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付記

本研究は，平成22年度科学研究費補助金基盤研究(S)「中高年者のこころの健康についての学際的大規模縦断研究—予防へのストラテジーの展開（課題番号18109007)」，及び平成24年度科学研究費学術研究助成基金助成金（若手研究（B))「中高年期における知能の経時変化とその維持・向上に有効な年代別ストラテジーの構築（課題番号23730640)」により行われた。

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資料 *潜在変数「知能」,「抑うつ」間の相関係数*

	知能 (Wave 1)	知能 (Wave 2)	知能 (Wave 3)	抑うつ (Wave 1)	抑うつ (Wave 2)	抑うつ (Wave 3)
知能（Wave 1）	—					
知能（Wave 2）	.970	—				
知能（Wave 3）	.964	.992	—			
抑うつ（Wave 1）	−.178	−.156	−.182	—		
抑うつ（Wave 2）	−.210	−.201	−.232	.703	—	
抑うつ（Wave 3）	−.235	−.236	−.249	.522	.739	—

注．Fullモデル（結果の3.）の下で計算された潜在変数の相関係数を示す。

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This study examined the reciprocal relationship between intelligence and depressive symptoms over time, in an elderly Japanese sample. Participants (age range=65–79: N=725) were from the first wave of the National Institute for Longevity Sciences Longitudinal Study of Aging (NILS-LSA). They were tested three times and followed for about 4 years. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression scale (CES-D) and intelligence was assessed by the Wechsler Adult Intelligence Scale-Revised Short Forms (WAIS-R-SF). Structural equation modeling with a cross-lagged panel design showed that intelligence was related to subsequent depressive symptoms at every time point, such that poorer cognitive functioning was related to higher depressive symptoms. However, depressive symptoms were unrelated to subsequent intelligence. These findings suggest that intellectual ability may predict depressive symptoms in community-dwelling Japanese elderly adults.

[Keywords] Intelligence, Depression, Elderly adults, Cross-lagged panel design

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ORIGINAL ARTICLE

Serum docosahexaenoic and eicosapentaenoic acid and risk of cognitive decline over 10 years among elderly Japanese

R Otsuka[1], C Tange[1], Y Nishita[1], Y Kato[1], T Imai[1,2], F Ando[1,3] and H Shimokata[1,4]

BACKGROUND/OBJECTIVES: To clarify the association of serum docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) levels with cognitive decline over 10 years.

SUBJECTS/METHODS: This study was part of the National Institute for Longevity Sciences - Longitudinal Study of Aging, and was conducted with 232 male and 198 female Japanese community-dwelling subjects aged 60–79 years in the second wave (2000–2002). Cognitive function was assessed with the Mini-Mental State Examination (MMSE) in both the second and seventh (2010–2012) waves. Fasting venous blood samples were collected in the morning, and serum DHA and EPA levels were measured. Multiple logistic regression analysis was performed among participants with an MMSE score $\geqslant 24$ in the second wave ($n = 430$) to estimate the odds ratio (OR) and 95% confidence interval (CI) for MMSE score $\leqslant 23$ or MMSE score decline $\geqslant 4$ 10 years later. These estimates were based on baseline tertiles of serum DHA or EPA levels, and controlled for age, sex, education, MMSE score at baseline, alcohol consumption, current smoking, body mass index and disease history.

RESULTS: Fifteen (3.5%) subjects whose MMSE score was $\leqslant 23$ and 36 (8.3%) subjects whose MMSE score declined to $\geqslant 4$ showed cognitive decline. Multivariate-adjusted OR (95% CI) for the lowest through highest tertiles of serum DHA to MMSE score $\leqslant 23$ or decline $\geqslant 4$ were 1.00 (reference), 0.11 (0.02–0.58) and 0.17 (0.04–0.74), or 1.00 (reference), 0.22 (0.08–0.61) and 0.31 (0.12–0.75), respectively (P for trend = 0.01 or 0.04). Serum EPA was not associated with cognitive decline.

CONCLUSIONS: The study gives some indication that a moderately high level of serum DHA might prevent cognitive decline among community-dwelling elderly Japanese individuals.

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Keywords: DHA; EPA; serum; cognition; Japanese; elderly

INTRODUCTION

An estimated two million people in Japan suffer from dementia and this number will likely increase as the population ages.[1] The essential n-3 polyunsaturated fatty acids (PUFA), docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) that constitute the predominant long-chain PUFAs of membrane phospholipids in mammalian brains and neural tissues, are crucial for maintenance of brain function.[2]

Fish consumption, particularly fatty fish, and intake of marine n-3 PUFA, DHA and EPA are thought to play a protective role against age-related cognitive decline.[3] However, results of cross-sectional and longitudinal studies examining the association between fish or n-3 PUFA intake and cognitive performance have been inconsistent, with some studies showing that high intake of n-3 PUFA was associated with better cognitive performance[4–6] and other studies showing no association.[3,5] One possible reason for these inconsistent results is the limited ability of dietary assessments to quantify blood levels of fatty acids (FA). Blood FA biomarkers can be measured to indicate differences in their delayed response to short- and long-term dietary intakes.[7,8] Studies using n-3 series PUFA in the blood have shown that higher concentrations of DHA in erythrocyte membranes,[9] DHA in plasma phosphatidylcholine[10] and plasma EPA[11] are associated with a lower risk of cognitive decline or Alzheimer's disease. Recently, lower red blood cell EPA and DHA levels were reported to be correlated with smaller brain volumes in elderly subjects without clinical dementia.[12] Furthermore, it has been proposed that FAs in the blood are associated with cognitive function.[13] However, other studies focusing on dementia not only reported no difference in DHA in plasma cholesterol esters and phospholipids,[14] but also reported significantly higher DHA in plasma phospholipids[15] or cholesteryl esters.[16,17] Hence, results of studies examining the association between blood FA and cognitive performance have been inconsistent.

Mean DHA and EPA intake/serum DHA/EPA levels among Caucasian subjects are substantially lower than those of Japanese subjects.[18–21] The effect of serum DHA/EPA levels on cognitive function may vary among Japanese subjects, and the association between serum DHA and EPA levels and cognitive decline among Japanese subjects remains unclear. In addition, studies that examined the effectiveness of serum DHA/EPA levels on cognition in Japanese subjects with high serum DHA/EPA levels would explain one of the reasons that DHA/EPA supplementation trials in Caucasians, in whom serum DHA/EPA levels were substantially low, demonstrated essentially no effect from DHA on cognitive impairment.[22,23] We considered that the duration of these intervention studies examining the effectiveness of DHA/EPA on cognitive performance were relatively short, and

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long-term effectiveness of DHA/EPA intake on cognitive performance would be easier to clarify among Japanese subjects because they are naturally exposed to higher DHA/EPA concentrations. No study in Japan and only a few studies among Asians have reported the association between blood FA and cognitive impairment.[24,25]

To clarify the effectiveness of serum DHA and EPA levels on cognitive decline among the Japanese whose DHA and EPA intake/serum DHA/EPA levels are higher than among Caucasians, and who are naturally exposed to high DHA/EPA concentrations, the present longitudinal study was carried out in elderly community-dwelling Japanese subjects and examined the associations of serum DHA and EPA levels with cognitive decline.

SUBJECTS AND METHODS

Participants

Data for this survey were collected as part of the National Institute for Longevity Sciences - Longitudinal Study of Aging (NILS-LSA). In this project, the normal aging process has been assessed over time using detailed questionnaires and medical checkups, anthropometric measurements, physical fitness tests and nutritional examinations. Participants in the NILS-LSA included randomly selected age- and sex-stratified individuals from the pool of non-institutionalized residents in the NILS neighborhood areas of Obu City and Higashiura Town in Aichi Prefecture. The first wave of the NILS-LSA was conducted from November 1997 to April 2000 and comprised 2267 participants (1139 men, 1128 women; age range, 40–79 years). Details of the NILS-LSA study have been reported elsewhere.[26]

The second wave of the NILS-LSA was conducted from April 2000 to May 2002 and comprised 2259 participants (1152 men, 1107 women; age range, 40–82 years). Among these participants, 1351 (690 men, 661 women) were also included in the seventh wave of the NILS-LSA, which was conducted from July 2010 to July 2012. The mean (±s.d.) interval between the second and seventh wave for each participant was 10.2 (±0.4) years.

Exclusion criteria were as follows: (1) those who were <60 years in the second wave ($n=868$), as cognitive function tested by the Mini-Mental State Examination (MMSE) was assessed only among participants aged 60 or older; (2) those who had an MMSE score ⩽23 in the second wave ($n=10$); and (3) those who did not complete either the alcohol intake assessments or the self-reported questionnaire ($n=43$). A total of 430 Japanese (232 men, 198 women) who had been between 60 and 79 years in the second wave of the NILS-LSA were available for analysis.

The study protocol was approved by the Committee of Ethics of Human Research of the National Center for Geriatrics and Gerontology (No. 369-2). Written informed consent was obtained from all subjects.

Blood sampling and serum FA analysis

Upon enrolment in the second wave of the NILS-LSA, venous blood was collected early in the morning after fasting for at least 12 h. Blood samples were centrifuged at 3500 *g* for 15 min. Serum was separated and frozen at −80 °C before analysis for FA content by a single technician. Serum DHA and EPA were measured by gas-liquid chromatography at a clinical laboratory (SRL, Tokyo, Japan). In brief, total lipids in the serum were extracted using the Folch procedure and FAs were then methylated with BF3/methanol. Transesterified FAs were then analyzed using a gas chromatograph (GC-17A; Shimadzu, Kyoto, Japan) with a capillary column (Omegawax 250; Supelco, Bellefonte, PA, USA). The weights of DHA and EPA (g/ml) as FA concentrations were identified by comparison with known standards. Intra- and inter-assay precision and accuracy values (coefficient of variation (CV)) were 2.7 and 6.9 CV% for EPA, and 1.9 and 6.9 CV% for DHA, respectively.

Assessment of cognitive function

Cognitive function was assessed by the Japanese version of the MMSE through interviews with a trained psychologist or clinical psychotherapist in both the second and seventh waves.[27,28] The MMSE is widely used as a brief screening test for dementia, and scores range from 0 to 30 points, with a higher score indicating better cognitive function. The MMSE includes questions on orientation of time and place, registration, attention and calculation, recall, language and visual construction. We used two different cutoff scores: (1) a decline of at least 4 points in the MMSE score from the second to seventh wave, which has been shown to be meaningful from a clinical point of view,[29–31] and (2) a cutoff score of ⩽23, which is traditionally used to represent 'suggestive cognitive impairment'[27,28] and thus was also used in the main analyses. Among participants in this study with an MMSE ⩾24 in the second wave ($n=430$), (1) 36 (8.3%) who had a decline of at least 4 points in the MMSE score from the second to seventh wave (10 years later), and (2) 15 (3.5%) who had an MMSE score ⩽23 in the seventh wave (10 years later) were classified as showing cognitive decline, respectively. We defined the second wave as baseline, as the MMSE method between the second and seventh wave was consistent, and there were slight modifications of the procedure between the first and second waves.

Nutritional assessments

Nutritional intakes were assessed using a 3-day dietary record after participation in the second wave survey. The dietary record was completed over three continuous days (both weekend days and 1 weekday),[32] and most subjects completed it at home and returned records within 1 month. Food was weighed separately on a scale (1-kg kitchen scales; Sekisui Jushi, Tokyo, Japan) before being cooked or portion sizes were estimated. Subjects used a disposable camera (27 shots; Fuji Film, Tokyo, Japan) to take photos of meals before and after eating. Dietitians used these photos to complete missing data and telephoned subjects to resolve any discrepancies or obtain further information when necessary. Averages for 3-day food and nutrient intakes were calculated according to the fifth edition of the Standard Tables of Foods Composition in Japan and other sources.[32] Alcohol intake in the previous year was assessed using a food frequency questionnaire; trained dietitians interviewed subjects using this questionnaire.

Other measurements

Medical history of heart disease, hypertension, hyperlipidemia, diabetes (past and current), education (⩽9, 10–12 or ⩾13 years of school) and smoking status (yes or no) were collected using self-report questionnaires. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Serum triacylglycerol levels were measured using enzymatic methods, and total and high-density lipoprotein-cholesterol levels were measured using the dehydrogenase method and direct method at a clinical laboratory (SRL). These measurements were assessed in the second wave.

Statistical analysis

All statistical analyses were conducted using statistical analysis system software version 9.1.3 (SAS Institute, Cary, NC, USA). The confounding variables were age (year, continuous), sex, education (⩽9, 10–12, ⩾13 years), MMSE score at baseline (continuous), alcohol consumption (ml/day), current smoking status (yes or no), BMI (kg/m^2), history of heart disease, hypertension, hyperlipidemia and/or diabetes (yes or no). Differences in proportions and means of covariates according to the MMSE score in the seventh wave (10 years later) were assessed using the χ^2-test or Fisher's exact probability test (if statistical expectation ⩽5) and independent *t*-test, respectively. Comparisons between baseline dietary intakes according to the MMSE score 10 years later were performed by independent *t*-test.

Multiple logistic regression analysis was performed to estimate the odds ratio (OR) and 95% confidence interval (CI) for (1) a decrease in MMSE score of at least 4 points or (2) an MMSE score ⩽23 in the seventh wave according to tertiles of serum DHA or EPA. The lowest tertile category was used as a reference. The independent variables in the first model were age, sex and education. The second model was further adjusted for MMSE score at baseline, alcohol consumption, current smoking status, BMI, history of heart disease, hypertension, hyperlipidemia and/or diabetes. Trend associations were assessed by assigning dummy variables of −1, 0 and 1 to tertiles of serum DHA or EPA. In the logistic regression analysis, we tested goodness-of-fit (Hosmer–Lemeshow test) using the lackfit option and calculated the generalized R^2 (Nagelkerke R^2) measure using the r^2 option. Age, sex and education-adjusted mean MMSE score according to tertiles of serum DHA or EPA were calculated using the PROC GLM procedure. To eliminate the effects of other confounding variables on MMSE score, a subsequent model included MMSE score at baseline, alcohol consumption, current smoking status, BMI, history of heart disease, hypertension, hyperlipidemia and diabetes as covariates. All reported *P* values are two-sided, and a P value < 0.05 was considered significant.

RESULTS

Baseline characteristics of subjects according to the MMSE score in the seventh wave (10 years later) and subjects excluded from the analyses are shown in Table 1. Fifteen subjects (3.5%) were classified as showing cognitive decline (MMSE score $\leqslant$23). Compared with subjects with an MMSE score $\geqslant$24, those with an MMSE score $\leqslant$23 were significantly less likely to be educated, significantly older and had a significantly higher BMI. Compared with subjects with both an MMSE score $\leqslant$23 and $\geqslant$24, subjects excluded from the analyses were older, more likely to be current smokers, and more likely to have a history of hyperlipidemia and diabetes. Mean serum EPA or DHA among subjects excluded from the analyses was intermediate between subjects with MMSE score $\leqslant$23 and $\geqslant$24.

Table 2 shows baseline dietary intakes of subjects according to MMSE score 10 years later. Compared with subjects with an MMSE score $\geqslant$24, those with an MMSE score $\leqslant$23 ate significantly less fat and vegetables and significantly more fruits and sweets.

Table 3 shows the ORs and 95% CIs for an MMSE score decline of at least 4 points in the seventh wave (10 years later) according to tertiles of serum FAs. In the age-, sex- and education-adjusted model, serum DHA levels were significantly associated with a decreased prevalence of cognitive decline. After further adjustment for other covariates, the association remained statistically significant. The multivariate-adjusted ORs (95% CIs) for the lowest through highest tertiles of serum DHA were 1.00 (reference), 0.22 (0.08–0.61) and 0.31 (0.12–0.75), respectively (P for trend = 0.004, goodness-of-fit Pr > 0.93, $R^2 = 0.22$). Serum EPA was not associated with cognitive decline.

Table 4 shows mean MMSE scores and ORs (95% CIs) for MMSE score $\leqslant$23 in the seventh wave (10 years later) according to tertiles of serum FAs. Mean MMSE scores according to tertiles of serum FAs were not statistically significant. In the age-, sex- and education-adjusted model, serum DHA levels were significantly associated with a decreased prevalence of cognitive decline. After further adjustment for other covariates, the association remained statistically significant; the multivariate-adjusted OR (95% CI) for the lowest through highest tertiles of serum DHA were 1.00 (reference), 0.11 (0.02–0.58) and 0.17 (0.04–0.74), respectively
(P for trend = 0.01, goodness-of-fit Pr > 0.85, $R^2 = 0.32$). Serum EPA was not associated with cognitive decline.

DISCUSSION

This study provides longitudinal evidence that low serum DHA levels were associated with a higher risk of cognitive decline over a 10-year period in community-dwelling Japanese adults aged 60 years and older. This association remained after controlling for baseline MMSE score and other variables. This is the first study to examine the association between serum DHA/EPA levels on cognitive decline among Japanese subjects whose DHA and EPA intake/serum DHA/EPA levels are higher than those seen in Caucasians and in whom ordinary exposure to DHA/EPA concentrations was high.

The ARIC (Atherosclerosis Risk in Communities) and Framingham Study studies, which examined n-3 series PUFA in the blood, showed that higher concentrations of these FAs were associated with a lower risk for cognitive decline.[10,14] Among elderly French subjects, DHA of erythrocyte membranes[9] and plasma EPA[11] have also been shown to be associated with a lower risk for cognitive decline. However, other studies focusing on dementia not only reported no difference in DHA in plasma cholesterol esters and phospholipids,[14] but also reported significantly higher DHA in either plasma phospholipids[15] or cholesteryl esters.[16,17] Hence, the results from studies examining the association between blood FA and cognitive performance have been inconsistent.

However, serum n-3 series PUFA differs markedly in middle-aged Japanese, Japanese-American and Caucasian (American) men.[33] DHA and EPA levels from the blood of Japanese men are

Table 1. Baseline characteristics of subjects according to the MMSE score 10 years later and subjects excluded from the analyses in the NILS-LSA study

	Subjects available for analyses (n = *430*)			*Subjects excluded from the analyses*[a] (n = *715*)[c]
	MMSE $\leqslant$*23*	*MMSE* $\geqslant$*24*	P-*value*[b]	
Number of subjects	15	415		
MMSE (mean ± s.d.)	27.7 ± 1.4	28.4 ± 1.4	0.04	27.5 ± 2.2
Age (mean ± s.d., years)	70.9 ± 5.9	66.4 ± 5.0	<0.01	71.3 ± 5.5
BMI (mean ± s.d., kg/m^2)	24.4 ± 2.7	22.8 ± 2.7	0.02	22.9 ± 3.3
Alcohol (mean ± s.d., ml/day)	10.2 ± 15.4	8.1 ± 13.5	0.55	7.5 ± 14.7
Female (%)	46.7	46.0	0.96	50.9
Education				
$\leqslant$9 years (%)	66.7	31.1	0.01	47.0
10–12 years (%)	6.7	15.7		21.8
$\geqslant$13 years (%)	26.7	53.3		31.2
Current smoking status (%)	6.7	15.4	0.35	17.4
History of hypertension (%)	53.3	31.1	0.07	42.5
History of hyperlipidemia (%)	13.3	21.5	0.45	21.9
History of diabetes (%)	6.7	7.2	0.93	12.8
Triacylglycerol (mean ± s.d., mg/dl)	85.9 ± 25.7	120.9 ± 62.1	0.03	117.7 ± 66.6
Total cholesterol (mean ± s.d., mg/dl)	219.1 ± 37.9	219.1 ± 33.7	0.99	216.5 ± 36.1
HDL cholesterol (mean ± s.d., mg/dl)	61.27 ± 16.1	59.9 ± 14.9	0.72	60.7 ± 15.8
Serum EPA (mean ± s.d., μg/ml)	74.9 ± 41.1	81.5 ± 39.7	0.53	77.5 ± 40.9
Serum DHA (mean ± s.d.,μg/ml)	145.0 ± 38.5	162.2 ± 45.2	0.15	157.1 ± 49.4

Abbreviations: BMI, body mass index; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL, high density lipid; MMSE, Mini Mental State Examination.
[a]Subjects excluded from the analyses included those who were older than 60 years in the second wave and those who did not participate in the seventh wave.
[b]For continuous variables, independent t-test was used; for categorical variables, χ^2test or Fisher's exact probability test was used. [c]The number of excluded subjects according to the characteristics listed ranged from 672 to 715.

Table 2. Baseline dietary intakes of subjects according to the MMSE score 10 years later in the NILS-LSA study

	MMSE⩽23	*MMSE⩾24*	P-*value*[a]
Number of subjects	15	415	
Energy (mean ± s.d., kcal/day)	2270.0 ± 371.5	2095.9 ± 394.8	0.85
Protein (mean ± s.d., energy%)	14.7 ± 1.5	15.7 ± 2.0	0.22
Fat (mean ± s.d., energy%)	21.5 ± 6.0	23.5 ± 4.3	0.03
Saturated fat (mean ± s.d., g/day)	16.2 ± 5.2	15.4 ± 5.1	0.85
Polyunsaturated fat (mean ± s.d., g/day)	12.2 ± 2.7	12.9 ± 3.6	0.25
DHA (mean ± s.d., mg/day)	543.0 ± 250.4	590.3 ± 1.4	0.07
EPA (mean ± s.d., mg/day)	302.5 ± 155.6	321.3 ± 383.0	0.11
Cereals (mean ± s.d., g/day)	475.0 ± 145.2	469.9 ± 139.5	0.74
Beans (mean ± s.d., g/day)	79.2 ± 35.6	72.8 ± 49.9	0.14
Vegetables (mean ± s.d., g/day)	283.9 ± 81.3	336.0 ± 130.5	0.04
Fruits (mean ± s.d., g/day)	259.8 ± 209.7	175.7 ± 129.1	0.002
Fish and shellfish (mean ± s.d., g/day)	113.6 ± 63.5	102.2 ± 50.3	0.16
Meats (mean ± s.d., g/day)	40.9 ± 23.8	56.7 ± 32.4	0.18
Eggs (mean ± s.d., g/day)	46.9 ± 29.5	46.7 ± 25.7	0.39
Milk and dairy products (mean ± s.d., g/day)	213.1 ± 120.5	165.6 ± 128.6	0.83
Sweets (mean ± s.d., g/day)	71.7 ± 53.8	38.3 ± 38.6	0.04

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MMSE, Mini Mental State Examination. [a]Independent *t*-test was used.

Table 3. ORs and 95% CIs for MMSE scores that declined at least 4 points during 10 years according to tertiles of serum fatty acids

	Tertiles of serum fatty acids			
	T1 (low)	*T2*	*T3 (high)*	*Trend* P[a]
EPA (range, μg/ml)	14.1–59.2	59.2< – 90.4	90.4< – 31.8	
Number of subjects MMSE score declined ⩾4/⩽3	12/129	13/129	11/136	
Age, sex, and education-adjusted OR (95% CI)[b]	1.00 (reference)	1.18 (0.50–2.79)	0.86 (0.35–2.09)	0.70
Multiple-adjusted OR (95% CI)[b,c]	1.00 (reference)	1.10 (0.44–2.75)	0.69 (0.27–1.76)	0.83
DHA (range, μg/ml)	59.3–138.5	138.5< – 175.6	175.6< – 354.6	
Number of subjects MMSE score declined ⩾4/⩽3	21/118	6/138	9/138	
Age, sex, and education-adjusted OR (95% CI)[b]	1.00 (reference)	0.23 (0.09–0.60)	0.35 (0.15–0.81)	0.003
Multiple-adjusted OR (95% CI)[b,c]	1.00 (reference)	0.22 (0.08–0.61)	0.31 (0.12–0.75)	0.004

Abbreviations: CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MMSE, Mini Mental State Examination; OR, odds ratio. [a]On the basis of multiple logistic regression analysis, assigning dummy variables – 1, 0, 1 to tertiles of serum fatty acids. [b]Adjusted ORs and CIs were based on multiple logistic regression analysis. [c]Adjusted for age (year, continuous), sex, education (⩽9, 10–12, ⩾13 years), MMSE score at baseline (continuous), alcohol consumption (ml/day), current smoking status (yes or no), body mass index (kg/m^2), and history of heart disease, hypertension, hyperlipidemia and diabetes (yes or no).

Table 4. Mean (s.e.) MMSE score and ORs (95% CIs) for MMSE scores ⩽23 10 years later according to tertiles of serum fatty acids

	Tertiles of serum fatty acids				
	T1 (low)	*T2*	*T3 (high)*	*ANCOVA* P	*Trend* P[a]
EPA (range, μg/ml)	14.1–59.2	59.2< – 90.4	90.4< – 31.8		
Age, sex and education-adjusted MMSE score[b]	27.78 (0.15)	27.53 (0.15)	27.77 (0.15)	0.44	0.99
Multiple-adjusted MMSE score[b,c]	27.79 (0.15)	27.57 (0.15)	27.72 (0.15)	0.43	0.74
Number of subjects with MMSE ⩽23/MMSE ⩾24	4/137	9/133	2/145		
Age, sex and education-adjusted OR (95% CI)[d]	1.00 (reference)	2.76 (0.78–9.72)	0.51 (0.08–2.91)		0.11
Multiple-adjusted OR (95% CI)[c,d]	1.00 (reference)	2.92 (0.74–11.54)	0.52 (0.08–3.24)		0.13
DHA (range, μg/ml)	59.3–138.5	138.5< – 175.6	175.6< – 354.6		
Age, sex and education-adjusted MMSE score[b]	27.48 (0.15)	27.89 (0.15)	27.70 (0.15)	0.18	0.29
Multiple-adjusted MMSE score[b,c]	27.47 (0.15)	27.90 (0.15)	27.68 (0.15)	0.17	0.32
Number of subjects with MMSE ⩽23/MMSE ⩾24	10/129	2/142	3/144		
Age, sex, and education-adjusted OR (95% CI)[d]	1.00 (reference)	0.16 (0.03–0.78)	0.26 (0.07–0.98)		0.02
Multiple-adjusted OR (95% CI)[c,d]	1.00 (reference)	0.11 (0.02–0.58)	0.17 (0.04–0.74)		0.01

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MMSE, Mini Mental State Examination; OR, odds ratio. [a]On the basis of the general linear model or multiple logistic regression analysis, assigning dummy variables – 1, 0, 1 to tertiles of serum fat [b]Adjusted MMSE scores (mean ± s.e.) were based on the general linear model. [c]Adjusted for age (year, continuous), sex, education (⩽9, 10–12, ⩾13 years), MMSE score at baseline (continuous), alcohol consumption (ml/day), current smoking status (yes or no), body mass index (kg/m^2), and history of heart disease, hypertension, hyperlipidemia and diabetes (yes or no). [d]Adjusted ORs and CIs were based on multiple logistic regression analysis.

significantly higher than those from the blood of Caucasian men.[33] Mean (±s.d.) serum EPA and DHA concentrations in our sample of subjects with an MMSE ⩾24 were 81.5 (±39.7) and 162.2 (±45.2) μg/ml, respectively. On the other hand, among cognitively healthy adults aged 70–79 years living in England, these plasma levels were 39.1 (±3.1) and 70.7 (±2.9) μg/ml, respectively.[34]

The biological mechanisms through which serum DHA exerts beneficial effects on cognition can be divided into vascular and non-vascular pathways. In terms of vascular pathways, the beneficial effects of DHA and EPA are well known, including blood pressure reduction[35] and pronounced effects on eicosanoid production[36] and two cardiovascular risk factors that may lead to cognitive decline.[37] In terms of non-vascular pathways, DHA is highly concentrated in membrane phospholipids of brain gray matter, and it has particular effects on membrane properties and cell signaling.[38] The precise mechanism of its effect, however, is unknown, although deficits in DHA could contribute to inflammatory signaling, apoptosis or neuronal dysfunction in the elderly.[39]

In terms of serum DHA levels, the multivariate-adjusted ORs for MMSE score decline of at least 4 points, and MMSE ⩽23 after 10 years were 1.00 (tertile 1, reference), 0.22 (0.08–0.61) and 0.31 (0.12–0.75) (P for trend = 0.004), or 1.00 (tertile 1, reference), 0.11 (0.02–0.58) and 0.17 (0.04–0.74) (P for trend = 0.01), respectively. Statistical significance was confirmed, but a dose–response relationship between serum DHA levels and cognitive decline was not observed. One of the possibilities for this finding is that serum DHA concentrations in our sample were substantially higher than the levels seen in Caucasian subjects,[33] and these higher blood levels of DHA might be above the threshold level to detect any effect on cognitive decline. In most previous studies of Caucasians, the mean DHA blood levels were in the lowest tertile seen in this study.[33,34] In addition, DHA/EPA supplementation trials in Caucasian subjects whose serum DHA/EPA levels were substantially lower demonstrated essentially no benefit of DHA on cognitive impairment.[22,23] One of the reasons these intervention studies failed might be due to the short duration used to examine the effectiveness of DHA/EPA on cognitive performance. In contrast, Japanese subjects, who have a normally high exposure to high DHA/EPA concentrations, might show different findings. No previous studies that we are aware of have examined serum DHA levels and cognitive decline among the people whose serum DHA/EPA levels were high. Hence, we cannot compare our findings with previous studies.[24,25] Our study presents the possibility that low DHA levels formed over time in blood are a risk factor for cognitive decline rather than that high DHA levels are a protective factor against cognitive decline among the population whose ordinary exposure to DHA/EPA concentrations is high.

Although the precise reason that the OR of the highest tertile in serum DHA was higher than that of the second tertile is unknown, we believe that one possible explanation is that the number of cases was too small. In fact, multiple-adjusted MMSE scores after 10 years according to tertiles of serum DHA were 27.47 (tertile 1), 27.90 (tertile 2) and 27.68 (tertile 3) and did not reach statistical significance (ANCOVA $P = 0.17$, P for trend = 0.32) because the number of cases was too small and no differences in MMSE scores could be detected. To address the small number of subjects, we performed subanalyses to examine the relationships between baseline serum DHA concentration and follow-up MMSE score using Pearson's correlation coefficients ($n = 430$). Even after controlling for age at baseline, no significant positive correlations between serum DHA concentrations and MMSE score at follow-up were observed (partial correlation coefficient $r = 0.029$, $P = 0.55$).

Dietary intakes might belie the association between serum DHA/EPA and MMSE score; for example, subjects with an MMSE score <23 might eat less of the traditional Japanese diet that includes high intakes of fish and rice, or eat more of the western diet that includes high intakes of meat and dairy products[40] compared with subjects with MMSE scores ⩾24. Recently, dietary patterns characterized by a high intake of soybeans, vegetables, algae, and milk and dairy products and a low intake of rice were reported to be associated with reduced risk of dementia in the general Japanese population.[41] However, in our study, subjects with an MMSE score ⩽23 had less intake of DHA (543.0 vs 590.3 mg/day, $P = 0.07$), significantly less intake of fat and vegetables and greater intake of fruits and sweets compared with subjects with an MMSE score ⩾24. Fish and shellfish intake between the two groups were not statistically different (113.6 vs 102.2 g/day, in Table 2). To eliminate the effects of dietary intake including sugar, sweets, fruits, fat and vegetables on MMSE decline, we performed multiple logistic regression analysis further adjusted for intakes of sugar, sweets, fruits, fat and vegetables. The association between serum DHA levels and MMSE decline held up even after controlling for these food intakes (data not shown). Hence, no specific dietary pattern or food intake seemed to bias the association between serum DHA/EPA and MMSE score.

Several limitations to the present study warrant consideration. First, we assessed cognitive function only using a general cognitive test, that is, the MMSE. Although the MMSE is widely used as a brief screening test for dementia, it could be affected by demographic variables such as educational level. Among older patients with a college education living in the United States, the MMSE cutoff score of 27 (sensitivity, 0.69; specificity, 0.91) or 28 (sensitivity and specificity, 0.78) has been shown to be better for detecting cognitive dysfunction compared to the value of ⩽23 used in this study (sensitivity, 0.66; specificity, 0.99).[42] Among our Japanese sample, 52% (224/430) had an education level of 13 years or more. Therefore, the MMSE cutoff point of ⩽23 may be inadequate to assess cognitive impairment. On the basis of this limitation, we used the other cutoff score that was (1) a decline of at least 4 points in MMSE score from the second to seventh wave (Table 3) and (2) an MMSE cutoff score of 28 in a subanalysis. The former analysis was consistent with the results when we used the MMSE cutoff point of ⩽23. However, in the latter subanalysis, an MMSE score ⩽27 was seen in 36% of our Japanese sample (118/326) in the seventh wave, although no significant association was observed between serum DHA/EPA levels and cognitive decline (data not shown). Because of the lack of a sufficient number of cases, when the serum DHA levels were divided into quartiles or quintiles, a few categories contained only one case, although there were still statistically significant findings in a few categories (OR of the fourth quartile: 0.21, $P = 0.05$, OR of the third quintile: 0.11, $P = 0.07$, data not shown).

Second, serum FA concentrations were assessed from a single blood sampling. However, Kobayashi *et al.* examined correlations between serum phospholipid FA levels collected twice and FA intake assessed from 7-day weighted dietary records among 87 Japanese men, and reported that a single measurement of serum phospholipids was a useful biomarker of n-3 PUFA.[8] Although that study used serum phospholipids, Ogura *et al.* reported that PUFA levels in plasma and erythrocyte phospholipids were nearly identical among 75 Japanese patients admitted for non-malignant diseases.[43] Third, attrition bias may have affected our results. Compared with included subjects, subjects excluded from the analyses were older, more likely to be current smokers, and more likely to have a history of hyperlipidemia and diabetes. Hence, excluded subjects might have been less healthy than subjects included in the final analysis. However, mean serum EPA or DHA among subjects excluded from the analyses was higher than those among subjects with an MMSE score ⩽23, and our results do not necessarily mean that subjects with lower serum EPA or DHA levels were more likely to drop out during the follow-up period. Fourth, DHA and EPA intake/serum levels among Japanese subjects are substantially higher than those of Caucasian subjects,[18–21] and the tissue n-3/n-6 ratio that would alter

eicosanoid patterns[44] might also differ between these groups. Furthermore, genetic factors, including APOE4, might also modify the metabolism of n-3 PUFA.[45] However, we could not assess the n-3/n-6 ratio or genetic factors in this study.

The main strengths of the present study are as follows: (1) the long average follow-up period of 10 years; (2) the use of an older sample of randomly selected age- and sex-stratified non-institutionalized individuals from the community; and (3) the use of serum FA levels to assess DHA or EPA status. Furthermore, a certain level of serum DHA is modifiable through the consumption of fish or dietary supplements in DHA.[46] Recently, red blood cell levels of DHA plus EPA were reported to be explained by DHA plus EPA intake (25%), heritability (24%) and fish oil supplementation (15%) in the Framingham Heart Study.[47] In our Japanese sample ($n = 430$), Pearson's correlation coefficient between serum DHA and DHA intake assessed by a 3-day dietary record was 0.18 ($P < 0.01$, data not shown). This finding means that serum DHA levels are an adjustable factor to some extent.

In conclusion, the findings of this study give some indication that a moderately high level of serum DHA among the Japanese, whose DHA and EPA intake/serum DHA/EPA levels are higher than among Caucasians, might prevent cognitive decline among elderly, community-dwelling Japanese individuals.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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◆編集

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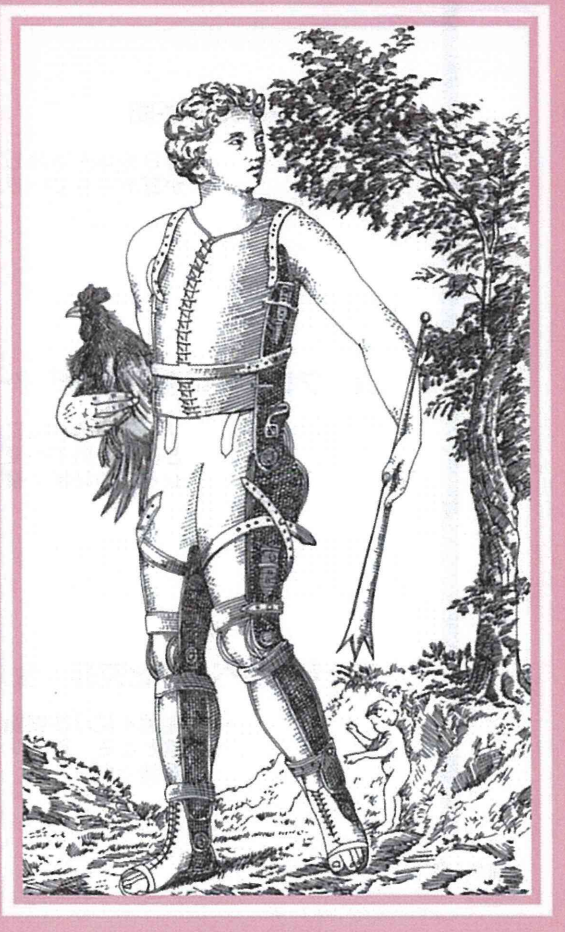

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特集／高齢者のフレイル（虚弱）とリハビリテーション

虚弱の危険因子

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Abstract　地域在住高齢者の虚弱の危険因子を見出し，予防対策に資することを目的に研究を行ってきた．無作為抽出された地域住民3,000人以上の6年間の追跡調査データから虚弱の危険因子について検討した．解析の結果，運動能力を中心に多くの指標が有意な要因として抽出されたが，特に，慢性疾患や抑うつの予防，十分に運動して，歩行能力や，体力を保つことが虚弱の予防には重要であることが確認することができた．また，地域在住の全高齢者を対象とした行政データからの解析では，生活機能全般の障害が虚弱の最大のリスクであり，次いで運動機能障害，うつ状態，栄養状態の不良の順でリスクが大きいことが明らかになった．虚弱の要因として老年症候群が重要である．老年症候群は，高齢者に特有の，あるいは高頻度にみられる諸症状であり，老年症候群の多くの症候が重積して虚弱を引き起こす．運動介入や栄養の単独の介入では虚弱の予防は難しい．高齢者に対しての生活全般のサポートによる対応が望まれる．

Key words：虚弱（frailty），高齢者（aged person），危険因子（risk factor），体力（physical fitness），老化（aging）

はじめに

日本人の平均寿命は年々長くなり，高齢者，特に後期高齢者の人口が急増している[1][2]．しかし，高齢になるほど虚弱となり，自立生活ができなくなって要支援・要介護となる者は増加する．一方で少子化が進み，今後は若い労働力が不足していくことが予想される．要支援・要介護となるような高齢者の虚弱を早期に見出して，その対策を行うことは高齢化が急速に進行する我が国において急務である．本稿では，地域住民のコホート追跡調査の解析からの結果を中心に，高齢者の虚弱の危険因子を明らかにし，その予防法を探る．

国立長寿医療研究センター・老化に関する長期縦断疫学研究

我々は1997年11月に「国立長寿医療研究センター・老化に関する長期縦断疫学研究（NILS-LSA）」を開始した[3)〜5)]．この研究は高齢化社会に対応し，地域住民の加齢変化を，医学・心理学・運動生理学・形態学・栄養学などの広い分野にわたっての調査を，詳細にかつ同一個人に対して長期にわたって実施し，老化や老年病の成因や危険因子を解明することを目的としている．1日の検査人数は7名で，毎日年間を通して詳細な老化に関連する検査を行ってきた．2000年4月に2,267名の基礎集団が完成し，以後は2年ごとに検査を繰り返し実施し，2012年7月に第7次調査を終了した．対象は調査開始時40〜79歳の地域住民から無作為に選ばれた男女である．追跡中の脱落者については，同じ人数の新たな補充を行うとともに，集団全体の年齢が高くならないように，40歳の男女を新たに加えて，定常状態として約2,400人の集団の追跡を行ってきた．抽出によって選定された者を説明会に招いて，検査の目的や方法などを十分に説明し，インフォームドコンセントを得たうえで検査を実施した．検査および調査はほ

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とんどすべて施設内に設けた専用の検査センターで行った．朝9時～夕方4時までの間に分刻みでスケジュールを組み，頭部MRI検査や心臓および頸動脈超音波断層検査，骨密度測定，腹部CT検査などの最新の機器を利用した医学検査のみならず，詳細な生活調査，栄養調査，運動機能調査，心理検査など広汎で学際的な，しかも精度の高い調査・検査を実施した．

要支援・要介護化の危険因子について，NILS-LSAの第4次調査から第7次調査までの6年間に調査に参加した40歳以上の地域在住中高年者3,126人(男性1,567人，女性1,559人)を対象とした．平均年齢は，男性58.4±13.2歳，女性58.9±13.5歳である．

今回の検討に用いた測定項目は，以下の通りである．

(1) **背景要因**：喫煙習慣(調査時点での喫煙の有無)，高血圧症，心疾患，脂質異常症，糖尿病，脳卒中既往歴，自覚的健康度(「とても良い」，「良い」，「普通」，「悪い」，「とても悪い」の5段階)，血圧，抑うつ(center for epidemilogic studies depression scale；CES-Dで16点以上を抑うつありとした[6])，認知機能(mini mental state examination；MMSEで23点以下を認知機能障害ありとした[7])．

(2) **体格**：BMI，大腿中部周囲長，下腿周囲長，上腕周囲長，体脂肪率(DXA法)

(3) **身体活動**：余暇身体活動量，総身体活動量，1日歩数

(4) **体力**：握力，開眼片脚立ち，閉眼片脚立ち，全身反応時間，脚伸展パワー，上体起こし，膝伸展筋力，普通歩速度，速歩速度

(5) **栄養摂取量**：総エネルギー摂取量，蛋白質，ビタミンD，イソロイシン，ロイシン，バリン，アルギニン(写真撮影を併用した3日間の秤量食事記録法により栄養素の摂取量を算出した)，血清アルブミン

(6) **身体機能**：SF36のphysical performance項目[8]．具体的な項目は，以下の通りである．軽度：体を前に曲げる，100 m以上歩く，中等度：適度の運動，階段を1階上まで登る，数100 m以上歩く，高度：階段を数階上まで登る，激しい運動，少し重い物を運ぶ，1 km以上歩く．これらの項目による得点が75点以下は要支援・要介護となる程度のADLの障害があると判定される．Physical performanceが75点以下となる6年間のリスクを各種要因について，一般推定方程式(GEE)で性別・年齢を調整して推定し，オッズ比を計算した(表1)．

喫煙はADLの低下とは有意な関連はみられなかった．高血圧症，心疾患，脂質異常症，糖尿病，脳卒中の有無は疾患を有する群でADLが低下するリスクは高かった．自覚的健康度は，「良い」群に比べ「悪い」，「普通」の群はADL低下のリスクが有意に高かった．オッズ比は3.2と高い値であった．血圧は有意な結果とならなかった．抑うつはある群に比べてない群で有意にADL低下のリスクが低くなっていた．認知機能は認知機能低下がない群でADL低下のリスクが下がっていた．

余暇活動量，総活動量，1日の歩数の身体活動指標は，いずれも高いほどADL低下のリスクを下げていた．体力の指標では，握力，開眼片脚立ち，閉眼片脚立ち，全身反応時間，脚伸展パワー，上体起こし，膝伸展筋力，普通歩速度，速歩速度と体力指標すべてで成績が悪いとADL低下のリスクとなっていた．

BMIは高くなるほどADL低下のリスクを上げていた．DXAで測定した体脂肪率は高いほどADL低下のリスクが高かった．肥満はADLの低下の要因になっていたが，大腿中部周囲長，下腿周囲長，上腕周囲長はADL低下との関連が認められなかった．エネルギー摂取量，蛋白質摂取量，ビタミンD摂取量，イソロイシン摂取量，ロイシン摂取量，バリン摂取量，アルギニン摂取量，血清アルブミンの栄養の指標はすべてADL低下の関連しており，数値が低いとADL低下のリスクとなっていた．

表 1. 生活習慣，背景要因などと ADL の低下との関連

項 目		オッズ比	95%信頼区間	p 値
喫煙	吸う vs 吸わない	1.070	0.796-1.437	NS
高血圧症	あり vs なし	1.564	1.324-1.846	<0.0001
心疾患	あり vs なし	1.768	1.329-2.352	<0.0001
脂質異常症	あり vs なし	1.266	1.055-1.521	0.0014
糖尿病	あり vs なし	1.739	1.321-2.291	<0.0001
脳卒中	あり vs なし	2.428	1.702-3.463	<0.0001
自覚的健康度	普通・悪い vs 良い	3.198	2.659-3.846	<0.0001
収縮期血圧	10 mmHg ごと	1.031	0.990-1.074	NS
拡張期血圧	10 mmHg ごと	1.008	0.939-1.081	NS
抑うつ	CES-D 15 以下 vs 16 以上	0.468	0.391-0.560	<0.0001
認知機能	MMSE 24 以上 vs 23 以下	0.702	0.530-0.930	0.0136
BMI	1 kg/m^2 ごと	1.080	1.045-1.116	<0.0001
大腿中部周囲長	1 cm ごと	0.999	0.995-1.002	NS
下腿周囲長	1 cm ごと	0.993	0.980-1.005	NS
上腕周囲長	1 cm ごと	1.004	0.985-1.023	NS
体脂肪率(DXA)	10% ごと	1.782	1.470-2.160	<0.0001
余暇身体活動量	100,000METS・min/y ごと	0.518	0.408-0.658	<0.0001
総身体活動量	100,000METS・min/y ごと	0.569	0.467-0.693	<0.0001
歩数	1,000 歩ごと	0.812	0.783-0.843	<0.0001
握力	10 kg ごと	0.377	0.307-0.462	<0.0001
開眼片脚立ち	10 秒ごと	0.942	0.923-0.962	<0.0001
閉眼片脚立ち	10 秒ごと	0.815	0.721-0.923	0.0012
全身反応時間	0.1 秒ごと	1.371	1.256-1.496	<0.0001
脚伸展パワー	10 W ごと	0.947	0.937-0.957	<0.0001
上体起こし	1 回／分ごと	0.926	0.904-0.948	<0.0001
膝伸展筋力	10 kg ごと	0.522	0.455-0.599	<0.0001
普通歩速度	1 m/分ごと	0.019	0.011-0.031	<0.0001
速歩速度	1 m/分ごと	0.944	0.937-0.951	<0.0001
総エネルギー摂取量	100 kcal/日ごと	0.940	0.918-0.963	<0.0001
蛋白質摂取量	10 g/日ごと	0.870	0.824-0.919	<0.0001
ビタミン D 摂取量	5 μg/日ごと	0.943	0.891-0.997	0.0379
イソロイシン摂取量	1 g/日ごと	0.763	0.678-0.858	<0.0001
ロイシン摂取量	1 g/日ごと	0.854	0.797-0.915	<0.0001
バリン摂取量	1 g/日ごと	0.790	0.714-0.873	<0.0001
アルギニン摂取量	1 g/日ごと	0.827	0.756-0.904	<0.0001
血清アルブミン	1 g/dl ごと	0.725	0.604-0.869	0.0005

SF36 physical performance が 75 点以下となる 6 年間のリスクを各種要因について，一般推定方程式(GEE)で性別・年齢を調整し全対象者で推定し，オッズ比を計算した．
NS：not significant

ADL 低下や虚弱の予防には多くのアプローチがあるが，NILS-LSA の解析から慢性疾患や抑うつの予防，十分に運動して，歩行能力や，体力を保つことが重要であることが確認することができた．

東浦町介護予防研究

愛知県東浦町の 2009 年 4 月 1 日現在の 65 歳以上全住民を対象として，3 年半後の 2012 年 10 月 1 日現在の要支援・要介護情報から，基本チェックリストの各項目や生活機能評価が，その後に要支援・要介護となるかを予測できるかという検討を行った．基本チェックリストは厚生労働省地域支援事業実施要綱に基づくもので，65 歳以上の高齢者を対象に要介護の原因となりやすい生活機能低下の危険性がないかどうかという視点で，運動，口腔，栄養，物忘れ，うつ症状，閉じこもり等の全 25 項目について，「はい」「いいえ」で記入する質問表である[9]．2009 年度には，東浦町では基本チェックリストを，65 歳以上の人口 9,374 人のう

表 2. 地域住民における 3 年半の追跡による基本チェックリストからの生活機能障害項目の要支援・要介護となるリスクのオッズ比

項　目	オッズ比	95%信頼区間	p 値
生活機能障害	3.82	3.05-4.78	p<0.001
運動機能障害	2.70	2.20-3.33	p<0.001
栄養状態の不良	2.44	1.31-4.54	p=0.005
口腔機能障害	1.59	1.27-1.99	p<0.001
閉じこもり	1.70	1.29-2.24	p<0.001
認知機能障害	1.80	1.50-2.15	p<0.001
うつ状態	2.54	2.09-3.09	p<0.001

性別・年齢を調整した多重ロジスティック回帰解析．オッズ比は各項目 1 点ごとの値．

ち，すでに要支援・要介護となっている者を除く 8,091 人の 69.6%にあたる 5,631 人に実施した．3 年半後には死亡者，転出者を除いて 603 名が要支援・要介護となった．多重ロジスティック回帰により性別，年齢を調整して要支援・要介護となるリスクについて検討を行った．項目別の検討ではチェックリスト項目すべてで有意となった．オッズ比が 2 倍以上となった項目は，「日用品の買い物をしていない」「階段をつたわらずに昇れない」「つかまらずに立てない」「15 分続けて歩くことはない」「1 年間に転んだことがある」「昨年より外出回数が減少」「生活に充実感がない」「楽しめなくなった」「億劫に感じる」「役に立つ人間だと思えない」であった．運動機能や抑うつに関連する項目でリスクが大きいことがわかる．基本チェックリストからの生活機能評価結果では，生活機能全般の障害が要支援・要介護の最大のリスクであり，オッズ比は 4 倍近くとなった．次いで，運動機能障害，うつ状態，栄養状態の不良の順でリスクが大きかった(表 2)．

老年症候群と虚弱

老年症候群は高齢者に特有の，あるいは高頻度にみられる諸症状であり，高齢者の ADL や QOL を阻害する[10]．老年症候群にはめまい，息切れ，やせ，食欲不振，抑うつ，転倒，関節痛，視力低下，聴力低下などが含まれる．これらの老年症候群の諸症状は高齢者虚弱との関わりが強い．図 1 に示すように，加齢，性別は高齢者の虚弱の要因として重要であるが，世帯年収や教育，住宅環境，家族構成などの社会経済的要因，喫煙，飲酒，身体活動，食生活などの生活習慣，糖尿病，脳血管障害，冠動脈疾患，COPD，骨折，関節炎，認知症，慢性炎症，アンドロポーズなどの慢性疾患や慢性的な病態が，高齢者の虚弱を引き起こす．こ

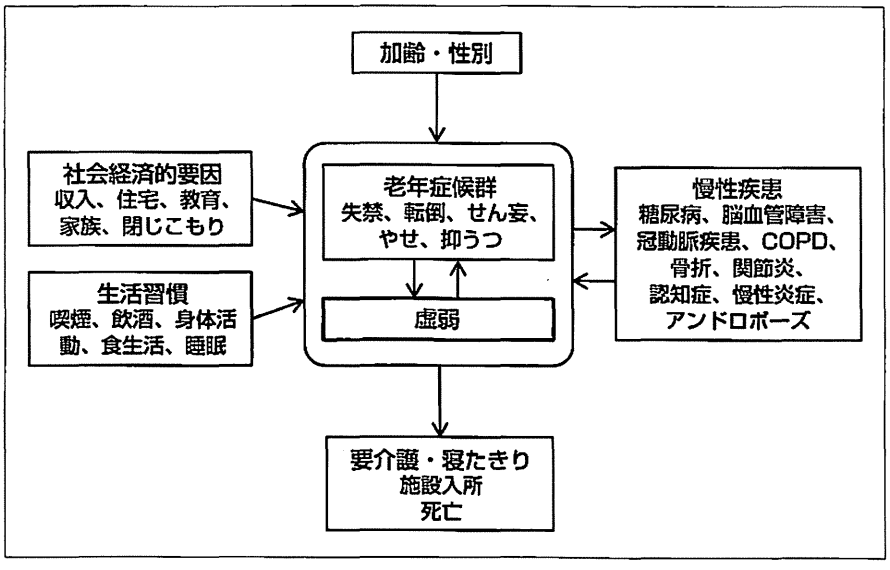

図 1. 高齢者の虚弱の危険因子と老年症候群

(文献 11 より)