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

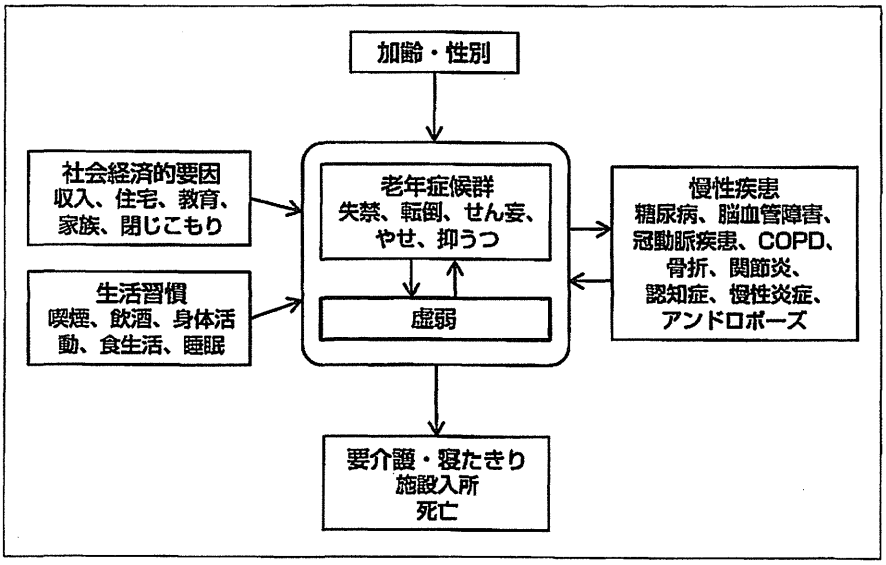

図 1. 高齢者の虚弱の危険因子と老年症候群

(文献 11 より)

れらの要因は同時に様々な老年症候群の要因にもなる．さらに高齢者の虚弱が老年症候群の原因ともなる．そして要介護や寝たきり，施設入所，最終的には死に至る．このように多くの要因が重積し虚弱を引き起こす．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[11]．

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ORIGINAL ARTICLE

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

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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 ⩽23). Compared with subjects with an MMSE score ⩾24, those with an MMSE score ⩽23 were significantly less likely to be educated, significantly older and had a significantly higher BMI. Compared with subjects with both an MMSE score ⩽23 and ⩾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 ⩽23 and ⩾24.

Table 2 shows baseline dietary intakes of subjects according to MMSE score 10 years later. Compared with subjects with an MMSE score ⩾24, those with an MMSE score ⩽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 ⩽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 ⩽23	*MMSE⩾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				
⩽9 years (%)	66.7	31.1	0.01	47.0
10–12 years (%)	6.7	15.7		21.8
⩾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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特集　生活習慣病・老年疾患と認知症

臨床に役立つQ&A

2. 喫煙が知能・認知機能に及ぼす影響と抗酸化食品の可能性

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KEY WORD ■喫煙 ■知能 ■認知機能 ■認知症 ■カロテノイド

SUMMARY

■わが国の成人の喫煙率は依然高く，特にこれから認知症年齢にさしかかる40～50歳代男性では約40%が喫煙している．喫煙と認知症(アルツハイマー病，脳血管性認知症)，認知機能低下，知能との関係は主に欧米で研究されており，「関係あり」とするものが多く，喫煙は知能・認知機能の多側面に悪影響を与えると考えられる．

■わが国での研究成果は乏しいが，40～79歳の地域住民の縦断研究では喫煙は知能の加齢変化に影響を与え，その効果は中高年に至るまでにある程度固定化され，それ以降継続すると推定された．野菜・果物に主に含まれる抗酸化物質であるカロテノイドには，喫煙の知能に対する負の効果を一部緩衝する作用が認められた．

はじめに

2013年の「全国たばこ喫煙者率調査」[1]によれば，喫煙率は20.9%(男性32.2%，女性10.5%)で，全国で約2,195万人が喫煙している．特に，これから認知症発症年齢を迎える40～50歳代の男性では，喫煙率はそれぞれ41.0%，36.4%と高く，喫煙本数も1日平均20本以上と推定されている．

喫煙と認知症(アルツハイマー病，脳血管性認知症)，認知機能低下，知能との関係に関する報告は欧米を中心に多数認められるが[2-11]，わが国の大きなコホートでの報告は乏しい[12]．本稿では喫煙と認知症・認知機能，知能との関係についての欧米の知見をまとめるとともに，わが国でのコホート研究の結果とその交絡要因としての抗酸化物質の作用についても言及する．

喫煙と認知症・認知機能との関連

2000年代前半までは横断的研究が多く，喫煙による他疾患発症・死亡による選択バイアスのため「喫煙はアルツハイマー病の予防に効果的」とする論文が認められた[2]が，その後の縦断的コホート研究のシステマティックレビューやメタアナリシスなどでは「喫煙は認知症全般，アルツハイマー病，脳血管性認知症，認知機能低下，知能の加齢変化に対して危険因子となる」という結論を得ているものが多い．

Reitzら[3]は，認知機能障害のない高齢者791人を5年以上追跡した結果，75歳以上の喫煙者は未喫煙者(喫煙経験のない者)・禁煙者より記憶力低下が大きかったと報告している．Ansteyら[4]らの2005年までの前向き研究19件についてのメタアナリシスでは，喫煙群は未喫煙群と比べてアルツハイマー病発症の相対リスクが

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1.79(95%信頼区間　1.43～2.23)．脳血管性認知症では1.78(1.28～2.47)，認知症全体でも1.27(1.02～1.60)と有意に高く，MMSE得点の低下率も高かった．禁煙群は喫煙群と比較すると，MMSE得点の低下率やアルツハイマー病の発症率は低かったが，そのほかの認知症では有意差は認められなかったという．その後の2つのメタアナリシスでも，認知症，特にアルツハイマー病と喫煙との関係は有意であった[5,6]．

Barnesら[7]はアルツハイマー病の危険因子に関わる多くの研究結果から，可変的な危険因子のアルツハイマー病への相対リスクと患者数への貢献度を推定している．世界的にみた場合，喫煙は浸透率が27.4%，アルツハイマー病への相対危険率は1.59で，これは低教育(1.59)，中年期の肥満(1.60)・高血圧症(1.61)とほぼ同等で糖尿病(1.39)よりも高かった．喫煙が発症に寄与していると推定されるアルツハイマー病患者は470万人で，低教育(650万人)に次いで第2位であり，低身体活動度(430万人)や抑うつ(360万人)を凌駕していた．

一方，対象者の年齢や特徴によっては，喫煙と認知機能との関係が有意ではないとする報告も認められる．直近のDi Marcoら[8]のシステマティックレビュー(2014年)によると，2013年までの生活習慣など可変要因と認知症に関する縦断観察研究75論文の中で，喫煙について解析されていた論文は15編であったが，結論は一定ではなく，おそらく喫煙や認知症(認知機能)の診断基準の問題とともに，対象者の年代も関連しており，認知機能障害と喫煙との関係を検討するためには，若い世代からの追跡が必要であるとコメントしている．実際に18歳男子20,221人を対象とした横断研究で，関係要因を調整した後も喫煙者は非喫煙者(喫煙していない群)より知能指数が低く，兄弟間でも喫煙者は非喫煙者より知能指数が低いという報告[9]があり，喫煙の知能や認知機能への影響は，より若い世代で始まっていると考えられる．

喫煙の認知機能・知能への作用

ニコチンには脳内のアセチルコリンの放出やニコチン受容体を増やし，短期的には集中力や情報処理能力を高める作用がある[2]．その一方で，喫煙は心血管疾患の発症リスクを高めることや喫煙と脳内コリン作動性ニコチン受容体との関係から，認知症やアルツハイマー病との関連が議論されており，このいずれのメカニズムにも喫煙による酸化ストレスが関与すると考えられている[2]．実際にSonnenら[13]は，初回調査時に認知症のなかった高齢者228症例を剖検したところ，喫煙者の大脳にはアルツハイマー病患者や頭部外傷者と同様のフリーラジカルによる障害が認められたと報告している．

それでは，喫煙は知能や認知機能のどのような側面に影響を与えるだろうか．スコットランドでのOkusagaら[10]の研究によれば，喫煙は言語流暢性を除く多くの知能の側面(語彙や言語学習，符号検査，注意・推論機能，知識量など)の低下に関連していた．Arntzenら[11]も，脳血管障害のない地域在住中高年者5,033人の7年間の追跡調査により，喫煙は言語記憶，符号検査，タッピングテストの低下に対しての独立した危険因子であったと報告しており，喫煙は知能や認知機能の多くの面に悪影響を与えると考えられる．

わが国での喫煙と認知機能に関する報告

「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：National Institute for Longevity Sciences — Longitudinal Study of Aging)」[14]では，愛知県大府市・知多郡東浦町在住の40～79歳の地域住民から無作為抽出された2,267人を対象として，約2年ごとに老化や老年病に関する幅広い追跡調査を行っている．この中には，ウェクスラー成人知能検査改訂簡易版(WAIS-R-SF：下位尺度「知識(一般的な事実についての知識量)」，「類似(論理的抽象的思考・語彙の知識)」，「絵画完成(視

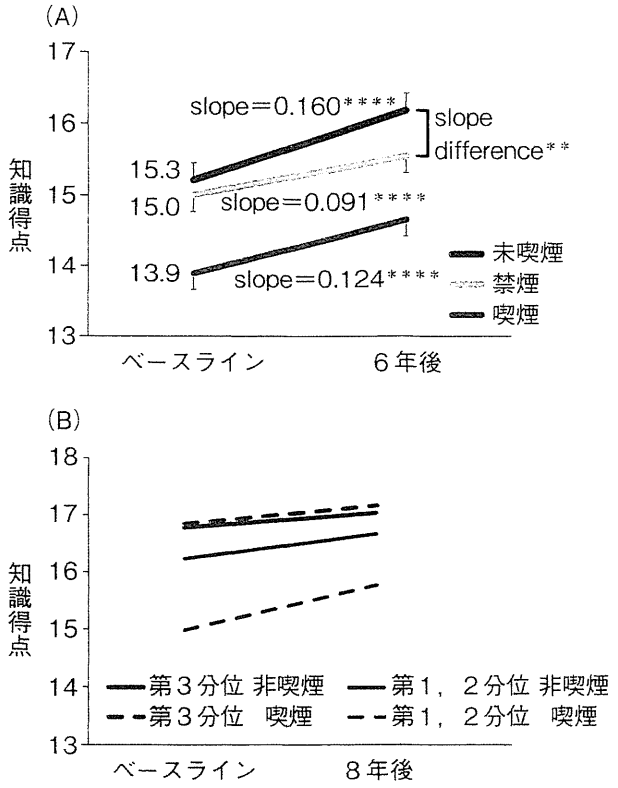

図1　知能の加齢変化に対する喫煙の影響(A)とカロテノイドの緩衝作用(B)

(A)ベースラインでの喫煙状況と「知識得点」の6年間の変化

喫煙はベースラインでの知識得点に有意な影響を与え，それは6年後も継続していた．

6年間で集団全体での知識得点は上昇したが，未喫煙群に比べて禁煙群ではその上昇の度合いは有意に低かった(年齢と性，個人差を調整した線形混合モデルによる，傾きの検定および傾きの差の検定，**：$p<0.01$，****：$p<0.0001$)．

(B)男性のαカロテン摂取量と喫煙状況が知識の加齢変化に及ぼす交互作用

ベースラインのαカロテンの摂取量(第1・2分位vs第3分位)と喫煙状況(非喫煙vs喫煙)で対象を4群に分け，ベースライン時の知識得点および8年間の知識得点の経過を示す．ベースライン時，8年後ともに，非喫煙の2群と喫煙・αカロテン第3分位群では得点に有意な差は認められなかった．しかし，喫煙・αカロテン第1・2分位群は，ベースライン・8年後ともにほかの3群よりも有意に知識得点が低かった(年齢と個人差を調整した線形混合モデルによる)．

同様の結果が女性では，知識得点とαカロテン摂取量，符号得点とβカロテン摂取量の関係において認められた．

覚的長期記憶の想起と照合)」，「符号(情報処理，課題遂行速度)」)・数唱やMini-Mental State Examination(MMSE)などの知能・認知機能検査や喫煙歴が含まれている．第3次調査(2002～2004年)から第6次調査(2008～2010年)までの6年間で，知能や認知機能の加齢変化に喫煙が及ぼす影響を検討したところ，知能(知識，類似，絵画完成，符号)得点に対し喫煙状況の効果は有意で，未喫煙群や禁煙群に対して喫煙群はベースラインでの得点が低く，その状況は6年後も継続していた(**図1-A**)．また，知識得点は経過中，全体では有意に上昇したが，未喫煙群に比べて禁煙群ではその上昇の度合いは有意に低かった(**図1-A**)．

興味深いことに，喫煙による知能低下作用は，野菜や果物に多く含まれる抗酸化物質であるカロテノイドによって緩和され，喫煙群でもカロテノイドを十分量摂取していた群では知能の加齢変化は非喫煙群と同等であったが，カロテノイド摂取量が少ない喫煙群では非喫煙群と比べて有意な知能低下が認められた(**図1-B**)．

まとめ

喫煙は高齢者の知能の幅広い側面に悪影響を与えると考えられるが，その影響は少なくとも中年期には既に始まっている．喫煙の知能に対する効果は，体内の過酸化やそれによる動脈硬化の二次的影響と考えられ，抗酸化物質の適正な摂取は喫煙の知能に対する悪影響を緩和する可能性がある．

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特集　生活習慣病・老年疾患と認知症

Seminar

7．難聴と認知症

杉浦　彩子　　内田　育恵　　中島　　務　　下方　浩史

KEY WORD　■難聴　■補聴器　■耳垢　■認知機能

SUMMARY

■難聴は高齢者に最も多くみられる感覚器障害であるが，認知症患者において難聴があると認知機能低下に拍車がかかることが報告されている．また認知症のない高齢者においても，難聴は認知症の独立したリスクファクターであるとする報告もある．一方で補聴器や耳垢栓塞除去といった難聴に対する介入で，認知機能が改善することも報告されているが，エビデンスの質は高くなく，今後の検討が必要である．認知症患者の診察において，聴力の把握と外耳道の観察は重要である．

はじめに

難聴は高齢者に最も多い病態の1つであり，補聴器装用が推奨される平均聴力レベル41 dB以上の難聴者は60歳代の1割弱，70歳代の1～2割，80歳代の3～4割，平均聴力レベル26 dB以上の軽度難聴者を含めると60歳代の2～3割，70歳代の5～6割，80歳代の7～8割にみられる[1]．認知症患者においても難聴の合併はよく認められ，国立長寿医療研究センターのもの忘れセンター受診患者の半数に難聴の自他覚がある．本稿では認知機能と難聴の関連について考察したい．

認知機能と難聴

認知症と難聴についての関連は古くから指摘されており，1960年代までさかのぼることができる．Petersらは認知症と診断されている患者において，難聴がある群とない群で約9カ月後のMini-Mental State Examination（MMSE）を比較し，難聴のない群ではMMSEスコアの低下は認めなかったのに対し，難聴がある群では−2.8±3.8点と有意な差を認めたことを報告している[2]．Uhlmannらもアルツハイマー型認知症と診断された患者において，難聴がある群とない群では有意に難聴のある群でMMSEスコアが低いこと[3]，さらに難聴のある群では1年後のMMSEも難聴のない群の−2.2点に対して−3.9点と有意に低下することを報告している[4]．

それでは，認知症のない高齢者における難聴の影響はどうであろうか？　一般地域住民を対象とした様々な調査において，難聴が認知機能へ与える影響について検討がなされてきた．500名を超える大規模な縦断研究では，難聴があると認知機能が有意に低下するという結果の文献と，年齢，性，教育歴，他疾患の合併などを調整すると有意な影響は認めないという結果の文献に分かれる．Study of Osteoporotic Fractures（SOF）では，ベースラインから4～5年後のMMSE低下のリスクが視覚障害では有意に高かったが，聴覚障害では有意ではなかった[5]．ただし，この研究では対象者が女性に限定されている．Hispanic Established Population for Epidemiologic Studies of the Elderly（H-EPESE）では，難聴の有無は2～7年後のMMSEスコアに有意な関連を認めなかった[6]．

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表1　聴力とMMSEの関連(NILS-LSA第7次調査より)

	正常 ～25 dB	軽度難聴 26～40 dB	中等度難聴 41～60 dB	高度難聴 61～80 dB	聾 81 dB～	計
人数(男性)	666(305)	403(224)	165(101)	10(7)	4(3)	1,248
年齢(歳)*	68.0±0.3	73.9±0.3	78.1±0.5	75.4±2.0	70.8±3.2	71.3±0.2
教育歴(年)*	12.2±0.1	11.5±0.1	10.7±0.2	10.3±0.8	11.3±1.3	11.7±0.1
MMSE*	28.1±0.1	27.6±0.1	26.9±0.2	26.1±0.6	26.8±1.0	27.7±0.1
MMSE**	27.9±0.1	27.8±0.1	27.4±0.2	26.6±0.6	26.9±1.0	

平均±標準誤差
*一般線形モデルにおいてp<0.0001
**一般線形モデルにおいて性別，年齢，教育歴を調整(p=0.04)

こちらの報告でも視覚障害は有意な関連を認めている．Alabama County Studyでは，5年後の認知機能低下に難聴が有意な相関を認めている．ただし，難聴の程度も認知機能の程度も簡易な問診によるスケール評価である[7]．そして近年Baltimore Longitudinal Study of Aging (BLSA)から，聴力が10 dB悪いと平均11.9年のフォローアップ中の認知症発症の危険率が1.27(95%CI 1.14～1.29)高まるという報告がなされた[8]．BLSAの筆頭著者であるLinは，その後も難聴と認知機能について精力的に研究を続けており，Health, Aging and Body Composition (Health ABC) studyのデータにおいてもModified Mini-Mental State(3MS)をはじめとした認知機能検査が，6年間のフォロー中に難聴のある群ではない群に比べて年齢などを調整しても有意に低下することを報告している[9]．また，同じくBLSAのデータより，難聴があると約6年後の脳容積が有意に小さくなるという解析結果も報告している[10]．

われわれは，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(National Institute for Longevity Sciences-Longitudinal Study of Aging：NILS-LSA)において，難聴の程度とMMSEスコアの関連について横断的に検討した．NILS-LSA第7次調査に参加した1,248人の一般地域住民参加者(60～94歳)において，**表1**に示すように聴力が悪いほど有意にMMSEスコアが低く(p<0.0001)，年齢，性別，教育歴を調整しても有意な関連を認めた(p=0.04)．縦断的な検討でも，聴力が悪いと有意に8年後のMMSEスコアが低下する危険率が高くなるという結果を得ている．

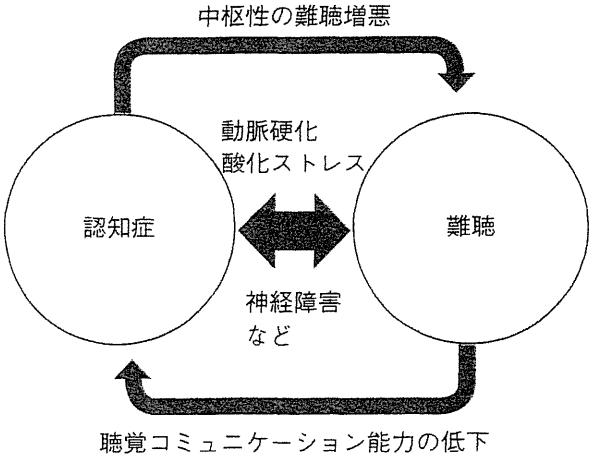

図1　認知症と難聴の関係

認知症と難聴の関連については**図1**に示すように，認知症と難聴に関連した共通の因子，例えば動脈硬化，神経変性，酸化ストレスなどがあるのと同時に，相互作用もあると推測される．認知症があれば中枢性難聴，すなわち聴力そのものはある程度保たれていても，言葉の聞き取りや雑音下での聴取といった音の弁別機能などが低下することとなる．また，難聴があれば聴覚刺激が少なくなり，聴覚コミュニケーションの不足から認知機能が悪化しやすくなるという面もある．

難聴に対する介入の認知機能への効果

それでは，難聴を補聴器などで補正すれば認知機能は低下しにくくなるのだろうか？　認知症患者において，補聴器装用が介護者の負担を軽減する可能性が報告されている[11]．この報告ではコントロールはないが，認知機能は補聴器装用前と比較して有意に低下していた．また，難聴高齢者における補聴器装用前後での認知機能を評価した報告は，アメリカ，オランダ，トルコ，ブラジルからある．Mulrowらは194人の退役軍人を対象に，補聴器装用群と非装用群に分けたランダム化比較試験を行った[12]．装用4カ月後のShort Portable Mental Status Questionare(SPMSQ)は，装用群で有意な改善を認めた．Van Hoorenらは難聴高齢者102人に対して補聴器の非ランダム化試験を行い，装用12カ月後のStroop Colour-Word Test（SC-WT）やConcept Shifting Task(CST)といった認知機能検査に有意差を認めなかったとしている[13]．Acarら[14]およびMagalhãesら[15]はそれぞれ3カ月後，7カ月後のMMSEが有意に改善したと報告している．ただし，どちらも50人以下の小規模な症例蓄積研究である．

個々の症例では，幻聴，認知機能低下でレビー小体型認知症が疑われた高度難聴高齢者に対して補聴器装用を開始したところ，幻聴が治まり，徐々に認知機能も改善した症例や，アルツハイマー型認知症のある高度難聴者に補聴器装用指導を定期的に行ったところ，歌を歌うようになったり，テレビに相槌を打つようになったりといった変化が認められ，認知機能も改善した症例を経験している．しかしながら，ほとんど効果の認められない患者もあり，今後の検討が必要である．

認知症患者で見逃してならないのが，耳垢栓塞である．小児，高齢者，知的障害者では耳垢栓塞のリスクが高いことが知られており，認知機能低下のある高齢者では6割に耳垢栓塞を認めたという報告もある[16]．高齢になると耳垢の排泄機能が低下するが，認知機能低下があると清潔への無関心から耳掃除をしなくなったり，誤った耳掃除の仕方でむしろ耳垢を鼓膜方向へ押し込んでしまったり，さらには耳へ異物を挿入したままにしている例もみかける．特に，耳垢の性状がねばねばしている湿性耳垢では，耳垢栓塞のリスクが高い．黄色人はかさかさした乾性耳垢が多いため，白人や黒人よりも耳垢栓塞になりにくいが，われわれの調査では，もの忘れセンター受診患者の7％に耳垢栓塞を認め，耳垢栓塞を除去することにより，聴力のみならず認知機能も改善する可能性が示唆された[17]．

おわりに

認知機能が低下すると難聴を訴えることが少なく，周りも難聴を見過ごすことが多い．耳垢栓塞による難聴であれば処置ですぐに改善するし，補聴器装用が有効な患者もある．認知症患者の診察において，外耳道チェックと聴力の把握は重要である．

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Short Communication

Moderate-Intensity Physical Activity, Cognition and APOE Genotype in Older Adults with Mild Cognitive Impairment

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Abstract

Mild Cognitive Impairment (MCI) is associated with an elevated risk of developing Alzheimer's disease (AD). The presence of the *APOE* ε4 allele is one of established risk factors for AD, and physical activity has been reported to be effective for preventing cognitive decline in older people. The aim of this cross-sectional study was to investigate the association between moderate levels of physical activity and cognitive function among older subjects who had MCI and were *APOE* ε4 carriers or non-carriers. Comprehensive neurocognitive assessments were conducted for 317 participants with MCI aged 65 or more (mean age 71.3 years, 54.6% women), and their physical activity levels were assessed using portable triaxial accelerometers. The activity group included participants who performed weekly physical activity for ≥150 minutes at an intensity of ≥3 metabolic equivalents. Among subjects with MCI who were *APOE* ε4 carriers, compared to the inactive group, the active group exhibited significantly better visual memory performance-delayed retention (age-adjusted $P = .039$), Rey Auditory Verbal Learning Test-immediate score (age-adjusted $P = .024$), and verbal fluency test performance (age-adjusted $P = .022$). In contrast, among MCI subjects who were *APOE* ε4 non-carriers, the active and inactive groups showed no statistical difference in performance on cognitive function tests. These results indicate that recommended moderate physical activity might have a greater impact on cognitive function in older adults with MCI who are *APOE* ε4 carriers than in those who are *APOE* ε4 non-carriers.

ABBREVIATIONS

MCI: Mild Cognitive Impairment; AD: Alzheimer's disease; APOE: Apolipoprotein E; METs: Metabolic Equivalents; WMS-R: Wechsler Memory Scale-Revised; RAVLT: Rey Auditory Verbal Learning Test; VFT: Verbal Fluency Test

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia and causes an immense burden on patients, caregivers, and society. The presence of the *APOE* ε4 allele is one of the few established risk factors for AD [1]. In addition to the *APOE* ε4 allele, which is one of the non-modifiable risk factor for dementia, several potential modifiable risk factors have been reported. For instance, physical activity is a modifiable risk factor for healthy aging and plays a role in AD prevention [2].

Recent systematic reviews and meta-analyses have suggested a significant and consistent effect of physical activity in preventing cognitive decline among older adults without dementia [3,4]. Although these previous findings are encouraging, majority of these studies were conducted on healthy subjects or did not define the cognitive status of subjects, such as whether they had Mild Cognitive Impairment (MCI). MCI is a heterogeneous condition associated with the transitional phase between normal cognitive aging and dementia, and is associated with an elevated risk of developing AD [5].

Another key limitation of most previous studies is that they examined the effects of physical activity on cognition utilizing self-reported questionnaires. Recent studies have used accelerometers in an attempt to assess the pattern of physical activity more accurately [6-8], and these studies have shown

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a positive relationship between habitual physical activity and cognitive functioning in healthy older adults [7]. In addition, to promote and maintain good health in older adults, moderate-intensity physical activity for a minimum of 30 min on 5 days each week is recommended [9]. A better understanding of the influences of moderate-intensity physical activity and the *APOE* genotype on cognitive function may help promote lifestyle changes to decrease the risk of conversion of MCI to AD.

Thus, the aim of this cross-sectional study was to investigate the association between moderate levels of physical activity and cognitive function among older subjects having MCI who were *APOE* ε4 carriers or non-carriers.

MATERIALS AND METHODS

In total, 317 participants with MCI who were aged 65 and more (mean age 71.3 years, 54.6% women) were examined. All participants met the following criteria for MCI [10,11]: having subjective memory complaints, exhibiting intact general cognitive functioning [scoring ≥ 24/30 on the Mini-Mental State Examination [12]], exhibiting age-adjusted objective cognitive impairment, not using Japanese long-term care insurance or not showing evidence of functional dependency (no need for supervision or external help to perform activities of daily living), and not fulfilling the clinical criteria for dementia. We assessed for age-adjusted objective cognitive impairment (age-adjusted score of ≤1.5 SDs below average) using the National Center for Geriatrics and Gerontology-Functional Assessment Tool [13,14]. We excluded participants who were diagnosed with dementia, had a history of major psychiatric illness (e.g., schizophrenia or bipolar disorder), other serious neurological or musculoskeletal diagnoses, or clinical depression, in this study. Informed consent was obtained from all participants prior to their inclusion in the study, and the Ethics Committee of the National Center for Gerontology and Geriatrics approved the study protocol.

All participants completed neurocognitive assessments and measurements of physical activity. The participants performed the neurocognitive assessments including tests of visual and verbal memory, working memory, language, attention/executive function, and processing speed domains under the supervision of licensed and well-trained clinical speech therapists. The Wechsler Memory Scale-Revised (*WMS-R) Visual* Reproduction subtest [15] was used to assess participants' visual memory. This test measures immediate (Visual Reproduction-I) and delayed retention (Visual Reproduction-II) of geometric figures. The Rey Auditory Verbal Learning Test (RAVLT) [16] performance was used to assess participants' verbal memory. We analyzed subjects' performance immediate (fifth trial score of five times free recall) and 30-min delayed recall from the RAVLT. We used the verbal forward and backward digit tests to assess working memory [17]. The difference between the digits forward test score and the digits backward test score was used as an index of working memory. To test language functions, we used the Verbal Fluency Test (VFT) [18]. In the VFT, participants were asked to name as many animals as possible in 1 minute. Attention and executive function were assessed using the tablet version of the trail making test [13]. This test consists of two parts (A and B) and we recorded the time (in seconds) taken to complete each task, within a maximum period of 90 s. A shorter time to complete the tasks represents better performance. We used the tablet version of the symbol digit substitution test to assess processing speed [13]. In this task, 9 pairs of numbers and symbols were presented at the top of the display. A target symbol was presented at the center of the display. Subjects then chose a number corresponding to a target symbol at the bottom of the display as rapidly as possible. The score was the number of correct numbers chosen within 90 s.

Physical activity levels were monitored using portable triaxial accelerometers (modified HJA-350IT, Active style Pro, Omron Healthcare Co., Ltd.) [19]. Participants were instructed to wear the accelerometer on an elastic band on their hip at all times for 2 weeks. The output was expressed in metabolic equivalents (METs, multiples of resting metabolic rate) [19,20]. Participants who did not record 75% or more of each daytime activity, daytime being from 6 A.M. to 6 P.M., for 7 days during the 2-week period were excluded from the study. During the 2-week period, the displays of accelerometers were disabled to prevent the participants from checking their counts and values, in order to ensure that they were pursuing their normal daily activity. The activity group included participants who satisfied the criterion of weekly physical activity for ≥150 minutes at an intensity of ≥3 METs (moderate-intensity physical activity) based on the recommendation of the American College of Sports Medicine and the American Heart Association [9].

All the data entry and analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 19.0 (SPSS Inc. Chicago, IL, USA). The significance threshold was 0.05. Means, standard deviations, and proportions were calculated. Student's *t*-tests and chi-square tests were used to compare characteristics between the active (weekly moderate-intensity physical activity for ≥150 min) and inactive (weekly moderate-intensity physical activity for <150 min) groups among both *APOE* ε4 carrier and non-carrier participants. We used analysis of covariance (ANCOVA) adjusted for age to compare group differences in performance of neurocognitive tests among the participants carrying and not carrying *APOE* ε4.

RESULTS AND DISCUSSION

Of the 317 participants, 67 (21.1%) were determined to be *APOE* ε4 carriers (ε2/ε4, ε3/ε4, ε4/ε4 genotypes). In both *APOE* ε4 carriers and non-carriers, the active and inactive groups showed no statistically significant differences in characteristics such as age, sex, education, body mass index, diagnosis, functional capacity, and blood markers (Table 1). Age-adjusted ANCOVA showed a significantly higher WMS-R-Visual recall II score (age-adjusted $P = .039$), RAVLT-immediate score (age-adjusted $P = .024$), and VFT performance (age-adjusted $P = .022$) in the active group than in the inactive group among *APOE* ε4 carriers with MCI. In contrast, among *APOE* ε4 non-carriers with MCI, the active and inactive groups showed no statistical differences in performance on neurocognitive tests (Table 2).

This study indicated that recommended moderate-intensity physical activity (≥150 minutes of weekly physical activity at an intensity ≥3 METs) affects cognitive function in older adults with MCI who were *APOE* ε4 carriers, but not in those who were *APOE* ε4 non-carriers.

Table 1: Participant characteristics.

	APOE ε4 carriers (n = 67)			*APOE* ε4 non-carriers (n = 250)		
	Active (n = 27)	Inactive (n = 40)	*P* value	Active (n = 109)	Inactive (n = 141)	*P* value
Age, years	70.4±3.1	72.4±5.4	0.08	70.7±4.5	71.6±4.3	0.084
Women, No. (%)	15 (55.6)	27 (67.5)	0.321[a]	58 (53.2)	73 (51.8)	0.821[a]
Education, years	11.5±2.6	11.4±3.0	0.937	10.8±2.1	10.8±2.1	0.842
Body mass index, kg/m^2	22.8±2.6	22.7±2.4	0.861	23.4±2.5	23.8±3.2	0.258
Diagnosis, No. (%)						
Hypertension	14 (51.9)	15 (37.5)	0.245[a]	39 (35.8)	55 (39.8)	0.571[a]
Diabetes mellitus	4 (14.8)	5 (12.5)	0.785[a]	11 (10.1)	17 (12.1)	0.611[a]
Heart disease	3 (11.1)	5 (12.5)	0.863[a]	9 (8.3)	21 (14.9)	0.109[a]
Osteoporosis	4 (14.8)	6 (15.0)	0.983[a]	8 (7.3)	15 (10.6)	0.371[a]
Functional capacity[†], score	12.5±0.9	12.5±0.8	0.933	12.4±1.1	12.4±1.1	0.838
Blood markers						
Albumin, g/ml	4.4±0.3	4.4±0.3	0.854	4.4±0.3	4.3±0.3	0.142
Total cholesterol, mg/dl	217.3±44.4	209.3±37.9	0.434	208.1±30.7	202.1±31.5	0.135
HbA1c, %	5.4±0.6	5.6±0.8	0.253	5.6±0.6	5.6±0.8	0.861

Note: Values are mean ± SD and numbers (proportion) for sex, APOE ε4, and diagnosis. *P*-value are based on t-test or chi-square ([a]). [†]The Tokyo Metropolitan Institute of Gerontology Index.

Table 2: Comparison of cognitive tests between active and inactive groups of *APOE* ε4 carriers and non-carriers.

	APOE ε4 carriers (n = 67)			*APOE* ε4 non-carriers (n = 250)		
	Active (n = 27)	Inactive (n = 40)	Age-adjusted *P* value	Active (n = 109)	Inactive (n = 141)	Age-adjusted P value
Visual memory						
WMS-R-Visual recall I, score	31.8 ± 6.8	27.7 ± 7.0	0.077	30.9 ± 5.7	30.8 ± 5.7	0.716
WMS-R-Visual recall II, score	25.0 ± 7.8	19.2 ± 9.0	0.039	22.5 ± 8.5	23.2 ± 8.7	0.248
Verbal memory						
RAVLT-immediate, score	10.9 ± 2.2	9.1 ± 2.6	0.024	9.7 ± 2.6	9.8 ± 2.5	0.556
RAVLT-delay, score	8.2 ± 2.7	6.5 ± 3.4	0.135	7.5 ± 3.3	7.6 ± 3.4	0.746
Working memory						
Digit Span: Forward–Backward, score	2.6 ± 1.6	3.1 ± 1.8	0.270	2.3 ± 1.9	2.6 ± 1.9	0.358
Language						
Verbal fluency test, score	17.6 ± 3.4	14.8 ± 4.7	0.022	15.7 ± 3.9	15.7 ± 4.0	0.715
Attention/Executive function						
Tablet TMT-A, sec	19.9 ± 4.9	21.5 ± 6.0	0.640	21.6 ± 7.6	21.8 ± 5.9	0.881
Tablet TMT-B, sec	36.7±12.1	44.2±18.1	0.288	41.3±15.9	44.1±15.8	0.446
Processing speed						
Tablet SDST, score	42.3 ± 6.9	38.1 ± 7.0	0.081	40.7 ± 6.9	38.5 ± 7.1	0.065

Abbreviations: *WMS-R:* Wechsler Memory Scale-Revised; RAVLT: Rey Auditory Verbal Learning Test; TMT: Trail Making Test; SDST: Symbol Digit Substitution Test

A previous longitudinal study indicated an association between physical inactivity in middle age and the risk of AD, especially among *APOE* ε4 carriers. Thus, *APOE* ε4 carriers might be more vulnerable to environmental factors, such as physical inactivity, dietary fat intake, consumption of alcohol, and smoking [21]. In contrast, in a previous prospective cohort study of community-dwelling older adults, an inverse association between physical activity and dementia risk was found for *APOE* ε4 non-carriers but not for *APOE* ε4 carriers [22]. Although both the presence of the *APOE* ε4 allele and low levels of physical