowledgments

We would like to thank Yoshiko Nakata, Yumi Tamura, and Nayoko Aota for their technical assistance. Author Contributions: Study concept and design (Y.T., I.T.). Acquisition of subjects and/or data (Y.T., T.W., W.-T.C., I.T.). Analysis and interpretation of data (Y.T., T.W., Y.S., W.-T.C., M.K., I.T.). Preparation of manuscript (Y.T., W.-T.C., I.T.).

Conflict of Interest

There are no potential conflicts of interest that relate to the manuscript.

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Preventive Medicine 59 (2014) 68–72

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Relationships between changes in time spent walking since middle age and incident functional disability

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ARTICLE INFO

Available online 27 November 2013

Keywords:
Walking
Physical activity
Disability
Cohort study
Longitudinal study

ABSTRACT

Objective. To examine the relationship between changes in time spent walking since middle age and incident functional disability.

Method. In 2006, we conducted a prospective cohort study of 7177 disability-free Japanese individuals aged ≥65 years who lived in Ohsaki City, Miyagi Prefecture, Japan. Participants were categorized into four groups according to changes in time spent walking based on two questionnaire surveys conducted in 1994 and in 2006. Incident functional disability was retrieved from the public Long-term Care Insurance database, and the subjects were followed up for 5 years. The Cox proportional hazards model was used to investigate the association between changes in time spent walking and the risk of incident functional disability.

Results. Compared with subjects who remained sedentary, the multivariate-adjusted hazard ratios (95% confidence intervals) were 0.69 (0.49–0.98) among those who became active and 0.64 (0.50–0.82) among those who remained active. These results did not alter when analyses were stratified by gender, age and motor function status.

Conclusion. An increase in time spent walking among sedentary adults is significantly associated with a lower risk of incident functional disability.

Introduction

Physical activity is a well-known modifiable behavior associated with lower risks of mortality (Haskell et al., 2009; Leitzmann Mf, 2007; Nelson et al., 2007; Wagner and Brath, 2012; Wen et al., 2011). In addition to keeping physically active, increasing physical activity is also known to be beneficial in terms of cardiovascular risk and longevity (Aadahl et al., 2009; Balboa-Castillo et al., 2011; Gregg et al., 2003; Petersen et al., 2012; Schnohr et al., 2003; Talbot et al., 2007; Wannamethee et al., 1998). Previous longitudinal studies have shown that, in comparison with individuals who remain sedentary, those who increase their physical activity have a total mortality risk reduction of more than 40% (Balboa-Castillo et al., 2011; Gregg et al., 2003; Schnohr et al., 2003; Wannamethee et al., 1998).

In countries with rapidly aging populations, such as Japan, the health and economic impacts of disability have been attracting increasing attention (Fried et al., 2001). Disability is the endpoint of the disablement process, which includes four distinct but correlated concepts: active pathology, impairment, functional limitation, and disability (Nagi, 1991). According to the Nagi's disablement model, functional limitation is a limitation in performance at the level of the whole organism or person, which includes motor dysfunction; disability is an inability or limitation in performing socially defined roles and tasks expected of an individual within a sociocultural and physical environment. During the disablement process, not only physical inactivity could be a predisposing risk factor, but changes in physical behavior may avoid, retard or reverse the outcomes (Verbrugge and Jette, 1994). However, data are limited regarding the effects of changes in physical activity on disability or functional status. One study of older American women has shown that in comparison with women who remained inactive after middle age, those who remained active or became active had fewer difficulties with activities of daily living (ADL), better scores in the Physical Performance Test, and faster walking speeds (Brach Js, 2003). Another two recent studies have also observed that increasing physical activity from middle age was associated with a lower disability score in old age (Berk et al., 2006; Gretebeck et al., 2012). Otherwise, the British Regional Heart Study has also shown that in comparison with men who had remained inactive, those who became active or remained active had a lower risk of mobility limitation (Wannamethee et al., 2005).

However, those studies mostly employed self-reported endpoints (Berk et al., 2006; Gretebeck et al., 2012; Wannamethee et al., 2005), and some had small numbers of participants (Berk et al., 2006; Brach Js, 2003); furthermore, none of them measured the incidence of disability. In Japan, Long-term Care Insurance (LTCI) certification of requiring assistance with ADL, based on a nationally uniform standard of functional disability, has been frequently used in previous epidemiological

Abbreviations: ADL, activities of daily living; LTCI, Long-term Care Insurance.

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http://dx.doi.org/10.1016/j.ypmed.2013.11.019

studies as a measure of incident functional disability in the elderly (Aida et al., 2012; Hozawa et al., 2010; Tomata et al., 2012). As the economic burden of taking care of older people with disability is increasing (Ministry of Health, 2012), studies of modifiable risk factors of functional disability have become necessary. To our knowledge, no prospective study has yet investigated the relationship between changes in physical activity since middle age and the risk of incident functional disability. Furthermore, the doubts of benefits of increasing or maintaining physical activity could result from younger age, better motor function or higher intensity of physical activity in men which allow those subjects to be more active than the others have not been well clarified.

In the present study, we chose to focus on walking, which is the most common type of physical activity among middle-aged or older individuals. Our previous studies have shown that spending a longer time walking per day is associated with lower medical costs and increased longevity (Fujita et al., 2004; Nagai et al., 2011; Tsuji et al., 2003). The objective of the present study was to investigate changes in time spent walking in relation to the risks of incident functional disability in a large community-dwelling population in Japan.

Methods

Study cohort

The present investigation used data from a population-based longitudinal study conducted in Ohsaki, a northern non-coastal rural area of Miyagi Prefecture, northeastern Japan. Between October and December 1994, all National Health Insurance beneficiaries aged 40 to 79 years who lived in the catchment area of Ohsaki Public Health Center (including one city and 13 towns) were invited to take part in a health survey with self-administered questionnaire on various lifestyle habits (1994 Survey) (Nagai et al., 2011; Tsuji et al., 2003). Among 54,996 eligible individuals, 52,029 (94.6%) responded.

During a period when a municipal merger occurred, one city and 6 towns in the study area were merged into a single new municipality, Ohsaki City, on 31 March 2006. Thereafter, we conducted a health survey on the citizens of Ohsaki City. Between 1 December and 15 December 2006, a self-administered questionnaire was distributed to subjects aged 65 years or older based on the Residential Registry for Ohsaki City (2006 Survey) (Koyama et al., 2010; Kuriyama et al., 2010; Nakaya et al., 2013; Tomata et al., 2012). Among 23,132 eligible individuals (aged 53 years or older in 1994 Survey), 12,676 (54.8%) responded. We considered the return of completed questionnaires to imply consent to participate in the 2006 Survey, and subsequent death and emigration were followed up. We also confirmed information regarding LTCI certification status after obtaining written consent from the subjects. The study protocol was approved by the Ethics Committee of Tohoku University School of Medicine.

For the present analysis, we further excluded 3610 persons who did not provide written consent for review of their LTCI information, one person who had been died, 973 persons who had already been certified as having disability by the LTCI at the time of the baseline survey, and 915 persons for whom responses to the questions on walking were missing. Thus, a final total of 7177 responses were analyzed for the purposes of this study.

Classification of exposures

Time spent walking was evaluated on the basis of the response to a specific question, 'How long do you walk a day, on average?' in both the 1994 and 2006 Surveys, and the subjects were asked to choose one out of three responses: '1 h or more', '30 min to 1 h' or '30 min or less'. The validity of self-reported time spent walking had been reported previously, which indicated that self-reported walking time was reasonably reproducible and sufficiently valid for studying the health effects of walking (Fujita et al., 2004; Nagai et al., 2011; Tsubono et al., 2002; Tsuji et al., 2003). According to the "Global Recommendations of Physical Activity for Health" developed by the WHO, at least a total of 150 min or 30 min of moderate-intensity activity 5 times per week is suggested for all adults (WHO, 2010). Therefore, participants who spent more than 30 min per day walking were considered to be active in this study. As shown in Table 1, four categories of changes in time spent walking were defined for each participant by his/her answers in 1994 and 2006: remained inactive (<30 min in both 1994 and 2006); became inactive (≥30 min in 1994 and <30 min in 2006); became active (<30 min in 1994 and ≥30 min in 2006); and remained active (≥30 min in both 1994 and 2006).

Table 1
Categories of changes in time spent walking (December 2006, Ohsaki City, Miyagi Prefecture, Northeastern Japan).

Time spent walking per day		2006 survey	
		≥30 min	≥30 min
1994 survey	<30 min	Remained inactive	Became active
	<30 min	Became inactive	Remained active

Follow-up and case ascertainment

The primary endpoint for the present analysis was incident functional disability defined as newly qualifying for LTCI certification and registration on the public LTCI database between 16 December 2006 and 30 November 2011. We collected LTCI certification data every year from the public LTCI database maintained by Ohsaki City. LTCI is a form of mandatory social insurance aimed at assisting the frail and elderly with daily activities (Ikegami, 1997; Imai et al., 2008; Ministry of Health, 2012; Tsutsui and Muramatsu, 2005). People aged 65 years or older who require assistance with ADL are eligible to apply for formal caregiving services, and undergo assessment by well-trained care managers based on a questionnaire developed by the Ministry of Health, Labour and Welfare. On the basis of standardized scores for functional and cognitive impairment calculated from the questionnaire and based on physician's judgment report including the elderly's disease status, physical and cognitive status and performance-based measures, the eligibility of applicants for insurance benefits is judged by the Municipal Certification Committee. LTCI certification has been used in previous epidemiological studies as a measure of incident functional disability in the elderly (Aida et al., 2012; Hozawa et al., 2010; Tomata et al., 2012).

All participants were followed up by reviewing information on the date of LTCI certification, death, or emigration from Ohsaki City, which had been transferred yearly each December from the Ohsaki City Government under an agreement related to Epidemiological Research and Privacy Protection.

Statistical analysis

The person-years of follow-up were calculated from 16 December 2006 to the date of incident functional disability, date of emigration from Ohsaki City, date of death, or 30 November 2011, whichever occurred first. Cox proportional hazards regression analysis was used to investigate the hazard ratios (HRs) and 95% confidence intervals (CIs) for incident functional disability according to changes in time spent walking, treating participants who had remained inactive as the reference category.

The following variables in the 2006 Survey, which were thought to be unfavorable conditions for being active and may be related to incident functional disability, were considered as potential confounders: age (in years), sex (men or women), body mass index (in kg/m^2), history of diseases (stroke, hypertension, myocardial infarction, arthritis, osteoporosis, cancer, falls or fractures), education level (junior high school, high school, or college or higher), smoking status (never smoked, smoked in the past, currently smoking <20 cigarettes/day or currently smoking ≥20 cigarettes/day), alcohol consumption (never drank, drank in the past or currently drinking), pain (none or mild pain, moderate pain or more), and motor function score based on the Kihon Checklist.

To assess whether the risk of incident functional disability associated with changes in time spent walking differed by gender, age or subjects' motor function, we further stratified the participants according to gender (men versus women), age at the time of the 2006 Survey (65–74 years versus ≥75 years) and motor function (without limitation versus with limitation). Motor function limitation was defined by a motor function score of 3 points or more based on the Kihon Checklist completed in the 2006 Survey. The motor function score based on the Kihon Checklist has been evaluated previously and shown to have predictive validity for functional disability (Fukutomi et al., 2013; Tomata et al., 2011). Statistical evidence for differences in effect between these subgroups was assessed on the basis of log-likelihood ratio tests of interaction.

All statistical analyses were performed using the SAS software package (version 9.2; SAS Institute, Inc., Cary, North Carolina, USA). All statistical tests described here were 2-sided, and differences at $P < 0.05$ were accepted as significant.

Results

From 1994 to 2006, 13.0% of the study participants remained inactive, 22.5% became inactive, 11.6% became active, and 52.9% remained active. The baseline characteristics of participants according to the changes in time spent walking categories are summarized in Table 2. Compared with the rest of the study participants, those who had become active were younger, included a higher proportion of men, included a higher proportion of current drinkers, were less likely to have a history of myocardial infarction, osteoporosis or cancer, and were less likely to have pain and motor function limitation.

During the 5 years of follow-up from 16 December 2006, we documented 712 incident functional disability (9.9%), 619 deaths (8.6%) and 59 losses to follow-up (0.8%) because of emigration. Table 3 shows the multivariate-adjusted HRs for incident functional disability according to the changes in time spent walking categories. In comparison with individuals who remained inactive, those who became active had a 31% lower risk of incident functional disability (HR = 0.69, 95% CI: 0.49–0.98), and those who remained active had a 36% lower risk of incident functional disability (HR = 0.64, 95% CI: 0.50–0.82). The risk of incident functional disability among individuals who became inactive was similar to that for individuals who remained inactive. Furthermore, we repeated the analyses after excluding individuals whose disability event occurred in the first year of follow-up (Model 3). When we excluded 253 such participants, the associations became slightly weaker but did not change substantially. The multivariate-adjusted HRs (95% CIs) for incident functional disability were 0.89 (0.66–1.19) for individuals who became inactive, 0.75 (0.50–1.12) for those who became active, and 0.64 (0.48–0.85) for those who remained active.

Table 4 shows the associations between changes in time spent walking and incident functional disability, after stratification by gender (men versus women), age at the time of the 2006 Survey (65–74 years versus ≥75 years) and motor function (without limitation versus with limitation). The associations did not vary substantially between men and women (p for interaction = 0.71). In women, became active or remained active was associated with a lower risk of incident functional disability, with HRs (95% CIs) of 0.61 (0.39–0.96) and 0.60 (0.44–0.80), respectively. Similar results were observed in men, but were not statistically significant. The risks of incident functional disability were not altered significantly by age (p for interaction = 0.10). The multivariate-adjusted HRs (95% CIs) for individuals who became active were 0.58 (0.24–1.37) for those aged 65–74 years and 0.73 (0.50–1.06) for those aged ≥75 years. Furthermore, irrespective of whether or not participants had motor function limitation, those who became active tended to have a lower risk of incident functional disability (p for interaction = 0.97). The multivariate-adjusted HRs (95% CIs) for became active were 0.75 (0.47–1.19) for individuals without motor function limitation and 0.69 (0.41–1.18) for those with motor function limitation, although this was not statistically significant.

Table 2
Baseline characteristics of participants according to the changes in time spent walking categories (December 2006, Ohsaki City, Miyagi Prefecture, Northeastern Japan).

	Remained inactive	Became inactive	Became active	Remained active	P-value[a]
Number at risk	937	1614	832	3794	
Age, mean (SD), years	75.8 (5.7)	76.1 (5.8)	74.0 (5.5)	74.2 (5.5)	<0.0001
Men (%)	43.3	41.3	46.9	45.9	0.0072
Body mass index, mean (SD), kg/m^2	23.9 (3.5)	23.6 (3.8)	23.7 (3.3)	23.4 (3.3)	0.0011
Current smoker (%)	12.4	14.0	12.4	13.5	0.7339
Current drinker (%)	33.6	30.2	38.8	37.3	<0.0001
Education until age 15 (%)	29.3	33.6	31.5	30.1	0.2239
History of diseases (%)					
Stroke	3.7	3.9	3.3	2.2	0.0021
Hypertension	47.1	50.7	42.2	40.1	<0.0001
Myocardial infarction	6.2	6.3	4.2	4.7	0.0244
Arthritis	20.3	19.0	15.1	14.8	<0.0001
Osteoporosis	14.1	13.4	8.5	9.7	<0.0001
Cancer	12.0	10.2	6.9	7.4	<0.0001
Falls or fractures	17.8	18.9	18.0	15.2	0.0036
Moderate pain or more (%)	36.8	37.4	24.0	24.7	<0.0001
Motor function limitation (%)[b]	38.3	40.6	18.0	16.7	<0.0001

[a] P-values were calculated by analysis of variance or chi-square test.
[b] With three points or more to the following five motor function questions in Kihon Checklist: 'Are you able to go upstairs without holding rail or wall?', 'Are you able to stand up from the chair without any aids?', 'Are you able to keep walking for about 15 min?', 'Have you fallen down during the past year?', 'Do you worry about falling down?'.

Discussion

In this large longitudinal population-based study of Japanese community-dwelling elderly, we observed that an increase in time spent walking among sedentary middle-aged adults was significantly associated with a lower risk of incident functional disability. Even in those who were very old or with limited motor function, becoming active from middle age tended to be associated with a lower risk of incident functional disability.

These results were consistent with previous longitudinal studies based on self-reported physical activity levels at different time points and subsequent functional status (Berk et al., 2006; Brach Js, 2003; Gretebeck et al., 2012; Wannamethee et al., 2005). Those studies found that in comparison with people who had always been inactive since middle age, those who increased their physical activity had better physical performance or lower disability scores in old age. In the present study, after 5 years of follow-up, we noticed that in a senior population aged more than 65 years, not only those who remained active also those who became active had lower risks of incident functional disability, than those who remained inactive for the previous 12 years. Furthermore, for those who became inactive, the risk of incident functional disability was similar to those who remained inactive, which was consistent with those of previous studies about changes in physical activity level and mortality (Balboa-Castillo et al., 2011; Gregg et al., 2003).

The British Regional Heart Study observed that the protective effects of maintaining or increasing physical activity against risks of mobility limitation were largely attenuated following adjustment for chronic diseases and clinical symptoms (Wannamethee et al., 2005). In the present study, after adjusting for possible confounders including history of diseases, body pain and motor function status, we found that an increase in time spent walking among sedentary middle-aged adults was still significantly associated with a lower risk of incident functional disability. Furthermore, the associations did not vary substantially by gender, age or motor function. This is important because it suggested that the lower risks of incident functional disability associated with increasing or maintaining physical activity level was not only a result of younger age, better motor function or higher intensity of physical activity in men. In our study population, even among individuals who were more than 75 years old or with motor function limitation, older adults who remained active since middle age had a significantly lower risk of incident functional disability. Therefore, even for those who may find it difficult to be physically active, maintaining or adopting an active lifestyle should be continuously promoted.

Most previous studies examining the health effect of changes in physical activity were focused on longevity (Balboa-Castillo et al., 2011; Gregg et al., 2003; Petersen et al., 2012; Schnohr et al., 2003; Talbot et al., 2007; Wannamethee et al., 1998). In the present study, we also observed that in comparison with individuals who remained inactive, those who became active tended to have lower risk of all-cause mortality (HR = 0.78, 95% CI: 0.54–1.09) (data not shown). We further observed that individuals who became active and those who remained active were also associated with a reduced risk of incident functional disability. The present study has expanded knowledge in this field because it showed that maintaining or adopting an active lifestyle not

Table 3
Hazard ratios (HRs) and 95% confidence intervals (CIs) for incident disability according to the changes in time spent walking categories (December 2006, Ohsaki City, Miyagi Prefecture, Northeastern Japan).

	No. of cases	Person-years	Model 1	Model 2	Model 3
			HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[c]
Remained inactive	134	3924	1.00	1.00	1.00
Became inactive	252	6679	1.14 (0.96–1.36)	0.98 (0.78–1.25)	0.89 (0.66–1.19)
Became active	62	3779	0.62 (0.46–0.84)	0.69 (0.49–0.98)	0.75 (0.50–1.12)
Remained active	264	17,266	0.56 (0.45–0.68)	0.64 (0.50–0.82)	0.64 (0.48–0.85)

[a] Model 1 was adjusted for age (years), sex.
[b] Model 2 was adjusted for age (years), sex, BMI (kg/m^2), history of stroke (yes/no), history of hypertension (yes/no), history of myocardial infarction (yes/no), history of arthritis (yes/no), history of osteoporosis (yes/no), history of cancer (yes/no), history of falls or fractures (yes/no), education (junior high school or less, high school, or college or higher), smoking status (never smoked, smoked in the past, currently smoking <20 cigarettes/day or currently smoking ≥20 cigarettes/day), alcohol consumption (never drank, drank in the past or currently drinking), pain (none or mild pain, moderate pain or more) and motor function limitations (yes/no).
[c] Model 3 was further excluded people whose event of disability occurred in the first year of follow-up.

only improved longevity, also resulted in healthier aging. Thus, for healthy aging, our message to those who are currently sedentary is that it is never too late to start walking.

This study had several strengths in addition to its prospective nature and large community-dwelling population base. First, we assessed the effects of several important confounding factors on changes in time spent walking and incident functional disability: history of diseases, body pain and motor function status. Subgroup analysis of motor function status was also conducted to confirm that there was no interaction between motor function limitation and time spent walking with incident functional disability. Second, the data on incident functional disability were more accurate than self-reported information because the outcome was obtained from the public LTCI database, which is based on uniform nationwide criteria of functional disability, and thus the data were considered reliable.

Several limitations should also be noted. First, we assessed walking using a simple questionnaire in which we asked the participants to report only the time spent walking and did not ask about walking pace, distance walked or any distinction between walking for exercise and other reasons, and there was no information about the reason of any change in time spent walking. However, physical activity level was noted to be affected by psychological distress and mental disorder in previous studies (Bonnet et al., 2005; Muhsen et al., 2010). It may be one reason for being or becoming inactive, where reverse causation may not be totally avoided. Second, we did not investigate the causes of functional disability in subjects who received LTCI certification. Thus, the most effective component responsible for reduction of functional disability by becoming or remaining active will need to be clarified in the future. Third, our endpoint could have been underestimated because the qualification process for obtaining LTCI benefit requires voluntary application. Furthermore, non-response bias and survival bias should be considered because the incidence rate of functional disability in the present study (9.9%) was much lower than that for all Japan (17.3%) (Ministry of Health, 2012).

Conclusion

An increase in time spent walking among sedentary middle-aged adults was significantly associated with a lower risk of incident functional disability. Even in those who were very old or with limited motor function, becoming active from middle age tended to be associated with a lower risk of incident functional disability. Our results suggest that, for healthy aging, active people should remain active as they age, and for those who are currently sedentary, it is never too late to start walking.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Acknowledgments

This study was supported by a Health Sciences Research Grant for Health Services (H24-Choju-Ippan-005, H23-Junkankitou (Seisyu)-Ippan-005, and H23-Junkankitou (Seisyu)-Wakate-015), from the Ministry of Health, Labour and Welfare, Japan. We are grateful to all the participants of this study.

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Table 4
Hazard ratios (HRs) and 95% confidence intervals (CIs) for incident disability according to the changes in time spent walking categories, by gender, age and motor function status (December 2006, Ohsaki City, Miyagi Prefecture, Northeastern Japan).

	Gender		Age		Motor function	
	Men	Women	65–74	≥75	No limitation	With limitation
Remained inactive (cases/n)	49/406	85/531	21/385	113/552	50/578	84/359
HR (95% CI)[a]	1.00	1.00	1.00	1.00	1.00	1.00
Became inactive (cases/n)	95/666	157/948	42/671	210/943	88/958	164/656
HR (95% CI)[a]	1.16 (0.77–1.74)	0.88 (0.65–1.18)	1.17 (0.64–2.15)	0.96 (0.74–1.25)	0.98 (0.67–1.43)	0.99 (0.72–1.35)
Became active (cases/n)	31/390	31/442	10/447	52/385	38/682	24/150
HR (95% CI)[a]	0.83 (0.48–1.43)	0.61 (0.39–0.96)	0.58 (0.24–1.37)	0.73 (0.50–1.06)	0.75 (0.47–1.19)	0.69 (0.41–1.18)
Remained active (cases/n)	103/1740	161/2054	52/2036	212/1758	169/3162	95/632
HR (95% CI)[a]	0.72 (0.48–1.09)	0.60 (0.44–0.80)	0.65 (0.36–1.18)	0.63 (0.48–0.82)	0.69 (0.49–0.98)	0.62 (0.44–0.88)
p for interaction	0.71		0.10		0.97	

[a] Model was adjusted for age (years), sex, BMI (kg/m^2), history of stroke (yes/no), history of hypertension (yes/no), history of myocardial infarction (yes/no), history of arthritis (yes/no), history of osteoporosis (yes/no), history of cancer (yes/no), history of falls or fractures (yes/no), education (junior high school or less, high school, or college or higher), smoking status (never smoked, smoked in the past, currently smoking <20 cigarettes/day or currently smoking ≥20 cigarettes/day), alcohol consumption (never drank, drank in the past or currently drinking), pain (none or mild pain, moderate pain or more) and motor function limitations (yes/no).

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血清総コレステロール値と要介護認定リスクに関する前向きコホート研究

鶴ヶ谷プロジェクト

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目的　地域高齢者における血清総コレステロール値と要介護認定リスクとの関連を前向きコホート研究により検討すること。

方法　仙台市宮城野区鶴ヶ谷地区の70歳以上の住民全員（2,925人）に対し，高齢者総合機能評価「寝たきり予防健診」を平成15年に行った。受診者（958人）のうち，研究の同意が得られ要介護認定非該当であった827人を解析対象者とし，平成21年6月まで6年間追跡した。血清総コレステロール値は5分位に分け，第四5分位群（212–230 mg/dL）を基準群とし，要介護認定リスクをCox比例ハザードモデルによりハザード比（HR）と95%信頼区間（95%CI）を算出した。

結果　6年間の追跡調査で214人が要介護認定（要支援1～要介護5）を受けた。血清総コレステロール低値と要介護認定リスクとの間には有意な負の関連があり，第四5分位群（212–230 mg/dL）を基準群として多変量調整したHR（95%CI）は177 mg/dL未満群（最低5分位群）で1.91（1.23–2.98），177–194 mg/dL群で1.36（0.85–2.18），195–211 mg/dL群で0.99（0.62–1.56），231 mg/dL以上群で1.38（0.88–2.17）であった。また，高感度C反応蛋白（CRP）が高値の者，がん・肝臓病既往歴ありの者，肝機能指標が基準値外の者を除外した解析でも，血清総コレステロール低値で要介護認定リスクの有意な上昇を認めた。

結論　様々な交絡要因を調整しても，血清総コレステロール低値で有意なリスク上昇を認めた。

Key words：血清総コレステロール値，要介護認定，地域高齢者，マーカー

I　緒　　言

高齢者の低栄養状態は，要介護発生のリスク要因となると考えられている[1,2]。そこで介護保険制度における介護予防事業では，低栄養状態のおそれがある高齢者を早期に把握し，栄養相談などを行うことで要介護状態の発生予防を目指している[3]。

血清総コレステロール値は，一般的で安価な血液マーカーであり，体内の栄養状態を反映する指標[4]である。血清総コレステロール値と死亡率との関連を調べた多くの研究では，U字型や逆J字型を示すことが示されており[5~7]，血清総コレステロールが低値でも高値でも，死亡リスクが上昇することが知られている[8~10]。

一方，血清総コレステロール値と要介護認定リスクとの関連に関する前向きコホート研究は，日本では3件しか行われていない。その結果は，血清総コレステロール値と負の関連があるものが1件[11]，関連がなかったものが2件[12,13]あり，結果は一致していない。その理由として，以下の方法の問題が挙げられる。それは，(1)血清総コレステロール値を連続変量で検討していること，(2)要介護発生のイベント数が少ない研究があること，(3)交絡因子の調整が不十分であることなどであり，わが国の地域在住高齢者におけるエビデンスが十分に確立しているとは言い難い。

本研究の目的は，血清総コレステロール値が低値または高値であることが，要介護状態の発生リスクを高めるかどうか検討することである。そのため仙台市鶴ヶ谷地区の70歳以上の地域在住の827人を6年間追跡し，血清総コレステロール値と要介護認定

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リスクとの関連について検討を行った。

Ⅱ　研究方法

1.　対象者

宮城県仙台市宮城野区鶴ヶ谷地区に居住する70歳以上（平成16年3月31日時点）の男女全員2,925人（男性：1,211人，女性：1,714人）に，高齢者総合機能評価「寝たきり予防健診」の案内状を郵送し，平成15年7月に「寝たきり予防健診」を実施した。このうち，健診の受診者は958人（男性：434人，女性：524人）で，参加率は32.8%であった。

健診では，身長，体重，喫煙歴，飲酒歴，既往歴，うつ傾向，認知機能，身体機能，血液検査，服薬情報，食物摂取頻度等を評価した。

2.　調査項目

本研究で調査した項目は，(1)アンケート調査：喫煙状況，飲酒状況，既往歴（脳卒中，骨粗鬆症，がん，肝臓病），(2)血液試料：血清総コレステロール値，血清アルブミン値，高感度C反応性蛋白（CRP），Alanine aminotransferase（ALT），Aspartate aminotransferase（AST），Gamma-glutamyl transpeptidase （γ-GTP），(3)その他：Body Mass Index（BMI），うつ傾向，認知機能，身体機能，高脂血症治療薬の服薬状況である。

血清総コレステロール値は，非空腹時に肘前静脈から真空採血した血液検体を，株式会社ビー・エム・エルに委託し，酵素法によって測定した。血清アルブミン値，高感度CRP，肝機能（ALT・AST・γ-GTP）も同様に，随時採血による血液検体を同株式会社に委託し，血清アルブミン値はブロムクレゾールグリーン法（BCG法）によって，高感度CRPはラテックス免疫比濁法によって，肝機能はJSCC標準化対応法によって測定した。

うつ傾向は，Geriatric depression Scale（GDS）で評価を行った[14]。認知機能検査はMini-Mental State Examination（MMSE）で評価を行った[15]。

身体機能はPhysical function scale of The Medical Outcomes Study（MOS）Short-form General Health Surveyで評価を行った[16]。これらは7段階の身体活動レベルのうち，最高の「強い運動を要する活動ができる」または次の「中等度以上の運動量の活動ができる」と回答した者を身体活動が良好と定義した。

服薬状況は健診当日，健康食品も含めた内服薬を受診者に持参してもらい，1人の薬剤師が内容を評価した。

3.　追跡調査

本研究は，介護保険の新規要介護認定（要支援・要介護）の発生をエンドポイントとした。また，死亡および転出は打ち切り（censored case）とした。介護保険の要支援・要介護認定状況の追跡にあたり，対象者本人に口頭および文書での説明を行い，対象者本人から書面による同意を得た。要介護認定状況の情報は，仙台市と東北大学大学院医学系研究科社会医学講座公衆衛生学分野との調査実施協定に基づき，仙台市に要介護認定の情報の閲覧に関する同意書の写しを提出した上で，平成15年7月1日から平成21年6月30日までの認定年月日と，要介護認定の区分についての情報提供を受けた。

4.　統計解析

総合機能評価の受診者958人のうち，948人が研究に同意した。そのうち，要介護認定に関する情報の閲覧の非同意者24人，すでに要介護認定を受けた者76人，採血の非同意者1人および採血データ欠損者20人を除外した827人（男性396人，女性431人）を解析対象とした。

解析では血清総コレステロール値を5分位（177 mg/dL未満，177–194 mg/dL，195–211 mg/dL，212–230 mg/dL，231 mg/dL以上）に分類し，要介護発生リスクとの関連を検討した。血清総コレステロール値と全死因死亡との間には逆J字型やU字型の関連を示すことが知られているため，第四5分位群を基準（212–230 mg/dL）として，各カテゴリーの要介護認定ハザード比（HR）と95%信頼区間（95% CI）を，Cox比例ハザードモデルで算出した。

調整項目は，性・年齢（連続変量）を調整したモデルをモデル1とした。モデル2は，性・年齢（連続変量），教育歴（最終学歴終了時の年齢；18歳以上，18歳未満，無回答），喫煙状況（現在喫煙者，過去喫煙者，非喫煙者，無回答），飲酒状況（現在飲酒者，過去・非飲酒者，無回答），うつ傾向（GDS；14点以上，14点未満，無回答），認知機能（MMSE；24点以上，24点未満，無回答），身体機能（MOS；0–5点，5点以上，無回答），血清アルブミン値（3.8 g/dL未満，3.8 g/dL以上），BMI（25.0未満，25.0以上），炎症マーカー（高感度CRP；連続変量），高脂血症治療薬服薬（あり，なし），既往歴（脳卒中，骨粗鬆症；あり，なし）を調整した。モデル3はモデル2に加え，肝機能（ALT・AST・γ-GTP；連続変量）や血清総コレステロール値に影響を与えうる既往歴（がん，肝臓病；あり，なし）を調整した多変量調整モデルを用いた。

以上の変数を多変量調整モデルに入れた理由は以下の通りである。年齢が高いこと[17]やBMIが低いこと[18]，喫煙者であること[18]，アルコール摂取量が

多いこと[19]，身体機能が低下すること[20]，炎症[21]やがん[9]，肝疾患[22]があることは血清総コレステロール値が低いことと関連がある。また，高脂血症治療薬は血清総コレステロール値が高い者が服用しており，血清総コレステロール値がコントロールされている可能性がある。なお，炎症，がん，肝疾患，肝機能の指標（ALT・AST・γ-GTP）については，基準外の者を除外し，基準値内の者だけでの解析を実施した。層別化解析に用いた変数（年齢，BMI，喫煙歴，飲酒歴，身体機能，高脂血症治療薬服用）と，除外解析に用いた変数（炎症マーカー低値の者のみ，がん既往歴なしの者のみ，肝臓病既往歴なしの者のみ，肝機能が基準値内の者のみ）のデータが欠損である者については，それぞれの解析で解析対象に含めなかった（たとえば，喫煙歴で層別化する場合に，喫煙歴のデータが欠損である者は，この解析に含まれない）。交互作用の解析は血清総コレステロール5分位群に層別化解析に用いたそれぞれの指標（2カテゴリー）を乗じたもの（cross product term）を多変量調整モデルに追加で投入した。層別化解析と交互作用の解析は，多変量調整モデル（モデル3）を用いた。

血清総コレステロール値全ての解析は，統計解析ソフト SAS Version 9.2（SAS Inc.Cary NC）を用いた。また，$P<0.05$を統計学的有意水準とした。

5.　倫理的配慮

本調査研究は，東北大学大学院医学系研究科倫理委員会の承認を得ている（承認番号：2002-040　平成14年5月20日）。要支援・要介護認定状況の追跡にあたり，「寝たきり予防健診」結果の調査研究の使用への同意，採血により得られた血液試料の調査研究への同意，医療機関の診療記録閲覧への同意について説明し，対象者本人から書面による同意を得た。

Ⅲ　結　　果

1.　ベースライン特性の比較

解析対象者の平均年齢（標準偏差）は75.2（4.5）歳であり，70歳から74歳までの者の割合は53.6%であった。ベースライン調査時の血清総コレステロール値の平均値（標準偏差）は204（32.9）mg/dL であり，高脂血症治療薬服用者は165人（解析対象者の20.0%）であった。6年間の追跡調査で，74人（同9.0%）が死亡，13人（同1.6%）が市外に転居

表1　ベースライン調査時の対象者の基本特性

	血清総コレステロール値（mg/dL）				
	＜177	177–194	195–211	212–230	231≦
	(n＝165)	(n＝153)	(n＝175)	(n＝167)	(n＝167)
男性（%）	74.6	58.8	44.6	33.5	29.5
年齢（歳）（平均±標準偏差）	75.8±4.6	74.9±4.2	75.5±4.7	74.9±4.7	74.7±4.0
Body Mass Index（kg/m^2）（平均±標準偏差）	23.3±3.3	24.3±3.4	24.3±3.3	24.6±3.5	24.3±3.1
現在喫煙者	15.3	15.4	6.3	8.5	8.6
現在飲酒者	57.7	50.7	46.3	45.8	34.4
うつ傾向の者（%）[a]	9.2	15.8	12.1	13.2	13.4
認知機能が低下している者（%）[b]	8.0	4.0	3.5	4.2	7.3
ADL が良好な者（%）[c]	61.7	57.5	58.4	55.5	57.4
脳卒中既往者（%）	5.5	1.3	2.9	3.6	3.0
骨粗鬆症既往者（%）	8.5	9.8	14.9	19.8	15.0
がん既往者（%）	15.2	12.4	5.7	6.6	5.4
肝臓病既往者（%）	7.3	5.2	6.9	6.0	5.4
高脂血症治療薬服用者（%）	15.8	23.5	18.9	24.6	17.4
高感度C反応性蛋白（mg/L）（平均±標準偏差）	0.3±0.8	0.2±0.6	0.1±0.2	0.1±0.3	0.1±0.3
Alanine aminotransferase（IU/L）(平均±標準偏差)	18.1±11.8	17.5±8.4	17.2±11.4	17.6±9.8	17.9±9.6
Aspartate aminotransferase（IU/L）（平均±標準偏差）	27.3±13.7	24.5±8.7	24.3±10.3	25.3±12.0	25.5±10.3
Gamma-glutamyl transpeptidase（IU/L）（平均±標準偏差）	38.7±36.7	39.3±46.0	30.9±22.0	33.3±36.8	38.1±59.2

a. Geriatric Depression Scale（GDS）が14点以上の者
b. Mini-Mental State Examination（MMSE）が24点以下の者
c. Physical function scale of The Medical Outcome Study Short-form General Health Survey（MOS）が5点以上の者

した。また要介護認定者の発生数は，214人（同25.9%）であった。

血清総コレステロール値を5分位にした対象者の基本特性を表1に示す。血清総コレステロール値最低5分位群では，男性，現在飲酒者，認知機能が低下している者，ADLが良好な者，脳卒中・がん・肝臓病既往者の割合が多かった。一方で，うつ傾向の者，高脂血症治療薬服用者が少なかった。

2. 血清総コレステロール値と要介護認定リスク

1) 全体の結果

血清総コレステロール値と要介護認定リスクとの関連を表2に示す。212–230 mg/dLを基準とした，全体の多変量調整のモデル3のHR（95%CI）は，177 mg/dL未満群で1.91（1.23–2.98），177–194 mg/dL群で1.36（0.85–2.18），195–211 mg/dL群で0.99（0.62–1.56），231 mg/dL以上群で1.38（0.88–2.17）であり，最低5分位群で有意なリスク上昇を認めた。

なお，要介護認定2以上をアウトカムとした解析も実施したが，結果は全認定区分と本質的に変わらなかった（表データなし）。

2) 男女別の結果

男女別に算出した結果では，男性での多変量調整のモデル3のHR（95%CI）は，177 mg/dL未満群で2.66（1.28–5.49），177–194 mg/dL群で0.91（0.40–2.10），195–211 mg/dL群で0.88（0.34–2.29），231 mg/dL以上群で0.60（0.20–1.81）であった（表2）。女性での多変量調整のモデル3のHR

表2　血清総コレステロール値と要介護認定リスク

	血清総コレステロール値（mg/dL）				
	＜177	177–194	195–211	212–230	231≤
全体					
追跡人年	754	761	890	873	843
イベント数	54	40	38	38	44
モデル1ハザード比(95%信頼区間)[a]	1.99(1.31–3.03)	1.55(0.99–2.43)	1.10(0.70–1.73)	1.00(reference)	1.39(0.90–2.16)
モデル2ハザード比(95%信頼区間)[b]	1.94(1.25–3.01)	1.39(0.87–2.22)	0.98(0.62–1.56)	1.00(reference)	1.36(0.87–2.15)
モデル3ハザード比(95%信頼区間)[c]	1.91(1.23–2.98)	1.36(0.85–2.18)	0.99(0.62–1.56)	1.00(reference)	1.38(0.88–2.17)
男性					
追跡人年	578	488	388	306	273
イベント数	38	13	12	8	5
モデル1ハザード比(95%信頼区間)[a]	2.41(1.26–4.63)	0.98(0.45–2.16)	1.06(0.43–2.61)	1.00(reference)	0.68(0.24–1.93)
モデル2ハザード比(95%信頼区間)[b]	2.55(1.26–5.14)	0.93(0.41–2.11)	0.85(0.33–2.18)	1.00(reference)	0.57(0.19–1.70)
モデル3ハザード比(95%信頼区間)[c]	2.66(1.28–5.49)	0.91(0.40–2.10)	0.88(0.34–2.29)	1.00(reference)	0.60(0.20–1.81)
女性					
追跡人年	177	274	502	567	570
イベント数	16	27	26	30	39
モデル1ハザード比(95%信頼区間)[a]	1.32(0.71–2.46)	2.09(1.22–3.59)	1.13(0.67–1.92)	1.00(reference)	1.64(0.99–2.70)
モデル2ハザード比(95%信頼区間)[b]	1.43(0.74–2.77)	1.95(1.09–3.50)	1.11(0.65–1.92)	1.00(reference)	1.87(1.10–3.18)
モデル3ハザード比(95%信頼区間)[c]	1.37(0.70–2.68)	1.90(1.05–3.44)	1.14(0.66–1.97)	1.00(reference)	1.92(1.13–3.27)

a. 性，年齢（連続変量）を調整
b. モデル1に加え，最終学歴（18歳以上，18歳未満，無回答），喫煙状況（現在喫煙者，過去喫煙者，非喫煙者，無回答），飲酒状況（現在飲酒者，過去・非飲酒者，無回答），うつ傾向（Geriatric Depression Scale；14点以上，14点未満，無回答），認知機能（Mini-Mental State Examination；24点以上，24点未満，無回答），身体機能（Physical function scale of The Medical Outcome Study Short-form General Health Survey；0–5点，5点以上，無回答），Body Mass Index（25.0未満，25.0以上），血清アルブミン値（3.8 g/dL未満，3.8 g/dL以上），高感度CRP（連続変量），高脂血症治療薬服用有無，脳卒中既往歴，骨粗鬆症既往歴を調整
c. モデル2に加え，肝機能（Alanine aminotransferase・Aspartate aminotransferase；連続変量），肝臓病既往歴，がん既往歴を調整

表3　項目別の血清総コレステロール値と要介護認定リスク

	血清総コレステロール値 (mg/dL)					
	<177	177–194	195–211	212–230	231≤	交互作用のP値[e]
年齢						
75歳未満 (n=443)						
イベント数	6	13	6	14	12	0.10
多変量ハザード比[a]	1.93(0.56–6.72)[d]	3.13(1.12–8.71)	2.20(0.81–5.97)	1.00(reference)	2.18(0.78–6.11)	
75歳以上 (n=384)						
イベント数	48	27	32	24	32	
多変量ハザード比	1.56(0.96–2.53)	0.91(0.52–1.58)	0.57(0.33–1.00)	1.00(reference)	0.98(0.58–1.64)	
Body Mass Index						
25.0 kg/m² 以下 (n=511)						
イベント数	39	22	25	23	24	0.19
多変量ハザード比	1.71(0.98–2.98)	0.96(0.52–1.77)	0.85(0.47–1.52)	1.00(reference)	0.86(0.48–1.53)	
25.0 kg/m² 以上 (n=316)						
イベント数	15	18	13	15	20	
多変量ハザード比	1.69(0.74–3.85)	2.54(1.16–5.53)	1.16(0.52–2.55)	1.00(reference)	1.96(0.89–4.29)	
喫煙歴						
現在・過去喫煙者 (n=351)						
イベント数	34	16	12	11	10	0.17
多変量ハザード比	2.69(1.30–5.58)	0.93(0.42–2.07)	0.69(0.28–1.73)	1.00(reference)	0.93(0.38–2.30)	
非喫煙者 (n=463)						
イベント数	19	23	26	27	33	
多変量ハザード比	1.26(0.66–2.39)	1.59(0.87–2.91)	1.04(0.60–1.81)	1.00(reference)	1.46(0.85–2.51)	
飲酒歴						
現在飲酒者 (n=355)						
イベント数	31	14	11	15	7	0.10
多変量ハザード比	2.92(1.38–6.21)	1.01(0.43–2.32)	1.19(0.52–2.74)	1.00(reference)	0.76(0.28–2.03)	
過去・非飲酒者 (n=401)						
イベント数	17	21	23	17	31	
多変量ハザード比	0.79(0.40–1.54)	0.95(0.51–1.80)	0.71(0.37–1.37)	1.00(reference)	1.11(0.64–1.93)	
身体機能						
低等度 (n=341)						
イベント数	26	30	22	23	24	0.50
多変量ハザード比	1.24(0.67–2.30)	1.35(0.75–2.43)	0.70(0.38–1.30)	1.00(reference)	1.16(0.63–2.14)	
中・高等度 (n=474)						
イベント数	15	5	8	8	9	
多変量ハザード比	3.32(1.67–6.60)	1.02(0.43–2.42)	1.44(0.69–3.04)	1.00(reference)	1.11(0.54–2.26)	
高脂血症治療薬服用						
あり (n=165)						
イベント数	9	10	9	6	13	0.02
多変量ハザード比	2.20(0.74–6.52)	1.29(0.45–3.73)	0.37(0.11–1.25)	1.00(reference)	1.89(0.66–5.38)	
なし (n=662)						
イベント数	45	30	29	32	31	
多変量ハザード比	1.75(1.05–2.92)	1.16(0.67–1.99)	1.01(0.60–1.70)	1.00(reference)	0.95(0.56–1.60)	
炎症マーカー低値[b]の者のみ (n=737)						
イベント数	40	33	34	33	41	
多変量ハザード比	1.63(1.00–2.64)	1.33(0.80–2.19)	0.77(0.47–1.26)	1.00(reference)	1.14(0.71–1.82)	
がん既往歴なしの者のみ (n=753)						
イベント数	43	35	33	36	41	
多変量ハザード比	1.71(1.06–2.77)	1.33(0.81–2.18)	0.94(0.58–1.54)	1.00(reference)	1.15(0.71–1.85)	
肝臓病既往歴なしの者のみ (n=776)						
イベント数	53	38	35	37	43	
多変量ハザード比	1.91(1.20–3.02)	1.29(0.80–2.08)	0.90(0.56–1.45)	1.00(reference)	1.19(0.75–1.88)	
肝機能が基準値内[c]の者のみ (n=645)						
イベント数	39	34	34	32	40	
多変量ハザード比	1.39(0.90–2.16)	0.95(0.60–1.51)	0.72(0.46–1.14)	1.00(reference)	1.09(0.71–1.69)	

a. 多変量ハザード比：性，年齢（連続変量），最終学歴（18歳未満，18歳以上，無回答），喫煙状況（現在喫煙者，過去喫煙者，非喫煙者，無回答），飲酒状況（現在飲酒者，過去・非飲酒者，無回答），うつ傾向（Geriatric Depression Scale；14点以上，14点未満，無回答），認知機能（Mini-Mental State Examination；24点以上，24点未満，無回答），身体機能（Physical function scale of The Medical Outcome Study Short-form General Health Survey；0–5点，5点以上，無回答），Body Mass Index（25.0未満，25.0以上），血清アルブミン値（3.8g/dL未満，3.8 g/dL 以上），高感度 CRP（連続変量），高脂血症治療薬服用有無，脳卒中既往歴，骨粗鬆症既往歴，肝機能（Alanine aminotransferase・Aspartate aminotransferase；連続変量），肝臓病既往歴，がん既往歴を調整

b. 高感度 CRP：0.3 mg/dL 以下

c. 基準値：ALT (6–43 IU/L), AST (11–33 IU/L), γ-GTP (10–50 IU/L)

d. ハザード比（95%信頼区間）

e. 血清総コレステロールカテゴリーと表中左に示す層別化解析に用いたそれぞれの指標（2カテゴリー）を乗じて算出した項目

(95%CI)は，177 mg/dL 未満群で1.37(0.70–2.68)，177–194 mg/dL 群で1.90（1.05–3.44)，195–211 mg/dL 群で1.14（0.66–1.97)，231 mg/dL 以上群で1.92（1.13–3.27）であった。すなわち，血清総コレステロール値最低5分位群のHRは，男性では2.66（1.28–5.49)，女性では1.37（0.70–2.68）と，男女とも血清総コレステロール低値でリスクが上昇していた。血清総コレステロール値最高5分位群は男性で0.60（0.20–1.81)，女性で1.92（1.13–3.27）であり，モデル3に血清総コレステロールカテゴリーと性別をかけあわせた交互作用項を追加した結果は有意な交互作用を認め，男女で異なる結果であった（交互作用のP値＝0.02)。

3）　層別化解析の結果

本研究では結果に影響を及ぼす可能性のある因子として年齢，BMI，喫煙歴，飲酒歴，身体機能，高脂血症治療薬服薬の有無で層別化を行った（表3)。どの因子も最低5分位群でリスク上昇を認めた。血清総コレステロールカテゴリーにこれらの変数を掛けあわせた交互作用項を追加したモデル3の結果において，高脂血症治療薬服薬は有意な交互作用を認め，あり群で高値の点推定値が高かったが，高脂血症治療薬服薬以外の因子では，有意な交互作用を認めなかった。

高感度CRP高値の者，既往歴（肝臓病・がん）ありの者を除外した場合でも，血清総コレステロール最低5分位群では有意なリスクの上昇を示した。肝機能の指標（ALT・AST・γ–GTP）が基準値外の者を除外した解析では，血清総コレステロール最低5分位群で有意なリスクの上昇を認めなかったが，1.43（0.97–2.12）と同様にリスクが高い傾向にあった。

Ⅳ　考　　察

本研究は，日本人の地域在住高齢者を対象とした前向きコホート研究において，血清総コレステロール値と要介護認定リスクとの関連について検討した。その結果，血清総コレステロール低値（最低5分位群；177 mg/dL 未満）で有意なリスク上昇を示した。

1.　先行研究との比較

血清総コレステロール値と要介護状態との関連を研究している先行研究3件のうち2件は，血清総コレステロール値を連続変量で検討していたが，血清総コレステロール値と要介護認定との間にU字型や逆J字型を示すかの検証をしていなかった[11,13]。本研究では5分位にて検討を行ったところ，血清総コレステロール値と要介護認定リスクとの関連は，死亡をアウトカムとした先行研究と同様に，血清総コレステロール低値（最低5分位群；177 mg/dL 未満）で有意な要介護のリスク上昇がみられた。また有意ではないものの，高値（最高5分位群；231 mg/dL 以上）において点推定値が1より高く，リスク上昇の傾向を認めた。そのため，要介護認定をアウトカムとした研究においても，連続変量ではない検討が必要であると考えられる。また，他の1件の研究では，1989年と1993年の両方の基本健診受診者を対象とした結果，血清総コレステロール低値は要介護状態のリスクを高める傾向にあったものの有意な関連ではなく，例数を増やす必要があると報告している[12]。これに対し本研究の方がイベント発生数が多く，統計学的な検出力が高かったために，有意な関連をみとめたと考えられる。

2.　交絡要因を検討した結果

本研究は血清総コレステロール値に対する様々な交絡要因を検討した。炎症マーカーである高感度CRPは血清総コレステロールと関連し，負の相関があることが知られている[21]。また，炎症は高齢者の要介護状態の要因であることが知られているため[23]，高感度CRPを調整して検討する必要があることが考えられた。しかし，高感度CRPが高い者を除外し検討を行っても，血清総コレステロール低値での要介護認定リスクは高い傾向にあった。

さらに血清総コレステロール低値は，がんや肝臓病との関連が知られている[9,22]。血清総コレステロール値と全死因死亡との関連を検討した国内の研究では，肝臓病既往者と5年以内の早期死亡者を除外したところ，160 mg/dL 未満のリスク上昇が減弱し，関連はみられなかった[24]。そのため，本研究でもがん既往歴ありの者，肝臓病既往ありの者・肝機能（ALT・AST・γ–GTP）が基準外であった者を除外した解析を行った。その結果，血清総コレステロール値が低い者でリスクが上昇した。

3.　本研究の長所・限界

本研究の長所として挙げられる点は，第1に地域在住の高齢者を対象としており，対象者の市外転居による観察期間中の追跡不能者が2%未満であった点である。第2に，考えられる様々な交絡因子を調整しており，肝臓病・肝機能やがん等をはじめ身体的要因，社会的要因，生活習慣を幅広く考慮している点である。

本研究の限界として挙げられる点は，第1に要介護認定を受けた理由が不明な点である。そのため，血清総コレステロール低値によって要介護認定に至ったメカニズムは不明であった。本研究結果では，血清総コレステロール値と要介護認定との関連は男

女で異なっていた。これは男女で要介護に至る原因が異なることが関連していると考えられる。平成22年の「国民生活基礎調査」によると介護が必要となった主な原因は，65歳以上の男性において脳血管疾患が全体の31.2%を占めるが，65歳以上の女性では，関節疾患と転倒・骨折が合わせて26.4%を占めている[25]。しかし，本研究では要介護状態に至った理由は不明であるため男女差の理由を明らかにすることができなかった。

第2に本研究の「寝たきり予防健診」の参加率は32.8%であり，健診対象者の健康状態は比較的良好で，よりリスクの高い者が解析対象に含まれていないことが考えられる点である。そのため血清総コレステロール高値の者が多く含まれておらず，影響を十分評価できていない可能性がある。

第3に本研究は要介護認定をエンドポイントとしているが，実際は要介護状態であっても認定調査を受けていないためにエンドポイントに誤分類が生じている可能性がある。しかし，血清総コレステロール値と誤分類（認定を申請しない）との間に明確な関連があると想定し難いので，この誤分類は非系統的なものであり誤分類の割合に偏りのない non-differential misclassification と考えられることから，結果を本質的に歪める可能性は低いと考えられる。

V　結　論

本研究は，地域在住高齢者を対象とした前向きコホート研究において，血清総コレステロール低値と要介護認定リスクとの間に有意なリスク上昇がみられた。今後血清総コレステロール値が，要介護認定リスクの高い高齢者を抽出するためのマーカーとなることが期待される。

（受付　2012. 1.26）
（採用　2013. 5.13）

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