

# Chapter 4

---

## Clinical Course and Treatment

---

# A | Risk Factors and Protective Factors of Dementia

## CQ 4A-1

### What are the risk factors and protective factors of dementia?

#### Answer

Risk factors for dementia include ageing, genetic risk factors (*APP*, *PS1*, *PS2*, *APOEε4*), vascular risk factors (hypertension, diabetes, dyslipidemia), lifestyle-related factors (such as smoking), and related diseases (metabolic syndrome, sleep apnea syndrome, depression, and bipolar disorder). Protective factors include moderate exercise, dietary factors, leisure activities, social participation, mental activity, and cognitive training. Acquired elements include education history and head trauma.

#### Comments and evidence

Risk factors that can be modified to prevent dementia include (midlife) hypertension, diabetes, (midlife) obesity, dyslipidemia, smoking, low physical activity, and depression<sup>1-3</sup>.

The effects of hypertension on dementia and cognitive impairment vary with age. Since midlife hypertension is a risk factor for dementia and cognitive impairment in older age, active treatment is recommended from the viewpoint of dementia prevention.

Diabetes is a risk factor for dementia (Alzheimer's disease dementia, vascular dementia, and mixed dementia); especially, glycemic control in midlife is necessary to prevent the onset of dementia.

Midlife dyslipidemia, especially hypercholesterolemia, has been shown to be a risk factor for Alzheimer's disease dementia, and strict control of dyslipidemia in midlife is desirable. In older people, report has indicated that higher serum cholesterol level is associated with a lower risk of developing Alzheimer's disease dementia. Therefore, statins have to be used with caution in older people.

An increasing number of reports suggest a relationship of metabolic syndrome with ageing-associated cognitive impairment, mild cognitive impairment, and vascular dementia, but the association with Alzheimer's disease dementia is not consistent. Many reports have shown that metabolic syndrome in midlife, in particular, is associated with cognitive impairment.

Smoking aggravates dementia [risk ratio (RR) 1.30], vascular dementia (RR 1.38), and Alzheimer's disease dementia (RR 1.40).

Many observational studies on exercise therapy have reported that regular physical activity prevents the onset of dementia and Alzheimer's disease dementia. Interventional trials on the effect of physical activity in older people report the protective effect of physical activity against cognitive impairment, and recommends active incorporation of exercise<sup>4</sup>.

Several observational studies report that a past history of depression and bipolar disorder increases the risk of dementia onset in later life<sup>5-7</sup>.

Leisure activities comprise intellectual, physical, and social elements. Many reports show that leisure activities have protective effects against the development of dementia and Alzheimer's disease dementia.

High-calorie diets containing mainly carbohydrates, low-protein diets, and low-fat diets tend to increase the risk of mild cognitive impairment and dementia. Moderate drinking has been reported to prevent dementia. Hyperhomocysteinemia has been reported to be a risk factor for Alzheimer's disease dementia and other types of dementia<sup>1</sup>. Sleep apnea syndrome and sleep-disordered breathing are known to be vascular risk factors associated with cognitive impairment.

A shorter education history is associated with increase in the risk of Alzheimer's disease dementia<sup>2</sup>.

Head injury increases the odds ratio (OR) of a pathological diagnosis of Alzheimer's disease dementia in men (OR 1.47), but not in women (OR 1.18)<sup>8</sup>.

#### ■ References

- 1) Deckers K, van Boxtel MPJ, Schiepers OJG, et al. Target risk factors for dementia prevention: a systematic review and Delphi consensus study on the evidence from observational studies. *Int J Geriatr Psychiatry*. 2015; 30(3): 234-246.
- 2) Beydoun MA, Beydoun HA, Gamaldo AA, et al. Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic

review and meta-analysis. *BMC Public Health*. 2014; 14: 643-676.

- 3) Plassman BL, Williams JW Jr, Burke JR, et al. Systematic review: Factors associated with risk for and possible prevention of cognitive decline in later life. *Ann Intern Med*. 2010; 153(3): 182-193.
- 4) So F, Valecchi D, Bacci D, et al. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. *J Intern Med*. 2011; 269(1): 107-117.
- 5) da Silva J, Goncalves-Pereira M, Xavier M, et al. Affective disorders and risk of developing dementia: systematic review. *Br J Psychiatry*. 2013; 202(3): 177-186.
- 6) Jorm AF. History of depression as a risk factor for dementia: an updated review. *Aust N Z J Psychiatry*. 2001; 35(6): 776-781.
- 7) Ownby RL, Crocco E, Acevedo A, et al. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. *Arch Gen Psychiatry*. 2006; 63(5): 530-538.
- 8) Abner EL, Nelson PT, Schmitt FA, et al. Self-reported head injury and risk of late-life impairment and AD pathology in an AD center cohort. *Dement Geriatr Cogn Disord*. 2014; 37(5-6): 294-306.

## Are hypertension control and antihypertensive drugs effective in dementia prevention?

### Recommendation

Hypertension in midlife is a risk factor for dementia, and should be treated actively. However, large-scale studies have not clearly shown the preventive effect of antihypertensive therapy against onset of dementia and cognitive impairment.

2C

### Comments and evidence

The effect of hypertension on dementia and cognitive impairment varies with age. In particular, hypertension in midlife is a risk factor for dementia in old age. Therefore, active treatment is recommended from the viewpoint of dementia prevention<sup>1)</sup>.

In a 12-year follow-up study of adults with no dementia at baseline, blood pressure at baseline had a greater effect on the speed of cognitive decline in subjects who were in midlife (aged under 65 years) at the start of the study compared with those who were in old age (aged 65 years or above). This finding suggests that blood pressure control in midlife has a pronounced effect on cognitive function<sup>2)</sup>.

The relationship between hypertension and dementia in old age is not consistent.

The dementia preventive effect of antihypertensive medications has been observed for dementia in general and for vascular dementia.

A Cochrane review reports a meta-analysis of large-scale double-blind interventional trials (SHEP, Syst-Eur, SCOPE, HYVET). The subjects of the analysis were older people (mean age 75 years) with hypertension. Blood pressure was adequately lower in the intervention group compared with the control group. However, with regard to the onset of dementia, the intervention group showed only a tendency of preventive effect [odds ratio (OR) 0.89, 95% confidence interval (CI) 0.74 to 1.07]<sup>3)</sup>.

A pooled meta-analysis of 8 large-scale clinical trials found that blood pressure lowering had no significant dementia prevention effect overall, but diuretics and calcium antagonists were effective<sup>4)</sup>.

In a pooled meta-analysis of 14 longitudinal studies on the relationship between antihypertensive therapy and onset of dementia or cognitive impairment in subjects without dementia at baseline, use of antihypertensive drugs had no significant preventive effect on the development of Alzheimer's disease dementia and cognitive impairment. However, there was a preventive effect on vascular dementia and dementia in general<sup>5)</sup>.

In a meta-analysis based on 19 randomized controlled trials (RCTs) and 11 observational studies on the prevention effects of antihypertensive drugs in patients with no history of stroke, the risk of developing dementia was significantly reduced by 9%. In a sub-analysis of the antihypertensive classes, angiotensin II receptor blocker (ARB) tended to be beneficial for cognitive function<sup>6)</sup>.

In another meta-analysis of 12 studies in older subjects without dementia or cerebrovascular disorders (4,076 subjects), hypertension significantly reduced episodic memory and global cognition<sup>7)</sup>.

In the Honolulu-Asia Aging Study, 2,197 male hypertensive patients (mean age 77 years) without dementia or cognitive impairment were followed. The risk of progression of cognitive decline was reduced in patients taking  $\beta$ -blockers as antihypertensive drug (incidence ratio 0.69, 95% CI 0.50 to 0.94)<sup>8)</sup>.

In the Hisayama study, the relative risk of developing vascular dementia increased linearly with increasing blood pressure from midlife to late life<sup>9)</sup>.

### References

- 1) Launer LJ, Hughes T, Yu B, et al. Lowering midlife levels of systolic blood pressure as a public health strategy to reduce late-life dementia: perspective from the Honolulu Heart Program/Honolulu Asia Aging Study. *Hypertension*. 2010; 55(6): 1352-1359.
- 2) Kohler S, Baars MA, Spauwen P, et al. Temporal evolution of cognitive changes in incident hypertension: prospective cohort study across the adult age span. *Hypertension*. 2014; 63(2): 245-251.
- 3) McGuinness B, Todd S, Passmore P, et al. Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. *Cochrane Database Syst Rev*. 2009; (4): CD004034.
- 4) Staessen JA, Thijs L, Richart T, et al. Placebo-controlled trials of blood pressure-lowering therapies for primary prevention of dementia. *Hypertension*.

2011; 57(2): e6-e7.

- 5) Chang-Quan H, Hui W, Chao-Min W, et al. e association of antihypertensive medication use with risk of cognitive decline and dementia: a meta-analysis of longitudinal studies. *Int J Clin Pract.* 2011; 65(12): 1295-1305.
- 6) Levi Marpillat N, Macquin-Mavier I, Tropeano AI, et al. Antihypertensive classes, cognitive decline and incidence of dementia: a network meta-analysis. *J Hypertens.* 2013; 31(6): 1073-1082.
- 7) Gifford KA, Badaracco M, Liu D, et al. Blood pressure and cognition among older adults: a meta-analysis. *Arch Clin Neuropsychol.* 2013; 28(7): 649-664.
- 8) Gelber RP, Ross GW, Petrovitch H, et al. Antihypertensive medication use and risk of cognitive impairment: The Honolulu-Asia Aging Study. *Neurology.* 2013; 81(10): 888-895.
- 9) Ninomiya T, Ohara T, Hirakawa Y, et al. Midlife and late-life blood pressure and dementia in Japanese elderly: the Hisayama study. *Hypertension.* 2011; 58(1): 22-28.

## ■ Search formula

PubMed search: June 13, 2015 (Saturday)

#1 (“Dementia/prevention and control” [Mesh]) OR (dementia AND prevent\*) OR “Cognition Disorders/prevention and control” [Mesh] OR (“cognition disorder\*” AND prevent\*) AND (“Antihypertensive Agents” [Mesh] OR “Antihypertensive Agents” [Pharmacological Action] OR antihypertensive agent\*)

Ichushi search: June 13, 2015 (Saturday)

#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI) AND (Antihypertensive agents/TH OR Antihypertensive agents/TI OR Antihypertensive agents /TI) AND (Prevention/TI OR Control/TI OR (SH = Prevention))

## Is diabetes control effective in dementia prevention?

### Recommendation

In many reports, including meta-analyses, diabetes is a risk factor for Alzheimer's disease dementia, vascular dementia, and mixed dementia. Especially, glycemic control in midlife is necessary for prevention of dementia onset. 2C

### Comments and evidence

Many meta-analysis and systematic reviews of observational studies have reported that diabetes is a risk factor for dementia (Alzheimer's disease dementia, vascular dementia, and mixed dementia) <sup>1-9)</sup>

A 9-year follow-up of older people aged 75 years and above, comprising 963 subjects with normal cognitive function and 302 subjects with mild cognitive impairments (120 with amnesic mild cognitive impairments, 182 without dementia but having other cognitive impairment), the rate of conversion to dementia was 2.87 times in the diabetes group and 4.96 times in the pre-diabetes group <sup>1)</sup>.

The mechanisms by which diabetes affects the pathology of Alzheimer's disease dementia presumably involve cell biological and molecular interactions of multiple factors including hyperinsulinemia and impaired insulin secretion <sup>2)</sup>. It remains unclear whether endogenous or exogenous insulin adversely affects cognitive function.

According to the results of the Hisayama study, diabetes is a significant risk for the development of Alzheimer's disease dementia and vascular dementia. The risk of developing vascular dementia increased with increased level of glucose tolerance impairment, and the risk of developing Alzheimer's disease dementia increased significantly with increased severity of diabetes (hazard ratio 2.1) <sup>3)</sup>.

A report indicates that controlling diabetes together with hypertension and lipids can reduce vascular events, and improve cognitive decline related to vascular dementia <sup>4)</sup>.

### References

- 1) Xu W, Caracciolo B, Wang HX, et al. Accelerated progression from mild cognitive impairment to dementia in people with diabetes. *Diabetes*. 2010; 59(11): 2928-2935.
- 2) Kopf D, Frolich L. Risk of incident Alzheimer's disease in diabetic patients: a systematic review of prospective trials. *J Alzheimers Dis*. 2009; 16(4): 677-685.
- 3) Ohara T, Doi Y, Ninomiya T, et al. Glucose tolerance status and risk of dementia in the community: the Hisayama study. *Neurology*. 2011; 77(12): 1126-1134.
- 4) McCrimmon RJ, Ryan CM, Frier BM. Diabetes and cognitive dysfunction. *Lancet*. 2012; 379(9833): 2291-2299.
- 5) Palta P, Schneider AL, Biessels GJ, et al. Magnitude of cognitive dysfunction in adults with type 2 diabetes: a meta-analysis of six cognitive domains and the most frequently reported neuropsychological tests within domains. *J Int Neuropsychol Soc*. 2014; 20(3): 278-291.
- 6) Cheng G, Huang C, Deng H, et al. Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. *Intern Med J*. 2012; 42(5): 484-491.
- 7) Luchsinger JA. Diabetes, related conditions, and dementia. *J Neurol Sci*. 2010; 299(1-2): 35-38.
- 8) Reijmer YD, van den Berg E, Ruis C, et al. Cognitive dysfunction in patients with type 2 diabetes. *Diabetes Metab Res Rev*. 2010; 26(7): 507-519.
- 9) Exalto LG, Whitmer RA, Kappelle LJ, et al. An update on type 2 diabetes, vascular dementia and Alzheimer's disease. *Exp Gerontol*. 2012; 47(11): 858-864.

### Search formula

PubMed search: June 13, 2015 (Saturday)

#1 (("Dementia" [Majr] OR dementia [TI] OR "Cognition Disorders" [Majr] OR "cognition disorder\*" [TI]) AND ("Diabetes Mellitus" [Majr] OR "diabetes mellitus" [TI] OR "Insulin Resistance" [Majr] OR "Insulin" [Majr] OR insulin [TI])) OR (("Dementia/prevention and control" [Mesh] OR (dementia AND prevent\*) OR "Cognition Disorders/prevention and control" [Mesh] OR ("cognition disorder\*" AND prevent\*)) AND ("Diabetes Mellitus/ therapy" [Mesh] OR ("diabetes mellitus" AND (therapy OR therapeutic OR treatment))))

Ichushi search: June 13, 2015 (Saturday)

#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI) AND (Diabetes/TH OR Diabetes/TI OR Insulin resistance/TH OR Insulin resistance/TI OR Insulin resistance/TI) AND (Prevention/TI OR Control/TI OR (SH = Prevention))

## Is treatment for dyslipidemia effective for dementia prevention?

### Recommendation

Dyslipidemia in midlife is a risk factor for dementia, especially Alzheimer's disease dementia. Statins have been reported to reduce the risk of dementia, and lipid control in midlife is desirable. Since the effects of serum cholesterol level on dementia in older people remain uncertain, statins should be used with caution in older people.

2C

### Comments and evidence

Research so far has shown that hypercholesterolemia is a risk for Alzheimer's disease dementia<sup>1)</sup>. Therefore, many studies have been conducted to examine the effect of administration of statins, therapeutic drugs for dyslipidemia, in preventing development of dementia including Alzheimer's disease dementia. However, the results of these studies are not consistent. In general, randomized controlled trials (RCT) have not yielded effective results, and data indicating effectiveness are largely reported by observational studies.

In a Cochrane review that analyzed two RCTs in patients with dyslipidemia and risk of developing dementia (cardiovascular and cerebrovascular disorder, lifestyle-related diseases), administration of statins was not associated with the onset of dementia, changes in various neuropsychological tests, or occurrence of adverse events<sup>2)</sup>.

Regarding the prevention of further cognitive decline by statin administration in persons with Alzheimer's disease dementia (including suspected cases), a Cochrane review reported a meta-analysis of only three large-scale RCTs with 748 subjects. No significant preventive effect of disease progression was observed in any of the three batteries: Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog), Mini Mental State Examination (MMSE), and Clinician's Global Impression of Change (CGIC)<sup>3)</sup>.

In a systematic review of observational studies that examined the effects of statins other than improvement of dyslipidemia in the general population, the incidence of dementia among statin users was low in 13 meta-analysis<sup>5)</sup>.

In a meta-analysis based on 8 prospective observational studies, statins reduced the risk of dementia by 38% [relative risk (RR) 0.62, 95% confidence interval (CI) 0.4 to 0.81]<sup>6)</sup>.

In a meta-analysis based on 20 studies (16 observational studies, 3 case-control studies, 1 RCT), statins reduced the risk of developing dementia by 38% (RR 0.62, 95% CI 0.43 to 0.82). Even when the endpoint was limited to Alzheimer's disease dementia, the risk of developing dementia was reduced by 24% (RR 0.76, 95% CI 0.65 to 0.90)<sup>7)</sup>.

The effect of dyslipidemia on cognitive decline varies with age. Midlife dyslipidemia, especially hypercholesterolemia, has been shown to be a risk factor for Alzheimer's disease dementia, and strict control of lipid abnormalities in midlife is desirable. There are also reports that higher serum cholesterol level in older people is associated with lower risk of developing Alzheimer's disease dementia. Therefore, statins have to be used with caution in older people.

In one report, statin treatment for mild cognitive impairment reduced the hazard risk of developing Alzheimer's disease dementia by 67%<sup>8)</sup>.

In another report, statin administration to older people with vascular risk factors did not prevent cognitive decline or prevent dementia<sup>9)</sup>.

### References

- 1) Shepardson NE, Shankar GM, Selkoe DJ. Cholesterol level and statin use in Alzheimer disease: I. Review of epidemiological and preclinical studies. *Arch Neurol*. 2011; 68(10): 1239-1244.
- 2) McGuinness B, Craig D, Bullock R, et al. Statins for the prevention of dementia. *Cochrane Database Syst Rev*. 2009; (2): CD003160.
- 3) McGuinness B, O'Hare J, Craig D, et al. Cochrane review on 'Statins for the treatment of dementia'. *Int J Geriatr Psychiatry*. 2013; 28(2): 119-126.
- 4) Richardson K, Schoen M, French B, et al. Statins and cognitive function: a systematic review. *Ann Intern Med*. 2013; 159(10): 688-697.
- 5) Macedo AF, Taylor FC, Casas JP, et al. Unintended effects of statins from observational studies in the general population: systematic review and meta-analysis. *BMC Med*. 2014; 12: 51.
- 6) Song Y, Nie H, Xu Y, et al. Association of statin use with risk of dementia: a meta-analysis of prospective cohort studies. *Geriatr Gerontol Int*. 2013; 13(4): 817-824.
- 7) Wong WB, Lin VW, Boudreau D, et al. Statins in the prevention of dementia and Alzheimer's disease: a meta-analysis of observational studies and an assessment of confounding. *Pharmacoepidemiol Drug Saf*. 2013; 22(4): 345-358.
- 8) Sparks DL, Kryscio RJ, Connor DJ, et al. Cholesterol and cognitive performance in normal controls and the influence of elective statin use after

conversion to mild cognitive impairment: results in a clinical trial cohort. *Neurodegener Dis.* 2010; 7(1-3): 183-186.

9) McGuinness B, Craig D, Bullock R, et al. Statins for the prevention of dementia. *Cochrane Database Syst Rev.* 2016; (1): CD003160.

## ■ Search formula

PubMed search: June 13, 2015 (Saturday)

#1 (“Dementia” [Majr] OR dementia [TI] OR “Cognition Disorders” [Majr] OR “cognition disorder\*” [TI]) AND (“Hypolipidemic Agents” [Majr] OR “antilipemic agent\*” [TI] OR “hypolipidemic agent\*” [TI]) OR (“Dementia/ prevention and control” [Mesh] OR dementia AND prevent\* OR “Cognition Disorders/prevention and control” [Mesh] OR (“cognition disorder\*” AND prevent\*)) AND (“Hypolipidemic Agents” [Mesh] OR “Hypolipidemic Agents” [Pharmacological Action] OR (“antilipemic agent\*” OR “hypolipidemic agent\*”) AND (therapy OR therapeutic OR treatment))

Ichushi search: June 13, 2015 (Saturday)

#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI) AND (Hypolipidemic agents/TH OR Hypolipidemic agents/TI OR Lipid improving agents/TI OR Antilipemic agent/TI OR Antilipidemic agent/TI OR Antilipidemic drug/TI OR Antilipemic drug/TI OR Antilipemic drug/ TI OR Antilipemic agent/TI OR Antilipemic drug/TI OR Antilipidemic drug/TI OR Lipid-lowering drug/TI OR Anticholesteremic agent/TI OR Anticholesteremic drug/TI OR Anticholesteremic agent/TI OR Anticholesteremic drug/TI) AND (Prevention/TI OR Control/TI OR (SH = Prevention))



## Does metabolic syndrome worsen dementia?

### Recommendation

There are many reports indicating that metabolic syndrome and its factors (abnormal glucose tolerance, obesity, hypertension, and dyslipidemia) are associated with ageing-related cognitive decline, mild cognitive impairment, and vascular dementia. However, opinions on Alzheimer's disease dementia are divided.

2C

### Comments and evidence

Many reports have shown that metabolic syndrome, especially in midlife, is associated with cognitive decline. Obesity in midlife is associated with an increase in risk of dementia [risk ratio (RR) 1.41], although the risk decreases at age 65 and above (RR 0.83)<sup>1)</sup>.

In one study of adults aged below 65 years, metabolic syndrome was associated with memory impairment, visuospatial impairment, and impaired executive function<sup>2)</sup>. In a 25-year longitudinal study of 3,555 subjects, patients who fulfilled multiple items of metabolic syndrome had increased risk of dementia, particularly vascular dementia, but no increase in risk of Alzheimer's disease dementia<sup>3)</sup>.

According to a 3.5-year longitudinal study of 2,097 persons aged 65 to 84 years, among subjects with mild cognitive impairment, those who had coexisting metabolic syndrome had a significantly higher risk of developing dementia compared with those without metabolic syndrome<sup>3)</sup>.

When 837 persons with mild cognitive impairment were observed for 5 years, 352 (42.1%) converted to Alzheimer's disease dementia, and these patients had significantly more vascular risk factors than those who remained having mild cognitive impairment (2.33 vs 1.15,  $p < 0.001$ )<sup>4)</sup>. In the group treated for all the vascular risk factors (hypertension, diabetes, and dyslipidemia) during the stage of mild cognitive impairment, the rate of conversion to Alzheimer's disease dementia was lower compared to the group not treated at all<sup>4)</sup>.

Persons with Alzheimer's disease dementia who had no cerebrovascular disorders and were treated for hypertension, diabetes, and dyslipidemia have slower decline in cognitive function compared with persons without any risk factors<sup>5)</sup>.

Even in persons with metabolic syndrome, treating risk factors for arteriosclerosis may prevent cognitive decline<sup>6)</sup>.

### References

- Pedditizi E, Peters R, Beckett N. The risk of overweight/obesity in mid-life and late life for the development of dementia: a systematic review and meta-analysis of longitudinal studies. *Age Ageing*. 2016; 45(1): 14-21.
- Yates KF, Sweat V, Yau PL, et al. Impact of metabolic syndrome on cognition and brain: a selected review of the literature. *Arterioscler Thromb Vasc Biol*. 2012; 32(9): 2060-2067.
- Panza F, Frisardi V, Capurso C, et al. Metabolic syndrome and cognitive impairment: current epidemiology and possible underlying mechanisms. *J Alzheimers Dis*. 2010; 21(3): 691-724.
- Li J, Wang, YJ, Zhang M, et al. Chongqing Ageing Study Group: Vascular risk factors promote conversion from mild cognitive impairment to Alzheimer disease. *Neurology*. 2011; 76(17): 1485-1491.
- Deschaintre Y, Richard F, Leys D, et al. Treatment of vascular risk factors is associated with slower decline in Alzheimer disease. *Neurology*. 2009; 73(9): 674-680.
- Arai A. Correction of metabolic syndrome and dementia prevention. *Japanese Journal of Clinical Medicine (Nihon Rinsho)* 2011; 69(1012 suppl 10): 202-206. (In Japanese)

### Search formula

PubMed search: June 13, 2015 (Saturday)

```
#1 ("Dementia" [Majr] OR dementia [TI] OR "Alzheimer's disease" [TI] OR "Alzheimer disease" [TI] OR "Cognition Disorders" [Majr] OR "cognition disorder*" [TI]) AND ("Metabolic Syndrome X" [Majr] OR "metabolic syndrome" [TI]) OR (("Dementia/prevention and control" [Mesh] OR ((dementia OR "Alzheimer's disease" OR "Alzheimer disease") AND prevent*) OR "Cognition Disorders/prevention and control" [Mesh] OR ("cognition disorder*" AND prevent*)) AND ("Metabolic Syndrome X" [Mesh] OR "metabolic syndrome"))
```

Ichushi search: June 13, 2015 (Saturday)

```
#1 (Dementia/TH OR Dementia/TI OR Alzheimer's disease/TI OR Alzheimer's disease/TI OR Cognitive impairment/TH OR Cognitive impairment/TI) AND (Metabolic syndrome/TH OR Metabolic syndrome/TI OR Metabolic syndrome/TI) AND (Risk factor/TH OR Risk factor/TI OR Risk factor/TI)
```

## Does smoking worsen dementia?

### Recommendation

Smoking worsens all-cause dementia, vascular dementia, and Alzheimer's disease dementia.

1B

### Comments and evidence

The results of 37 large-scale studies show that smoking worsens dementia [risk ratio (RR) 1.30], vascular dementia (RR 1.38), and Alzheimer's disease dementia (RR 1.40). The risk of Alzheimer's disease dementia is significantly higher in current smokers who are APOE ε4 non-carriers. People aged between 65 and 75 who smoke have an increased risk of all-cause dementia and Alzheimer's disease dementia compared with those who do not smoke<sup>1,3</sup>.

Smoking 20 cigarettes a day increases the risk of all-cause dementia (RR 1.34)<sup>1</sup>. Persons who have ever smoked are at higher risk for all-cause dementia (RR 1.13) and vascular dementia (RR 1.25) than those who never smoke. On the other hand, those who smoked before but have quit smoking do not have an increased risk for all-cause dementia<sup>1</sup>.

In recent large-scale trials, smoking is often reported as a risk factor for all-cause dementia<sup>1,3</sup>.

The global smoking rate is 27.4%. The increase in risk of Alzheimer's disease dementia due to smoking has a RR of 1.59, and the population attributable risk (PAR) is 13.9%. Approximately 14% of Alzheimer's disease dementia worldwide is reported to be caused by smoking<sup>3</sup>.

### References

- 1) Zhong G, Wang Y, Zhang Y, et al. Smoking is associated with an increased risk of dementia: a meta-analysis of prospective cohort studies with investigation of potential effect modifiers. *PLoS One*. 2015; 10(3) : e0118333.
- 2) Cataldo JK, Prochaska JJ, Glantz SA. Cigarette smoking is a risk factor for Alzheimer's Disease: an analysis controlling for tobacco industry affiliation. *J Alzheimers Dis*. 2010; 19(2) : 465-480.
- 3) Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol*. 2011; 10(9) : 819-828.

### Search formula

PubMed search: June 13, 2015 (Saturday)

```
#1 (("Dementia" [Majr] OR dementia [TI] OR "Alzheimer's disease" [TI] OR "Alzheimer disease" [TI] OR "Cognition Disorders" [Majr] OR "cognition disorder*" [TI]) AND ("Smoking" [Majr] OR smoking [TI])) OR (("Dementia/ prevention and control" [Mesh] OR ((dementia OR "Alzheimer's disease" OR "Alzheimer disease") AND prevent*)) OR "Cognition Disorders/prevention and control" [Mesh] OR ("cognition disorder*" AND prevent*)) AND ("Smoking" [Mesh] OR "smoking"))
```

Ichushi search: June 13, 2015 (Saturday)

```
#1 (Dementia/TH OR Dementia/TI OR Alzheimer's disease/TI OR Alzheimer's disease/TI OR Cognitive impairment/TH OR Cognitive impairment/TI) AND (Smoking/TH OR Smoking/TI) AND (Risk factor/TH OR Risk factor/TI OR Risk factor/TI)
```

## Is exercise effective in preventing dementia?

### Recommendation

Many observational studies have reported that regular physical activity is associated with reduced incidence of all-cause dementia and Alzheimer's disease dementia. Interventional studies in older persons without dementia and older persons with mild cognitive impairment report that physical activity protects against cognitive decline. Active incorporation of exercise is recommended.

1B

### Comments and evidence

Decreased walking speed and reduced grip strength in middle-aged to older persons are related to cognitive impairment<sup>1)</sup>. Physical activity and habitual exercise during middle age to old age have been shown to be associated with reduced incidence of dementia and Alzheimer's disease dementia<sup>2, 3)</sup>.

A meta-analysis has reported that intervention of physical activity for older persons without dementia improves attention and judgment<sup>4)</sup>. In a meta-analysis of 14 randomized controlled trials (RCT) that studied older people aged 65 years and above with mild cognitive impairment or Mini Mental State Examination (MMSE) scores of 24-28 points, exercise intervention significantly improved verbal fluency, but did not significantly improve executive function, memory or information processing<sup>5)</sup>. In a RCT studying older Japanese persons with mild cognitive impairment, implementation of a combination of physical exercise and cognitive tasks that stimulate attention and memory (such as calculation and word chain), so-called "cognicise", improved logical memory and MMSE score as well as prevented the progression of hippocampal atrophy<sup>6)</sup>.

### References

- 1) Clouston SA, Brewster P, Kuh D, et al. The dynamic relationship between physical function and cognition in longitudinal aging cohorts. *Epidemiol Rev.* 2013; 35: 33-50.
- 2) Morgan GS, Gallacher J, Bayer A, et al. Physical activity in middle-age and dementia in later life: Findings from a prospective cohort of men in Caerphilly, South Wales and a meta-analysis. *J Alzheimers Dis.* 2012; 31(3): 569-580.
- 3) Sofi F, Valecchi D, Bucci D, et al. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. *J Intern Med.* 2011; 269(1): 107-117.
- 4) Kelly ME, Loughrey D, Lawlor BA, et al. The impact of exercise on the cognitive functioning of healthy older adults: a systematic review and meta-analysis. *Ageing Res Rev.* 2014; 16: 12-31.
- 5) Gates N, Fiatarone Singh MA, Sachdev PS, et al. The effect of exercise training on cognitive function in older adults with mild cognitive impairment: a meta-analysis of randomized controlled trials. *Am J Geriatr Psychiatry.* 2013; 21(11): 1086-1097.
- 6) Suzuki T, Shimada H, Makizako H, et al. A randomized controlled trial of multicomponent exercise in older adults with mild cognitive impairment. *PLoS One.* 2013; 8(4): e61483.

### Search formula

PubMed search: June 2, 2015 (Tuesday)

```
#1 (("Dementia/prevention and control" [Mesh] OR "Cognition Disorders/prevention and control" [Mesh] OR "Alzheimer Disease/therapy" [Majr] OR "Mild Cognitive Impairment/therapy" [Majr]) AND ("Exercise" [Majr] OR "Exercise therapy" [Majr])) OR (("Dementia/prevention and control" [Majr] OR "Cognition Disorders/prevention and control" [Majr]) AND ("Exercise" [Mesh] OR "Exercise therapy" [Mesh]))
```

Ichushi search: June 2, 2015 (Tuesday)

```
#1 (Dementia/TH OR Dementia/TI) AND (Preventive medicine/TH OR (SH = Prevention) OR Prevention/TI) AND (Physical exercise/TH OR Sports/TH OR Exercise therapy/TH)
```

## Are leisure activities, social participation, mental activities, cognitive training, and artistic activities such as music effective in preventing dementia and cognitive decline in older people?

### Recommendation

The effect of cognitive training is not consistent. While some reports show that cognitive training is effective in preventing cognitive decline, other reports find no significant difference. Cognitive training and exercise reduce the risk of cognitive decline. For leisure activities, since the definitions are not clear, further analysis is needed in the future.

2C

### Comments and evidence

Leisure activities include intellectual elements (such as games, chess, mahjong, and going to movies or theater), physical elements (such as sports, walking, and aerobics, etc.), and social elements (such as meeting friends, volunteer activities, and travelling). Many reports have shown that leisure activities are effective in preventing the onset of dementia and Alzheimer's disease dementia. Although observational studies<sup>1,2</sup> report that leisure activities from middle age to old age reduce the risk of developing Alzheimer's disease dementia, the definition of leisure activity is not clear<sup>3</sup>. Therefore, further analysis is necessary.

While reports have indicated a possibility that cognitive training (see CQ3A-7-1) is effective in preventing functional decline with respect to memory<sup>4,5</sup>, other report shows no significant difference<sup>6</sup>. Some randomized controlled trials (RCT) report that cognitive training and exercise reduce the risk of cognitive impairment<sup>7-9</sup>.

There are 12 reports on meditation therapy, including 6 RCTs. The results suggest that meditation may prevent cognitive decline<sup>10</sup>.

The preventive effect of music therapy for cognitive decline is unknown, but a meta-analysis of RCTs in patients with dementia finds that rather than cognitive function, music therapy is effective in improving behavioral and psychological symptoms of dementia (BPSD) as well as anxiety<sup>11</sup>.

There are only case reports and reports of small-scale study on the effect of art therapy<sup>12,13</sup>.

### References

- 1) Stern C, Munn Z. Cognitive leisure activities and their role in preventing dementia: a systematic review. *Int J Evid Based Healthc*. 2010; 8(1): 2-17.
- 2) Wang HX, Jin Y, Hendrie HC, et al. Late life leisure activities and risk of cognitive decline. *J Gerontol A Biol Sci Med Sci*. 2013; 68(2): 205-213.
- 3) Wang HX, Xu W, Pei JJ. Leisure activities, cognition and dementia. *Biochim Biophys Acta*. 2012; 1822(3): 482-491.
- 4) Gates NJ, Sachdev PS, Fiatarone Singh MA, et al. Cognitive and memory training in adults at risk of dementia: a systematic review. *BMC Geriatr*. 2011; 11: 55-69.
- 5) Smith GE, Housen P, Yaffe K, et al. A cognitive training program based on principles of brain plasticity: results from the Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) study. *J Am Geriatr Soc*. 2009; 57(4): 594-603.
- 6) Martin M, Clare L, Altgassen AM, et al. Cognition-based interventions for healthy older people and people with mild cognitive impairment. *Cochrane Database Syst Rev*. 2011; (1): CD006220.
- 7) Bherer L. Cognitive plasticity in older adults: effects of cognitive training and physical exercise. *Ann N Y Acad Sci*. 2015; 1337: 1-6.
- 8) Middleton LE, Yaffe K. Promising strategies for the prevention of dementia. *Arch Neurol*. 2009; 66(10): 1210-1215.
- 9) Barnes DE, Santos-Modesitt W, Poelke G, et al. The Mental Activity and eExercise (MAX) trial: a randomized controlled trial to enhance cognitive function in older adults. *JAMA Intern Med*. 2013; 173(9): 797-804.
- 10) Gard T, Holzle BK, Lazar SW. The potential effects of meditation on age-related cognitive decline: a systematic review. *Ann N Y Acad Sci*. 2014; 1307: 89-103.
- 11) Chang YS, Chu H, Yang CY, et al. The efficacy of music therapy for people with dementia: A meta-analysis of randomised controlled trials. *J Clin Nurs*. 2015; 24(23-24): 3425-3440.
- 12) Chancellor B, Duncan A, Chatterjee A. Art therapy for Alzheimer's disease and other dementias. *J Alzheimers Dis*. 2014; 39(1): 1-11.
- 13) Hattori H, Hattori C, Hokao C, et al. Controlled study on the cognitive and psychological effect of coloring and drawing in mild Alzheimer's disease patients. *Geriatr Gerontol Int*. 2011; 11(4): 431-437.

## ■ Search formula

PubMed search: June 15, 2015 (Monday)

#1 (“Dementia/prevention and control” [Mesh] OR (dementia AND prevent\*) OR “Cognition Disorders/prevention and control” [Mesh] OR (“cognition disorder\*” AND prevent\*)) AND (“Leisure Activities” [Mesh] OR leisure activity\* OR “Learning” [Mesh] OR “memory training” OR cognitive activity\* OR “Neuronal Plasticity” [Mesh] OR “cognitive plasticity” OR (physical AND social component\*) OR “Psychotherapy” [Mesh] OR “music therapy” OR “art therapy”)

Ichushi search: June 15, 2015 (Monday)

#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI) AND (Leisure activities/TH OR Leisure activities/TI OR Leisure/TI OR Social participation/TH OR Social participation/TI OR Social participation/TI OR mental activities/AL OR Cognitive training/AL OR Perceptive art therapy/TH OR Art therapy/TI OR Music therapy/TI) AND (Prevention/TI OR Management/TI OR (SH = Prevention))

## Are there dietary factors associated with dementia?

### Recommendation

There are many reports on dementia, diet and nutrition. High-calorie diets composed mainly of carbohydrates, low-protein diets and low-fat diets tend to increase the risk of mild cognitive impairment and dementia. No definitive results are available for individual nutrients.

2C

### Comments and evidence

Many studies on dementia and dietary factors have been reported, most of which are observational studies. While these observational studies have accumulated a vast amount of knowledge about the relationship between diet, nutrition and cognitive function, no definitive conclusions have been reached on the specific foods, nutrients, or dietary patterns that increase the risk of developing dementia or prevent the development of dementia. Some randomized controlled trials (RCTs) have been performed, but they have not yielded any definitive results so far.

High-calorie diets composed of mainly carbohydrates may increase the risk of mild cognitive impairment and dementia. As a possible cause, diets with high blood glucose load may have adverse effects on glucose and insulin metabolism. On the other hand, low-protein diets and low-fat diets also tend to increase the risk of mild cognitive impairment and dementia<sup>1)</sup>.

According to reports of the Hisayama study on the relation between dietary patterns and risk of dementia, consumption of soybeans, soybean products, vegetables, seaweed, milk and dairy products reduces the risk of dementia, while consuming larger quantity of rice increases the risk of dementia<sup>2, 3)</sup>.

The Rotterdam study reports on the relation between antioxidants and dementia. Consumption of foods high in vitamin E slightly reduces the risk of dementia over the long term. On the other hand, vitamin C, beta-carotene, and flavonoids are not associated with the risk of dementia. Furthermore, consumption of fish and omega-3 fatty acid is also not related to the risk of dementia<sup>4, 5)</sup>.

Opinions are divided on caffeine, coffee, and tea. In general, the degree of cognitive decline tends to be lower in consumers of the above products. However, the level of consumption related to this effect remains unclear<sup>6)</sup>.

### References

- 1) Roberts RO, Roberts LA, Geda YE, et al. Relative intake of macronutrients impacts risk of mild cognitive impairment or dementia. *J Alzheimers Dis.* 2012; 32(2): 329-339.
- 2) Ozawa M, Ohara T, Ninomiya T, et al. Milk and dairy consumption and risk of dementia in an elderly Japanese population: the Hisayama Study. *J Am Geriatr Soc.* 2014; 62(7): 1224-1230.
- 3) Ozawa M, Ninomiya T, Ohara T, et al. Dietary patterns and risk of dementia in an elderly Japanese population: the Hisayama Study. *Am J Clin Nutr.* 2013; 97(5): 1076-1082.
- 4) Devore EE, Grodstein F, van Rooij FJ, et al. Dietary intake of fish and omega-3 fatty acids in relation to long-term dementia risk. *Am J Clin Nutr.* 2009; 90(1): 170-176.
- 5) Devore EE, Grodstein F, van Rooij FJ, et al. Dietary antioxidants and long-term risk of dementia. *Arch Neurol.* 2010; 67(7): 819-825.
- 6) Arab L, Khan F, Lam H. Epidemiologic evidence of a relationship between tea, coffee, or caffeine consumption and cognitive decline. *Adv Nutr.* 2013; 4(1): 115-122.

### Search formula

PubMed search: June 15, 2015 (Monday)

#1 ("Dementia/etiology"[Mesh] OR "Dementia/epidemiology"[Mesh] OR (dementia AND (etiology\* OR epidemiology\*)) OR "Cognition Disorders/etiology" [Mesh] OR "Cognition Disorders/epidemiology" [Mesh] OR ("cognition disorder\*" AND (etiology\* OR epidemiology\*))) AND ("Food and Beverages" [Mesh] OR food OR beverage\*) AND ("Risk" [Mesh] OR risk)

Ichushi search: June 15, 2015 (Monday)

#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI) AND (Foods and drinks/TH OR Foods/TI OR Drinks/TI OR Diet/TH OR Diet/TI) AND (Risk/TH OR Risk/TI OR Risk/TI)

## Is moderate drinking effective in preventing cognitive decline and dementia?

### Recommendation

A report has shown that moderate drinking of alcoholic drinks has preventive effect on dementia. Caution should be exercised in interpreting this finding, because the definition of “moderate drinking” differs depending on race and on individuals. This should not be recommended to persons who cannot drink.

2C

### Comments and evidence

Alcohol is inherently neurotoxic, and heavy drinking causes atrophy of the brain. On the other hand, moderate drinking has been reported to prevent dementia. In particular, appropriate consumption of red wine has been reported to prevent cognitive decline.

According to observational studies in persons with a healthy lifestyle, low to moderate alcohol consumption reduces the odds ratio of cognitive decline or dementia<sup>1)</sup>, but heavy alcohol consumption increases the risk of conversion from mild cognitive impairment to dementia<sup>2)</sup>. While red wine has a preventive effect against cognitive decline, other alcoholic beverages such as beer, white wine, fortified wine (wine with high alcohol content), spirits (such as gin and vodka) have no such effect, suggesting that ingredients other than alcohol in red wine may have a preventive effect<sup>3)</sup>. In addition, a case-control study has found that habitual drinking in older people protects against the development of vascular dementia (odds ratio 0.48)<sup>4)</sup>.

Note that the relationship between drinking and cognitive function has not been proven by randomized controlled trial (RCT) due to ethical restrictions.

### ■ References

- 1) Elwood P, Galante J, Pickering J, et al. Healthy lifestyles reduce the incidence of chronic diseases and dementia: evidence from the Caerphilly cohort study. *PLoS One*. 2013; 8(12): e81877.
- 2) Xu G, Liu X, Yin Q, et al. Alcohol consumption and transition of mild cognitive impairment to dementia. *Psychiatry Clin Neurosci*. 2009; 63(1): 43-49.
- 3) Nooyens AC, Bueno-de-Mesquita HB, van Gelder BM, et al. Consumption of alcoholic beverages and cognitive decline at middle age: the Doetinchem Cohort Study. *Br J Nutr*. 2014; 111(4): 715-723.
- 4) Takahashi PY, Caldwell CR, Targonski PV. Effect of alcohol and tobacco use on vascular dementia: a matched case control study. *Vasc Health Risk Manag*. 2011; 7: 685-691.

### ■ Search formula

PubMed search: June 15, 2015 (Monday)

#1 (“Dementia/prevention and control” [Mesh] OR (dementia AND prevent\*) OR “Cognition Disorders/prevention and control” [Mesh] OR (“cognition disorder\*” AND prevent\*)) AND (“Alcohol Drinking” [Mesh] OR alcohol drinking\* OR “Alcoholic Beverages” [Mesh] OR alcoholic beverage\*)

Ichushi search: June 15, 2015 (Monday)

#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI) AND (Alcoholic beverage/TH OR Alcohol/TI OR Drinking/TH OR Drinking/TI)

## Does sleep apnea syndrome worsen cognitive function?

### Recommendation

Sleep apnea syndrome, while being a vascular risk factor, is also associated with cognitive impairment. Continuous positive airway pressure therapy improves cognitive impairment.

2C

### Comments and evidence

Many observational studies have shown that sleep apnea syndrome and sleep-disordered breathing are vascular risk factors, and at the same time are associated with cognitive decline. In addition, although continuous positive airway pressure therapy, which is used as a treatment for sleep apnea syndrome, is expected to contribute to the improvement of cognitive function, there remain many unclear aspects about the relationship between severity and therapeutic effect.

A report from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study has shown that the presence of sleep apnea syndrome accelerates the development of mild cognitive impairment and Alzheimer's disease dementia, and that treatment with continuous positive airway pressure delays the progression of dementia<sup>1)</sup>.

A meta-review of reports suggesting that sleep apnea syndrome affects cognitive function indicates that sleep apnea is related to deficits in attention, long-term visual and verbal memory, visuospatial cognitive function, and executive function, but does not affect language ability and psychomotor function<sup>2,3)</sup>. In older women, reports have shown that shortened sleep time, hypoxia during sleep, and sleep apnea increase the risk of cognitive decline<sup>4,5)</sup>.

Several observational studies<sup>1,2)</sup> and randomized controlled trials (RCT)<sup>6,7)</sup> have reported that continuous positive airway pressure therapy improves the decline of cognitive functions associated with sleep apnea.

### References

- 1) Osorio RS, Gumb T, Pirraglia E, et al. Sleep-disordered breathing advances cognitive decline in the elderly. *Neurology*. 2015; 84(19): 1964-1971.
- 2) Bucks RS, Olaithe M, Eastwood P. Neurocognitive function in obstructive sleep apnoea: a meta-review. *Respirology*. 2013; 18(1): 61-70.
- 3) Yaffe K, Falvey CM, Hoang T. Connections between sleep and cognition in older adults. *Lancet Neurol*. 2014; 13(10): 1017-1028.
- 4) Chang WP, Liu ME, Chang WC, et al. Sleep apnea and the risk of dementia: a population-based 5-year follow-up study in Taiwan. *PLoS One*. 2013; 8(10): e78655. CQ 4A.11 141
- 5) Yaffe K, Laffan AM, Harrison SL, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA*. 2011; 306(6): 613-619.
- 6) Sanchez AI, Martinez P, Miro E, et al. CPAP and behavioral therapies in patients with obstructive sleep apnea: effects on daytime sleepiness, mood, and cognitive function. *Sleep Med Rev*. 2009; 13(3): 223-233.
- 7) Kushida CA, Nichols DA, Holmes TH, et al. Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients: The Apnea Positive Pressure Long-term Efficacy Study (APPLES). *Sleep*. 2012; 35(12): 1593-1602.

### Search formula

PubMed search: June 17, 2015 (Wednesday)

#1 ("Dementia" [Mesh] OR dementia OR "Cognition Disorders" [Mesh] OR cognition disorder\*) AND ("Sleep Apnea Syndromes" [Mesh] OR "sleep apnea syndrome")

Ichushi search: June 17, 2015 (Wednesday)

#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI) AND (sleep apnea syndrome/TH OR sleep apnea syndrome/TI)



## Are depression and bipolar disorder risk factors for dementia?

### Recommendation

Multiple observational studies have reported that a history of depression **1B** or bipolar disorder **2C** is associated with increased risk of developing dementia.

### Comments and evidence

Many studies have reported that a history of depression is associated with increased risk of developing dementia in older age<sup>1,2</sup>. Although the possibility that depression symptoms *per se* may be the initial symptoms of dementia has been noted, the relationship between early-onset depression and development of dementia in old age, as well as the relationship between the number of episodes of depressive symptoms and the risk of dementia have been reported<sup>3</sup>, supporting the notion that depressive symptoms are a risk factor for dementia.

While many studies focus on Alzheimer's disease dementia, there are reports indicating that a history of depression is also a risk factor for vascular dementia (VaD).

A few reports have shown that a history of bipolar disorder increases the development of dementia, but there is opinion that a bias may be present since patients with bipolar disorder are in an environment that facilitates a diagnosis of dementia compared to control patients<sup>1</sup>. Although observational studies have reported that the rate of developing dementia decreases with continuous treatment with antidepressants for depression and lithium for bipolar disorder<sup>4,5</sup>, there is no clear evidence from interventional study that these treatments reduce the development of dementia.

### References

- 1) da Silva J, Goncalves-Pereira M, Xavier M, et al. Affective disorders and risk of developing dementia: systematic review. *Br J Psychiatry*. 2013; 202(3): 177-186.
- 2) Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol*. 2011; 10(9): 819-828.
- 3) Dotson VM, Beydoun MA, Zonderman AB. Recurrent depressive symptoms and the incidence of dementia and mild cognitive impairment. *Neurology*. 2010; 75(1): 27-34.
- 4) Kessing LV, Forman JL, Andersen PK. Do continued antidepressants protect against dementia in patients with severe depressive disorder? *Int Clin Psychopharmacol*. 2011; 26(6): 316-322.
- 5) Kessing LV, Forman JL, Andersen PK. Does lithium protect against dementia? *Bipolar Disord*. 2010; 12(1): 87-94.

### Search formula

PubMed search: June 3, 2015 (Wednesday)

#1 ("Dementia/etiology" [Mesh] AND ("Mood Disorders/complications" [Mesh] OR "Depression/complications" [Mesh]) AND "Risk Factors" [Mesh]) OR ("Dementia/epidemiology" [Majr] AND ("Mental Disorders/epidemiology" [Majr] OR "Mood Disorders/epidemiology" [Majr]) AND "Age Factors" [Mesh] AND "Epidemiologic Methods" [Mesh] AND risk [TI]) OR (risk [TI] AND dementia [TI] AND (depression OR "bipolar disorder"))

Ichushi search: June 3, 2015 (Wednesday)

#1 (Dementia/TH OR Dementia/TI) AND (Depression OR Depression OR bipolar disorder) AND (Risk factor OR Risk)

## B | Mild Cognitive Impairment

### CQ 4B-1

## What are the prevalence and incidence of mild cognitive impairment (MCI)?

### Answer

---

Although the data vary from study to study, the prevalence of MCI is estimated to be 15-25% in older people aged 65 years and above, and the incidence is estimated to be 20-50 per 1,000 people per year.

---

### Comments and evidence

#### 1. Prevalence<sup>1-4)</sup>

The original diagnostic criteria for MCI was published by Petersen et al.<sup>1)</sup>. Since then, various criteria for diagnosis of mild cognitive impairment have been used in epidemiological studies, which greatly affect the prevalence and incidence obtained from these studies. Since a large amount of epidemiological data focuses on amnesic mild cognitive impairment, which is a subtype of mild cognitive impairment restricted to memory impairment, this situation also causes some confusion. Moreover, the prevalence would differ depending on whether subject recruitment of an epidemiological study is community-based or population-based. The range of the results obtained also differs depending on the magnitude (how high or how low) and the range of the subjects' ages.

If one only views the data without considering the above factors, the statistics would yield a prevalence of approximately 15-25% in most studies. When limited to amnesic mild cognitive impairment, prevalence with a range from 2.4% to 28.3% in those aged 65 and above has been reported.

#### 2. Incidence<sup>4, 5)</sup>

Since the age of the cohort participating in survey varies from study to study, the incidence ranges from 20 to 50 per 1,000 person per year. When limited to amnesic mild cognitive impairment, the incidence has been reported to be 9.9-40.6 per 1,000 persons per year.

The prevalence is higher in recent reports.

### ■ References

- 1) Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol*. 1999; 56(3): 303-308.
- 2) Petersen RC. Early diagnosis of Alzheimer's disease: is MCI too late? *Curr Alzheimer Res*. 2009; 6(4): 324-330.
- 3) Luck T, Lupp M, Briel S, et al. Incidence of mild cognitive impairment: a systematic review. *Dement Geriatr Cogn Disord*. 2010; 29(2): 164-175.
- 4) Ward A, Arrighi HM, Michels S, et al. Mild cognitive impairment: disparity of incidence and prevalence estimates. *Alzheimers Dement*. 2012; 8(1): 14-21.
- 5) Roberts R, Knopman DS. Classification and epidemiology of MCI. *Clin Geriatr Med*. 2013; 29(4): 753-772.

### ■ Search formula

PubMed search: June 5, 2015 (Friday)

#1 ("Mild Cognitive Impairment/epidemiology" [Mesh] OR "Mild Cognitive Impairment" AND "Cognition Disorders/epidemiology" [Mesh]) AND "Morbidity" [Mesh]

Ichushi search: June 5, 2015 (Friday)

#1 (mild cognitive impairment/TH OR mild cognitive impairment/TI) AND (prevalence OR incidence OR incidence)

## What is the conversion rate from mild cognitive impairment (MCI) to dementia, and the reversion rate from MCI to cognitive normal?

### Answer

The conversion rate from mild cognitive impairment to dementia is estimated to be approximately 5-15% per year. The reversion rate is estimated to be approximately 16-41% per year.

### Comments and evidence

The data for conversion from mild cognitive impairment to dementia varies from study to study. In addition, it should be noted that the results differ depending on whether the study involves follow-up by medical specialists or is community-based. Naturally, the conversion rate would be high if follow-up is done by specialists. Conversion occurs at a rate of approximately 5-15% per year. By type of dementia, the rate of conversion diagnosed by specialists is 8.1% for Alzheimer's disease dementia and 1.9% for vascular dementia. In community-based studies, the conversion rates for the two types are 6.8% and 1.6%, respectively, with higher rate for Alzheimer's disease dementia.

On the other hand, the reversion rates from mild cognitive impairment to a cognitive normal state range widely from 16 to 41% per year.

### ■ Further reading

- 1) Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia--meta-analysis of 41 robust inception cohort studies. *Acta Psychiatr Scand.* 2009; 119(4): 252-265.
- 2) Roberts R, Knopman DS. Classification and epidemiology of MCI. *Clin Geriatr Med.* 2013; 29(4): 753-772.

### ■ Search formula

PubMed search: June 5, 2015 (Friday), August 14, 2015 (Friday)

```
#1 (("Mild Cognitive Impairment" [Mesh] OR ("Mild Cognitive Impairment" AND "Cognition Disorders" [Mesh])) AND "Dementia" [Mesh] AND("conversion rate" OR "conversion rates" OR "reversion rate" OR "reversion rates" OR ((convert [TI] OR conversion [TI] OR reversion [TI] OR revert [TI]) AND (rate [TI] OR rates [TI]))) OR (("Mild Cognitive Impairment/epidemiology" [Majr] OR ("Mild Cognitive Impairment" [TI] AND "Cognition Disorders/epidemiology" [Majr])) AND "Dementia/epidemiology" [Mesh] AND ("Incidence" [Mesh] OR "Prevalence" [Mesh]))
```

Ichushi search: June 5, 2015 (Friday)

```
#1 (mild cognitive impairment/TH OR mild cognitive impairment/TI) AND (Dementia/TH OR Dementia/TI) AND (Convert OR Conversion OR Revert OR Reversion)
```

## What are the useful biomarkers for predicting conversion of mild cognitive impairment (MCI) to dementia?

### Answer

Abnormal cerebrospinal fluid levels of A $\beta$ 42, phosphorylated tau, and total tau; presence of APOE gene  $\epsilon$ 4 polymorphism; and abnormal findings on amyloid PET and <sup>18</sup>F-DG-PET have been considered to be useful biomarkers for predicting conversion from mild cognitive impairment (MCI) to dementia.

B

### Comments and evidence

Most studies on risk factors for conversion of mild cognitive impairment to dementia focus on Alzheimer's disease. The clinical state of MCI due to Alzheimer's disease coincides with the pathological stage of completion of A $\beta$  and phosphorylated tau accumulation in the brain. Persons showing an Alzheimer's disease pattern in biomarker study tend to convert to dementia.

#### 1. Humoral markers

##### a. Cerebrospinal fluid<sup>1)</sup>

In a meta-analysis that analyzed 10 studies, cerebrospinal fluid biomarkers predicted conversion from MCI to dementia with the following performance: abnormal A $\beta$ 42 level with 79% sensitivity and 72% specificity, abnormal total tau level with 72% sensitivity and 70% specificity, abnormal phosphorylated tau with 84% sensitivity and 93% specificity, and abnormal ratio of A $\beta$ 42/phosphorylated tau with 85% sensitivity and 79% specificity.

##### b. Genes<sup>2)</sup>

A meta-analysis of 8 studies found that carriers of APOE  $\epsilon$ 4 polymorphism tended to convert from MCI to dementia, with a relative risk of 2.09.

##### c. Blood

Reports of research on various blood biomarkers including proteins and microRNA have been published, but none of the biomarkers showed consistent performance that is reproducible in multiple studies.

#### 2. Imaging biomarkers

##### a. MRI

Cohort studies have reported that the volumes of hippocampus, amygdala, and entorhinal cortex at the start of study were reduced in the group showing conversion compared to the group that did not convert. Moreover, higher atrophy rates of hippocampus, entorhinal cortex, and temporal cortex depicted on serial images taken over time were associated with higher rate of conversion. However, no conclusion has been reached as to the site and size of atrophy, and the rate of atrophy that best predicts conversion<sup>3-7)</sup>.

##### b. FDG-PET<sup>8)</sup>

In a meta-analysis analyzing 14 studies, <sup>18</sup>F-DG-PET predicted conversion with 76% sensitivity and 82% specificity.

##### c. Amyloid PET<sup>9)</sup>

In a meta-analysis that analyzed 11 studies using <sup>11</sup>C-labelled Pittsburgh Compound-B (<sup>11</sup>C-PIB)-PET, this method predicted conversion of MCI to dementia with 96% sensitivity and 58% specificity. There is no meta-analysis of studies using <sup>18</sup>F ligand preparations.

##### d. SPECT<sup>10)</sup>

Although SPECT is a frequently used examination in Japan, this method is not widely used globally. In a meta-analysis of 8 studies, this test predicts conversion with 83.8% sensitivity and 70.4% specificity.

## ■ References

- 1) Ferreira D, Rivero-Santana A, Perestelo-Perez L, et al. Improving CSF biomarkers' performance for predicting progression from mild cognitive impairment to Alzheimer's disease by considering different confounding factors: a meta-analysis. *Front Aging Neurosci.* 2014; 6: 287.
- 2) Fei M, Jianhua W. Apolipoprotein  $\epsilon 4$ -allele as a significant risk factor for conversion from mild cognitive impairment to Alzheimer's disease: a meta-analysis of prospective studies. *J Mol Neurosci.* 2013; 50(2): 257-263.
- 3) Davatzikos C, Bhatt P, Shaw LM, et al. Prediction of MCI to AD conversion, via MRI, CSF biomarkers, and pattern classification. *Neurobiol Aging.* 2011; 32(12): 2322. e19-e27.
- 4) Vemuri P, Wiste HJ, Weigand SD, et al. MRI and CSF biomarkers in normal, MCI, and AD subjects: predicting future clinical change. *Neurology.* 2009; 73(4): 294-301.
- 5) Gomar JJ, Conejero-Goldberg C, Davies P, et al. Extension and refinement of the predictive value of different classes of markers in ADNI: Four-year follow-up data. *Alzheimer's & Dementia.* 2014; 10(6): 704-712.
- 6) Risacher SL, Shen L, West JD, et al. Longitudinal MRI atrophy biomarkers: Relationship to conversion in the ADNI cohort. *Neurobiology of Aging.* 2010; 31(8): 1401-1418.
- 7) Risacher SL, Saykin AJ, West JD, et al. Baseline MRI predictors of conversion from MCI to probable AD in the ADNI cohort. *Current Alzheimer Research.* 2009; 6(4): 347-361.
- 8) Smailagic N, Vacante M, Hyde C, et al. 18F-FDG PET for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). *Cochrane Database Syst Rev.* 2015; 1: CD010632.
- 9) Zhang S, Smailagic N, Hyde C, Noel-Storr AH, Takwoingi Y, McShane R, Feng J. 11C-PIB-PET for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). *Cochrane Database Syst Rev.* 2014; 7: CD010386.
- 10) Yuan Y, Gu ZX, Wei WS. Fluorodeoxyglucose-positron-emission tomography, single-photon emission tomography, and structural MR imaging for prediction of rapid conversion to Alzheimer disease in patients with mild cognitive impairment: a meta-analysis. *AJNR Am J Neuroradiol.* 2009; 30(2): 404-410.

## ■ Search formula

PubMed search: June 27, 2016 (Monday)

#1 ("Mild Cognitive Impairment" [Mesh] OR Mild Cognitive Impairment\* [TIAB]) AND (convert [TIAB] OR conversion [TIAB] OR reversion [TIAB] OR revert [TIAB]) AND ("Biomarkers" [Mesh] OR biomarker\* [TIAB] OR marker\* [TIAB] OR predict\* [TIAB] OR marked\* [TIAB])

Ichushi search: June 27, 2016 (Monday)

#1 (mild cognitive impairment/TH OR mild cognitive impairment/TI) AND (Convert OR Conversion OR Revert OR Reversion) AND (Biomarker/TH OR Marker)

## What rating scales are recommended when mild cognitive impairment (MCI) is suspected?

### Answer

The Mini Mental State Examination (MMSE) is not adequate to detect mild cognitive impairment (MCI). Therefore, the Montreal Cognitive Assessment-Japanese version (MoCA-J) is recommended. Instead of MMSE alone, adding slightly complex memory tasks such as sentence memorization facilitates the diagnosis of amnesic mild cognitive impairment.



### Comments and evidence

The MoCA-J is more challenging than MMSE because the memory task requires recall of five words and the scale also includes tests of frontal lobe function, and is therefore suitable for the diagnosis of MCI. When the cutoff score for MoCA was set at 25/26 out of 30, MCI is diagnosed with 95% sensitivity and 50% specificity for the English version, and 93% sensitivity and 87% specificity for the Japanese version<sup>1, 2)</sup>

Addenbrooke's Cognitive Examination-Revised (ACE-R) is an MMSE test with the addition of other elements including anterograde/retrograde memory, naming words, and visuospatial cognitive function. When the cut-off score is 88/100, ACE-R differentiates MCI with better sensitivity and specificity than MMSE<sup>3)</sup>.

Amnesic MCI can be detected more easily by adding detailed memory tests such as Wechsler Memory Scale-Revised (WMS-R) and Rey Auditory Verbal Learning Test (RAVLT). Although the clock drawing test is widely used, this test has been reported to be unsuitable for the discrimination of MCI because of low sensitivity (58.2%) and specificity (57.3%)<sup>4)</sup>.

Regarding evaluation based on questionnaires and interviews with caregivers, reports have indicated the effectiveness of questionnaires on instrumental activities of daily living and total score of Clinical Dementia Rating (CDR) for diagnosing MCI<sup>5, 6)</sup>. Some studies use CDR 0.5 as a test for MCI, for convenience. Cognitive Function Instrument (CFI), which asks the patient and the family about changes in cognitive activities compared to one year ago, has been reported to be useful for the evaluation of functional abilities before onset of Alzheimer's disease dementia<sup>7)</sup>.

### ■ References

- 1) Smith T, Gildeh N, Holmes C. e Montreal Cognitive Assessment: validity and utility in a memory clinic setting. *Can J Psychiatry* 2007; 52(5): 329-332.
- 2) Fujiwara Y, Suzuki H, Yasunaga M, et al. Brief screening tool for mild cognitive impairment in older Japanese: validation of the Japanese version of the Montreal Cognitive Assessment. *Geriatr Gerontol Int*. 2010; 10(3): 225-232.
- 3) Crawford S, Whitnall L, Robertson J, et al. A systematic review of the accuracy and clinical utility of the Addenbrooke's Cognitive Examination and the Addenbrooke's Cognitive Examination-Revised in the diagnosis of dementia. *Int J Geriatr Psychiatry* 2012; 27(7): 659-669.
- 4) Ehreke L, Lupp M, Luck T, et al. Is the clock drawing test appropriate for screening for mild cognitive impairment? Results of the German study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe). *Dement Geriatr Cogn Disord*. 2009; 28(4): 365-372.
- 5) Zoller AS, Gaal IM, Royer CA, et al. SIST-M-IR activities of daily living items that best discriminate clinically normal elderly from those with mild cognitive impairment. *Curr Alzheimer Res*. 2014; 11(8): 785-791.
- 6) Duara R, Loewenstein DA, Greig-Custo MT, et al. Diagnosis and staging of mild cognitive impairment, using a modification of the clinical dementia rating scale: the mCDR. *Int J Geriatr Psychiatry*. 2010; 25(3): 282-289.
- 7) Amariglio RE, Donohue MC, Marshall GA, et al. Tracking early decline in cognitive function in older individuals at risk for Alzheimer disease dementia: the Alzheimer's Disease Cooperative Study Cognitive Function Instrument. *JAMA Neurol*. 2015; 72(4): 446-454.

## How is mild cognitive impairment (MCI) diagnosed?

### Answer

Mild cognitive impairment (MCI) is originally a concept centered on memory impairment. MCI is classified into amnesic MCI and non-amnesic MCI by the presence or absence of memory impairment. Furthermore, it is divided into single-domain or multiple-domain depending on whether the impairment involves a single cognitive function domain or multiple domains. Similar concept is also found in Clinical Dementia Rating (CDR) 0.5; mild neurocognitive disorder in Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> edition (DSM-5); and mild cognitive disorder (MCD) in International Statistical Classification of Diseases and Related Health Problems, 10<sup>th</sup> revision (ICD-10).

### Comments and evidence

Petersen established the concept that the state of mild cognitive impairment may represent the prodrome stage of dementia<sup>1)</sup>. The diagnostic criteria for MCI were defined in 1995<sup>2)</sup>. Since then, some additions and corrections have been made based on research and books, but the fundamental concept remains unchanged. As subtypes of mild cognitive impairment, amnesic mild cognitive impairment is defined as predominantly memory impairment, and non-amnesic mild cognitive impairment is defined as impairment of other functions including execution, attention, language, and visuospatial cognition<sup>3)</sup>. It should be noted that MCI is a diagnosis based on symptoms, and the pathological background is diverse.

#### 1. Criteria of Petersen<sup>2, 4, 5)</sup>

Mild cognitive impairment is a concept centered on memory impairment, and refers to a state (not dementia) in a person who complains of memory loss and who has low scores in memory tests adjusted for age and years of education. The detailed criteria are as follows.

- Cognitive function has declined compared to before, which is reported by the patient and corroborated by informant and experienced clinical doctor.
- Has impairment in at least one of the following cognitive function domains: memory, execution, attention, language, and visuospatial cognition.
- Is independent in activities of daily living. May require more time than before, or become inefficient, or make mistakes.
- Not dementia.

#### 2. Diagnostic criteria of DSM-5<sup>6)</sup>

In DSM-5, dementia is renamed major neurocognitive disorder, and mild cognitive impairment is termed mild neurocognitive disorder. The diagnostic criteria for mild neurocognitive disorder in DSM-5 include mild decline in one or more cognitive domains that can be confirmed from cognitive function tests and a reliable informant, but the impairment does not interfere with daily life. These criteria are not much different from other diagnostic criteria. On the other hand, regarding the results of neuropsychological test battery, the decline in cognitive function is described as -1 to -2SD. This range differs slightly from the NIA-AA criteria, which will be described later.

#### 3. Diagnostic criteria of ICD-10<sup>7)</sup>

In ICD-10, mild cognitive disorder (MCD) is adopted as a concept equivalent to mild cognitive impairment.

#### 4. Clinical Dementia Rating (CDR) 0.5<sup>8)</sup>

The CDR evaluates memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care; each scored on a 5-grade scale of 0, 0.5, 1, 2, and 3. The overall score is determined after weighting. An overall score of 0.5 corresponds to mild cognitive impairment.

#### 5. Diagnostic criteria of National Institute on Aging–Alzheimer’s Association workgroup (NIA-AA)<sup>9, 10)</sup>

In addition to clinical diagnostic criteria, biomarker criteria are provided in the NIA-AA criteria. The degree of cognitive decline based on the neuropsychological test battery is described as -1 to -1.5 SD compared with age- and education-matched peers, which is slightly different from that described in DSM-5.

## 6. Criteria of International Working Group-2 <sup>11)</sup>

In the diagnostic criteria for Alzheimer's disease published in 2014, an attempt was made to change the conventional division of "preclinical Alzheimer's disease", "prodromal Alzheimer's disease", and "Alzheimer's disease dementia" into two groups: "preclinical Alzheimer's disease" and "Alzheimer's disease". In other words, the concept is not to distinguish between mild cognitive impairment and dementia based on the pathological background of Alzheimer's disease, but to diagnosis Alzheimer's disease when clinical symptoms are present, including amnesia alone.

### ■ References

- 1) Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment clinical characterization and outcome. *Arch Neurol.* 1999; 56(3): 303-308.
- 2) Petersen RC, et al., Apolipoprotein E status as a predictor of the development of Alzheimer's disease in memory-impaired individuals. *JAMA.* 1995; 273(16): 1274-1278.
- 3) Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med.* 2004; 256(3): 183-194.
- 4) Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. *Arch Neurol.* 2001; 58(12): 1985-1992.
- 5) Petersen RC. Clinical practice. Mild cognitive impairment. *New Engl J Med.* 2011; 364(23): 2227-2234.
- 6) American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition: DSM-5.* Arlington VA: American Psychiatric Association; 2013.
- 7) World Health Organization. *International Statistical Classification of Diseases and Related Health Problems. 10th Revision.* Geneva: World Health Organization; 1993.
- 8) Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology.* 1993; 43(11): 2412-2414.
- 9) Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011; 7(3): 270-279.
- 10) Arai H. Diagnosis of mild cognitive impairment with Alzheimer's disease in the background: proposal from the National Institute on Aging-Alzheimer's Association workgroups. *Cognition Dementia* 2012; 11(3): 19-27. (In Japanese)
- 11) Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol.* 2014; 13: 614-629.

### ■ Search formula

PubMed search: June 5, 2015 (Friday), August 26, 2015 (Wednesday)

```
#1 "Mild Cognitive Impairment/diagnosis" [Majr] OR ("Mild Cognitive Impairment" AND "Cognition Disorders/diagnosis"[Majr]) OR ("Mild Cognitive Impairment" [TI] AND "Cognition Disorders/diagnosis"[Mesh] AND criteria [TIAB]) AND ("Diagnosis, Differential" [Mesh] OR ("diagnostic criteria")) OR ("Alzheimer Disease/diagnosis" [Majr] AND "diagnostic criteria" [TI]) OR ("clinical dementia rating" AND "Dementia/psychology" [Majr] AND "Psychiatric Status Rating Scales" [Majr])
```

Ichushi search: June 5, 2015 (Friday)

```
#1 (mild cognitive impairment/MTH OR mild cognitive impairment/TI) AND (SH = Diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, radionuclide diagnosis, ultrasound diagnosis)
```



## Are there methods to prevent progression from mild cognitive impairment (MCI) to dementia?

### Recommendation

Control of hypertension, diabetes, dyslipidemia and other risk factors, as well as continued practice of moderate exercise are recommended. There is no sufficient evidence that anti-dementia drugs should be used for the purpose of preventing progression to dementia in persons with mild cognitive impairment.

2C

### Comments and evidence

Methods for preventing progression from mild cognitive impairment to dementia include pharmacotherapy, non-pharmacological therapies, and interventions for risk factors.

For pharmacotherapy, the effect of cholinesterase inhibitors in improving cognitive function has been confirmed in patients with mild cognitive impairment, but the effect of preventing progression from mild cognitive impairment to dementia remains unclear<sup>1-3</sup>). Estrogen therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), extract from leaves of ginkgo tree (*Ginkgo biloba*), and vitamin E have been studied, but the effect of preventing progression from mild cognitive impairment to dementia has not been confirmed for any of these treatments.

Non-pharmacological therapies including moderate physical activity, aerobic exercise, Mediterranean diet, cocoa, and smoking cessation have been suggested to be effective, but most studies were conducted in a small number of subjects and hence do not provide sufficient evidence<sup>4-6</sup>). Several studies suggest that cognitive rehabilitation or cognitive training is effective in maintaining and improving cognitive function, but further intervention studies are needed to standardize intervention and assessment methods<sup>7-10</sup>) (see CQ4A).

Studies have clarified that a history of hypertension, diabetes, dyslipidemia (hypercholesterolemia) or cerebrovascular disorders is a risk factor that promotes progression from mild cognitive impairment to dementia, not only for vascular dementia but also for Alzheimer's disease dementia<sup>11</sup>). Although there is still insufficient evidence that controlling these risk factors can prevent progression to dementia, appropriate control is recommended for patients with these risk factors (see CQ4A).

### References

- 1) Doody RS, Ferris SH, Salloway S, et al. Donepezil treatment of patients with MCI: a 48-week randomized, placebo-controlled trial. *Neurology*. 2009; 72(18): 1555-1561.
- 2) Russ TC, Morling JR. Cholinesterase inhibitors for mild cognitive impairment: Cochrane Database Syst Rev. 2012; (9): CD009132.
- 3) Tricco AC, et al. Efficacy and safety of cognitive enhancers for patients with mild cognitive impairment: a systematic review and meta-analysis. *CMAJ*. 2013; 185: 1393-1401.
- 4) Baker LD, Frank LL, Foster-Schubert K, et al. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Arch Neurol*. 2010; 67(1): 71-79.
- 5) Etgen T, Sander D, Bickel H, et al. Mild cognitive impairment and dementia: the importance of modifiable risk factors. *Dtsch Arztebl Int*. 2011; 108(44): 743-750.
- 6) Scarmeas N, Stern Y, Mayeux R, et al. Mediterranean diet and mild cognitive impairment. *Arch Neurol*. 2009; 66(2): 216-225.
- 7) Teixeira CVL, Gobbi LT, Corazza DI, et al. Non-pharmacological interventions on cognitive functions in older people with mild cognitive impairment (MCI). *Arch Gerontol Geriatr*. 2012; 54(1): 175-180.
- 8) Simon SS, Yokomizo JE, Bottino CM, et al. Cognitive intervention in amnesic Mild Cognitive Impairment: a systematic review. *Neurosci Biobehav Rev*. 2012; 36(4): 1163-1178.
- 9) Gates NJ, Sachdev PS, Fiatarone Singh MA, et al. Cognitive and memory training in adults at risk of dementia: a systematic review. *BMC Geriatr*. 2011; 11: 55. doi: 10.1186/1471-2318-11-55.
- 10) Law LL, Barnett F, Yau MK, et al. Effects of functional tasks exercise on older adults with cognitive impairment at risk of Alzheimer's disease: a randomised controlled trial. *Age Ageing*. 2014; 43(6): 813-820.
- 11) Li J, Wang YJ, Zhang M, et al. Vascular risk factors promote conversion from mild cognitive impairment to Alzheimer disease. *Neurology*. 2011; 76(17): 1485-1491.

## ■ Search formula

PubMed search: July 17, 2015 (Friday), August 26, 2015 (Wednesday)

#1 ("Mild Cognitive Impairment" [Majr] OR ("mild cognitive impairment" [TI] OR MCI [TI]) AND (prevent\* OR improvement OR therapy OR therapeutic OR treatment OR training OR rehabilitation OR intervention OR program OR prophylaxis\*)) OR ("mild cognitive impairment" [TI] OR MCI [TI]) AND "Cognition Disorders/therapy" [Mesh]) AND ("Dementia/prevention and control" [Mesh] OR (dementia AND (prevent\* OR prophylaxis\*)) OR "Cognition Disorders/prevention and control" [Mesh] OR ((cognition disorder\* OR cognitive disorder\*) AND (prevent\* OR prophylaxis\*))) OR ("mild cognitive impairment" [TI] OR MCI [TI]) AND "Cognition Disorders" [Majr] AND "Dementia/epidemiology" [Majr] AND prevent\*)

Ichushi search: July 17, 2015 (Friday)

#1 (Mild cognitive impairment/TH OR Mild cognitive impairment/TI OR MCI/TI) AND ((SH = Therapeutic use, Treatment, Drug treatment, Surgical treatment, Transplantation, Dietary treatment, Psychiatric treatment, Radiologic treatment, Rehabilitation, Prevention) OR Treatment/TH OR Treatment/TI OR Therapy/TI OR Rehabilitation/TI OR Training/TI OR Training/TI OR Program/TI) AND (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI OR Cognitive function impairment/TI) AND ((SH = Prevention) OR Prevention/TH OR Prevention/TI)

## What kinds of guidance and support are available for people with mild cognitive impairment (MCI)?

### Answer

It is necessary to provide proper information about mild cognitive impairment to the patients as well as caregivers in order to promote correct understanding of the disease.

Provide support to enable the patients to continue living independently for as long as possible by introducing assistive devices utilizing information technology (IT), practicing the use of calendars and notebooks, and modifying the living environment.



### Comments and evidence

Unlike those with dementia, persons at the stage of mild cognitive impairment (MCI) are independent in basic activities of daily living (ADL). Therefore, daily care and support for these persons are not necessary. However, in situations such as heart failure where self-care is required, MCI may worsen the prognosis.

The memory support system (MSS) that trains patients to enter schedules and events in calendars and notebooks can be expected to improve ADL and self-efficacy of patients with MCI and reduce the burden on caregivers<sup>1)</sup>. Acquiring a habit of using calendars and notebooks would also be helpful in the future when mild cognitive impairment has progressed to dementia.

Risk factors for lifestyle-related diseases such as hypertension, diabetes, and dyslipidemia can become risk factors that promote progression from mild cognitive impairment to dementia. Therefore, it is necessary to provide guidance on lifestyle modification and medication management.

It is necessary to first of all help the patient and family understand correctly that mild cognitive impairment is an unstable condition that may progress to dementia or may return to normal cognition, and then provide guidance to prepare for progression to dementia in the future.

See also CQ3A-1.

### ■ References

- 1) Greenaway MC, Duncan NL, Smith GE. e memory support system for mild cognitive impairment: randomized trial of a cognitive rehabilitation intervention. *Int J Geriatr Psychiatry*. 2013; 28(4): 402-409.

### ■ Search formula

PubMed search: July 18, 2015 (Saturday), July 23, 2015 (Thursday)

```
#1 (("Mild Cognitive Impairment" [Mesh] OR "mild cognitive impairment" [TI] OR MCI [TI]) AND ("Patient Care" [Mesh] AND management* OR "Health Education" [Mesh] OR education [TI] OR support* [TI] OR guidance[TI] OR instruction [TI] OR service* [TI])) OR ("Mild Cognitive Impairment" [Mesh] OR "mild cognitive impairment" [TI] OR MCI [TI]) AND ("Health Education" [Mesh] OR education [TI] OR support* [TI] OR guidance [TI] OR instruction [TI] OR service* [TI]) AND ("Patient Care" [Mesh] OR "Patient Care Management" [Mesh] OR patient* [TI] OR management* [TI] OR care [TI]))
```

Ichushi search: July 17, 2015 (Friday)

```
#1 (Mild cognitive impairment/TH OR <Mild cognitive impairment/TI OR MCI/TI) AND (Patient care management/TH OR Health education/TH OR Home care support service/TH OR Social support/TH OR Mental support/TH) AND (Support/TI OR Guidance/TI OR Education/TI OR Support/TI OR Support/TI OR Guidance/TI OR Instruction/TI OR Service/TI)
```

# C | Disease Severity and Interventions According to Severity

## CQ 4C-1

### What kind of guidance and support can be given to persons with mild to moderate dementia?

#### Answer

Case management (care management) has been reported to be effective in reducing admission to care facilities and costs of care in the short term. Education on dementia and peer support are effective in improving the patients' depressive state and quality of life (QOL).



#### Comments and evidence

Case management is carried out by professionals such as nurses and social workers, and involves a variety of activities including coordination of care and formulation of a care plan according to the needs of the persons with dementia living in the community. According to a review of 13 randomized controlled trials (RCTs), case management is effective in reducing admission to care facilities and long-term care costs in the short term, but the long-term effect is uncertain<sup>1)</sup>.

Social support groups for people with dementia provide a venue for education related to dementia, mutual assistance, peer support, and information exchange. They are effective in improving the patients' depression state, QOL, and self-esteem<sup>2)</sup>.

A multi-disciplinary educational program for persons with early-stage dementia and their families should contain a core component of medical knowledge about the symptoms and progression of dementia<sup>3)</sup>.

Many cognitive training or cognitive rehabilitation programs are conducted for the purpose of improving cognitive function centered on memory. Cognitive rehabilitation has been suggested to improve ADL in patients with mild Alzheimer's disease dementia<sup>4)</sup>. Cognitive training provides training of specific tasks targeting cognitive functions, while cognitive rehabilitation introduces compensatory approaches to meet patients' needs.

Many research articles have suggested the effectiveness of non-pharmacological therapies such as reminiscence therapy, validation therapy, music therapy, exercise, aromatherapy<sup>5)</sup>, and light therapy<sup>6)</sup>. However, there are issues in these reports concerning the quality of evidence. Therefore these therapies cannot be actively recommended.

Assistive devices using computer and robotic assistance for ADL and entertainment activities are being evaluated in clinical trials, and future development can be expected. A system that prompts bathing and other activities at specific time is effective for persons with mild dementia<sup>7)</sup>. In a study of persons with moderate Alzheimer's disease dementia, presenting pictorial step-by-step instructions of work procedures on a computer allowed the patients to make coffee and snacks by themselves<sup>8)</sup>. In addition, the patients were able to enjoy music by choosing from music options by themselves<sup>8)</sup>.

#### ■ References

- 1) Reilly S, Miranda-Castillo C, Malouf R, et al. Case management approaches to home support for people with dementia. *Cochrane Database Syst Rev.* 2015; 1: CD008345.
- 2) Leung P, Orrell M, Orgeta V. Social support group interventions in people with dementia and mild cognitive impairment: a systematic review of the literature. *Int J Geriatr Psychiatry.* 2015; 30(1): 1-9.
- 3) Seike A, Sumigaki C, Takeda A, et al. Developing an interdisciplinary program of educational support for early-stage dementia patients and their family members: an investigation based on learning needs and attitude changes. *Geriatr Gerontol Int.* 2014; 14 Suppl 2: 28-34.
- 4) Bahar-Fuchs A, Clare L, Woods B. Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia. *Cochrane Database Syst Rev.* 2013; (6): CD003260.
- 5) Forrester LT, Maayan N, Orrell M, et al. Aromatherapy for dementia. *Cochrane Database Syst Rev.* 2014; (2): CD003150.
- 6) Forbes D, Blake CM, Thiessen EJ, et al. Light therapy for improving cognition, activities of daily living, sleep, challenging behaviour, and psychiatric disturbances in dementia. *Cochrane Database Syst Rev.* 2014; (2): CD003946.
- 7) Mokhtari M, Aloulou H, Tiberghien T, et al. New trends to support independence in persons with mild dementia: a mini-review. *Gerontology.* 2012; 58(6): 554-563.
- 8) Lancioni GE, Singh NN, O'Reilly MF, et al. Persons with moderate Alzheimer's disease use simple technology aids to manage daily activities and leisure occupation. *Res Dev Disabil.* 2014; 35(9): 2117-2128.

## ■ Search formula

PubMed search: July 17, 2015 (Friday), August 26, 2015 (Wednesday)


#1 (("Dementia" [Majr] OR dementia [TI] OR alzheimer\* [TI]) AND ("early stage" [TI] OR mild [TI] OR moderate [TI] OR "Patient Acuity" [Mesh])) OR ((dementia OR alzheimer\*) AND ("early stage" OR mild OR moderate)) AND ("Patient Care" [Mesh] OR "Health Education" [Mesh]) AND (education [TI] OR support\* [TI] OR guidance [TI] OR instruction [TI] OR service\* [TI] OR management [TI])

Ichushi search: July 17, 2015 (Friday)

#1 (Dementia/TH OR Dementia/TI) AND (Mild/TI OR Moderate/TI OR severity/TH) AND (Patient care management/TH OR Health education/TH OR Home care support service/TH OR Social support/TH OR Mental support/TH) AND (Support/TI OR Guidance/TI OR Education/TI OR Support/TI OR Support/TI OR Guidance/TI OR Instruction/TI OR Service/TI)

## What kind of guidance and support can be given to caregivers of persons with mild to moderate dementia?

### Answer

Educational support for caregivers of persons with dementia is effective in lessening their care burden and depressive state. Telephone counseling and Internet educational programs are also effective. 

### Comments and evidence

Caregivers of persons with dementia often report feeling the care burden and depressive symptoms. According to a meta-analysis of studies that provide educational interventions for caregivers of persons with dementia, a moderate beneficial effect on care burden and a small beneficial effect on the depressive state were observed, but the effects of improving quality of life (QOL) and reducing admission to care facilities were not clear<sup>1)</sup>.

A meta-analysis on counseling using telephone found a significant effect in improving the caregivers' depressive state<sup>2)</sup>.

There is also a study suggesting the effectiveness of caregiver education via the Internet<sup>3)</sup>, and this method may be further developed by the widespread use of the Internet.

An Italian study was conducted using reduction of caregiver burden and avoidance of admission of persons with dementia to care facilities as markers of effectiveness of an intervention program for caregivers. In this study, case management, visits by nurses, and introduction of technological devices were effective in reducing care burden and avoiding admission to care facilities<sup>4)</sup>.

A meta-analysis of 78 studies on caregiver interventions showed significant improvements in caregivers' feeling of care burden, depression, subjective well-being, satisfaction, and ability/knowledge, as well as care receivers' symptoms. The intervention effect for caregivers of persons with dementia was less than that for other groups of caregivers. Psychoeducational or psychotherapeutic interventions showed the most consistent short-term effects<sup>5)</sup>.

See also CQ3A-1.

### ■ References

- 1) Jensen M, Agbata IN, Canavan M, et al. Effectiveness of educational interventions for informal caregivers of individuals with dementia residing in the community: systematic review and meta-analysis of randomised controlled trials. *Int J Geriatr Psychiatry*. 2015; 30(2): 130-143.
- 2) Lins S, Hayder-Beichel D, Rucker G, et al. Efficacy and experiences of telephone counselling for informal carers of people with dementia. *Cochrane Database Syst Rev*. 2014; (9): CD009126.
- 3) Blom MM, Zarit SH, Groot Zwaafink RB, et al. Effectiveness of an Internet intervention for family caregivers of people with dementia: results of a randomized controlled trial. *PLoS One*. 2015; 10(2): e0116622.
- 4) Chiatti C, Rimland JM, Bonfranceschi F, et al. The UP-TECH project, an intervention to support caregivers of Alzheimer's disease patients in Italy: preliminary findings on recruitment and caregiving burden in the baseline population. *Aging Ment Health*. 2015; 19(6): 517-525.
- 5) Sorensen S, Pinquart M, Duberstein P. How effective are interventions with caregivers? An updated meta-analysis. *Gerontologist*. 2002; 42(3): 356-372.

### ■ Search formula

PubMed search: July 17, 2015 (Friday)

```
#1 (((("Dementia" [Majr] OR dementia [TI] OR alzheimer* [TI]) AND ("early stage" [TI] OR mild [TI] OR moderate [TI])) AND ("Caregivers" [Mesh] OR "Family" [Mesh] OR caregiver* [TI] OR family* [TI]) AND ("Patient Care" [Mesh] OR "Health Education" [Mesh] OR education [TI] OR support* [TI] OR guidance [TI] OR instruction [TI] OR service* [TI])) OR ((dementia OR alzheimer*) AND ("early stage" OR mild OR moderate) AND (caregiver* OR family) AND (education OR support* OR guidance OR instruction OR service*)))
```

Ichushi search: July 17, 2015 (Friday)

```
#1 (Dementia/TH OR Dementia/TI) AND (Mild/TI OR Moderate/TI OR severity/TH) AND (Caregiver/TH OR Caregiver/TI OR Care personnel/TH OR Family/TH OR Family/TI) AND (Patient care management/TH OR Health education/TH OR Home care support service/TH OR Social support/TH OR Mental support/TH OR Support/TI OR Guidance/TI OR Education/TI OR Support/TI OR Support/TI OR Guidance/TI OR Instruction/TI OR Service/TI)
```

## What kind of guidance and support can be given to persons with severe dementia?

### Answer

For persons with severe dementia, it is desirable to help them receive medical and long-term care continuously without changing their living environment or lifestyle as far as possible.



### Comments and evidence

Persons with severe dementia have increased frequencies of physical symptoms including loss of appetite, sleep disturbance, urinary disorders such as incontinence, defecation disorders such as constipation, and gait disturbance. There are also more emergency admissions for infections, cerebrovascular disorders, and undernutrition. A study has found when these patients require emergency admission, admission to a special ward cared by a team comprising doctor, nurse, physiotherapist, social worker, and counselor, and then having the same team in charge of home care after discharge resulted in significantly less behavioral disturbance, use of fewer antipsychotic drugs, and less caregiver stress compared to admission to a general ward<sup>1)</sup>. It is desirable to coordinate the system to enable patients to receive continuous medical and long-term care, so that they can receive medical care in a familiar environment without changing their lifestyle.

For persons with severe dementia, admission to care facilities is an important consideration. A report has shown that while appropriate home care management can delay admission to care facilities, it is ultimately impossible to avoid facility admission for persons with severe dementia<sup>2)</sup>. In addition, it is also known that the cost of nursing care increases as the severity of dementia increases<sup>3)</sup>. Compared to mild and moderate cases, the difference between the costs of institutional care and the costs of home care is small.

There is no research with high-level evidence on the treatment of pneumonia and nutritional disorders in persons with severe dementia. For management of dysphagia, hand feeding of small portions by a caregiver (comfort feeding by hand) with mouth care is preferable to tube feeding<sup>4)</sup>.

In a survey of a nursing home in the United States, patients with severe dementia were given quinolone and cephalosporin antibiotics without adequate evidence, resulting in extensive colonization of multidrug-resistant bacteria. Comfort is the goal of care for many patients with advanced dementia, and more sensible use of antibacterial drugs is desirable<sup>5, 6)</sup>.

### References

- 1) Tibaldi V, Aimonino N, Ponzetto M, et al. A randomized controlled trial of a home hospital intervention for frailty elderly demented patients: behavioral disturbances and caregiver's stress. *Arch Gerontol Geriatr Suppl.* 2004; (9): 431-436.
- 2) Eloniemi-Sulkava U, Norkola IL, Hentinen M, et al. Effects of supporting community-living demented patients and their caregivers: a randomized trial. *J Am Geriatr Soc.* 2001; 49(10): 1282-1287.
- 3) Lopez-Bastida J, Serrano-Aguilar P, Perestelo-Perez L, et al. Social-economic costs and quality of life of Alzheimer disease in the Canary Islands, Spain. *Neurology.* 2006; 67(12): 2186-2191.
- 4) Arcand M. End-of-life issues in advanced dementia: Part 2: management of poor nutritional intake, dehydration, and pneumonia. *Can Fam Physician.* 2015; 61(4): 337-341.
- 5) Mitchell SL, Shaffer ML, Loeb MB, et al. Infection management and multidrug-resistant organisms in nursing home residents with advanced dementia. *JAMA Intern Med.* 2014; 174(10): 1660-1667.
- 6) Yates E, Mitchell SL, Habtemariam D, et al. Interventions associated with the management of suspected infections in advanced dementia. *J Pain Symptom Manage* 2015; 50(6): 806-813.

### Search formula

PubMed search: July 17, 2015 (Friday)

```
#1 (((“Dementia” [Majr] OR dementia [TI] OR alzheimer* [TI]) AND (advanced [TI] OR severe [TI])) OR ((dementia OR alzheimer*) AND (advanced OR severe))) AND (“Patient Care” [Mesh] OR “Health Education” [Mesh]) AND (education [TI] OR support* [TI] OR guidance [TI] OR instruction [TI] OR service* [TI] OR management [TI]))
```

Ichushi search: July 17, 2015 (Friday)

```
#1 (Dementia/TH OR Dementia/TI) AND Advanced/TI AND (Patient care management/TH OR Health education/TH OR Home care support service/TH OR Social support/TH OR Mental support/TH) AND (Support/TI OR Guidance/TI OR Education/TI OR Supprt/TI OR Support/TI OR Guidance/TI OR Instruction/TI OR Service/TI)
```

## What kind of guidance and support can be given to caregivers of persons with severe dementia?

### Answer

Providing support to caregivers can help maintain the quality of life (QOL) of the caregivers and reduce their psychological burden. Support given by a multidisciplinary team is recommended to enable patients with dementia to receive continuous medical and long-term care.



### Comments and evidence

A family booklet about comfort care for persons with severe dementia may be useful<sup>1)</sup>. The contents of the booklet consist of symptoms, decision-making, and treatments accompanying progression of Alzheimer's disease dementia, and the booklet is perceived as acceptable and useful by bereaved families of persons with dementia in Canada, Holland and Italy.

Support through telephone is also effective. Sixteen telephone conversations in six months from therapists who provided educational instructions to caregivers systematically improved caregivers' depressive symptoms and reactions to care recipients' behaviors<sup>2)</sup>.

Since caring for persons with severe dementia imposes heavy burden on caregivers 24 hours a day, 365 days a year, the use of respite care is recommended. However, there are few high-quality studies on respite care, and the benefits and adverse effects have not been clarified so far<sup>3)</sup>.

### ■ References

- 1) van der Steen JT, Arcand M, Toscani F, et al. A family booklet about comfort care in advanced dementia: three-country evaluation. *J Am Med Dir Assoc.* 2012;13(4): 368-375.
- 2) Tremont G, Davis JD, Papandonatos GD, et al. Psychosocial telephone intervention for dementia caregivers: A randomized, controlled trial. *Alzheimers Dement.* 2015;11(5): 541-548.
- 3) Maayan N, Soares-Weiser K, Lee H. Respite care for people with dementia and their carers. *Cochrane Database Syst Rev.* 2014;(1): CD004396.

### ■ Search formula

PubMed search: July 17, 2015 (Friday)

#1 (("Dementia" [Majr] OR dementia [TI] OR alzheimer\* [TI]) AND (advanced [TI] OR severe [TI])) AND ("Caregivers" [Mesh] OR "Family" [Mesh] OR caregiver\* [TI] OR family\* [TI]) AND ("Patient Care" [Mesh] OR "Health Education" [Mesh] OR education [TI] OR support\* [TI] OR guidance [TI] OR instruction [TI] OR service\* [TI] OR management\* [TI]) OR ((dementia OR alzheimer\*) AND (advanced OR severe) AND (caregiver\* OR family) AND (education OR support\* OR guidance OR instruction OR service\* OR management\*))

Ichushi search: July 17, 2015 (Friday)

#1 (Dementia/TH OR Dementia/TI) AND Severity/TI AND (Caregiver/TH OR Caregiver/TI OR Care personnel/TI OR Family/TH OR Family/TI) AND (Patient care management/TH OR Health education/TH OR Home care support service/TH OR Social support/TH OR Mental support/TH OR Support/TI OR Guidance/TI OR Education/TI OR Support/TI OR Support/TI OR Guidance/TI OR Instruction/TI OR Service/TI)



## How should end-of-life care be given to persons with dementia?

### Answer

In the terminal stage of persons with advanced dementia, providing medical care and general care with an emphasis on alleviating the person's pain is desirable.



### Comments and evidence

The survival prognosis for persons with advanced dementia is extremely poor. A survey conducted at nursing homes in the United States on 323 persons (median age 86.0 years) with Global Deterioration Scale (GDS) stage 7 dementia found a 24.7% probability of death within 6 months and a median survival duration of 478 days, which was equivalent to the life expectancy of metastatic breast cancer and stage IV congestive heart failure<sup>1)</sup>.

No method has been established to predict the survival prognosis of persons with dementia<sup>2)</sup>. Medicare in the United States requires Functional Assessment Staging (FAST) stage 7c as a requirement for initiation of palliative care, but this is not a reliable predictor of death after 6 months<sup>2)</sup>.

Persons with advanced dementia may experience pain, breathing difficulty, and anorexia, as in patients with terminal stage cancer, but control of these conditions is extremely inadequate in persons with dementia<sup>3)</sup>. In the terminal stage of persons with advanced dementia, care based on advance care planning (ACP)<sup>4)</sup> aiming at comfort of the person rather than prolonging life is desirable, but the introduction of ACP is not easy in clinical practice<sup>3)</sup>. According to observational studies, tube feeding is not recommended because the benefits are unclear. Report suggests the effectiveness of palliative care or hospice care<sup>4)</sup>. Appropriate assessment and management of pain as well as effective management of behavioral problems can improve the quality of life (QOL) of persons with severe dementia<sup>6)</sup>.

Persons with advanced dementia often have difficulties with self-determination and confirmation of intent. As an alternative, decision has to be based on presumed intent, proxy intent, or prior intent. Based on the opinions of the family, speculate the patient's intent as far as possible and respect it. As a tool that supports the decision-making process through discussions between the parties concerned, the Japan Geriatrics Society has published the "Guidelines for the decision-making process in medical and long-term care for the elderly: focusing on the initiation of artificial hydration and nutrition"<sup>7)</sup>.

The family plays an important role in end-of-life care. At the same time, since the family is under great mental and physical stress, support for the family is important. In addition, after the person with dementia has died, grief care for the family is necessary.

### References

- 1) Mitchell SL, Teno JM, Kiely DK, et al. The clinical course of advanced dementia. *N Engl J Med.* 2009;361(16): 1529-1538.
- 2) Brown MA, Sampson EL, Jones L, et al. Prognostic indicators of 6-month mortality in elderly people with advanced dementia: a systematic review. *Palliat Med.* 2013;27(5): 389-400.
- 3) Sampson EL. Palliative care for people with dementia. *Br Med Bull.* 2010;96: 159-174.
- 4) Mitchell SL. Clinical Practice. Advanced dementia. *N Engl J Med.* 2015;372(26): 2533-2540.
- 5) Sampson EL, Jones L, Thune-Boyle IC, et al. Palliative assessment and advance care planning in severe dementia: an exploratory randomized controlled trial of a complex intervention. *Palliat Med.* 2011;25(3): 197-209.
- 6) Corder Z, Blass DM, Rabins PV, et al. Quality of life in nursing home residents with advanced dementia. *J Am Geriatr Soc.* 2010;58(12): 2394-2400.
- 7) Japan Geriatrics Society. Guidelines for the decision-making processes in medical and long-term care for the elderly: focusing on the initiation of artificial hydration and nutrition. *Japanese Journal of Geriatrics.* (Nihon Ronen Igakkai Zasshi) 2012; 49(5): 632-645 (In Japanese)

### Search formula

PubMed search: July 17, 2015 (Friday)

```
#1 ("Dementia" [Mesh] OR dementia [TI] OR alzheimer* [TI]) AND (advanced [TI] OR severe [TI]) AND ("Terminal Care" [Mesh] OR "Advance Care Planning" [Mesh] OR "Palliative Care" [Mesh] OR "terminal care" [TI] OR hospice [TI] OR "palliative care" [TI] OR "end of life" [TI] OR bereavement* [TI]) OR ((dementia OR alzheimer*) AND (advanced OR severe) AND ("terminal care" OR hospice OR "palliative care" OR "end of life" OR bereavement*))
```

Ichushi search: July 18, 2015 (Saturday)

```
#1 (Dementia/TH OR Dementia/TI) AND (Severe/TI OR Advanced dementia/AL OR End-stage dementia/AL) AND (Terminal care/TH OR Terminal care/TI OR Advance care plan/TH OR Advance care plan/TI OR Palliative care/TH OR Palliative care/TI OR Hospice/TH OR Hospice/TI OR Bereavement/TH OR Bereavement/TI)
```