資　料　２
櫻井構成員提供資料
H30.5.31
食事摂取基準策定検討会

認知症と栄養

国立長寿医療研究センター　もの忘れセンター
櫻井　孝

日本人の食事摂取基準（2015年版）

認知機能低下及び認知症と栄養との関連

- 栄養素と認知機能低下・認知症との関係には十分な証拠がない
- ホモシステイン（Hcy)、葉酸、ビタミンB6、ビタミンB12：アルツハイマー型認知症、血管性認知症ではHcyが高い、Hcy高値は認知症のリスク。Hcy高値の高齢者に葉酸⇒認知機能は良好、B6, B12の効果はなし。
- N-3系脂肪酸：認知機能への影響は、いまだ不明
- ビタミンD：アルツハイマー型認知症では、25（OH)Dが低値、25（OH)D低値は認知機能低下と関連する。RCTでは関連なし。
- 抗酸化と関連するビタミン（ビタミンE、ビタミンC、ベータカロテン）：結論に至らない（今のところ否定的）

認知症疾患診療ガイドライン2017

CQ　認知症と関連する食事因子はあるか

認知症と食事、栄養に関する多くの報告がある。炭水化物を主とする高カロリー食や低蛋白症および低脂肪食は、軽度認知障害や認知症のリスクを高める傾向にある。
個々の栄養素では確定的な結果は得られていない。

エビデンスレベル２C

概要

- 多くは観察研究、特定の食物・栄養素、食事パターンの効果については確定していない。RCTでも確定なし。
- 炭水化物を主とする高カロリー食はMCIや認知症のリスクを高めるかもしれない
- 低蛋白食や低脂肪食もリスクを高める傾向
- 大豆、大豆食品、野菜、藻類、牛乳・乳製品の摂取は認知症のリスクを軽減（久山町研究）
- ビタミンEを多く含む食物はリスクを軽減、ビタミンC、ベータカロチン、フラボノイドは関連なし（Rotterdam研究）
- 魚およびomega-3脂肪酸は関連しない
- ADでは、葉酸、ビタミンA、B12、C,Eは有意に低下。ビタミンD、亜鉛、銅、鉄は差がない。
- カフェイン、コーヒー、茶については、総じて摂取者のほうが認知障害は緩やか

認知症疾患診療ガイドライン2017

CQ　適度な飲酒は認知機能の低下や認知症の予防に有効か

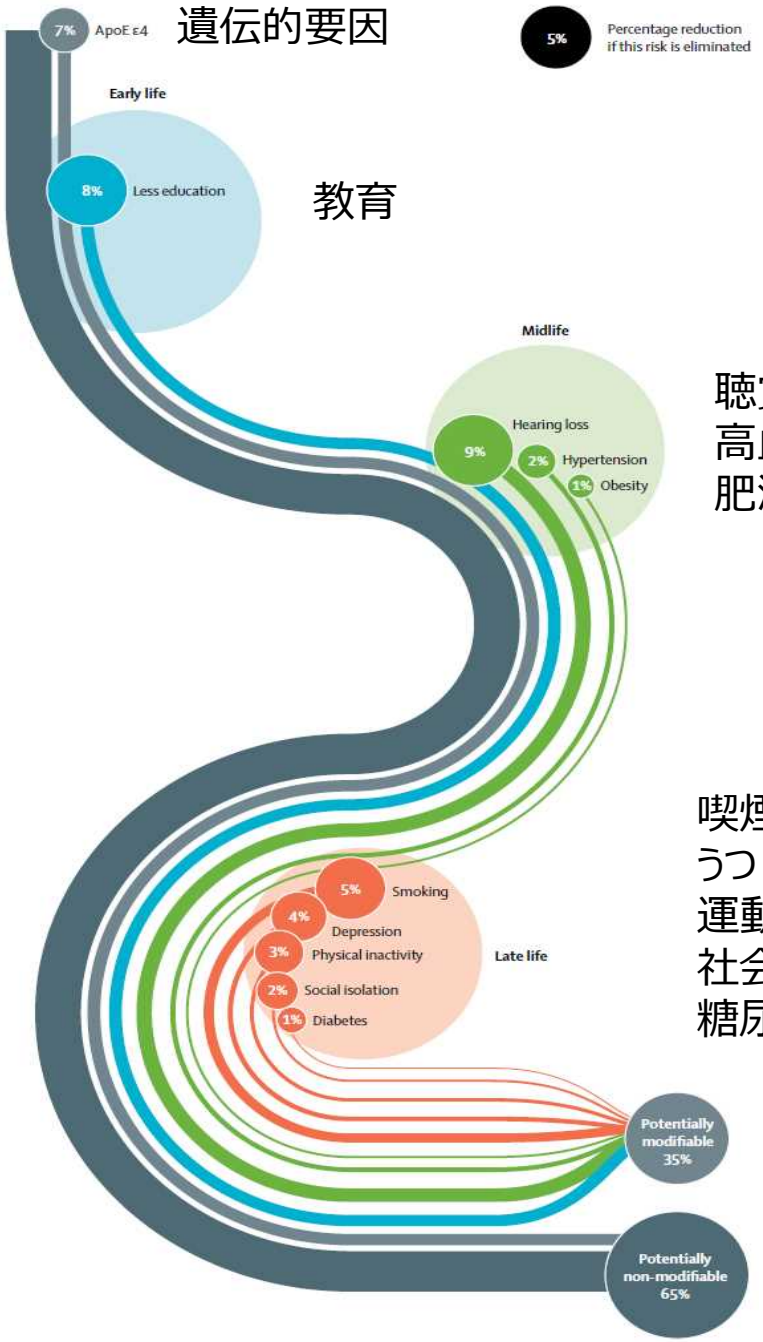
適度の飲酒が認知症の予防的効果があるという報告がある。“適度な飲酒量”には人種さ、個人差の違いがあるので注意が必要である。飲酒ができない人には勧めるべきではない。

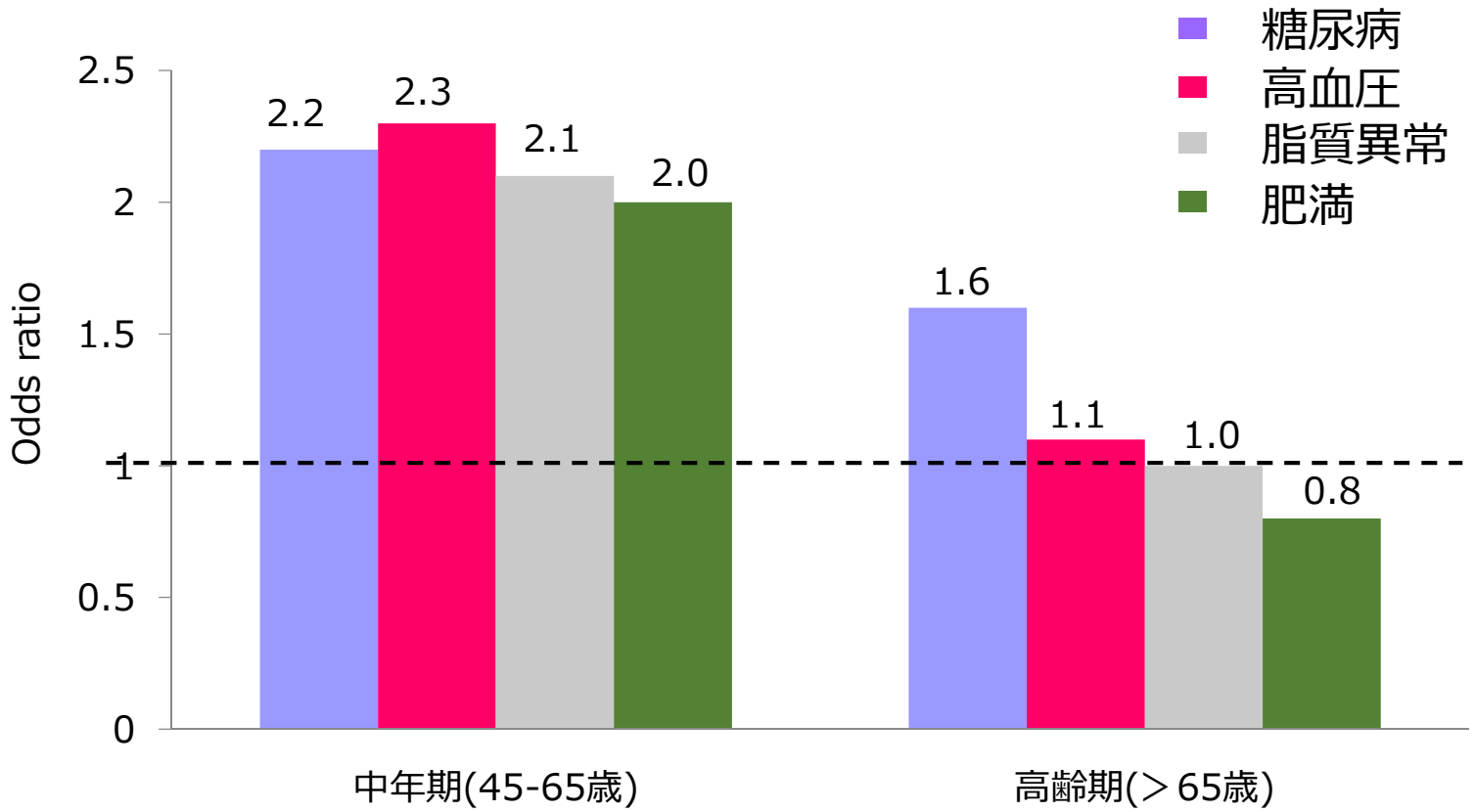
エビデンスレベル２C

概要

- 低・適度の飲酒では認知機能低下ないし認知症のオッズ比が低下する。大量の飲酒ではMCIから認知症への移行リスクが高まる
- 赤ワインには認知機能低下の予防的効果がある。ビール、白ワイン、酒精強化ワイン、スピリッツにはその効果がない
- 高齢者の習慣的飲酒はVaDの発症を抑制する
- 飲酒と認知機能の関連についてはRCTは倫理的制約のためそぐわない

認知症の危険因子



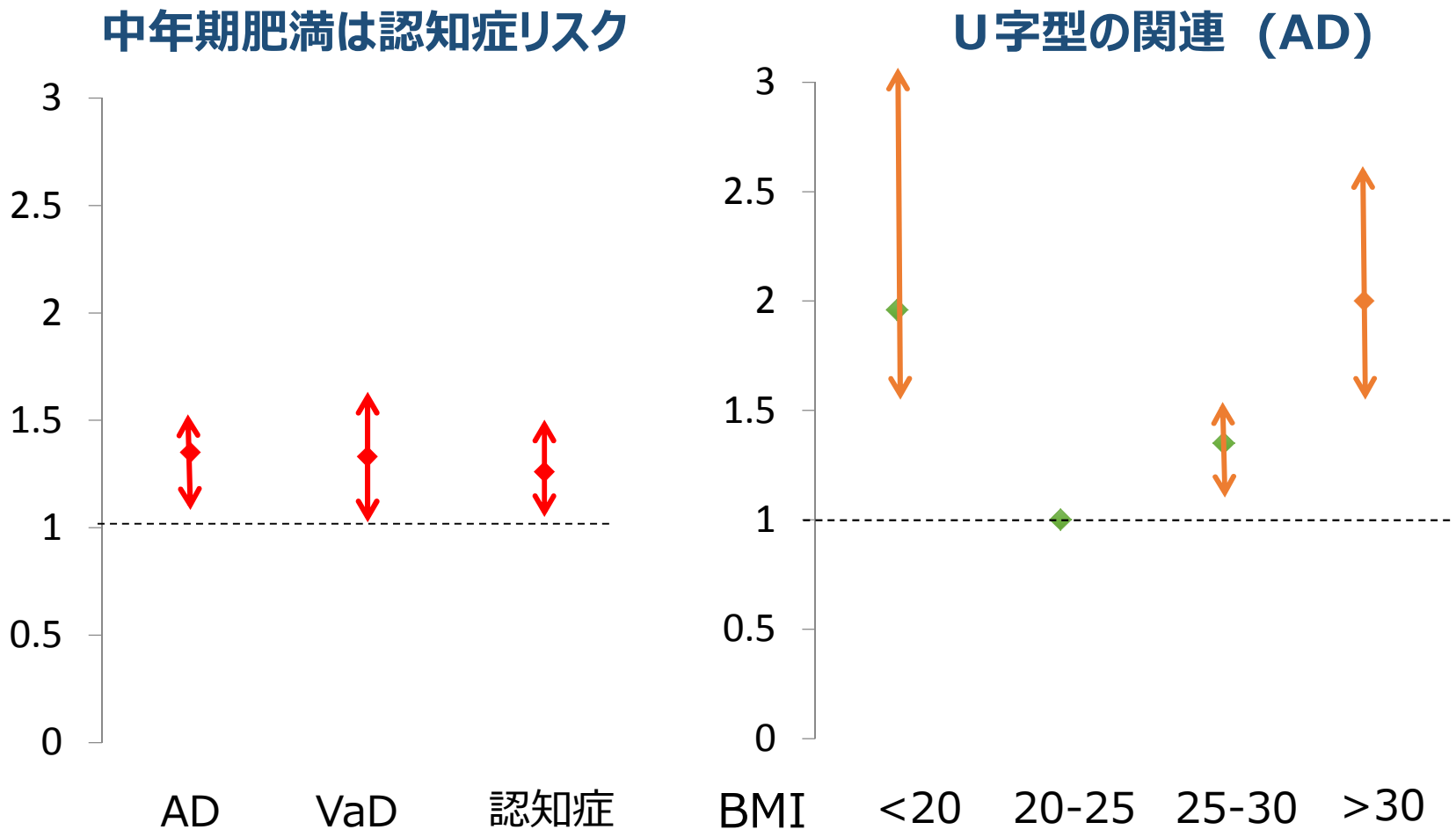


Eur J Pharmaco 2008; 585: 97-108

www.thelancet.com Published online July 20, 2017
http://dx.doi.org/10.1016/S0140-6736(17)31363-6

中年期の肥満は認知症リスク

メタ解析



Anstey et al. 2011

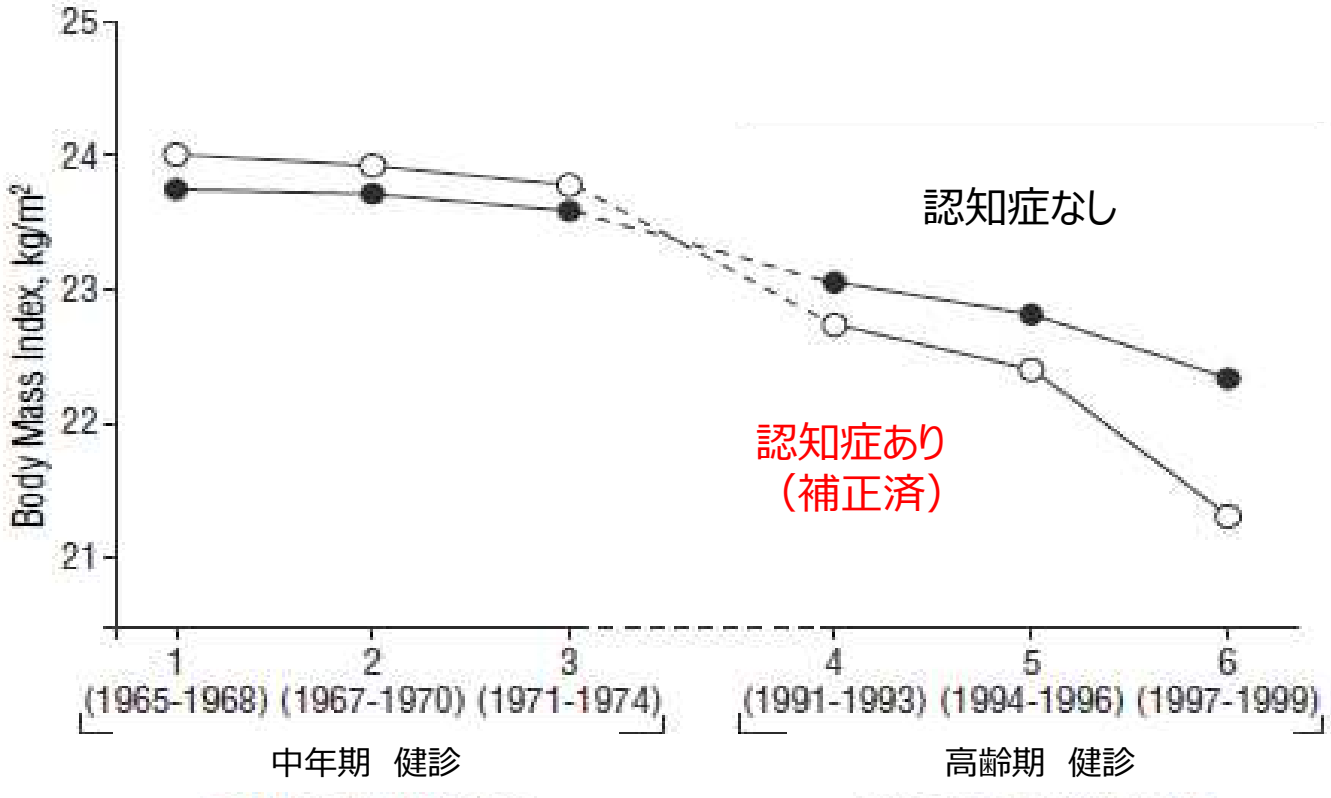
高齢期の肥満は認知症を抑制

TABLE 1 Overview of results of meta-analysis comparing different ranges of BMI with normal weight

Age	Indication	BMI (vs. 20-24,99)	Pooled RR	95% CI
		<20	1.39	0.66, 2.91
		25-29,99	1.44	0.96, 2.15
	AD	>30	1.98	1.24, 3.14
		25-29,99	1.34	1.08, 1.66
40-59	Dementia	>30	1.91	1.4, 2.62
		>30	0.8	0.67, 0.95
60+	Dementia	>25	0.79	0.69, 0.9

Loef et al. 2013

認知症発症10年前から体重は減少する



→体重減少の原因は明らかになっていない
（筋肉量の低下、摂取/吸収の低下？　消費の亢進？）

Stewart et al. Arch Neurol. 2005

BMI低下とアルツハイマー型認知症

Exposure	Model 1		Model 2		Model 3	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Midlife BMI	1.05 (0.98, 1.12)	0.17	1.03 (0.96, 1.11)	0.36	1.04 (0.96, 1.12)	0.36
Late-life BMI	0.92 (0.85, 1.00)	0.050	0.90 (0.82, 0.99)	0.030	0.89 (0.81, 0.98)	0.022
Decrease in BMI*	1.21 (1.11, 1.33)	<0.001	1.19 (1.08, 1.32)	<0.001	1.20 (1.09, 1.33)	<0.001
Midlife BMI category						
<25 kg/m^2	1.00 (reference)		1.00 (reference)		1.00 (reference)	
25–30 kg/m^2	0.98 (0.53, 1.81)	0.94	0.92 (0.49, 1.73)	0.80	0.89 (0.47, 1.68)	0.72
>30 kg/m^2	1.87 (0.95, 3.68)	0.07	1.57 (0.78, 3.17)	0.21	1.57 (0.75, 3.29)	0.23
Late-life BMI category						
<25 kg/m^2	1.00 (reference)		1.00 (reference)		1.00 (reference)	
25–30 kg/m^2	0.77 (0.39, 1.52)	0.46	0.61 (0.3, 1.24)	0.17	0.57 (0.27, 1.19)	0.13
>30 kg/m^2	0.52 (0.22, 1.25)	0.15	0.45 (0.17, 1.14)	0.09	0.40 (0.15, 1.08)	0.07

Model 1 is adjusted for age, gender, *APOEε4*-status and region of residence. Model 2 is as Model 1 plus additional adjustment for smoking status, education and income. Model 3 is as Model 2 plus additional adjustment for diabetes, cerebro/cardiovascular disease and systolic blood pressure and serum total cholesterol. *Absolute change in BMI, calculated as BMI in midlife-BMI in late-life.

Tolppanena, Kivipelto et al. JAD 38:201, 2014

高齢期のBMI低下と認知症

- 高齢男性4181人の8年間追跡研究
  BMI変化がなく維持されている状態がもっとも認知症リスクが低い
  Power et al. Int Psychogeriatr 2013: 35:467

- Kame project:日系アメリカ人1836人の追跡研究
  過体重と肥満の人で、BMIが急速に減現象することが認知症のリスク
  Hughes et al. Neurology 2009:72:1741

- Kungsholmen project: 3年間の追跡研究
  BMIの10%以上の減少が認知症のリスク
  Driscoll et al. Obesity 2011;19:1595

Cochrane review

Title	Studies	Intervention	subjects	Results	conclusion
Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people, 2008	8 RCTs	folic acid, with or without vitamin B12	elderly healthy or demented people	healthy elderly with high homocysteine levels, folic acid showed benefit	cholinesterase inhibitors with folic acid with improvement
Thiamine for Alzheimer's disease, 2010	3	Vit B1	AD	not significant	No conclusions
Omega-3 fatty acids for the treatment of dementia, 2016		Omega-3 polyunsaturated fatty acids (omega-3 PUFAs)	mild to moderate AD	no evidence of a benefit from omega-3 PUFAs on cognitive function	no convincing evidence
L-carnitine for cognitive enhancement in people without cognitive impairment, 2017	2 RCTs	L-carnitine	people without cognitive impairment	no effect of L-carnitine on cognition	unable to draw any conclusions
Vitamin E for Alzheimer's dementia and MCI, 2017	4 trials	vitamin E	MCI and dementia due to AD	no evidence of effect of vitamin E on cognition	no evidence

未読：Carbohydrates for improving the cognitive performance of independent-living older adults with normal cognition or mild cognitive impairment

Nutritional trials (1)

PubMed検索：“Nutrition” “dementia”, clinical trial & >65 y.o. （2013-2018）126件ヒット⇒絞り込み 19件

Title	Design	Intervention	subjects	Results
24-month intervention with a specific multi-nutrient in people with prodromal Alzheimer's disease (LipiDiDiet), 2017	RCT	specific multi-nutrient	AD	no significant effect
Cognitive Changes with Omega-3 Polyunsaturated Fatty Acids in Non-Demented Older Adults with Low Omega-3 Index, 2017		omega 3 polyunsaturated fatty acid (n-3 PUFA)	Non-Demented Old Adults	less decline on the Controlled Oral Word Association Test
A high-glycemic diet is associated with cerebral amyloid burden in cognitively normal older adults, 2017	cross-sectional	A high-glycemic diet	cognitively normal OLD	greater cerebral amyloid burden
Efficacy and Blood Plasmalogen Changes by Oral Administration of Plasmalogen in Patients with Mild Alzheimer's Disease and Mild Cognitive Impairment: A Multicenter, Randomized, Double-blind, Placebo-controlled Trial, 2017	RCT	Plasmalogen	Mild AD	Pls may improve cognitive functions
Folic Acid Supplementation Mitigates Alzheimer's Disease by Reducing Inflammation: A Randomized Controlled Trial.	RCT	Folic Acid	AD	MMSE was slightly increased

Nutritional trials (2)

Title	Design	Intervention	subjects	Results
Maintenance of Cognitive Performance and Mood for Individuals with Alzheimer's Disease Following Consumption of a Nutraceutical Formulation: A One-Year, Open-Label Study, 2016		folate, vit E, B12, S-adenosyl methioinine, N-acetyl cysteine, acetyl-L-carnitine	Postmeno pausal Women	maintained cognitive performance and BPSD
Impact of Omega-3 Fatty Acid Supplementation on Memory Functions in Healthy Older Adults, 2016		Omega-3 Fatty Acid	Healthy OLD	positive effects on memory functions
Omega-3 Fatty Acid Status Enhances the Prevention of Cognitive Decline by B Vitamins in Mild Cognitive Impairment. 2016		B vitamins (FA, vit B6, B12) + omega-3	MCI	Better verbal delayed recall, global cognition
Consumption of anthocyanin-rich cherry juice for 12 weeks improves memory and cognition in older adults with mild-to-moderate dementia, 2015		Dietary flavonoids, including anthocyanins	mild-to-moderate dementia	improve specific cognitive outcomes
Plasma Fatty Acid Profiles in Relation to Cognition and Gender in Alzheimer's Disease Patients During Oral Omega-3 Fatty Acid Supplementation: The OmegAD Study, 2015		Oral Omega-3	AD	preservation of cognition

Nutritional trials (3)

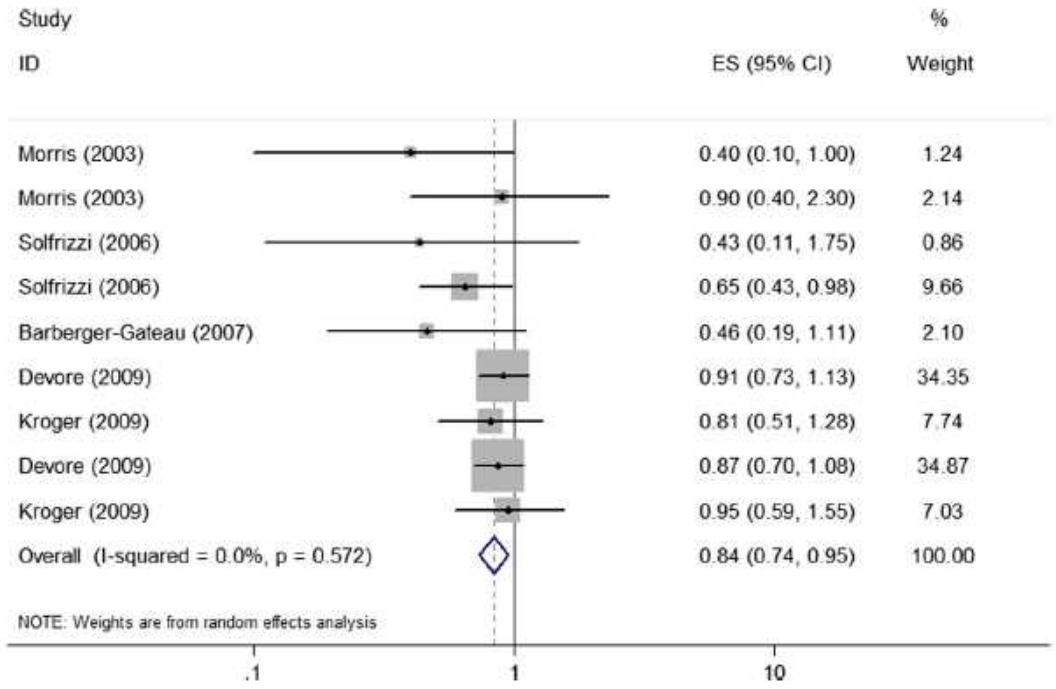
Title	Design	Intervention	subjects	Results
A Nutritional Formulation for Cognitive Performance in Mild Cognitive Impairment: A Placebo-Controlled Trial with an Open-Label Extension, 2015	RCT	folate, vit E, B12, S-adenosyl methioinine, N-acetyl cysteine, acetyl-L-carnitine		improved in the Dementia Rating Scale
Mediterranean Diet and Age-Related Cognitive Decline: A Randomized Clinical Trial, 2015		Mediterranean diet		improved cognitive function
Brain atrophy in cognitively impaired elderly: the importance of long-chain ω-3 fatty acids and B vitamin status in a randomized controlled trial, 2015	RCT	high-dose B vitamin (folic acid, vit B6, vit B12)	cognitively impaired elderly	beneficial effect of B vitamin on brain atrophy
A Phase II Randomized Clinical Trial of a Nutritional Formulation for Cognition and Mood in Alzheimer's Disease, 2015	RCT	folate, vit E, B12, S-adenosyl methioinine, N-acetyl cysteine, acetyl-L-carnitine	AD	improved cognitive performance and mood/behavior
Turmeric improves post-prandial working memory in pre-diabetes independent of insulin, 2014		turmeric with white bread		increases working memory

Nutritional trials (4)

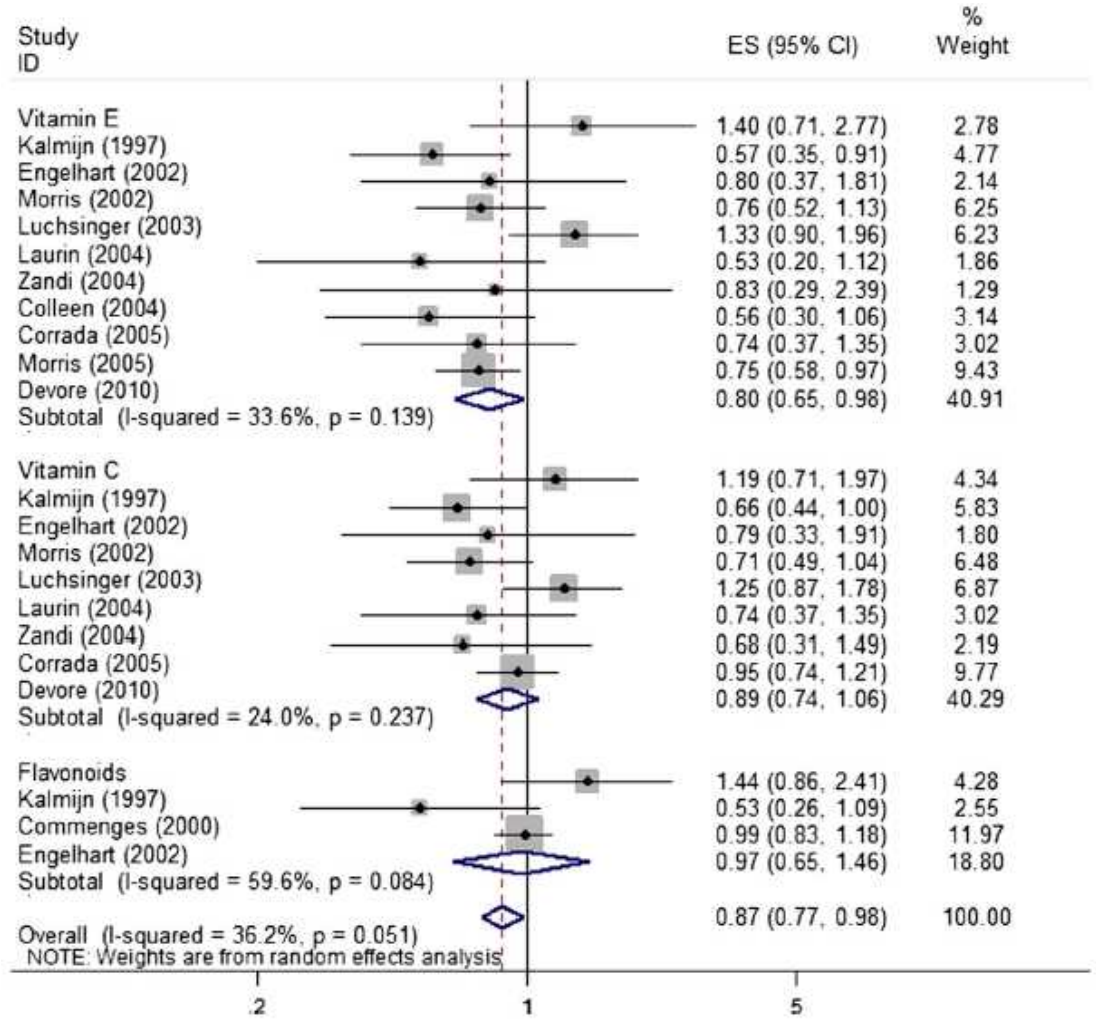
Title	Design	Intervention	subjects	Results
Tolerability and safety of Souvenaid in patients with mild Alzheimer's disease: results of multi-center, 24-week, open-label extension study, 2015		specific multi-nutrient	AD	increase in the exploratory memory
Retrospective lifetime dietary patterns predict cognitive performance in community-dwelling older Australians, 2014	observation	dietary patterns	cognitively healthy sample	Higher coffee, high-sugar, high-fat extras' predicted poorer performance, 'vegetable and non-processed' pattern better
Virgin olive oil supplementation and long-term cognition: the PREDIMED-NAVARRA randomized, trial, 2013	RCT	two MedDiets		better cognitive function
The effect of an aloe polymannose multinutrient complex on cognitive and immune functioning in Alzheimer's disease、2013	open-label trial	aloe polymannose multinutrient complex	AD	ADAS-cog cognition score significantly improved

Dietary Patterns and Risk of Dementia: a Systematic Review and Meta-Analysis of Cohort Studies

Unsaturated fatty acids and dementia



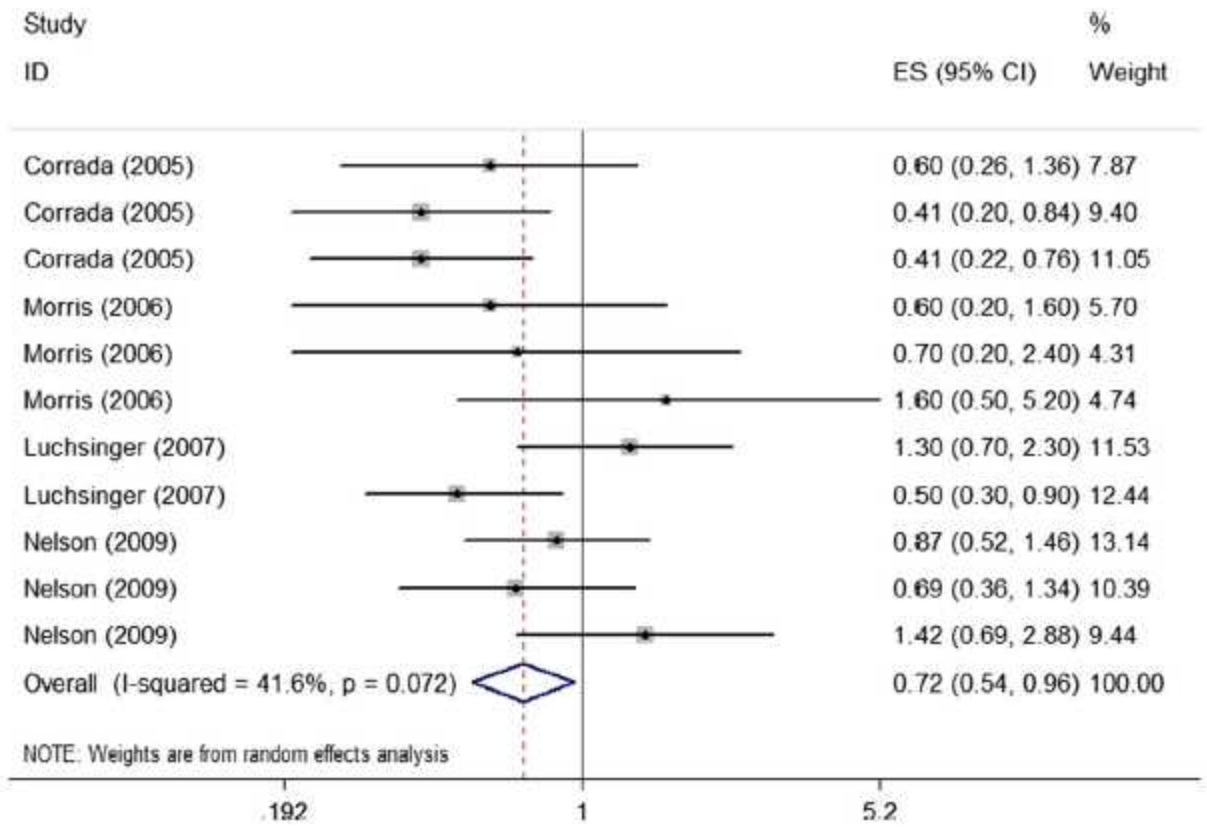
Antioxidants and dementia



Mol Neurobiol (2016) 53:6144–6154

Dietary Patterns and Risk of Dementia: a Systematic Review and Meta-Analysis of Cohort Studies

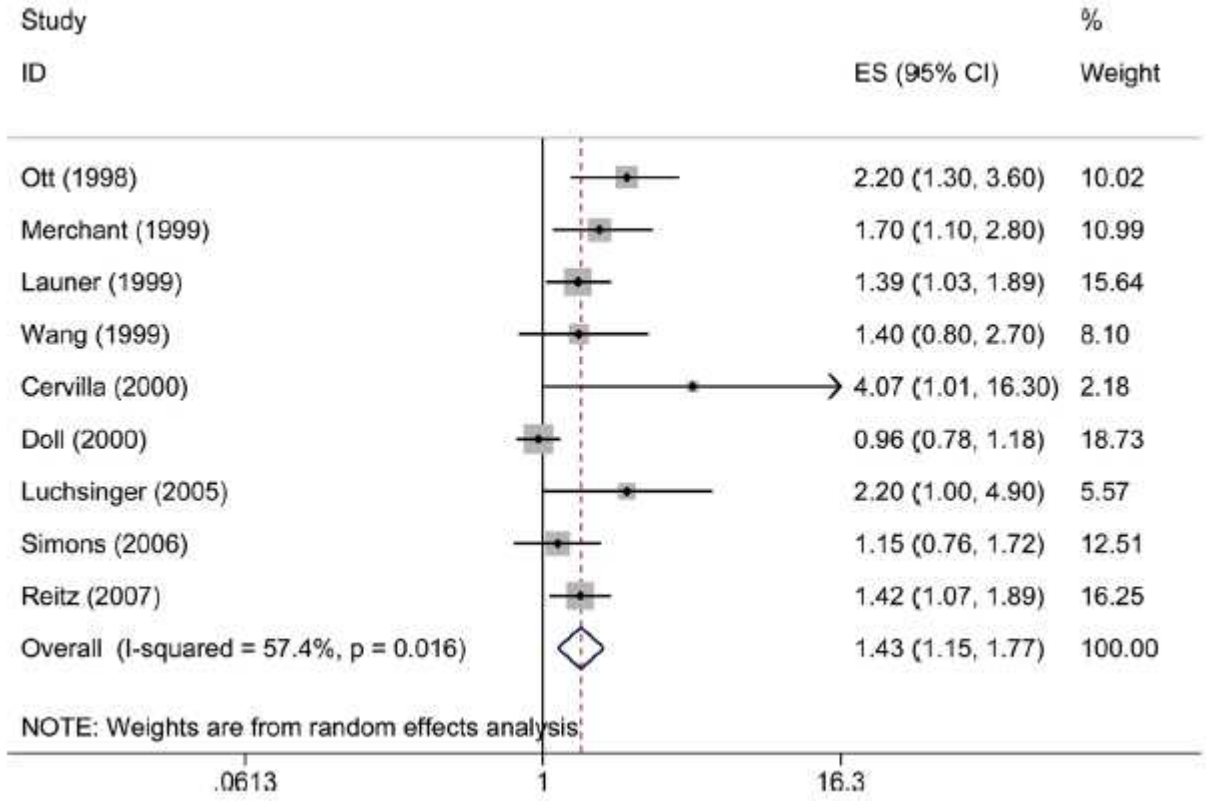
Vitamins B and dementia



Mediterranean diet

low levels of vitamin D

Smoking and dementia



Mol Neurobiol (2016) 53:6144–6154

Nutrition and Dementia: Evidence for Preventive Approaches? A systematic review of RCT

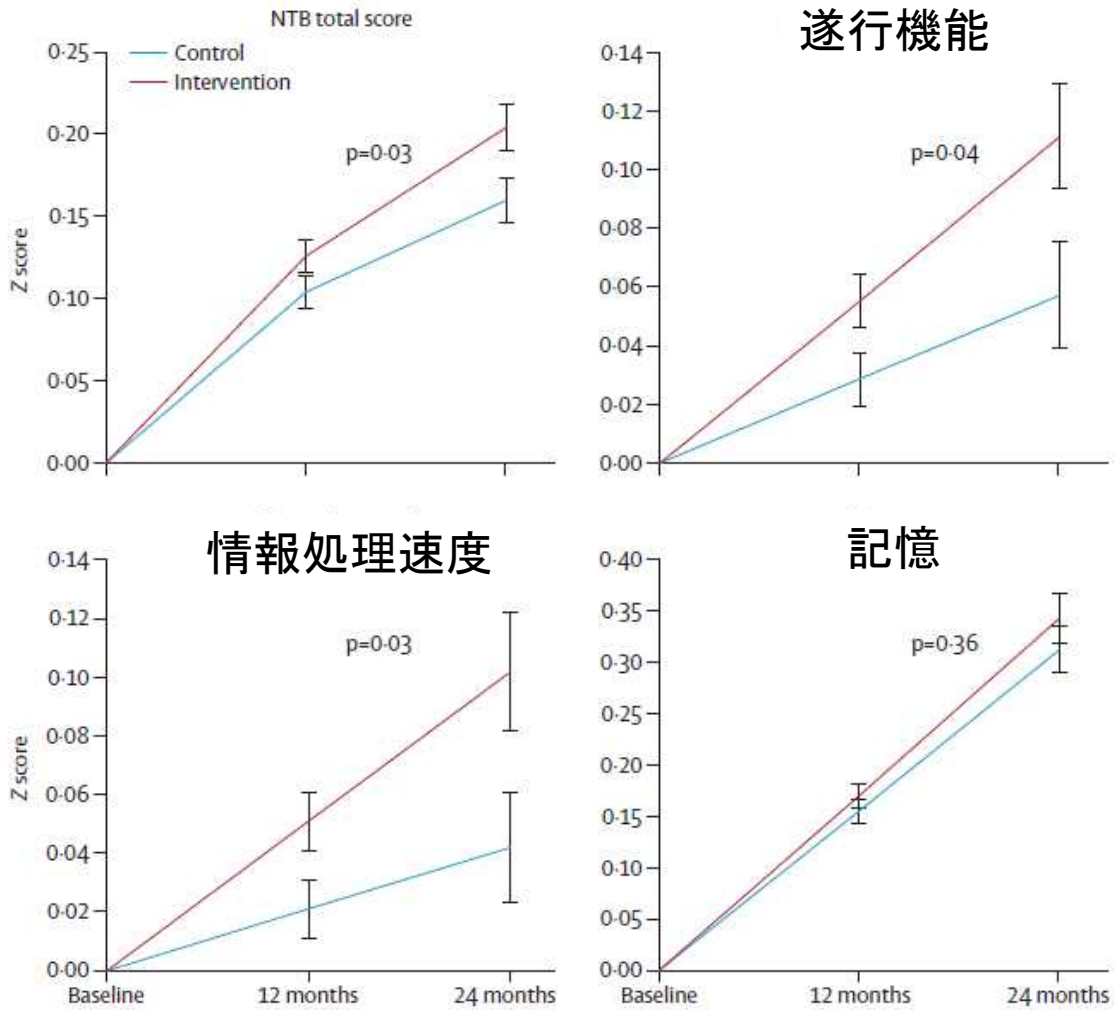
Reference	Study Sample	Intervention(s)	Duration	Cognitive Outcome(s)	Main Results
Alves et al.2013 [13]	n = 56 healthy older women (mean age 66.8 years)	(1) Creatine (20 g/day for 5 days, then 5 g/day) (2) Creatine + strength training (3) Placebo (4) Placebo + strength training	24 weeks	MMSE; Stroop test; TMT; Digit Span; Delayed recall test	Creatine supplementation did not promote any significant cognitive benefit
Bin Sayeed et al. 2013 [14]	n = 40 healthy elderly males (mean age 55.8 years)	(1) Nigella sativa Linn. Seeds (1000 mg/day) (2) Placebo	9 weeks	WMS; Digit Span; ROCF; LCT; TMT; Stroop test; Logical memory test	Significant improvement of all the cognitive scores in the Nigella sativagroup
Brickman et al. 2014 [15]	n = 37 healthy, sedentary older subjects (mean age 57.7 years)	(1) High flavanol intake (900 mg cocoa flavanols and 138 mg of (−)-epicatechin/day) + exercise (2) High flavanol intake (3) Low flavanol intake (10 mg cocoa flavanols and <2 mg (−)-epicatechin/day) + exercise (4) Low flavanol intake	12 weeks	ModBent task	A high-flavanol intervention had a significant effect on ModBent performance, independent of exercise
Kean et al.2015 [16]	n = 37 healthy older subjects (mean age 66.7 years)	(1) High flavanone drink (305 mg/day) (2) Low flavanone drink (37 mg/day)	8 weeks	CERAD; SWM; DSST; LM; Go-NoGo; Letter Fluency; Serial sevens; WMS	Significant improvement of global cognitive function in the high flavanone group
Màrtinez-Lapiscina et al. 2013 [17] *	n = 268 older subjects at high vascular risk (mean age 74.1 years)	(1) MedDiet + EVOO (1 L/w) (2) MedDiet + mixed nuts (30 g/day) (3) Control diet (advice to reduce dietary fat)	6.5 years	MMSE; CDT; WMS; FAS; RAVLT; ROCF; BNT; CDR; TMT; WAIS; Digit span Cognitive status	Significant improvement of fluency and memory tasks in MedDiet + EVOO group. Reduced MCI incidence
Màrtinez-Lapiscina et al. 2013 [18]	n = 522 older subjects at high vascular risk (mean age 67.4 years)	(1) MedDiet + EVOO (1 L/week) (2) MedDiet + mixed nuts (30 g/day) (3) Control diet (advice to reduce dietary fat)	6.5 years	MMSE; CDT	Significant improvement of cognitive performance in the two MedDiet groups
Ngandu et al. 2015 [19]	n = 1260 older subjects at high risk of cognitive decline (mean age 69.3 years)	(1) Diet (Finnish Nutrition Recommendations) + exercise + cognitive training + vascular risk monitoring (2) General health advice	2 years	Comprehensive neuropsychological test battery (CERAD)	Significant improvement of global cognition, executive functioning and processing speed
Nilsson et al. 2012 [20]	n = 40 healthy older subjects (mean age 63.3 years)	(1) Fish oil n-3 PUFA (3 g/day) (2) Placebo	5 weeks	Working memory and selective attention tests	n-3 PUFA intervention significantly improved working memory
Valls-Pedret et al. 2015 [11]	n = 447 cognitively healthy older subjects (mean age 66.9 years)	(1) MedDiet + EVOO (1 L/week) (2) MedDiet + mixed nuts (30 g/day) (3) Control diet (advice to reduce dietary fat)	4.1 years (median)	MMSE; WMS; RAVLT; WAIS; CTT; FAS; Digit span Cognitive status	Significant improvement of all the cognitive functions in the 2 MedDiet groups. No difference in MCI incidence
van de Rest et al. 2014 [21]	n = 127 frail or pre-frail older subjects (mean age 79 years)	(1) Protein (30 g/day) (2) Protein + exercise (3) Placebo (4) Placebo + exercise	24 weeks	MMSE; TMT; Stroop test; WMS; WLT; VFT; Reaction time tasks; Digit span	Exercise training in combination with protein supplementation improved information processing speed
van der Zwaluw et al. 2014 [22]	n = 65 frail or pre-frail older subjects (mean age 79 years)	(1) Protein (30 g/day) (2) Placebo	24 weeks	MMSE; TMT; Stroop test; WMS; WLT; VFT; Reaction time tasks; Digit span	Improvement of reaction time in the protein su

Multi-domain dementia prevention trials

	PreDIVA (Netherlands)	FINGER (Finland)	MAPT (France)
Sample size	3526	1200	1680
Inclusion criteria	Not demented 70-78 y	Dementia risk score >6; 60-77 y	Memory complaint or frailty, >70 y
intervention	Multi-domain (2 arms)	Multi-domain (2arms)	Multi-domain (4 arms)
Diet	tailored lifestyle advice	nutritional guidance	Omega-3 supplementation
Follow-up	6 y	2 y	3 y
Baseline MMSE	28 (27-29)	26.8	27.5
Primary outcome	dementia	Change in cognitive function	Change in cognitive function

FINGER研究

食事、運動、生活習慣病を同時に介入



食の多様性と認知機能

対象：「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）」

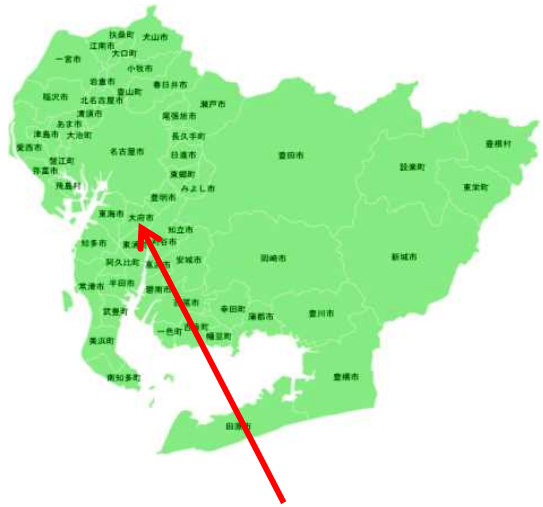
愛知県大府市および知多郡東浦町の地域住民からの無作為抽出者（観察開始時年齢40～79歳）

1st Wave	2nd	3rd	4th	5th	6th	7th
1997-	2000-	2002-	2004-	2006-	2008-	2010-2012
n=2,267	n=2,259					

第2次調査　参加者（60歳以上）　n=1,145

条件
・第2次調査の認知機能正常（MMSE28以上）
・第2次調査と、第3-7次調査に1回以上参加
・解析に必要な項目　欠損なし

解析対象者　n=570　（男性n=298、女性n=272）

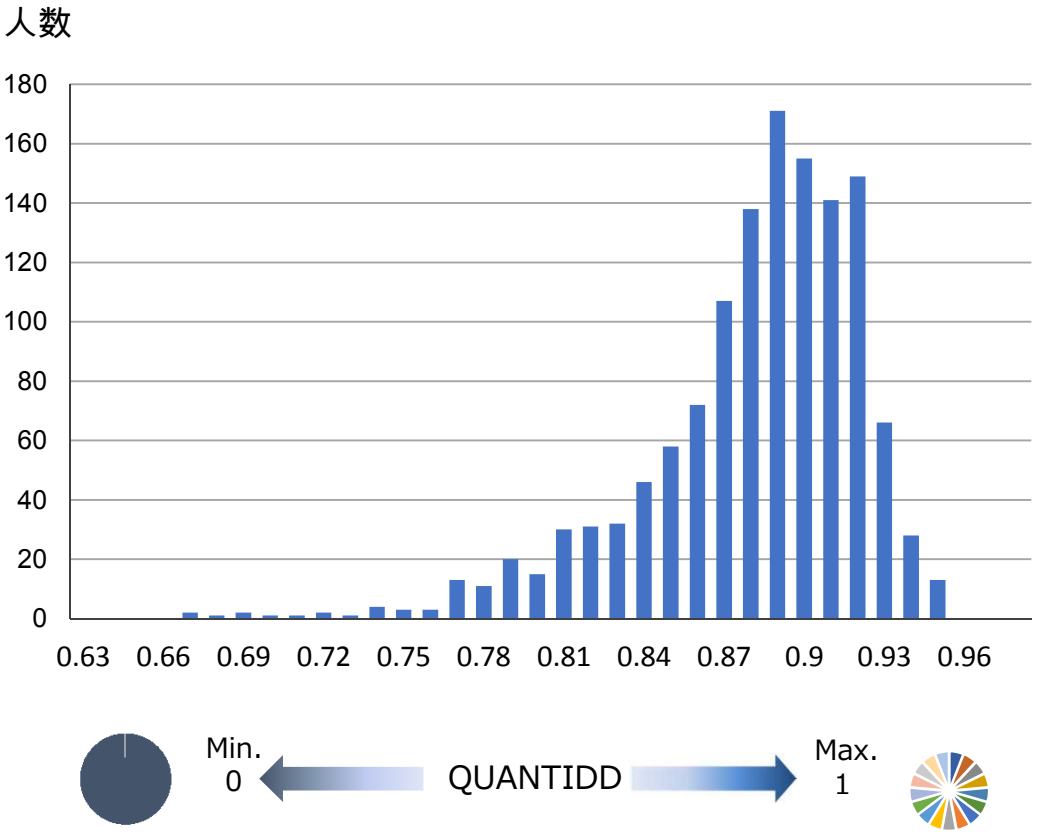


国立長寿医療研究センター

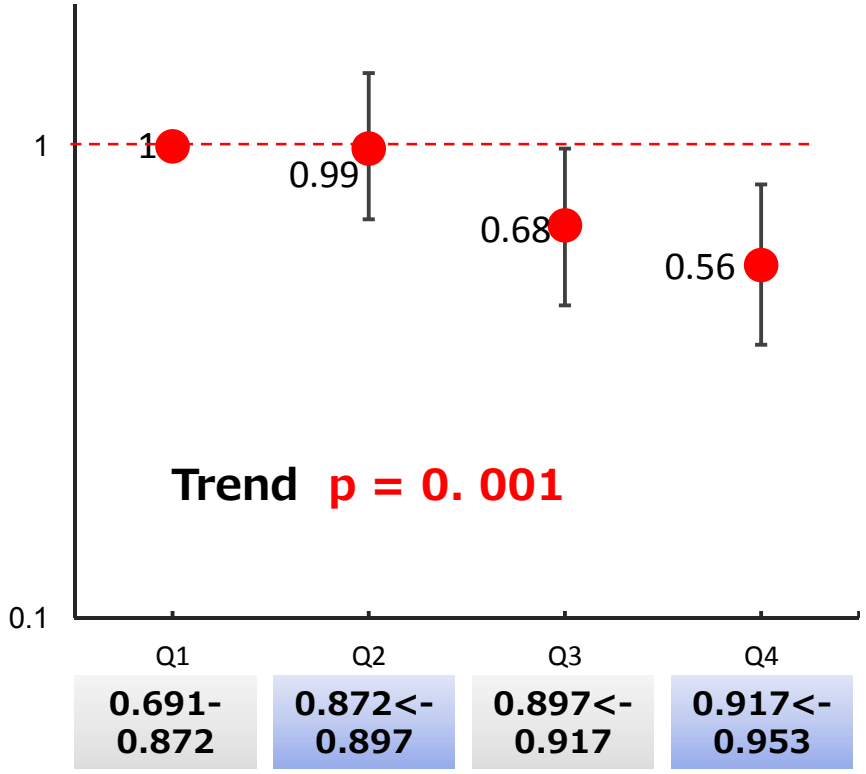
Otsuka et al. Geriatr Gerontol Int (2016)

食品摂取の多様性と認知機能

多様性スコア（QUANTIDD)の度数分布



QUANTIDD 1標準偏差(0.04) 上昇に伴う
認知機能低下リスク*



中高年期に様々な食品を摂取することは、認知機能低下リスクを抑制する

認知症と栄養：レビューのポイント

◆ 高齢者の体重減少と認知症（認知障害）は関連する。また、MCIから栄養障害は生じている

◆ 個々の栄養素では確定的な結果は得られていないが、近年、関連を示すエビデンスレベルの高い報告がみられる

◆ 関連のあり得る栄養素：
- 炭水化物を主とする高カロリー食
- 低蛋白食や低脂肪食
- ビタミンE、ビタミンC、ベータカロチン、フラボノイド、魚/omega-3脂肪酸
- 葉酸、ビタミンA、B12、ビタミンD、亜鉛、銅、鉄
- カフェイン、コーヒー、茶
- 赤ワイン

◆ 食事パターン：地中海食、日本食

◆ 多因子介入試験（栄養+運動+社会活動）