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Special Article

Brain Health: The Importance of Recognizing Cognitive Impairment: An IAGG Consensus Conference



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ABSTRACT

Keywords: Cognitive impairment Alzheimer disease Cognitive impairment creates significant challenges for patients, their families and friends, and clinicians who provide their health care. Early recognition allows for diagnosis and appropriate treatment, education, psychosocial support, and engagement in shared decision-making regarding life planning,

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case finding cognitive frailty MCI health care, involvement in research, and financial matters. An IAGG-GARN consensus panel examined the importance of early recognition of impaired cognitive health. Their major conclusion was that case-finding by physicians and health professionals is an important step toward enhancing brain health for aging populations throughout the world. This conclusion is in keeping with the position of the United States' Centers for Medicare and Medicaid Services that reimburses for detection of cognitive impairment as part the of Medicare Annual Wellness Visit and with the international call for early detection of cognitive impairment as a patient's right. The panel agreed on the following specific findings: (1) validated screening tests are available that take 3 to 7 minutes to administer; (2) a combination of patient- and informant-based screens is the most appropriate approach for identifying early cognitive impairment; (3) early cognitive impairment may have treatable components; and (4) emerging data support a combination of medical and lifestyle interventions as a potential way to delay or reduce cognitive decline.

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Cognition (the ability to learn, solve problems, remember, and appropriately use stored information) is a key to successful health and aging. A variety of conditions, many age-associated, adversely affect cognition. After the age of 70, numerous studies suggest that approximately 16% of persons have mild cognitive impairment (MCI) and 14% experience dementia. 1-5 Approximately two-thirds of persons with dementia identified in population studies have Alzheimer disease (AD), either alone or in combination with other diseases.⁵ Because of the importance of the maintenance of cognitive health or brain health to both the individual and society, the International Association of Gerontology and Geriatrics (IAGG) and its Global Aging Research Network (GARN) convened an expert consensus panel to (1) determine the role of screening and/or case-finding to identify early cognitive impairment, (2) establish the minimum workup/advice that providers should give to a person with early cognitive impairment, (3) explore if the management of persons with subjective cognitive impairment should differ from that of persons with objective cognitive impairment, and (4) decide if cognitive frailty (a mixture of both mental and physical frailty) is a useful concept for research and clinical care. 10-12

An expert panel (referred to hereafter as "panel"), including neurologists, psychiatrists, geriatricians, social workers, and psychologists, was convened in St Louis, MO, in March 2015. The methodology followed a modified Delphi approach, which has been used previously to obtain consensus. 13,14 Before the conference, the panelists were surveyed using a series of questions pertinent to the objectives. During the panel meeting, the results of the survey were made available to the participants, along with results of focus groups of persons with dementia (n = 6), care partners (n = 8), and staff and volunteers (n = 9). The panel discussed in detail several key areas: Preferred terminology for early cognitive impairment; the distinction between screening and case-finding; screening instruments; postscreening recommendations, including the role of antidementia drugs and treatment of potentially remediable components of cognitive impairment, possible nutritional and exercise (physical and cognitive) interventions, and utility of biomarkers for etiological diagnosis; the interaction between physical and cognitive failure; and possible next steps. A draft manuscript was then developed, circulated, and revised until the panelists arrived at consensus on the content.

Cognition is a Key to Good Health

Cognitive impairment is recognized as being either syndromic (eg, MCI, subjective cognitive decline, mild neurocognitive disorder, or cognitive frailty) or etiologic (eg, prodromal AD or early symptomatic AD). The premeeting survey results identified that 60% of participants favored MCI as the term of choice, but panel members recognized the importance of framing the issue in the more positive terms

of "cognitive (brain) health" to reduce public fears that may impede early detection and to encourage positive steps toward preserving cognitive function throughout the life course.

A stimulus in the United States toward providing guidelines relative to the recognition and management of cognitive health is the creation of a new Medicare benefit, the Annual Wellness Visit (AWV), under the Patient Protection and Affordable Care Act of 2010. Among the reimbursable components of the AWV is detection of any cognitive impairment. In a 1996 study, physicians at the Mayo Clinic in Minnesota found the Mini-Mental State Examination (MMSE), 17 in 4000 persons 60 to 102 years of age to be of little value from the physician's point of view. 8 On the other hand, in southern France, family practitioners have found a very brief screen for memory problems and physical frailty to be highly useful to determine need for specialist referral when coupled with the ability to refer patients to a specialty clinic for further evaluation. 9 Screening for cognitive impairment has been carried out in primary care and community settings. 20–23

Cognitive impairment and dementia, when present, are either not recognized or recognized and not documented, in more than half of patients seen by primary care physicians. ^{24–28} The US Preventive Services Task Force, using a systematic review, determined that, "there is no empirical evidence that screening improves decision making." ²⁹ We note that this conclusion was based on limited studies reporting health outcomes in persons with dementia. The Gerontological Society of America (GSA) has issued a report providing 9 potential benefits of early diagnosis of dementia (https://www.geron.org/images/gsa/documents/gsaciworkgroup2015report.pdf). The GSA report also provided a 4-step approach to the diagnosis and management for detection of cognitive impairment and/or dementia, while recognizing that the approach still requires validation.

The panel recognized the important public health distinction between screening and case-finding. By definition, screening is universal and involves a brief assessment of all individuals within a certain category (for example, all of a certain age). It is wellestablished that the strongest risk factor for AD and other dementias is age.³⁰ Although the panel was split on whether universal screening should be carried out, many members supported 70 years as an appropriate age threshold for screening. The focus groups (persons with dementia, care partners, and direct practice staff and volunteers) were generally supportive of universal screening with several caveats, including the need for standardization of screening tools and adequate training for the provider administering the screening tool. Interestingly, the focus groups believed that screening at age 70 years was too late and advocated for earlier (by age 55 years) screening. In contrast to screening, case-finding is the assessment of a subgroup of individuals identified on the basis of known risk factors (eg, subjective cognitive concerns or family history of dementia) to be carried out by physicians and other health

Table 1Application of the World Health Organization (Wilson's Criteria) Screening Criteria to Cognitive Impairment and Dementia

	Cognitive Impairment	Dementia
1 The condition should be an important health problem	YES	YES
2 There should be treatment for the condition	Some	Slow Deterioration
3 Facilities for diagnosis and treatment should be available	Some	Some
4 There should be a latent stage of disease	Uncertain	YES
5 There should be a test or examination for the condition	YES	YES
6 The test should be acceptable to the population	YES	YES
7 The natural history of the disease should be adequately understood	Possibly	YES
8 There should be an agreed on policy of who to treat	Possibly	YES
9 The total cost of finding a case should be economically balanced	YES	YES
10 Case-finding should be a continuous process, not just a "once-and-for-all project"	YES	YES

professionals. Table 1 depicts the way in which screening for cognitive impairment and dementia might fulfill the World Health Organization (Wilson's criteria) guidelines for screening.

The IAGG panel strongly endorses the viewpoint that international studies must determine the most cost-effective approach to identification and management of cognitive impairment in different settings and populations. However, like the GSA, the panel determined that, at a minimum, case-finding by physicians and other health professionals is important to enhance brain health throughout the world.

Screening Instruments

More than half of the panelists believe that an ideal screening instrument should be less than 5 minutes, although 5 to 7 minutes for screening was also considered reasonable. A number of validated screening instruments are available (Table 2). Of these, the Ascertain Dementia 8 (AD8) is an informant-based screening tool, which also may be useful in patients with MCI.^{31–34} The items in the AD8 address memory, temporal orientation, judgment, and function. It has a sensitivity of 85% and specificity of 92%. Informant report has a better association with disease than self-rated report.³⁵ The AD8 has been validated in Korea, Brazil, Spain, Japan, China, and Taiwan.^{36–41}

A number of objective screening tests are available. The MiniCog meets the criterion of taking less than 3 minutes to administer. ^{42–45} The Rapid Cognitive Screen (RCS), developed from the Saint Louis University Mental Status (SLUMS) examination, also takes less than 3 minutes and validations are available in 2 studies. ⁴⁶ SLUMS has excellent receiver operating curves to distinguish both MCI and dementia. From an international perspective, the SLUMS is available in 24 languages (http://aging.slu.edu/index.php?page=saint-louis-university-mental-status-slums-exam). ^{47–49} "The 5-word test" has

been validated in AD (specificity 87%). It has a positive predictive value of 83% and a negative predictive value of 93%. To takes 2 minutes to administer and is widely used in France. The panel agreed that all of these tools, as well as others, were acceptable for screening and selection should be left to the discretion of the provider.

Figure 1 illustrates that screening implementation requires a variety of components to allow for successful administration. These include training of the physicians and other health care professionals who administer the instrument, appropriate preparation of the patient/informant, immediate follow-up, and later follow-up.

Screening is typically accomplished by a simple test with a single score at a single point in time, to identify those patients who deserve a more complete diagnostic assessment by an expert clinician. An individual's performance at a single point in time provides no information about the course of his or her cognitive functioning over time. The diagnosis of the progressive dementias, such as probable AD, depends on the patient experiencing cognitive decline over time. At the initial assessment, this information is typically obtained from the history. Ideally, decline should be identified based on serial objective assessments (repeated cognitive testing) over time (Figure 2). By using a well-validated cognitive test with established normative values for a range of age and educational groups, the clinician can compare a given patient's actual performance on the test, even on a single occasion, with the expected values for an individual of the same age and education. Test performance below the expected range strongly suggests that decline has occurred.

An example of an optimal, 2-pronged, approach to assessment might include administering an objective test to the patient, while the care partner or informant completes a questionnaire such as the AD8. Overall an "ideal" screening tool should be brief, have no copyrighted costs, and be able to be administered by any

Table 2Potential Screening Instruments for Early Cognitive Impairment

Instrument	Administration Time, min	Items	Туре	Detects MCI	Copyright*
Ascertain Dementia 8 (AD8)	3	8	Informant	Yes	Yes
MiniCog	3	2	Patient	Yes	Yes
The 5 Words	3	1	Patient	No	Yes
Rapid Cognitive Screen (RCS)	3	3	Patient	Yes	No
Memory Impairment Screen	4	3	Patient	Yes	Yes
General Practitioners Assessment of Cognition	4-5	4(P), 6(I)	Patient/Informant	No	Yes
Kokmen Short Test of Mental Status	5	8	Patient	Yes	Yes
St Louis University Mental Status Examination (SLUMS)	7	14	Patient	Yes	No
7-Minute Screen (7MS)	7-10	11	Patient	No	Yes
Mini-Mental Status Exam (MMSE)	7-10	19	Patient	Yes	Yes
Telephone Interview for Cognitive Status	7-10	11	Patient	Yes	Yes
Informant Questionnaire on Cognitive Decline in the Elderly (Short IQCODE)	10-15	16	Informant	Yes	Yes
Addenbrook's Cognitive Exam	15	30+	Patient	Yes	Yes

^{*}The MMSE is both copyrighted and requires a fee to use in the United States. Most of the other copyrighted instruments require no fee at the present time.

TRAIN HEALTH CARE PROFESSIONALS TO ADMINISTER SCREEN

Prepare Patient/Informant

- EXPLAIN SCREENING
- DETERMINE PREFERENCES

Administration of Screener

- CREATE ENVIRONMENT THAT MAXIMIZES PERFORMANCE
- USE STANDARDIZED
 ADMINISTRATION AND SCORING

Immediate Follow-up

- SHARE RESULTS SIMPLY & CLEARLY
- CHECK FOR UNDERSTANDING
- GAUGE DISTRESS
- OFFER RECOMMENDATIONS
- VERBAL/WRITTEN FEEDBACK

Later Follow-up

- CHECK FOR RECALL AND COMPREHENSION
- GAUGE DISTRESS
- QUERY ABOUT ACTIONS TAKEN
- OFFER RECOMMENDATIONS

Fig. 1. Process for implementing screening.

appropriately trained individual. There are limitations of many screening instruments in low education/illiterate populations. In addition, there is a need for culturally fair instruments.

The use of biomarkers (Table 3) for etiological diagnosis furthers our understanding of disease trajectories, but should be limited to use

by specialists after an extensive clinical evaluation. $^{51-55}$ This emerging area of interest has led to different opinions from the National Institute on Aging/Alzheimer's Association and the International Working Group as to the role of biomarkers in the clinical evaluation of the patient. $^{56-58}$

Potential Benefits of Early Diagnosis of Cognitive Impairment

When screening or case-finding reveals cognitive impairment, the health care professional can take the appropriate steps toward diagnosis and treatment. When testing fails to find cognitive impairment, this reassurance allows persons to re-focus on enjoying their "brain health." A negative screen may bring relief to older persons who fear that their normal age-related cognitive changes represent the beginnings of AD.

Whether or not the screening information is shared with the patient and family, physicians and other health professionals should know that their patient is cognitively impaired. Management of chronic medical conditions requires the patient to enter into an active partnership with his or her health care professionals to obtain the best outcome. Besides failing to take their medications, cognitively impaired patients often fail to carry out other simple instructions from their physicians. These patients may not understand the explanation of their disease given to them by their physician or its implications. The same may be true of family members who are present when the diagnosis is given. ⁵⁹ Therefore, the clinician delivering the diagnosis should check for comprehension in both the patient and family members.

There also are numerous potentially reversible causes of cognitive impairment, including some which are clearly treatable when diagnosed early. These include anticholinergic medications, $^{60-62}$ polypharmacy, 63,64 depression, 65 metabolic disorders such as hypothyroidism and hypercalcemia, 66 normal-pressure hydrocephalus, 67 space-occupying lesions in the brain, infections, and sleep apnea. 68,69 Defects in vision and hearing can lead to poor performance on cognitive screening and prolonged sensory isolation can result in cognitive impairment. 62

Patients with white matter hyperintensities on magnetic resonance imaging (MRI), suggestive of ischemic brain damage, may have treatable conditions that when controlled could slow down further ischemic brain damage and possibly the development of AD. These include hypertension, diabetes, hyperlipidemia, smoking, and atrial fibrillation. Both heart failure and chronic obstructive pulmonary disease are associated with an increased risk of cognitive impairment. This suggests early treatment and improvement of oxygenation may slow the development of cognitive impairment.

Persons with diabetes mellitus have early onset of cognitive impairment and a higher likelihood of developing dementia. $^{79-81}$ Hyperglycemia has been associated with reversible cognitive impairment in humans and animals. $^{82-84}$

There are a number of lifestyle changes that have reasonable evidence for slowing down the rate of cognitive deterioration. Epidemiological studies support that persons consuming Mediterranean-style diets are less likely to have cognitive impairment. In addition, the PREDIMED-NAVARRA study showed that a Mediterranean diet slowed the development of cognitive impairment after 6.5 years compared with a low-fat diet. Extravirgin olive oil improves memory and reduces oxidative damage in the SAMP8 mouse and extra-virgin olive oil was slightly better than nuts in improving cognition in the PREDIMED-NAVARRA study. Mediterranean diet characteristics include fruit and vegetables, fish 2 times a week, olive oil, nuts, legumes, and whole grains. The "MIND-diet," which incorporates elements of both the Mediterranean

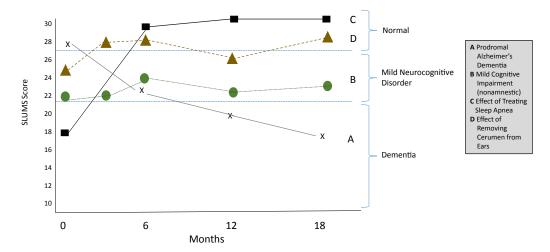


Fig. 2. Schematic demonstrating the importance of intra-individual change in confirming the diagnosis.

diet and the "DASH diet," has been linked with a lower risk of cognitive impairment⁹¹ and the development of AD.⁹² It is recognized that association in epidemiological studies does not prove causality. The FINGER and PREDIMED-NAVARRA studies were controlled interventional studies, helping to confirm causality.

Although epidemiological studies have found that foods rich in antioxidant vitamins reduce the risk of AD, 93 intervention studies with antioxidant vitamins have been disappointing, 94,95 although 2000 IU per day of vitamin E did result in a slight, but significantly less, decline in the Alzheimer's Disease Co-operative Study/Activities of Daily Living Inventory. 96 Similarly, supplementation with B-vitamin supplements has not been effective except in cases of clear vitamin B deficiency or in countries where bread is not fortified with folate. 94,97-100 Preclinical studies have shown that a combination of nutrients involved in the Kennedy pathway for biosynthesis of neuronal membranes (including uridine monophosphate, choline and phospholipids) increased surrogate markers for synapse formation. In addition, in vivo studies showed that dietary enrichment with these nutrients improved neurotransmission, learning, and memory. 101 It has been shown that patients with AD may be partially deficient in some of these essential nutrients. 102 This led to the development of a specific nutrient combination (Souvenaid), which has been tested in humans. Although the results were negative in persons with established dementia, improvement in immediate and delayed verbal memory was seen in early cognitive dysfunction 103,104 and was sustained over a 12-month period without any safety issues being

Table 3Potential Biomarkers for Persons With Cognitive Impairment

Biomarker	Utility	
MRI	Ischemic disease (white matter hyperintensities), normal-pressure hydrocephalus, space- occupying lesions, vasculitis; AD (hippocampal volume, cortical thinning)	
Cerebral spinal fluid		
Amyloid β and Tau	AD	
Positron emission tomography		
Fluorodeoxyglucose	AD/Lewy body dementia	
Pittsburgh compound β	AD	
Florbetapir	AD	
Florbetaben	AD; frontotemporal dementia and	
Tau	parkinsonism linked to chromosome	
	17 (FTDR-17)	
Single-photon emission computerized tomography		
Dopamine transporter	Lewy body dementia	

observed. A European Union—funded trial (Lipidiet Consortium) is examining the effects in persons with prodromal AD. Medium-chain triglycerides (Axona), which are metabolized to ketone bodies, have been shown to have a small effect on memory in APOE4-negative individuals, but more studies are needed. Overall, the consensus group concluded that a Mediterranean-type diet is a reasonable recommendation for persons with early cognitive dysfunction, whereas further evidence in early AD or MCI is awaited. Further studies are necessary to provide evidence for the efficacy for special dietary formulations.

An analysis of population-based data found that the population attributable risk for AD in the United States, Europe, and the United Kingdom was highest for physical inactivity. 107 Å meta-analysis of prospective studies in persons without dementia (n = 33.816) found that physical exercise was protective against cognitive decline. ¹⁰⁸ The Cochrane meta-analysis suggested physical exercise had effects on delayed memory functions and auditory attention. 109 Another metaanalysis involving 14 randomized controlled trials (RCTs) found exercise had a very small significant effect on improving verbal fluency and no other significant effects. 110 Wang et al 111 found an effect of exercise on global cognitive function. Many of these studies were conducted over relatively short periods. A year-long aerobic exercise training study in older adults improved memory and hippocampal volume. 112 However, in another smaller study, the investigators failed to show an effect on cognition over a year. ¹¹³ In a study of resistance training in persons with MCI, there was a significant improvement in global cognitive function and maintenance of executive function over 18 months. 114 In the Fitness for Aging Brain study, physical activity enhanced cognitive scores, compared with an educational program over the 18-month follow-up. 115 A meta-analysis of 2533 participants found that Tai Chi enhanced both executive function and global cognitive function. 116 This was reinforced by a recent study. 117 Despite strong epidemiological evidence for a relationship between physical fitness and cognition, 118 the intervention studies have not shown large effects and none has shown protection against markers of neurodegenerative diseases, including AD. Moreover, none of the studies showed that the positive cognitive effects translated to everyday life; that is, the effects were not clinically meaningful. As physical exercise has many benefits for older persons and is generally recommended, the panel endorsed this recommendation for persons with cognitive impairment.

Epidemiologically, there is less cognitive decline in persons who have higher levels of engagement in intellectual activity, play a musical instrument, or dance. The Advanced Cognitive Training

for Independent and Vital Elderly (ACTIVE) study provided cognitive exercises once a week for 10 weeks in 2832 older persons. ¹²² Participants in this intervention showed improvement in memory, reasoning, and processing even after 5 years of follow-up, although transfer of cognitive training benefits to improvements in real-world activities remains to be established. ¹²³ In persons with mild to moderate dementia, cognitive stimulation therapy (CST) has been shown to improve cognition. ^{124–130} CST also improves quality of life and is at least as effective as cholinesterase inhibitors in persons with dementia. ¹³¹ Reminiscence therapy has been shown to have a small effect on cognition and possibly quality of life. ^{132–135} Combinations of cognitive and exercise training can enhance cognitive function and functional status in older adults, but more studies are needed. ¹³²

Video game training produces positive effects on global cognition, memory, reaction time, and attention in older adults. 136,137

The Agency for Healthcare Research and Quality produced a metaanalysis examining factors associated with cognitive decline. ²⁹ Overall, the evidence suggested that physical and cognitive activities were associated with lesser cognitive decline in aging. However, there is no evidence for a causal relationship, and the National Institute on Aging State-of-the-Science Conference could not make confident recommendations for preserving cognitive health based on existing evidence. ¹³⁸

Given that cognitive impairment and dementia/AD are multifactorial disorders, targeting several risk factors simultaneously may be needed for optimal preventive effect.¹³⁹ The Finnish geriatric intervention study to prevent cognitive impairment and disability (FINGER)¹⁴⁰ is the first large, long-term RCT showing that multidomain lifestyle-based intervention can maintain cognitive function and reduce cognitive decline in older at-risk individuals. In this study, 1260 persons aged 60 to 77 years were included and screened based on the Dementia Risk Score. 141 Half were randomly allocated to the multidomain intervention group (consisting of physical exercise, healthy diet, cognitive diet, and vascular risk monitoring), and half were allocated to a control group that received regular health advice only. After 2 years, the intervention group had significantly better Neuropsychological Test Battery score (primary outcome) and lower risk for cognitive decline compared with the controls. 140 Extended follow-up (up to 7 years) is ongoing to determine the effect on incidence of dementia and AD, other health outcomes, and long-term adherence to lifestyle intervention.

There are 2 other large, multidomain RCTs in Europe aiming to prevent cognitive impairment and dementia: The MAPT trial in France, and the pre-DIVA study in the Netherlands. ¹³⁹ Both of these trials have been recently finalized and results are awaited. Research groups from these 3 trials (FINGER, MAPT, pre-DIVA) have established European Dementia Prevention Initiative (EDPI; www.edpi.org) aiming to better use the available data. Through combined data analyses (totaling >6000 participants) and sharing of experiences about methodological issues, EDPI aims to improve multidomain preventive strategies that can be tested in larger studies.

The IAGG panelists recognized the paucity of high-quality randomized trials to make recommendations, but were in general agreement that positive lifestyle changes, such as those embodied in FINGER, should be recommended to all persons with early cognitive impairment.

Cholinesterase inhibitors do not improve cognition in persons with MCI (with the possible exception of prodromal AD). Memantine should not be used in early AD.

Cognitive impairment at any level of severity creates significant challenges for both individuals and family members. ¹⁴³ Early recognition sets the stage for ongoing engagement of patients, family members, and clinicians in person-centered, individualized partnerships to optimize both medical and psychosocial outcomes over time.

Table 4

Recommendations for the Management of Early Cognitive Impairment

- Spend enough time with the patient and, when appropriate, family
 members, to ensure maximum understanding of the condition and
 recommended care. Provide written instructions. When necessary, engage
 a care partner to help carry out recommendations.
- Identify all potentially reversible causes of cognitive impairment.
- Provide advice regarding lifestyle practices and follow-up on implementation:
 - i. The Mediterranean or similar diet including olive oil
 - ii. Physical exercise
 - iii. Intellectual activities
 - iv. CST for persons with early or moderate AD
- Discuss the potential use of cholinesterase inhibitors in persons with AD
- Encourage the person to develop advanced directives for health, legal, and financial matters, and follow-up on whether this was done
- Educate the patient and family through recognized specialty organizations (eg, the Alzheimer's Association in the US)
- Address, and take steps to avoid, major risks associated with cognitive impairment (eg, money management, "safe return" bracelet, appropriate disposition of unsafe tools and guns, driving)
- Encourage identification and use of support services (eg, support groups, family and friend engagement activities)
- Talk about potential research participation and help the person to make his or her own informed decisions

Early recognition of cognitive impairment allows the person to reprioritize personal life goals, and to develop advanced directives for health, legal, and financial matters that fit with their preferences. This also allows the person to work with his or her family to identify and avoid major potential risks (eg, susceptibility to theft; wandering; unsafe use of tools, appliances, and guns; and operating motor vehicles). Early recognition also allows education for the person and the family on the effects of cognitive impairment and to engage both in activities that mitigate stress. Finally, early detection gives individuals the opportunity to make their own informed decisions about participation in research.

The recommendations that health care professionals should provide to persons with cognitive impairment are outlined in Table 4.

Cognitive Frailty

Cognitive frailty is a term that has recently emerged in the geriatrics literature inspired by potential parallel links to and possible common underlying mechanisms with the physical frailty syndrome. Physical frailty has been defined as "a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death." ¹⁴ Recently it has been recognized that a subgroup of persons with cognitive impairment have reduced resilience and functional decline that interacts with physical frailty. Converging evidence suggests that the cognitive status represents an important dimension of the frailty syndrome. Epidemiological studies have shown an association between frailty and late-life cognitive decline, incident MCI and AD, and non-AD dementias. 144 It has been suggested that cognitive frailty can be defined as a reduced cognitive function (clinical dementia rating score = 0.5) with the cognitive impairment being due to either physical or brain disease, 29,145 or accelerated brain aging in the absence of evident brain disease. Physical frailty has to coexist to evoke the term cognitive frailty. It manifests commonly with executive dysfunction (frontal cortex) and less with pure amnestic defects (mesial temporal cortex). Others have suggested that the deficits in frail and prefrail patients in executive function and memory may be similar in size.14

There is some evidence that, even with normal aging, both cognitive decline and physical frailty often coexist. ^{147–149} Cross-sectional studies find a high level of coexistence between rates of cognitive impairment and dementia and physical frailty. ¹⁵⁰ Frailty predicts cognitive decline and incident dementia, ^{151,152} and cognitive impairment predicts frailty. ^{153,154} in longitudinal studies. Loss of executive function and poor attention are particularly associated with slow gait. ¹⁵⁵ There is increasing evidence that persons with white matter hyperintensities have poor balance, poor get up and go performance, slow gait speed, and increased falls. ^{156–158} White matter hyperintensities also predict functional decline. ¹⁵⁹

The panelists agreed that persons with cognitive decline should be screened for physical frailty and vice versa. Although the concept of cognitive frailty may eventually yield useful insights and expanded predictability of function and disease outcomes, the panelists, however, considered it premature to incorporate cognitive frailty into the diagnostic lexicon and agreed that more studies on the interaction of the 2 entities and their pathophysiology are needed.

Conclusion

There was consensus that all persons 70 years and older should have their cognitive function (subjectively and objectively) evaluated when visiting their health care provider, at least once a year. The objectives of this assessment are to identify treatable disease, provide lifestyle guidance to try to slow cognitive impairment, to allow recognition of patients who may struggle understanding a physician's instructions, and to allow patients and their families to adequately prepare if they are at risk for developing dementia. Although this will vary by setting and circumstance, it was agreed that screening instruments should take less than 3 to 7 minutes to administer. The need to follow an individual longitudinally (ie, serial assessments) to demonstrate a deterioration in his or her performance was considered an important component of case-finding. The concept of cognitive frailty was viewed as being of interest but needs further research and development. The panel supports the Institute of Medicine's Report Brief that there is a need for a greater societal commitment to promote cognitive health (http://www.iom.edu/ reports/2015/cognitive-aging.aspx). It is suggested that when communicating with the public, the term "cognitive (brain) health" may be more acceptable than talking about cognitive impairment or dementia.

References

- Petersen RC. Clinical practice. Mild cognitive impairment. N Engl J Med 2011; 364:2227–2234.
- Morley JE. Mild cognitive impairment—a treatable condition. J Am Med Dir Assoc 2014;15:1–5.
- Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment—beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. J Intern Med 2004;256:240–246.
- Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: A Delphi consensus study. Lancet 2005;366:2112–2117.
- Hugo J, Ganguli M. Dementia and cognitive impairment: Epidemiology, diagnosis, and treatment. Clin Geriatr Med 2014;30:421–442.
- Tomlinson BE, Blessed G, Roth M. Observations on the brains of demented old people. J Neurol Sci 1970;11:205–242.
- Chui HC, Ramirez-Gomez L. Clinical and imaging features of mixed Alzheimer and vascular pathologies. Alzheimers Res Ther 2015;7:21.
- Zhang Y, Xu Y, Nie H, et al. Prevalence of dementia and major dementia subtypes in the Chinese populations: A meta-analysis of dementia prevalence surveys, 1980–2010. J Clin Neurosci 2012;19:1333–1337.
- de Pedro-Cuesta J, Virues-Ortega J, Vega S, et al. Prevalence of dementia and major dementia subtypes in Spanish populations: A re-analysis of dementia prevalence surveys, 1990–2008. BMC Neurol 2009;9:55.
- Kelaiditi E, Cesari M, Canevelli M, et al. Cognitive frailty: Rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. J Nutr Health Aging 2013;17:726–734.

- Malmstrom TK, Morley JE. Frailty and cognition: Linking two common syndromes in older persons. | Nutr Health Aging 2013;17:723–725.
- 12. Fitten IJ. Thinking about cognitive frailty. J Prev Alzheimers Dis 2015;2:7–10.
- Morley JE, Abbatecola AM, Argiles JM, et al. Sarcopenia with limited mobility: An international consensus. J Am Med Dir Assoc 2011;12:403

 –409.
- Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: A call to action. J Am Med Dir Assoc 2013;14:392–397.
- Morris JC, Blennow K, Froelich L, et al. Harmonized diagnostic criteria for Alzheimer's disease: Recommendations. J Intern Med 2014;275:204–213.
- Cordell CB, Borson S, Boustani M, et al. Alzheimer's Association recommendations for operationalizing the detection of cognitive impairment during the Medicare Annual Wellness visit in a primary care setting. Alzheimers Dement 2013:9:141–150
- Folstein MF, Folstein SE, McHugh PR. "Mini-mental State." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
- Tangalos EG, Smith GE, Ivnik RJ, et al. The Mini-Mental State Examination in general medical practice: Clinical utility and acceptance. Mayo Clin Proc 1996; 71:829–837.
- Subra J, Gillette-Guyonnet S, Cesari M, et al. The integration of frailty into clinical practice: Preliminary results from the Gerontopole. J Nutr Health Aging 2012;16:714

 –720.
- McCarten JR, Anderson P, Kuskowski MA, et al. Screening for cognitive impairment in an elderly veteran population: Acceptability and results using different versions of the Mini-Cog. J Am Geriatr Soc 2011;59:309–313.
- Bayley PJ, Kong JY, Mendiondo M, et al. Findings from the national memory screening day program. J Am Geriatr Soc 2015;63:309

 –314.
- Cruz-Oliver DM, Malmstrom TK, Allen CM, et al. The Veterans Affairs St. Louis
 University mental status exam (SLUMS exam) and the Mini-mental status
 exam as predictors of mortality and institutionalization. J Nutr Health Aging
 2012;16:636–641.
- 23. Woo J, Yu R, Wong M, et al. Frailty screening in the community using the FRAIL scale. I Am Med Dir Assoc 2015:16:412–419.
- Ross GW, Abbott RD, Petrovitch H, et al. Frequency and characteristics of silent dementia among elderly Japanese-American men. The Honolulu-Asia Aging Study. JAMA 1997;277:800–805.
- Jansen AP, van Hout HP, Nijpels G, et al. Yield of new method to detect cognitive impairment in general practice. Int J Geriatr Psychiatry 2007;22: 590–597.
- Miller DK, Morley JE, Rubenstein LZ, et al. Formal geriatric assessment instruments and the care of older general medical outpatients. J Am Geriatr Soc 1990;38:645–651.
- 27. Alzheimer's Association. 2015 Alzheimer's disease facts and figures. Available at: www.alz.org/facts/overview.asp. Accessed March 29, 2015.
- Tierney MC, Naglie G, Upshur R, et al. Factors associated with primary care physicians' recognition of cognitive impairment in their older patients. Alzheimer Dis Assoc Disord 2014;28:320–325.
- Lin JS, O'Connor E, Rossom RC, et al. Screening for cognitive impairment in older adults: An evidence update for the U.S. Preventive services task force. Agency for healthcare research and quality (US). 2013 (Nov) report No:14-05198-EF-1. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24354019. Accessed March 25, 2015.
- Imtiaz B, Tolppanen AM, Kivipelto M, Soininen H. Future directions in Alzheimer's disease from risk factors to prevention. Biochem Pharmacol 2014; 88:661–670.
- Chin R, Ng A, Narasimhalu K, Kandiah N. Utility of the AD8 as a self-rating tool for cognitive impairment in an Asian population. Am J Alzheimers Dis Other Demen 2013;28:284–288.
- 32. Malmstrom TK, Miller DK, Coats MA, et al. Informant-based dementia screening in a population-based sample of African Americans. Alzheimer Dis Assoc Disord 2009;23:117–123.
- **33.** Galvin JE, Roe CM, Powlishta KK, et al. The AD8: A brief informant interview to detect dementia. Neurology 2005;65:559–564.
- 34. Galvin JE, Roe CM, Xiong C, Morris JC. Validity and reliability of the AD8 informant interview in dementia. Neurology 2006;67:1942–1948.
- Rueda AD, Lau KM, Saito N, et al, Alzheimer's Disease Neuroimaging Initiative. Self-rated and informant-rated everyday function in comparison to objective markers of Alzheimer's disease [published online ahead of print November 15, 2014]. Alzheimers Dement; 2014. http://dx.doi.org/10.1016/j.jalz.2014.09. 002
- Meguro K, Kasai M, Nakamura K. Kurihara Project members. Reliability and validity of the Japanese version of the AD8. Nihon Ronen Igakkai Zaashi 2015; 52:61–70.
- Xie Y, Gao Y, Jia J, et al. Utility of AD8 for cognitive impairment in a Chinese physical examination population: A preliminary study. ScientificWorldJournal 2014;2014:804871.
- Chen CH, Wang LC, Ma TC, Yang YH. A walk-in screening of dementia in the general population in Taiwan. ScientificWorldJournal 2014;2014: 243738.
- Li T, Wang HL, Yang YH, et al. The reliability and validity of Chinese version of AD8 [Chinese]. Zhonghua Nie Ke Za Zhi 2012;51:777–780.
- Carnero Pardo C, de la Vega Cotarelo R, López Alcalde S, et al. Assessing the diagnostic accuracy (DA) of the Spanish version of the informant-based AD8 questionnaire. Neurologia 2013;28:88–94.

- Correia CC, Lima F, Junqueira F, et al. AD8-Brazil: Cross-cultural validation of the ascertaining dementia interview in Portuguese. J Alzheimers Dis 2011;27: 177–185.
- Borson S, Scanlan J, Brush M, et al. The mini-cog: A cognitive 'vital signs' measure for dementia screening in multi-lingual elderly. Int J Geriatr Psychiatry 2000;15:1021–1027.
- Scanlan J, Borson S. The Mini-Cog: Receiver operating characteristics with expert and naïve raters. Int J Geriatr Psychiatry 2001;16:216–222.
- Borson S, Scanlan JM, Chen P, Ganguli M. The Mini-Cog as a screen for dementia: Validation in a population-based sample. J Am Geriatr Soc 2003;51: 1451–1454.
- **45.** Setter SM, Neumiller JJ, Johnson M, et al. The mini-cog: A rapid dementia screening tool suitable for pharmacists' use. Consult Pharm 2007;22:855–861.
- 46. Malmstrom TK, Voss VB, Cruz-Oliver DM, et al. Rapid Cognitive Screen (RCS): A point-of-care screening for dementia and mild cognitive impairment. J Nutr Health Aging 2015;19:741–744.
- Tariq SH, Tumosa N, Chibnall JT, et al. Comparison of the Saint Louis University mental status examination and the mini-mental state examination for detecting dementia and mild neurocognitive disorder—a pilot study. Am J Geriatr Psychiatry 2006;14:900–910.
- Feliciano L, Horning SM, Klebe KJ, et al. Utility of the SLUMS as a cognitive screening tool among a nonveteran sample of older adults. Am J Geriatr Psychiatry 2013;21:623

 –630.
- Cummings-Vaughn LA, Chavakula NN, Malmstrom TK, et al. Veterans Affairs Saint Louis University mental status examination compared with the Montreal cognitive assessment and the short test of mental status. J Am Geriatr Soc 2014;62:1341–1346.
- Dubois B, Touchon J, Portet F, et al. "The 5 words": A simple and sensitive test for the diagnosis of Alzheimer's disease [French]. Presse Med 2002:31:1696–1699.
- Wicklund M, Petersen RC. Emerging biomarkers in cognition. Clin Geriatr Med 2013;29:809

 –828.
- Morris JC, Kimberly A, Quaid K, et al. Role of biomarkers in studies of presymptomatic Alzheimer's disease. Alzheimers Dement 2005;1:145–151.
- Ariza M, Kolb HC, Moechars D, et al. Tau positron emissions tomography (PET) imaging: Past, present, and future. J Med Chem 2015;58:4365–4382.
- McCleery J, Morgan S, Bradley KM, et al. Dopamine transporter imaging for the diagnosis of dementia with Lewy bodies. Cochrane Database Syst Rev 2015;(1):CD010633.
- Bocchetta M, Galluzzi S, Kehoe PG, et al. The use of biomarkers for the etiologic diagnosis of MCI in Europe: An EADC survey. Alzheimers Dement 2015; 11:195–206 e1
- 56. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia 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;7:263—269.
- Prestia A, Caroli A, Wade SK, et al. Prediction of AD dementia by biomarkers following the NIA-AA and IWG diagnostic criteria in MCI patients from three European memory clinics [published online ahead of print January 31, 2015]. Alzheimers Dement; 2015. http://dx.doi.org/10.1016/j.jalz.2014.12.001.
- Cummings JL, Dubois B, Molinuevo JL, Scheltens P. International Work Group criteria for the diagnosis of Alzheimer disease. Med Clin North Am 2013;97: 363–368
- Zaleta AK, Carpenter BD, Porensky EK, et al. Agreement on diagnosis among patients, companions, and professionals after a dementia evaluation. Alzheimer Dis Assoc Disord 2012;26:232–237.
- Morley JE. Anticholinergic medications and cognition. J Am Med Dir Assoc 2011;12:543–543.e1.
- Campbell N, Boustani M, Limbil T, et al. The cognitive impact of anticholinergics: A clinical review. Clin Inter Aging 2009;4:225–233.
- Cruz-Oliver DM, Malmstrom TK, Roegner M, et al. Cognitive deficit reversal as shown by changes in the Veterans Affairs Saint Louis University Mental Status (SLUMS) examination scores 7.5 years later. J Am Med Dir Assoc 2014;15:687. e5–687.e10.
- 63. Morandi A, Bellelli G, Vasilevskis EE, et al. Predictors of rehospitalization among elderly patients admitted to a rehabilitation hospital: The role of polypharmacy, functional status, and length of stay. J Am Med Dir Assoc 2013; 14:761–767.
- 64. Tsai R, Noone M, Johnson B, et al. Potentially inappropriate medication use in individuals with mild cognitive impairment: Results from the Kerala Einstein Study. | Am Geriatr Soc 2012;60:1369—1370.
- Thakur M, Blazer DG. Depression in long-term care. J Am Med Dir Assoc 2008; 9:82–87.
- Osterweil D, Syndulko K, Cohen SN, et al. Cognitive function in non-demented older adults with hypothyroidism. J Am Geriatr Soc 1992;40:325–335.
- Suchorska B, Kunz M, Schniepp R, et al. Optimized surgical treatment for normal pressure hydrocephalus: Comparison between gravitational and differential pressure valves. Acta Neurochir (Wien) 2015;157:703–709.
- Olaithe M, Bucks RS. Executive dysfunction in OSA before and after treatment: A meta-analysis. Sleep 2013;36:1297–1305.
- Lal C, Strange C, Bachman D. Neurocognitive impairment in obstructive sleep apnea. Chest 2012;141:1601–1610.
- Van der Flier WM, van Straaten EC, Barkhof F, et al. Small vessel disease and general cognitive function in nondisabled elderly: The LADIS study. Stroke 2005;36:2116–2120.

- Kloppenborg RP, Nederkoorn PJ, Geerlings MI, van den Berg E. Presence and progression of white matter hyperintensities and cognition: A meta-analysis. Neurology 2014;82:2127–2138.
- Overdorp EJ, Kessels RP, Claassen JA, Oosterman JM. Cognitive impairments associated with medial temporal atrophy and white matter hyperintensities: An MRI study in memory clinic patients. Front Aging Neurosci 2014:6:98.
- Wakefield DB, Moscufo N, Guttmann CR, et al. White matter hyperintensities predict functional decline in voiding, mobility, and cognition in older adults. | Am Geriatr Soc 2010;58:275–281.
- Pantoni L. Cerebral small vessel disease: From pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol 2010;9:689

 –701.
- Pantoni L, Poggesi A, Inzitari D. Cognitive decline and dementia related to cerebrovascular diseases: Some evidence and concepts. Cerebrovasc Dis 2009; 27:191–196.
- Ganguli M, Fu B, Snitz BE, et al. Mild cognitive impairment: Incidence and vascular risk factors in a population-based cohort. Neurology 2013;80: 2112–2120.
- Singh B, Mielke MM, Parsaik AK, et al. A prospective study of chronic obstructive pulmonary disease and the risk for mild cognitive impairment. JAMA Neurol 2014;71:581–588.
- Ampadu J, Morley JE. Heart failure and cognitive dysfunction. Int J Cardiol 2015;178:12—23.
- Cheng G, Huang C, Deng H, Wang H. Diabetes as a risk factor for dementia and mild cognitive impairment: A meta-analysis of longitudinal studies. Intern Med J 2012;42:484–491.
- Geijselaers SL, Sep SJ, Stehouwer CD, Biessels GJ. Glucose regulation, and brain MRI in type 2 diabetes: A systematic review. Lancet Diabetes Endocrinol 2015;3:75–89.
- 81. Biessels GJ, Reijmer YD. Brain changes underlying cognitive dysfunction in diabetes: What can we learn from MRI? Diabetes 2014;63:2244–2252.
- McNeilly GS, Cheung E, Tessier D, et al. The effect of improved glycemic control on cognitive functions in the elderly patient with diabetes. J Gerontol 1993;48:M117—M121.
- Reaven GM, Thompson LW, Nahum D, Haskins E. Relationship between hyperglycemia and cognitive function in older NIDDM patients. Diabetes Care 1990;13:16–21.
- **84.** Flood JF, Mooradian AD, Morley JE. Characteristics of learning and memory in streptozocin-induced diabetic mice. Diabetes 1990;39:1391–1398.
- Psaltopoulou T, Sergentanis TN, Panagiotakos DB, et al. Mediterranean diet, stroke, cognitive impairment, and depression: A meta-analysis. Ann Neurol 2013;74:580–591.
- 86. Singh B, Parsaik AK, Mielke MM, et al. Association of mediterranean diet with mild cognitive impairment and Alzheimer's disease: A systematic review and meta-analysis. J Alzheimers Dis 2014;39:271–282.
- Solfrizzi V, Panza F. Mediterranean diet and cognitive decline. A lesson from the whole-diet approach: What challenges lie ahead? J Alzheimers Dis 2014; 39:283–286.
- Martinez-Lapiscina EH, Clavero P, Toledo E, et al. Mediterranean diet improves cognition: The PREDIMED-NAVARRA randomised trial. J Neurol Neurosurg Psychiatry 2013;84:1318–1325.
- Martinez-Lapiscina EH, Clavero P, Toledo E, et al. Virgin olive oil supplementation and long-term cognition: The PREDIMED-NAVARRA randomized trial. J Nutr Health Aging 2013;17:544–552.
- 90. Farr SA, Price TO, Dominguez LJ, et al. Extra virgin olive oil improves learning and memory in SAMP8 mice. J Alzheimers Dis 2012;28:81–92.
- Tangney CC, Li H, Wang Y, et al. Relation of DASH- and Mediterranean-like dietary patterns to cognitive decline in older persons. Neurology 2014;83: 1410–1416.
- Morris MC, Tangney CC, Wang Y, et al. MIND diet associated with reduced incidence of Alzheimer's disease [published online ahead of print February 11, 2015]. Alzheimers Dement; 2015. http://dx.doi.org/10.1016/jj.jalz.2014.11.
- Barnard ND, Bush AI, Ceccarelli A, et al. Dietary and lifestyle guidelines for the prevention of Alzheimer's disease. Neurobiol Aging 2014;35:S74–S78.
- 94. Shah R. The role of nutrition and diet in alzheimer disease: A systematic review. J Am Med Dir Assoc 2013;14:398–402.
- 95. Farina N, Isaac MG, Clark AR, et al. Vitamin E for Alzheimer's dementia and mild cognitive impairment. Cochrane Database Syst Rev 2012;(11):CD002854.
- Dysken MW, Sano M, Asthana S, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: The TEAM-AD VA cooperative randomized trial. JAMA 2014;311:33

 –44.
- Li MM, Yu JT, Wang HF, et al. Efficacy of vitamin B supplementation on mild cognitive impairment and Alzheimer's disease: A systematic review and meta-analysis. Curr Alzheimer Res 2014;11:844–852.
- Dangour AD, Whitehouse PJ, Rafferty K, et al. B-Vitamins and fatty acids in the prevention and treatment of Alzheimer's disease and dementia: A systematic review. J Alzheimers Dis 2010;22:205–224.
- Malouf R, Areosa Sastre A. Vitamin B12 for cognition. Cochrane Database Syst Rev 2003;(3):CD004326.
- 100. Cheng D, Kong H, Pang W, et al. B vitamin supplementation improves cognitive function in the middle aged and elderly with hyperhomocysteinemia [published online ahead of print June 18, 2014]. Nutr Neurosci; 2014.

- 101. van Wijk N, Broersen LM, de Wilde MC, et al. Targeting synaptic dysfunction in Alzheimer's disease by administering a specific nutrient combination. J Alzheimers Dis 2014;38:459–479.
- 102. Olde Rikkert MG, Verhey FR, Sijben JW, et al. Differences in nutritional status between very mild Alzheimer's disease patients and healthy controls. J Alzheimers Dis 2014;41:261–271.
- **103.** Shah RC, Kamphuis PJ, Leurgans S, et al. The S-Connect study: Results from a randomized, controlled trial of souvenaid in mild-to-moderate Alzheimer's disease. Alzheimers Res Ther 2013;5:59.
- 104. Olde Rikkert MG, Verhey FR, Blesa R, et al. Tolerability and safety of souvenaid in patients with mild Alzheimer's disease: Results of multi-center, 24-week, open-label extension study. J Alzheimers Dis 2015;44:471–480.
- 105. Sharma A, Bemis M, Desilets AR. Role of medium chain triglycerides (Axona(R)) in the treatment of mild to moderate Alzheimer's disease [published online ahead of print January 9, 2014]. Am J Alzheimers Dis Other Demen; 2014
- 106. Henderson ST, Vogel JL, Barr LJ, et al. Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: A randomized, double-blind, placebocontrolled, multicenter trial. Nutr Metab (Lond) 2009;6:31.
- 107. Norton S, Matthews FE, Barnes DE, et al. Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. Lancet Neurol 2014;13:788–794.
- 108. Sofi F, Valecchi D, Bacci D, et al. Physical activity and risk of cognitive decline: A meta-analysis of prospective studies. J Intern Med 2011;269:107–117.
- 109. Angevaren M, Aufdemkampe G, Verhaar HJ, et al. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. Cochrane Database Syst Rev 2008;(3):CD005381.
- Gates N, Fiatarone Singh MA, Sachdev PS, Valenzuela M. 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;21:1086–1097.
- 111. Wang C, Yu JT, Wang HF, et al. Non-pharmacological interventions for patients with mild cognitive impairment: A meta-analysis of randomized controlled trials of cognition-based and exercise interventions. J Alzheimers Dis 2014;42:663—678.
- Erickson KI, Voss MW, Prakash RS, et al. Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci U S A 2011;108: 3017–3022.
- 113. Voss MW, Heo S, Prakash RS, et al. The influence of aerobic fitness on cerebral white matter integrity and cognitive function in older adults: Results of a one-year exercise intervention. Hum Brain Mapp 2013;34:2972–2985.
- 114. Fiatarone Singh MA, Gates N, Saigal N, et al. The study of mental and resistance training (SMART) study—resistance training and/or cognitive training in mild cognitive impairment: A randomized, double-blind, double-sham controlled trial. J Am Med Dir Assoc 2014;15:873–880.
- 115. Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for alzheimer disease: A randomized trial. JAMA 2008;300:1027–1037.
- **116.** Wayne PM, Walsh JN, Taylor-Piliae RE, et al. Effect of tai chi on cognitive performance in older adults: Systematic review and meta-analysis. J Am Geriatr Soc 2014;62:25–39.
- 117. Lam LC, Chau RC, Wong BM, et al. A 1-year randomized controlled trial comparing mind body exercise (Tai Chi) while stretching and toning exercise on cognitive function in older Chinese adults at risk of cognitive decline. J Am Med Dir Assoc 2012;13:568.e15–568.e20.
- 118. 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.
- 119. Verghese J, Lipiton RB, Katz MJ, et al. Leisure activities and the risk of dementia in the elderly. N Engl J Med 2003;348:2508—2516.
- Verghese J, Wang Cuiling, Katz MJ, et al. Leisure activities and risk of vascular cognitive impairment in older adults. J Geriatr Psychiatry Neurol 2009;22: 110–118.
- 121. Hall CB, Lipton RB, Sliwinski M, et al. Cognitive activities delay onset of memory decline in persons who develop dementia. Neurology 2009;73: 356–361.
- **122.** Unverzagt FW, Guey LT, Jones RN, et al. ACTIVE cognitive training and rates of incident dementia. J Int Neuropsychol Soc 2012;18:669–677.
- 123. Jones RN, Marsiske M, Ball K, et al. The ACTIVE cognitive training interventions and trajectories of performance among older adults. J Aging Health 2013;25:1865–208S.
- **124.** Woods B, Aguirre E, Spector AE, Orrell M. Cognitive stimulation to improve cognitive functioning in people with dementia. Cochrane Database Syst Rev 2012;(2):CD005562.
- 125. Simon SS, Yokomizo JE, Bottino CMC. Cognitive intervention in amnestic mild cognitive impairment: A systematic review. Neurosci Biobehav Rev 2012;36: 1163—1178.
- **126.** D'Amico F, Rehill A, Knapp M, et al. Maintenance cognitive stimulation therapy: An economic evaluation within a randomized controlled trial. J Am Med Dir Assoc 2015;16:63–70.
- 127. Loraine J, Taylor S, McAllister M. Cognitive and physical stimulation therapy. J Am Med Dir Assoc 2014;15:140–141.
- 128. Kawashima R, Hiller DL, Sereda SL, et al. SAIDO learning as a cognitive intervention for dementia care: A preliminary study. J Am Med Dir Assoc 2015;16:56–62.

- 129. Karlin BE, Visnic S, McGee JS, Teri L. Results from the multisite implementation of STAR-VA: A multicomponent psychosocial intervention for managing challenging dementia-related behaviors of veterans. Psychol Serv 2014;11: 200–208.
- **130.** Teri L, Huda P, Gibbons L, et al. STAR: A dementia-specific training program for staff in assisted living residencies. Gerontologist 2005;45:686–693.
- Woods B, Thorgrimsen L, Spector A, et al. Improved quality of life and cognitive stimulation therapy in dementia. Aging Ment Health 2006;10:219–226.
- 132. Law LLF, Barnett F, Yau MK, Gray MA. Effects of combined cognitive and exercise interventions on cognition in older adults with and without cognitive impairment: A systematic review. Ageing Res Rev 2014;15:61–75.
- 133. Wingbermuehle C, Bryer D, Berg-Weger M, et al. Baseball reminiscence league: A model for supporting persons with dementia. J Am Med Dir Assoc 2014:15:85–89.
- **134.** van Bogaert P, Van Grinsven R, Tolson D, et al. Effects of SolCos model-based individual reminiscence on older adults with mild to moderate dementia due to alzheimer disease: A pilot study. J Am Med Dir Assoc 2013;14:528. e9–528.e13.
- Woods B, Spector A, Jones C, et al. Reminiscence therapy for dementia. Cochrane Database Syst Rev 2005;(2):CD001120.
- 136. Toril P, Reales JM, Ballesteros S. Video game training enhances cognition of older adults: A meta-analytic study. Psychol Aging 2014;29:706–716.
- Kueider AM, Parisi JM, Gross AL, Rebok GW. Computerized cognitive training with older adults: A systematic review. PLoS One 2012;7:e40588.
- 138. Daviglus ML, Bell CC, Berrettini W, et al. National Institutes of Health State-ofthe-Science Conference statement: Preventing Alzheimer disease and cognitive decline. Ann Intern Med 2010;153:176–181.
- 139. Solomon A, Mangialasche F, Richard E, et al. Advances in the prevention of Alzheimer's disease and dementia. J Intern Med 2014;275:229–250.
- 140. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A randomized controlled trial. Lancet 2015;385:2255—2263.
- **141.** Kivipelto M, Ngandu T, Laatikainen T, et al. Risk score for the prediction of dementia risk in 20 years among middle aged people: A longitudinal, population-based study. Lancet Neurol 2006;5:735–741.
- 142. Knopman DS, Petersen RC. Mild cognitive impairment and mild dementia: A clinical perspective. Mayo Clin Proc 2014;89:1452–1459.
- **143.** Dean K, Wilcock G. Living with mild cognitive impairment: The patient's and carer's experience. Int Psychogeriatr 2012;24:871–881.
- 144. Panza F, Solfrizzi V, Barulli MR, et al. Cognitive frailty—epidemiological and neurobiological evidence of an age-related clinical condition: A systematic review [published online ahead of print March 26, 2015]. Rejuvenation Res; 2015
- 145. Morris JC. The clinical dementia rating (CDR): Current version and scoring rules, Neurology 1993;43:2412–2414.
- **146.** Robertson DA, Savva BM, Coen RF, Kenny RA. Cognitive function in the prefrailty and frailty syndrome. J Am Geriatr Soc 2014;62:2118–2124.
- 147. Malmstrom TK, Morley JE. The frail brain. J Am Med Dir Assoc 2013;14: 453–455
- 148. Shimada H, Makizako H, Doi T, et al. Combined prevalence of frailty and mild cognitive impairment in a population of elderly Japanese people. J Am Med Dir Assoc 2013;14:518–524.
- 149. Nishiguchi S, Yamada M, Fukutani N, et al. Differential association of frailty with cognitive decline and sarcopenia in community-dwelling older adults. J Am Med Dir Assoc 2015;16:120–124.
- **150.** Mitnitski A, Fallah N, Rockwood MR, Rockwood K. Transitions in cognitive status in relation to frailty in older adults: A comparison of three frailty measures. J Nutr Health Aging 2011;15:863–867.
- 151. Avila-Funes JA, Pina-Escudero SD, Aguilar-Navarro S, et al. Cognitive impairment and low physical activity are the components of frailty more strongly associated with disability. J Nutr Health Aging 2011;15:683–689.
- **152.** Auyeung TW, Lee JS, Kwok T, Woo J. Physical frailty predicts future cognitive decline—a four-year prospective study in 2737 cognitively normal older adults. J Nutr Health Aging 2011;15:690–694.
- 153. Parihar R, Mahoney JR, Verghese J. Relationship of gait and cognition in the elderly. Curr Transl Geriatr Exp Gerontol Rep 2013;2.
- 154. Halil M, Cemal Kizilarslanoglu M, Emin Kuyumcu M, et al. Cognitive aspects of frailty: Mechanisms behind the link between frailty and cognitive impairment. J Nutr Health Aging 2015;19:276–283.
- 155. McCough EL, Kelly VE, Logsdon RG, et al. Associations between physical performance and executive function in older adults with mild cognitive impairment: Gait speed and the timed "up & go" test. Phys Ther 2011;91: 1198–1207.
- 156. Ogama N, Sakurai T, Shimizu A, Toba K. Regional white matter lesions predict falls in patients with amnestic mild cognitive impairment and Alzheimer's disease. J Am Med Dir Assoc 2014;15:36–41.
- 157. Bolandzadeh N, Liu-Ambrose T, Aizenstein H, et al. Pathways linking regional hyperintensities in the brain and slower gait. Neuroimage 2014; 99:7–13.
- **158.** Callisaya ML, Beare R, Phan T, et al. Progression of white matter hyperintensities of presumed vascular origin increases the risk of falls in older people. J Gerontol A Biol Sci Med Sci 2015;70:358–364.
- Prins ND, Scheltens P. White matter hyperintensities, cognitive impairment and dementia: An update. Nat Rev Neurol 2015;11:157–165.