Yonago Acta Medica 2022;65(3):184–190 doi: 10.33160/yam.2022.08.001

Dementia Prevention and Aromatherapy in Japan

Katsuya Urakami*

** Department of Dementia Prevention, School of Health Science, Faculty of Medicine, Tottori University, Yonago 683-8503, Japan*

ABSTRACT

Until recently, it was thought that dementia prevention was not possible. However, a recent paper reported that 40% of the risk factors for developing dementia are modifiable. Large-scale clinical studies on dementia prevention and various initiatives to reduce the risk of developing dementia have been made worldwide. In addition to the introduction of a global initiative in dementia prevention, I also introduce the results of our research on the development of the Tottori method dementia prevention program and aromatherapy to approach olfactory impairment in Alzheimer's disease.

Key words Alzheimer's disease; aromatherapy; MCI; non-pharmacological treatment; olfactory impairment

Currently, there is no cure for dementia; therefore, its prevention has gathered increasing attention.[1] In the case of Alzheimer's disease, a dementia-causing disease, deposition of amyloid β-protein appeared as an early pathological change.[2] The aggregation of amyloid β-protein becomes insoluble.[3] This leads to the formation of senile plaques, followed by changes in neurofibrillary tangles through the deposition of phosphorylated tau protein, which finally results in neuronal cell death.[4] It was believed that neurodegeneration pathway was irreversible. In recent years, however, it has become clear that amyloid β-proteins can, in fact by solublilised,[5] not only by drugs[6] but also by non-drugs.[7] The former is the fundamental medical treatment for Alzheimer's disease, while the latter is being taken up as a preventive treatment. This study focuses on preventive treatments for dementia, specifically on aromatherapy, which has recently attracted attention.

Corresponding author: Katsuya Urakami, MD, PhD
kurakami@tottori-u.ac.jp
Received 2021 October 13
Accepted 2022 June 30
Online published 2022 August 1
Abbreviations: ADAS, Alzheimer's disease assessment scale; GBS scale, the Gottfries-Brane-Steen scale; MCI, mild cognitive impairment; OSIT-J, the Odor Stick identification test for Japanese, ROC, Receiver Operating Characteristic; SAMP8 mice, senescence-accelerated 8 mice; TDAS, Touch panel-type dementia assessment scale

DEFINITION OF DEMENTIA PREVENTION

For all diseases, including dementia, there are different types of prevention. Primary prevention refers to predicting the onset of diseases. Secondary prevention involves the early detection and treatment of diseases. Tertiary prevention entails stopping the progression of diseases. In general, people associate preventive treatments with primary prevention, but the broader definition of prevention, from primary to tertiary, should be kept in mind for the prevention of all diseases. Since dementia is no longer considered a special disease, it is appropriate to use this broader concept for its prevention as well. The present study describes primary prevention strategies for dementia.

RISK FACTORS FOR DEMENTIA

In 2017,[8] it was revealed that 35% of the identified risk factors for dementia can be modified among the risk factors. Previously, none of the risk factors were known to be modifiable. Further, risk factors differ among age groups. For instance, in early life, risk factors for dementia include less education,[9] in midlife they include hearing loss,[10] hypertension,[11] and obesity,[12] and in late life they include smoking,[13] depression,[14] physical inactivity,[15] social isolation,[16] and diabetes.[17] Therefore, prevention strategies should be tailored to specific age groups.

For example, obesity is a risk factor in midlife, but not in late life. Therefore, taking measures against obesity in midlife is useful, but taking similar measures in other life stages would not contribute to dementia prevention. Specifically, aerobic exercise is highly recommended as a measure against obesity, but continuing such exercises in late life is likely to lead to muscle volume loss and weakness. Instead in late life, muscle training should be emphasised.

Surprisingly, hearing loss (9%) is considered the highest risk factor.[8] Thus, hearing loss treatment should be sought immediately, and hearing aids should be worn as soon as possible. Hearing training for less severe cases of hearing loss will also be needed in the near future.

More recently, in 2020, a review[18] of the literature on risk factors for dementia reported an increase in the percentage of risk factors that are modifiable (i.e. 40%). It is expected that more factors will be found to

be modifiable in the future, including traumatic brain injury[19] and excessive alcohol intake[20] in midlife, and air pollution[21] in late life.

DEMENTIA PREVENTION ACTIVITIES

The most appropriate target for dementia prevention activities is people with mild cognitive impairment (MCI).[22] MCI is commonly referred to as the pre-stage of dementia.[23] While dementia is irreversible, MCI is a reversible condition.[24] As of 2012, 4 million people had been diagnosed with MCI in Japan.[25] It is, of course, important for people with normal cognitive function to engage in dementia prevention activities, but they are less likely to develop dementia than those with MCI. Therefore, the outcome of prevention activities is unknown for people with normal cognitive function.

MCI has been found to progress to dementia in 10–20% of cases each year, which highlight is why people with MCI are the most suitable subjects for dementia prevention from an outcome perspective.[26] However, it is not easy to detect MCI. Consequently, I have developed computer-based screening method with touch-panel type for early and easy detection of MCI.[27, 28] As a primary screening method, a program for forgetfulness consultation was created, which evaluates the three most important cognitive functions for the early detection of dementia: delayed recall, orientation of time, and visuospatial ability. These questions can be answered within 3–5 minutes. The results are then obtained by means of Receiver Operating Characteristic (ROC) analysis with 96% sensitivity and 97% specificity (i.e. extremely high accuracy). Scores range from 0 (i.e. all incorrect) to 15 (i.e. all correct). Since this non-invasive screening method is convenient to carry around and is not affected by administration bias, it is considered to be an optimum tool for forgetfulness detection.[27] For individuals with scores from 7–13, MCI is suspected and secondary medical examination is recommended for the doctor (dementia specialist) and/or public health nurse to explain the results and provide counselling. The TDAS computer system and the Alzheimer's Disease Assessment Scale (ADAS) significantly correlated[28] suggesting they evaluate the same things. The ADAS is a reliable scale, that has been used worldwide to assess drugs for Alzheimer's disease treatment. Unfortunately, the ADAS is rarely used in clinical practice because it has to be administered by a clinical psychologist or licensed professional and it takes about one hour to complete. In rural Japan, there are very few licensed clinical psychologists, making it difficult for the ADAS to be employed as screening tool. Even if we luckily employ one person, it is only 8 people maximum we can examine ADAS through the whole day. In order to solve these problems, we developed the TDAS program. The TDAS, on the other hand, can be completed in 10–15 minutes without a specialist or licensed clinical psychologist.

TDAS scores of 6 or less indicates normal cognitive state, scores from 7–13 indicates MCI, and scores of 14 or more suggest suspected dementia. For people with normal cognitive state, we recommend that they undergo screening for forgetfulness in next year. For those who score 14 or more, we recommend that they visit a medical hospital specializing in dementia. Finally, for those who the score 7–13, indicating MCI, we recommend that they participate in dementia prevention classes. These classes include 12 weekly sessions of two hours each for three months. Prevention activities in this class consist of three components: physical exercise, intellectual activities and communication. Physical exercise includes a range of activities, from workouts to elements of game property. Intellectual activities involve keeping the mind active from learning actions to incorporating elements of game property. Communication activities entail enjoying and participating in conversation with other participants and staff members. Communication is important, especially for elderly people living alone since a lifestyle with little conversation predisposes to dementia.

Difference of TDAS before and after MCI in dementia prevention class with suitable three components for prevention was statistically significant.[29] In addition, we found that MCI had been kept in good condition for three years. At the same time, we validated the economic effects in Kotoura-cho (study field), Tottori prefecture. This initiative became one of the factors contributing to the 26 (1.5%reduction overall) and 78 (4.3% reduction overall) million yen reduction in care insurance in 2014 and 2018, respectively. Although it is not so high as a percentage, it is quite a large amount (tens of millions of yen) in terms of the amount, and highly appreciated by many people. Such reductions can increase if we maintain our efforts. This initiative, which started in Kotoura-cho, Tottori prefecture has been implemented in numerous cities, towns, and villages in the Tottori prefecture and others.

APPROACH AND ISSUE ON THE PROGRAM FOR FORGETFULNESS AND DEMENTIA PREVENTION CLASSES

Although both the forgetfulness detection survey and dementia prevention classes have been successful. For instance, the number of participants is not increasing, possibly due to social prejudices about dementia. We

have spread enlightenment that "dementia can be treated and prevented if it occurs at an early stage, but is not yet knoun"

Specifically, human resources development should be established in the dementia prevention class. Seven dementia prevention classes were conducted during around the same times. Although all participants showed improved TDAS scores after participation, the degree of improvement varied greatly among class groups, despite similar programs being imparted.[30] This might be due to differences in the class coordinators' knowledge and skills for dementia prevention. While volunteer work can be accepted, we think that it would be desirable to involve professionals with expertise in dementia prevention.

Therefore, the Japanese Society of Dementia Prevention has established a specialist system for the prevention of dementia and has been developing human resources for the same.

DEVELOPMENT AND DISSEMINATION OF THE TOTTORI METHOD DEMENTIA PREVENTION PROGRAM

The study of Tottori Method Dementia Prevention Program Development was conducted in Houki-cho with the aim of upgrading the dementia prevention initiative in Kotoura-cho, Tottori Prefecture, which has been conducted since 2004, and to provide scientific evidence of its effectiveness.[31] The method used in Kotoura-cho was to select individuals with diagnosed with MCI from among older adults living in the community using the forgetfulness consultation program system and TDAS, and to examine the effectiveness of the dementia prevention class by dividing the individuals into two groups: (intervention-first and observation-first). The former received the intervention in the first half of the program, and observation only in the latter half. The observation-first group received observation in the former half and intervention in the latter half. Significant differences were obtained between the intervention and observation periods. The contents of the dementia prevention class were upgraded versions of the exercises and intellectual, and communication activities that had been conducted in Kotoura-cho. The exercise programs included warm-ups, aerobic, muscle strength training, and cool-down sessions. Since too much aerobic exercise is not good for the elderly, a good balance of aerobic and muscle strength exercises was provided. Stretching exercises were included in the warm-up and cooling-down exercises to improve flexibility. Intellectual activities were designed to stimulate all eight types of cognitive functions and were divided into individual and group activities. Communication activities included having a chat over a cup of tea during breaks between exercise and intellectual activities.

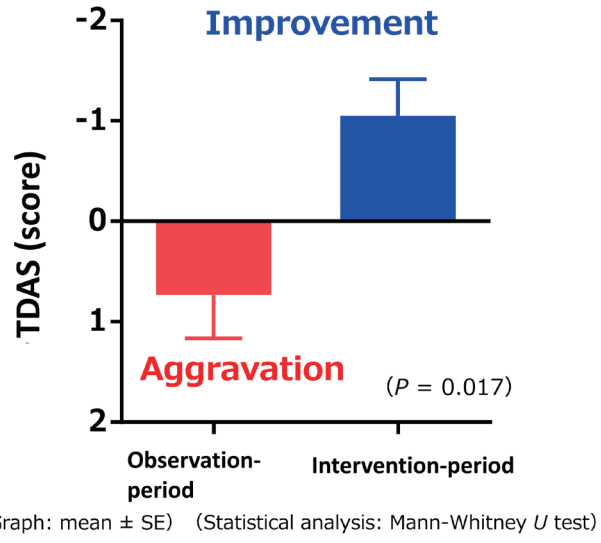

Fig. 1. Improvement in cognitive function through intervention. Improvement in cognitive function was observed through intervention with the prevention program using the TDAS ($P = 0.017$). Mann-Whitney U test was used for statistical analysis. The vertical axis shows the TDAS score. TDAS, Touch panel type dementia assessment scale.

Cognitive function was assessed using the TDAS, and significant improvement was observed as a result of the intervention (i.e. dementia prevention classes: Fig. 1).[32] The physical activity assessment showed significant improvements in upper limb strength, lower limb strength and flexibility (Fig. 2).[32] Improvement in lower limb muscle strength can help prevent falls by allowing the patient balance themselves when about to fall. Flexibility also helps prevent fractures in case of falls. Bone fractures in the elderly are known to be a risk for the progression and worsening of dementia; thus, preventing falls is essential for dementia prevention.

As I have been able to scientifically verify the effectiveness of the Tottori Method Dementia Prevention Program, we are now promoting this program in Tottori Prefecture and throughout Japan.

IMPROVEMENT OF DEMENTIA WITH AROMATHERAPY

Given that Alzheimer's disease is caused by olfactory dysfunction,[33] we investigated the possibility of early detection of dementia by olfactory testing and prevention of dementia by stimulating the olfactory nerve with aromatherapy. There are many diseases that cause dementia, but Alzheimer's disease accounts for

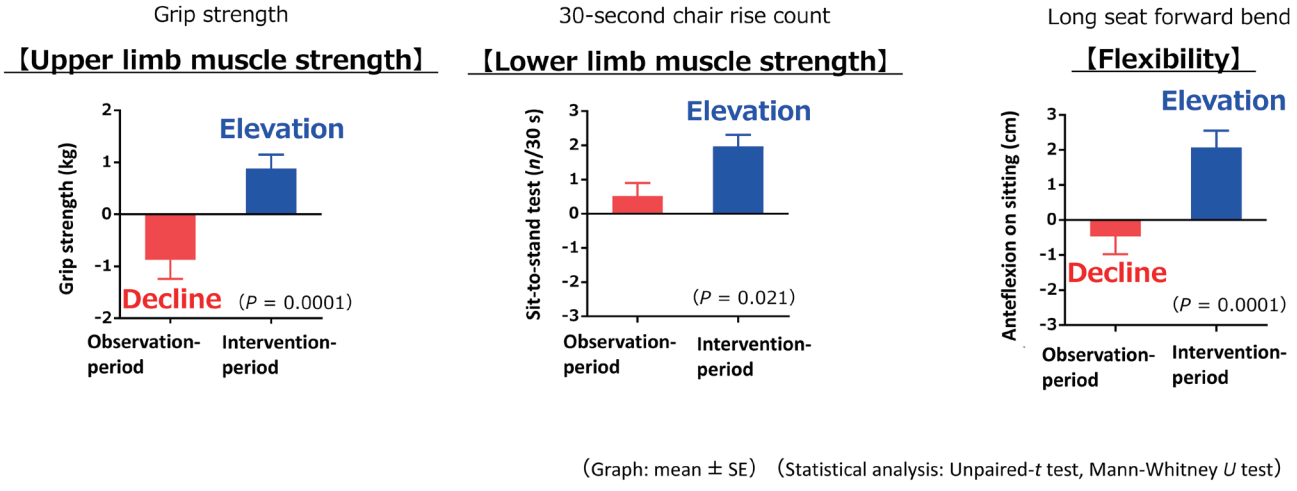

Fig. 2. Improvement of body function through intervention. The physical activity assessment showed significant improvements between intervention and observation period in upper limb strength ($P < 0.0001$), lower limb strength ($P < 0.0021$) and flexibility ($P < 0.0001$) through intervention with the prevention program. Unpaired-*t* test and Mann-Whitney *U* test were used for statistical analysis.

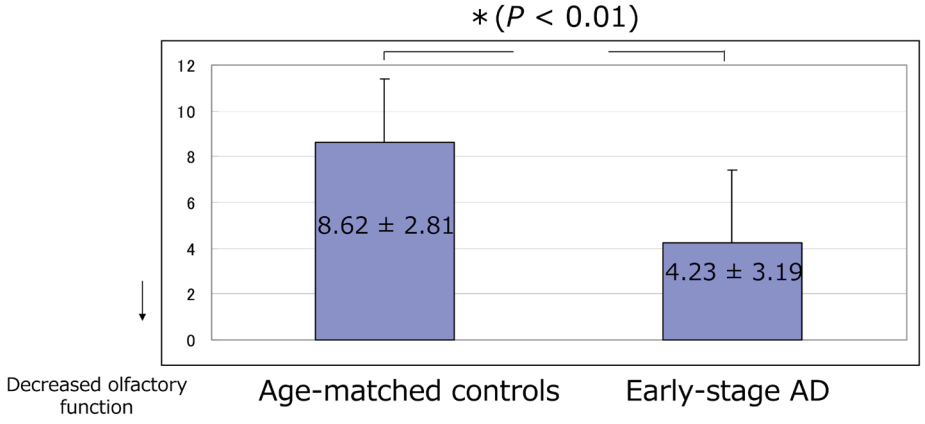

Fig. 3. Olfactory impairment in AD compared to age-matched controls (OSIT-J). Olfactory impairment in early stage of AD is shown compared to age-matched controls using OSIT-J kit ($P < 0.01$). Mann-Whitney *U* test was used for statistical analysis. The vertical axis shows the OSIT-J score, the lower the score, the lower the sense of smell. AD, Alzheimer's disease; OSIT-J, the Odor Stick identification test for Japanese.

about 70% of all dementia cases.[34] The first symptom of Alzheimer's disease has been said to be memory impairment, but in reality, the first symptom is olfactory impairment due to damage to the olfactory nerve. Using the Odor Stick Identification test for Japanese people (OSIT-J), it was found that the olfactory function of Alzheimer's disease patients is lower than that of age-matched controls.[35] Furthermore, we confirmed that their olfactory function was impaired from an early stage of Alzheimer's disease (Fig. 3). Pathologically, it has been reported that amyloid-β protein accumulates in the olfactory nerve in Alzheimer's disease from its onset.[36] As Alzheimer's is a neurodegenerative disease, the olfactory nerve is systematically damaged, followed by the hippocampal nerve. Therefore, if we can effectively stimulate the olfactory nerve in the early stages of the disease to promote olfactory nerve regeneration, we may be able to prevent dementia.

Aromatherapy was administered to patients with mild Alzheimer's disease, who showed significant improvement in cognitive function on the Gottfries-Brane-Steen scale (GBS scale) (Fig. 4). From before to after (1), aromatherapy was not performed as the control period. We conduct aromatherapy between after (1) and after (2). In GBS-A points (cognitive function) in Alzheimer's disease (AD), there is no significant difference between before and after (1), but a significant difference has been obtained before and after (2) ($P < 0.05$). On the other

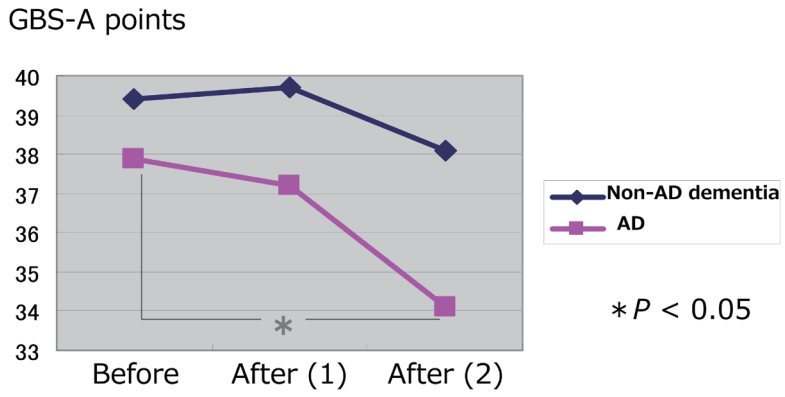

Fig. 4. Aromatherapy improve cognitive function in Alzheimer's disease (AD). The effects of aromatherapy on cognitive function were examined. From before to after (1), aromatherapy is not performed as the control period. We conduct aromatherapy between after (1) and after (2). In GBS-A points (cognitive function) in AD, there is no significant difference between before and after (1), but a significant difference has been obtained between before and after (2) ($P < 0.05$). On the other hand, in GBS-A points (cognitive function) in non-AD dementia, there is no significant difference between before and after (1), and there is also no significant difference between before and after (2). ANOVA was used for statistical analysis. AD, Alzheimer's disease (olfactory dysfunction); non-AD dementia, non Alzheimer's disease dementia (no olfactory dysfunction).

hand, in GBS-A points (cognitive function) in non-Alzheimer's disease (non-AD) dementia, there is no significant difference between before and after (1), and there is also no significant difference between before and after (2). The most effective essential oil combinations were rosemary camphor and lemon for daytime use, and genuine lavender and sweet orange for night time use.[37] As for usage, the authors recommend using an aroma pendant for daytime use so that the scent of the essential oil can reach the user even if they move, and ordinary diffuser for nighttime use in the bedroom.

In an animal study using senescence-accelerated mice (SAMP8), the above-mentioned aroma combination treatment was found to improve memory learning ability. In biochemical experiments, both amyloid-β protein and phosphorylated tau protein levels were significantly decreased in the hippocampus and olfactory bulb of the aroma-treated mice.[38] We found that our recommended combination of aromatic oils may have a useful effect on the brain pathology of Alzheimer's disease.

Dementia prevention is a long term process, more similar to running a marathon than to a 100-meter race. Aromatherapy is easy to enjoy and can be continued for a long time; thus, it is one of the most important prevention tools.

CONCLUSION

Worldwide, one person is diagnosed with dementia every three seconds.[39] Japan is facing a super-aging society, and it is estimated that the number of dementia patients will reach 7 million by 2025.[40] Therefore, dementia prevention is an urgent issue. I must create useful scientific evidences and raise awareness of dementia prevention.

Acknowledgments: We would like to thank Editage (https://www.editage.jp) for the English language review.

CONFLICT OF INTEREST

The author owns patents on the forgetfulness consultation program system and the TDAS, and receives royalties from Nihon Koden corporation.

REFERENCES

1 Prince M, Albanese E, Guerchet M, Prina M. World Alzheimer report 2014: Dementia and risk reduction - An analysis of protective and modifiable factors [Internet]. London: Alzheimer's Disease International; 2014 [cited 2022 May 31]. Available from: https://www.alzint.org/u/WorldAlzheimerReport2014.pdf
2 Selkoe DJ. The molecular pathology of Alzheimer's disease. Neuron. 1991;6:487-98. DOI: 10.1016/0896-6273(91)90052-2, PMID: 1673054
3 Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. Science. 1992;256:184-5. DOI: 10.1126/science.1566067, PMID: 1566067
4 Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002;297:353-6. DOI: 10.1126/science.1072994, PMID: 12130773
5 Shoji M, Golde TE, Ghiso J, Cheung TT, Estus S, Shaffer LM, et al. Production of the Alzheimer amyloid beta protein by normal proteolytic processing. Science. 1992;258:126-9. DOI: 10.1126/science.1439760, PMID: 1439760

6 Schenk D, Barbour R, Dunn W, Gordon G, Grajeda H, Guido T, et al. Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse. Nature. 1999;400:173-7. DOI: 10.1038/22124, PMID: 10408445

7 Jankowsky JL, Melnikova T, Fadale DJ, Xu GM, Slunt HH, Gonzales V, et al. Environmental enrichment mitigates cognitive deficits in a mouse model of Alzheimer's disease. J Neurosci. 2005;25:5217-24. DOI: 10.1523/JNEUROSCI.5080-04.2005, PMID: 15917461

8 Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. Lancet. 2017;390:2673-734. DOI: 10.1016/S0140-6736(17)31363-6, PMID: 28735855

9 Meng X, D'Arcy C. Education and dementia in the context of the cognitive reserve hypothesis: a systematic review with meta-analyses and qualitative analyses. PLoS One. 2012;7:e38268. DOI: 10.1371/journal.pone.0038268, PMID: 22675535

10 Vassilaki M, Aakre JA, Knopman DS, Kremers WK, Mielke MM, Geda YE, et al. Informant-based hearing difficulties and the risk for mild cognitive impairment and dementia. Age Ageing. 2019;48:888-94. DOI: 10.1093/ageing/afz099, PMID: 31437275

11 Walker KA, Power MC, Gottesman RF. Defining the relationship between hypertension, cognitive decline, and dementia: A review. Curr Hypertens Rep. 2017;19:24. DOI: 10.1007/s11906-017-0724-3, PMID: 28299725

12 Pugazhenthi S, Qin L, Reddy PH. Common neurodegenerative pathways in obesity, diabetes, and Alzheimer's disease. Biochim Biophys Acta Mol Basis Dis. 2017;1863:1037-45. DOI: 10.1016/j.bbadis.2016.04.017, PMID: 27156888

13 Durazzo TC, Mattsson N, Weiner MW; Alzheimer's Disease Neuroimaging Initiative. Smoking and increased Alzheimer's disease risk: A review of potential mechanisms. Alzheimers Dement. 2014;10(suppl):S122-45. DOI: 10.1016/j.jalz.2014.04.009, PMID: 24924665

14 Kessing LV. Depression and the risk for dementia. Curr Opin Psychiatry. 2012;25:457-61. DOI: 10.1097/YCO.0b013e328356c368, PMID: 22801361

15 Kivimäki M, Singh-Manoux A, Pentti J, Sabia S, Nyberg ST, Alfredsson L, et al.; IPD-Work consortium. Physical inactivity, cardiometabolic disease, and risk of dementia: an individual-participant meta-analysis. BMJ. 2019;365:l1495. DOI: 10.1136/bmj.l1495, PMID: 30995986

16 Evans IEM, Llewellyn DJ, Matthews FE, Woods RT, Brayne C, Clare L; CFAS-Wales research team. Social isolation, cognitive reserve, and cognition in healthy older people. PLoS One. 2018;13:e0201008. DOI: 10.1371/journal.pone.0201008, PMID: 30118489

17 Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. Nat Rev Endocrinol. 2018;14:591-604. DOI: 10.1038/s41574-018-0048-7, PMID: 30022099

18 Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020;396:413-46. DOI: 10.1016/S0140-6736(20)30367-6, PMID: 32738937

19 Graham NSN, Sharp DJ. Understanding neurodegeneration after traumatic brain injury: from mechanisms to clinical trials in dementia. J Neurol Neurosurg Psychiatry. 2019;90:1221-33. DOI: 10.1136/jnnp-2017-317557, PMID: 31542723

20 Xu W, Wang H, Wan Y, Tan C, Li J, Tan L, et al. Alcohol consumption and dementia risk: a dose–response meta-analysis of prospective studies. Eur J Epidemiol. 2017;32:31-42. DOI: 10.1007/s10654-017-0225-3, PMID: 28097521

21 Peters R, Ee N, Peters J, Booth A, Mudway I, Anstey KJ. Air pollution and dementia: A systematic review. J Alzheimers Dis. 2019;70:S145-63. DOI: 10.3233/JAD-180631, PMID: 30775976

22 Urakami K. [Prevention of dementia]. Jpn J Clin Med. 2016;74:395-8. PMID: 27025075 PMID: 27025075 Japanese with English abstract.

23 Petersen RC. Clinical practice. Mild cognitive impairment. N Engl J Med. 2011;364:2227-34. DOI: 10.1056/NEJMcp0910237, PMID: 21651394

24 Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol. 1999;56:303-8. DOI: 10.1001/archneur.56.3.303, PMID: 10190820

25 Ninomiya T, Nakaji S, Maeda T, Yamada M, Mimura M, Nakashima K, et al.; JPSFC-AD Study Group. Study design and baseline characteristics of a population-based prospective cohort study of dementia in Japan: the Japan Prospective Studies Collaboration for Aging and Dementia (JPSC-AD). Environ Health Prev Med. 2020;25:64. DOI: 10.1186/s12199-020-00903-3, PMID: 33129280

26 Bruscoli M, Lovestone S. Is MCI really just early dementia? A systematic review of conversion studies. Int Psychogeriatr. 2004;16:129-40. DOI: 10.1017/S1041610204000092, PMID: 15318760

27 Inoue M, Jinbo D, Nakamura Y, Taniguchi M, Urakami K. Development and evaluation of a computerized test battery for Alzheimer's disease screening in community-based settings. Am J Alzheimers Dis Other Demen. 2009;24:129-35. DOI: 10.1177/1533317508330222, PMID: 19150968

28 Inoue M, Jimbo D, Taniguchi M, Urakami K. Touch Panel-type Dementia Assessment Scale: a new computer-based rating scale for Alzheimer's disease. Psychogeriatrics. 2011;11:28-33. DOI: 10.1111/j.1479-8301.2010.00345.x, PMID: 21447106

29 Urakami K. Examination and preventive intervention of dementia from the point of view of life style. Jpn J Geriatr. 2011;48:118-9. DOI: 10.3143/geriatrics.48.118, PMID: 21778622

30 Ito Y, Urakami K. Evaluation of dementia-prevention classes for community-dwelling older adults with mild cognitive impairment. Psychogeriatrics. 2012;12:3-10. DOI: 10.1111/j.1479-8301.2011.00397.x, PMID: 22416823

31 Kouzuki M, Kato T, Wada-Isoe K, Takeda S, Tamura A, Takanashi Y, et al. A program of exercise, brain training, and lecture to prevent cognitive decline. Ann Clin Transl Neurol. 2020;7:318-28. DOI: 10.1002/acn3.50993, PMID: 32068975

32 Tottori Prefecture Web Site [Internet]. Tottori: Tottori Prefecture [cited 2022 May 22]. [Dementia-related measures]. Available from: https://www.pref.tottori.lg.jp/item/1198192.htm. Japanese.

33 Silva MM, Mercer PBS, Witt MCZ, Pessoa RR. Olfactory dysfunction in Alzheimer's disease Systematic review and meta-analysis. Dement Neuropsychol. 2018;12:123-32. DOI: 10.1590/1980-57642018dn12-020004, PMID: 29988355

34 Ikejima C, Hisanaga A, Meguro K, Yamada T, Ouma S, Kawamuro Y, et al. Multicentre population-based dementia prevalence survey in Japan: a preliminary report. Psychogeriatrics. 2012;12:120-3. DOI: 10.1111/j.1479-8301.2012.00415.x, PMID: 22712646

35 Jimbo D, Inoue M, Taniguchi M, Urakami K. Specific feature of olfactory dysfunction with Alzheimer's disease inspected by the Odor Stick Identification Test. Psychogeriatrics. 2011;11:196-204. DOI: 10.1111/j.1479-8301.2011.00387.x, PMID: 22151238

36 Kovács T, Cairns NJ, Lantos PL. Beta-Amyloid deposition and neurofibrillary tangle formation in the olfactory bulb in ageing and Alzheimer's disease. Neuropathol Appl Neurobiol. 1999;25:481-91. DOI: 10.1046/j.1365-2990.1999.00208.x, PMID: 10632898

37 Jimbo D, Kimura Y, Taniguchi M, Inoue M, Urakami K. Effect of aromatherapy on patients with Alzheimer's disease. Psychogeriatrics. 2009;9:173-9. DOI: 10.1111/j.1479-8301.2009.00299.x, PMID: 20377818

38 Okuda M, Fujita Y, Takada-Takatori Y, Sugimoto H, Urakami K. Aromatherapy improves cognitive dysfunction in senescence-accelerated mouse prone 8 by reducing the level of amyloid beta and tau phosphorylation. PLoS One. 2020;15:e0240378. DOI: 10.1371/journal.pone.0240378, PMID: 33052945

39 Prince M, Wimo A, Guerchet M, Ali GC, Prina M. World Alzheimer report 2015: Global impact of dementia: An analysis of prevalence, incidence, cost and trends. Dementia. Alzheimer's Disease International. 2015 September; London; 1–26.

40 Ninomiya T. [A study on future estimates of the elderly population with dementia in Japan] [Internet]. Wako: National Institute of Public Health [cited 2022 May 31]. Available from: https://mhlw-grants.niph.go.jp/system/files/2014/141031/201405037A_upload/201405037A0003.pdf. Japanese.