CCCDTD5 recommendations on early non cognitive markers of dementia: A Canadian consensus

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Abstract

Introduction: Cognitive impairment is the hallmark of Alzheimer’s disease (AD) and related dementias. However, motor decline has been recently described as a prodromal state that can help to detect at-risk individuals. Similarly, sensory changes, sleep and behavior disturbances, and frailty have been associated with higher risk of developing dementia. These clinical findings, together with the recognition that AD pathology precedes the diagnosis by many years, raises the possibility that non-cognitive changes may be early and non-invasive markers for AD or, even more provocatively, that treating non-cognitive aspects may help to prevent or treat AD and related dementias.

Methods: A subcommittee of the Canadian Consensus Conference on Diagnosis and Treatment of Dementia reviewed areas of emerging evidence for non-cognitive markers of dementia. We examined the literature for five non-cognitive domains associated with future dementia: motor, sensory (hearing, vision, olfaction), neuro-behavioral, frailty, and sleep. The Grading of Recommendations Assessment, Development, and...
Evaluation system was used to assign the strength of the evidence and quality of the recommendations. We provide recommendations to primary care clinics and to specialized memory clinics, answering the following main questions: (1) What are the non-cognitive and functional changes associated with risk of developing dementia? and (2) What is the evidence that sensory, motor, behavioral, sleep, and frailty markers can serve as potential predictors of dementia?

**Results:** Evidence supported that gait speed, dual-task gait speed, grip strength, frailty, neuropsychiatric symptoms, sleep measures, and hearing loss are predictors of dementia. There was insufficient evidence for recommending assessing olfactory and vision impairments as a predictor of dementia.

**Conclusions:** Non-cognitive markers can assist in identifying people at risk for cognitive decline or dementia. These non-cognitive markers may represent prodromal symptoms and several of them are potentially amenable to treatment that might delay the onset of cognitive decline.

**KEYWORDS**
behavior, biomarker, cognitive impairment, dementia, frailty, gait, hearing, olfaction, parkinsonism, prediction, risk, sleep, vision

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1 | **INTRODUCTION**

Cognitive impairment is the hallmark of Alzheimer’s disease (AD) and related dementias. Motor decline has recently been described as an early prodromal feature that can help to detect individuals at risk.1,2 Similarly, sensory changes (vision, olfaction, and hearing), sleep and behavior disturbances, and frailty have been associated with higher risk of developing dementia.3,4 These clinical findings, together with the recognition that AD pathology develops over many years, raises the possibility that specific sensory or motor changes may be early non-invasive biomarkers for AD or, even more provocatively, that treating these aspects may help to prevent or treat AD and related dementias. However, guidelines and recommendations for assessing non-cognitive markers of dementia are scarce.

Since 1989, the Canadian Consensus Conference on Diagnosis and Treatment of Dementia (CCCDTD) has convened to generate expert clinical guidelines for dementia.2,5 As the field has evolved, so have the guidelines, and for the first time, non-cognitive markers have been included as a topic based on a steering committee needs assessment. The 5th CCCDTD was conducted in 2019–2020 to comprehensively review and update guidelines for cognitive disorders; the summary paper of all guidelines has now been published.6 Here, we review the development and rationale for the recommendations on early non-cognitive markers to dementia.

The goal was to provide recommendations for primary care physicians that care for older adults, and also for specialized clinics in geriatric medicine, neurology, and psychiatry evaluating older adults at risk of dementia.

2 | **METHODS**

A subcommittee was formed to create guidelines on early non-cognitive markers of dementia, which included experts representing the disciplines of geriatric medicine, neurology, psychiatry, psychology, and physical medicine and rehabilitation. Areas for recommendations were identified by expert knowledge. Subcommittee members then performed targeted systematic literature searches to identify evidence with potential to change practice in these non-cognitive domains selected based on reported associations with cognitive status or decline in older adults. The non-cognitive domains identified were as follows: motor, sensory (hearing, vision, and olfaction), neuro-behavioral, frailty, and sleep. Systematic reviews and important original studies were included. We performed systematic searches that are described in the supporting information for each non-cognitive domain category. In our searches, we included studies that: (1) were original research, (2) assessed motor or gait function, (3) assessed frailty, (4) assessed behavior disturbances, (5) assessed sleep, (6) assessed sensory function, (7) measured incident dementia, (8) included adult human participants, and (9) were written in English language.

Guidelines were drafted by committee members and the Grading of Recommendations Assessment, Development, and Evaluation system was used to describe the strength of recommendation and quality of evidence (Table 1).6 Recommendations were reviewed and revised until internal subcommittee consensus was obtained. All subcommittee recommendations were then voted on by all CCCDTD5 conference attendees, with a majority of 80% or higher agreement required to pass. The final set of recommendations were presented at
2.1 | Motor function as a marker of late-onset dementia

Cognition and motor function decline with aging, and it has been shown that motor impairments can precede cognitive impairment. Therefore, motor changes have been proposed as potential clinical biomarkers to help predict dementia syndromes. Several motor domains have been associated with cognition, with lower limb motor performance (including gait performance) being more commonly studied. Changes in gait speed have been found up to 12 years before clinical diagnosis of mild cognitive impairment (MCI). Previous systematic reviews of potential dementia motor markers have shown that gait speed is associated with future dementia in general. Please see the supporting information for details on our search strategy.

2.1.1 | Results stratified by motor markers and recommendations

Gait speed test
A high-quality study in older adults with Parkinson’s disease found that each standard deviation (SD = 0.20 meter/second [m/s]) decrease in gait speed was associated with an estimated 59% increased short-term risk of incident dementia and 47% increased short-term risk of incident AD (n = 3663, follow-up = 9 years). Another high-quality study found that slow gait speed, measured by the Timed Up and Go Test, was not independently associated with incident dementia (n = 80, follow-up = 4.4 years). A study of early PD found that quantitative gait measures predicted cognitive decline in specific cognitive domains. Another non-PD study did not find slow gait speed (<0.6 m/s) significantly associated with incident dementia or AD, but it was associated with an estimated 113% increased short-term risk of incident non-AD dementia (n = 2619, follow-up = 6.5 years). A cohort study found pre-specified categories for slow gait velocity based on age and sex were not associated with incident dementia of any type, but slow gait was associated with an estimated 4.5 times increase in the short-term risk of incident vascular dementia (VaD) (n = 767, follow-up = 3 years). Six cohort studies using different methods to quantify slow gait speed (continuous m/s, cut-off values, quartiles) with different levels of risk of bias, consistently found significant associations with incident dementia. Finally, one cohort study classified quantitative gait performance into three factors: pace, rhythm, and variability (n = 399, follow-up = 2 years). Pace was not associated with incident dementia, but it was the only factor associated with increased risk of VaD, specifically. Gait rhythm was associated with incident dementia unless baseline memory was controlled for. Gait variability was associated with incident dementia unless executive function was controlled for. Attrition bias may be present in this study. Five studies combined in a meta-analysis revealed that slow gait speed (defined as a dichotomous exposure, as below 0.8 m/s) was associated with an estimated 94% increased short-term risk of incident dementia. Funnel plots suggest some publication bias toward larger studies reporting positive associations, and thus, the summary hazard ratio (HR) found may be an overestimation.

*Recommendation 1*. There is strong evidence that slower gait speed is associated with future dementia, in population studies. When gait speed (cut-off gait speed below 0.8 m/s) is associated with incident dementia unless executive function was controlled for. Gait variability was associated with incident dementia unless executive function was controlled for. Attrition bias may be present in this study. Five studies combined in a meta-analysis revealed that slow gait speed (defined as a dichotomous exposure, as below 0.8 m/s) was associated with an estimated 94% increased short-term risk of incident dementia. Funnel plots suggest some publication bias toward larger studies reporting positive associations, and thus, the summary hazard ratio (HR) found may be an overestimation.

RESEARCH IN CONTEXT

1. Systematic review: Using expert knowledge and systematic reviews searches of previous articles published in English, the writing committee identified clinical questions for guideline development. For each question and non-cognitive domain associated with dementia risk assessed, a search strategy was created and searched in Medline database on September 9, 2019, using PubMed.

2. Interpretation: Recommendations and suggestions are offered to guide the use of non-cognitive markers in the detection of individuals at risk of developing dementia.

3. Future directions: Research will be needed on how our recommendations influence clinical practice. The supporting evidence for the predictive role of non-cognitive early markers dementia found is strong, so future research also can evaluate if managing or treating these markers could help to prevent or stabilize Alzheimer’s disease and related dementias.

HIGHLIGHTS

- Cognitive impairment is the hallmark of Alzheimer’s disease and related dementias.
- However, non-cognitive markers can also help detect individuals at risk of dementia.
- We reviewed non-cognitive markers and reached evidence-based recommendations.
- We recommend testing gait speed, dual-task gait, grip strength, frailty, behavioral symptoms, sleep, and hearing loss.
- Some of the markers are amenable to treatment to delay onset of cognitive decline.
coupled with cognitive impairment (subjective or objective) the risk is higher. We recommend testing gait speed in clinics in those patients with cognitive complaints/impairments if time/resources are available. 1B. Note. Standardized protocols on how to assess gait speed with stopwatch are available. Test takes, on average, 3 minutes to perform.

Dual-task gait

Dual-task gait (DTG), walking while performing a concurrent cognitively demanding task, can be seen as a brain stress test that can evaluate the cognitive-motor interface and it has been postulated as a biomarker that can detect older adults at risk of progressing to dementia. One cohort study showed that DTG is associated with progression from MCI to dementia and from normal to MCI and motoric cognitive risk syndrome (MCR).21,22 Five studies evaluated DTG and cognitive performance and dementias.21-25 Two cross-sectional studies showed the feasibility to perform the DTG test in clinic scenarios.23,24 One of these studies also addresses the potential ability of DTG to differentiate cognitive subtyping.23

There is no consensus regarding which cognitive challenge task (eg, naming items or animals, calculations, reciting alphabet letters) should be paired with walking, or the predicted ability of one task over another. Thus, these different variations of the dual-task paradigm should not be considered interchangeable. Dual-task cost—defined as the percent change between single (S) and dual-task (D) gait speeds: \[ \frac{(S-D)/S}{100} \] of >20% slowing significantly predicts increasing risk of progression to dementia in older adults with MCI, with higher cost having progressively higher risk with shorter time to dementia.8 DTG has been also associated with future dementia in at least one large cohort of community-dwelling older adults.19 Published consensus protocols on how to assess DTG for dementia risk with just a stopwatch are available.2,26

**Recommendation 2:** Dual-task gait impairment (lower speed or higher cost) is associated with future incident dementia. In MCI samples, dual-task gait was shown to predict time to progression to dementia. Variability in the delivery of testing protocols is noted. We recommend that dual-task gait test may be used in specialized clinics (memory clinics) to help identify mild cognitive impairment in older adults at higher risk of progression to dementia if time/resources are available. 2B.

Grip strength

Studies showed mixed results. Two large high-quality studies (n = 2619, follow-up = 6.5 years,14 and n = 2046, follow-up = 11 years27) failed to find an association between low grip strength and incident dementia. However, a separate high-quality cohort study (n = 2288, follow-up = 5.9 years) found each quartile increase in grip strength was associated with 13% decreased risk of incident dementia.15 Another cohort study (n = 877, follow-up = 5.7 years) found each point increase in grip strength was associated with 1% decreased risk of incident AD.28

**Recommendation 3:** Grip strength test is associated with future dementia and may be used in specialized memory clinics (moderate quality evidence). Because this involves using an instrument, this test may be used when handheld dynamometers are available. 2B (weak recommendation due to feasibility).

Global parkinsonism

Six studies assessing parkinsonism (presence vs absence) for incident dementia showed mixed results. Parkinsonism was defined as having rigidity, bradykinesia, or parkinsonian gait in the absence of a clinical diagnosis of PD. Three studies including community-dwelling older adults (n = 394, follow-up = 6 years),29 MCI (n = 111, follow-up = 3.9 years),30 and PD (n = 61, follow-up = 2 years)31 failed to find significant associations. Significant associations were found in two studies32,33 including cognitively healthy older adults.34 Nine studies evaluated severity of parkinsonism as a continuous variable using validated scales. Significant associations with incident dementia were found in older adults with MCI (n = 189, follow-up = 10 years),35 PD (n = 173, follow-up = 3.6 years),36 MCI and PD (n = 49, follow-up = 5 years),37 and in four studies of community-dwelling older adults (n = 115, follow-up = 2.6 years;38 n = 746, follow-up = 4.8 years;39 n = 919, follow-up = 4.7 years;40 and n = 1028, follow-up = 5.7 years).34,41

In contrast, two studies including only PD patients found severity of parkinsonism was not associated with incident dementia (n = 80, follow-up = 4.4 years12,13 and n = 24, follow-up = 6 years).42

A meta-analysis combining studies which defined overall parkinsonism as a dichotomous exposure and used an odds ratio as the effect estimate found that parkinsonism increases the odds of developing dementia by three times.29,34

**Recommendation 4:** The presence of parkinsonism may increase by three times the odds of developing dementia. We recommend routinely assessing parkinsonism as a marker of risk of dementia in memory clinics. 1B.

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TABLE 1  Evidence grading system (GRADE)

| Strength of recommendation | 1 | Strong: benefits clearly outweigh undesirable effects |
|-----------------------------|---|----------------------------------------------------|
|                             | 2 | Weak, or conditional: either lower quality evidence or desirable and undesirable effects are more closely balanced |

| Quality of evidence | A | High: “further research is unlikely to change confidence in the estimate of effect” |
|---------------------|---|----------------------------------------------------------------------------------|
|                     | B | Moderate: “further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate” |
|                     | C | Low: “further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate” |

Note: Strength and quality levels are based on the GRADE system.
| Domains          | Assessment/variable          | Recommendation                                                                 | Grade | Key findings from synthesis search                                                                                     |
|------------------|-----------------------------|---------------------------------------------------------------------------------|-------|---------------------------------------------------------------------------------------------------------------------|
| Motor            | Gait speed                  | To detect individuals at risk of dementia, we recommend testing gait speed in    | 1B    | Slow gait was consistently associated with incident dementia in older adults without Parkinson’s disease              |
|                  |                             | clinics in patients with cognitive complaints/impairments if time/resources are  |       |                                                                                                                     |
|                  |                             | available                                                                         |       |                                                                                                                     |
|                  | Dual-task gait              | We recommend that dual-task gait test may be used in specialized clinics (memory | 1B    | Dual-task gait test was associated with future dementia in MCI and cognitive healthy populations                      |
|                  |                             | clinics) to help identify mild cognitive impairment (MCI) older adults at higher  |       |                                                                                                                     |
|                  |                             | risk of progression to dementia if time/resources are available                 |       |                                                                                                                     |
|                  | Global parkinsonism         | We recommend routinely assessing parkinsonism as a marker of risk of dementia in | 2B    | Parkinsonism and upper limb motor domains showed mixed results across older populations                               |
|                  |                             | memory clinics                                                                   |       |                                                                                                                     |
|                  | Grip strength               | Grip strength test performance is associated with future dementia and may be     | 1B    | Studies with showed mixed results, however, two large studies supported the association between grip strength and dementia |
|                  |                             | used in specialized memory clinics                                              |       |                                                                                                                     |
| Frailty          | Frailty index               | We recommend that frailty is assessed as a marker of future dementia in primary   | 1B    | Frailty is cross-sectional associated with cognitive impairment and dementia                                        |
|                  | Frailty phenotype           | care and memory clinics                                                          |       |                                                                                                                     |
|                  | Clinical frailty scale      | We recommend that frailty is included/or adjusted in prediction models of        | 1B    | Frailty at baseline has been associated with risk of future dementia                                               |
|                  |                             | dementia, for clinician research studies                                         |       |                                                                                                                     |
| Neuro-behavioral | Neuropsychiatric symptoms   | Older adults presenting with neuropsychiatric symptoms (NPS) should be assessed  | 1B    | There is an association between later life onset of psychiatric symptoms and dementia diagnosis 5–11 years later      |
|                  | (NPS)                       | with respect to the natural history of symptoms. Those with first episode        |       |                                                                                                                     |
|                  |                             | psychiatric symptoms in later life should be assessed for a psychiatric          |       |                                                                                                                     |
|                  |                             | condition, with a high index of suspicion for a neurocognitive disorder          |       |                                                                                                                     |
|                  |                             | Referral to a memory clinic may be considered for those with later life          | 2B    |                                                                                                                     |
|                  |                             | emergent and sustained NPS, for additional investigation and work up             |       |                                                                                                                     |
|                  | Neuropsychiatric Inventory  | Corroborative information from a reliable informant, if available, regarding    | 1B    | The emergence of new neuropsychiatric symptoms in later life, that are persistent for at least 6 months and are       |
|                  | (NPI-Q)                     | neuropsychiatric symptoms is recommended. Using the Neuropsychiatric Inventory   |       | associated with risk of incident cognitive decline and all-cause dementia, can manifest in any of the following 5     |
|                  | Mild Behavioral Impairment  | (NPI-Q) or Mild Behavioral Impairment Checklist (MBI-C) can operationalize        |       | domains:                                                                                                            |
|                  | Checklist (MBI-C)           | assessments of NPS, especially in primary care                                   |       | 1) Impaired drive and motivation                                                                                     |
|                  |                             |                                                                                   |       | 2) Emotional dysregulation                                                                                           |
|                  |                             |                                                                                   |       | 3) Impulse dyscontrol                                                                                              |
|                  |                             |                                                                                   |       | 4) Social inappropriateness                                                                                         |
|                  |                             |                                                                                   |       | 5) Abnormal thoughts and perception                                                                                 |
| Sleep            | Sleep history               | A careful sleep history, sleep time, insomnia, daytime sleepiness, napping, and   | 1A    | Idiopathic REM sleep behavior disorder is associated with future risk of a synucleinopathy.                        |
|                  |                             | rapid eye movement (REM) sleep behavior disorder, may facilitate identification of    |       | Long sleep, excessive daytime sleepiness, and napping in older adults, particularly of new onset, is associated with |
|                  |                             | pre-clinical dementia or high risk of developing dementia, and should be included  |       | future risk of dementia and cognitive decline.                                                                     |
|                  |                             | in assessments in both the primary care and specialized memory clinic settings    |       | Insomnia in middle-aged and older adults may be associated with future risk of dementia and cognitive decline.        |
TABLE 2  (Continued)

| Domains | Assessment/variable                     | Recommendation                                                                 | Grade | Key findings from synthesis search                                                                                                                                                                                                 |
|---------|----------------------------------------|---------------------------------------------------------------------------------|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         | Sleep actigraphy or polysomnography    | Objective assessment of sleep using actigraphy or polysomnography may facilitate identification of individuals at high risk of developing dementia. Individuals, in whom a careful sleep history, taken in the context of a work-up for cognitive impairment or dementia, suggests the possibility of a sleep abnormality, and should be referred to a specialized sleep clinic for further assessment | 1C    | Sleep fragmentation in older adults, quantified by actigraphy or electroencephalography (EEG), is associated with future risk of dementia and cognitive decline, may accentuate the effect of genetic factors such as apolipoprotein E (APOE) genotype, and may be a marker of tau and/or amyloid pathology. Decreased non-REM (NREM) slow wave activity on polysomnography may be associated with amyloid and tau pathology in older adults. Altered EEG sleep spindles and EEG REM may be associated with AD pathology and future risk of dementia and cognitive decline. |
| Sensory | Hearing                                | There is enough observation evidence that hearing impairment is associated with the development of dementia. We recommend assessing and recording hearing impairment in primary clinics as a dementia risk factor                                              | 1B    | Hearing impairment is associated with dementia                                                                                      |
|         | Vision                                 | There is insufficient evidence to support assessment of vision impairment for dementia risk. However, vision assessment and correction outweigh burden and vision correction could improve cognitive functioning | 1C    | Vision correction may improve cognitive functioning                                                                                   |

TABLE 3  Summary of the suggestions and key findings from synthesis search of non-cognitive biomarkers of dementia risk

| Domains | Assessment/variable | Grade | Suggestion                                      | Key findings from synthesis search                                                                                                                                                                                                 |
|---------|---------------------|-------|------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Motor   | Manual dexterity    | 1C    | Manual dexterity tests should not be used as predictors of dementia | Manual dexterity showed mixed results when assessing its association with dementia                                                                                                                                                                                                            |
|         | Finger tapping      | 1C    | Finger tapping tests should not be used as predictors of dementia | The only study did not find an association between finger tapping and incident dementia                                                                                                                                                                                                       |
|         | Tremor              | 1B    | Tremor should not be used as a predictor of dementia | Tremor was not significantly associated with dementia syndromes in any population                                                                                                                                                                                                            |
|         | Bradykinesia        | 1C    | There is not enough evidence to recommend assessing bradykinesia as a marker of future dementia | Studies showed mixed results when assessing the association of bradykinesia with dementia                                                                                                                                                                                                           |
|         | Balance             | 2B    | There is not enough evidence to recommend assessing balance as a marker of future dementia | The evidence from three studies is low quality and the association between balance performance and dementia needs further research                                                                                                                                                     |
| Sensory | Olfaction           | 1B    | There is moderate to strong evidence to support assessment of olfaction for dementia risk | There is evidence from five studies that support associations of olfaction for dementia risk                                                                                                                                                                                                     |

* This item is a Suggestion and not a Recommendation because it was not able to be submitted for voting.

2.1.2  Findings that do not qualify for recommendation

The following findings did not qualify for recommendation, as they did not reach the recommendation threshold in the voting process.

Manual dexterity

Two studies with overall high quality used the Purdue Pegboard Test (PPT) to assess manual dexterity. One PD cohort study found each one-point PPT increase was associated with 33% decreased odds of developing dementia (n = 80, follow-up = 4.4 years). The second, an
MCI cohort, did not find a significant association (n = 189, follow-up = 10 years).35

**Finger-tapping**

An MCI study did not find associations with finger tapping speed and incident dementia (n = 90, follow-up = 2 years).44

**Tremor**

Five studies did not find a significant association between incident dementia and tremor measured using different versions of the Unified Parkinson’s Disease Rating Scale (UPDRS). These studies included participants with PD (n = 61, follow-up = 2 years),31 MCI (n = 189, follow-up = 10 years)35 and n = 111, follow-up = 3.9 years,30 MCI and PD (n = 49, follow-up = 5 years),37 and community-dwelling older adults (n = 3891, follow-up = 6.6 years).45 Incident dementia was also not significantly associated with clinician classification of resting tremor in two PD studies (n = 96, follow-up = 4.9 years46 and n = 2056, follow-up = 3.8 years47), nor with essential tremor in community-dwelling older adults (n = 84, follow-up = 5.4 years48). A meta-analysis combining the studies, which defined tremor as a dichotomous exposure, did not find a statistically significant overall association with incident dementia.46–48

**Bradykinesia**

Five studies assessed bradykinesia by summing scores from relevant sections of the UPDRS or mUPDRS. Specifically, the UPDRS motor examination (part III) section was used. Each 1-point increase in severity of bradykinesia was associated with 9% increased risk of incident dementia in one PD study (n = 173, follow-up = 3.6 years).36 However, a separate PD study failed to find associations between bradykinesia scores and progression to dementia (n = 61, follow-up = 2 years).31 This study had a shorter follow-up and did not control for potential confounders. An MCI study found every 1% increase in bradykinesia score was associated with a 2% increased risk of dementia (n = 189, follow-up = 7.2 years).35 A separate MCI study failed to find an association between bradykinesia and incident AD (n = 111, follow-up = 3.9 years).30

**Balance**

Three studies were found. One cohort study found that inability to perform a “one leg balance” test was associated with a 127% increased odds of incident dementia (n = 1775, follow-up = 6 years),49 while a second study found each 1-point (range 0-4) increase on a “standing balance test” was associated with an estimated 13% decreased short-term risk of incident dementia (n = 2288, follow-up = 5.9 years).15 A PD study found failing the “pull test” was associated with an estimated 245% increased risk of incident dementia (n = 96, follow-up = 4.9 years).66

### 2.2 Frailty as a marker of late onset dementia

One of the most challenging expressions of aging is frailty. Frailty is “a state of increased vulnerability to poor resolution of homeostasis after a stressor event, which increases the risk of adverse outcomes, including falls, delirium, and disability.”56 Two approaches predominate the quantification of frailty: the frailty index and the frailty phenotype. The frailty index, also known as the deficit accumulation approach, considers frailty as a health state and identifies levels of frailty by counting the number of health problems present out of a number of health variables assessed.51 In contrast, the frailty phenotype considers frailty a clinical syndrome and identifies a frail or pre-frail state commonly operationalized by measuring five features: weight loss, low grip strength, physical inactivity, slow walking speed, and fatigue. Having none of these indicates “robust,” presence of one or two is deemed “pre-frail,” while three or more indicates “frail.”92

While many chronic conditions have been reported to be associated with frailty, these relationships are complex and poorly understood. The relationship between frailty and cognitive function has been established, largely via observational studies53–56 typically where frailty is considered to precede cognitive impairment.57–59 More severe frailty is associated with worse cognition and more rapid cognitive decline60,61 and severity of frailty predicts MCI.60 Several studies have also explored the relationship of frailty with dementia status. A systematic review concluded that among five studies including patients with AD, the pooled prevalence of frailty (four of which used a modified version of the frailty phenotype, and one a frailty index) was 31.9%.62 Although evidence is scarce for specific tools used to measure frailty in relation to cognition in clinical settings, the most widely cited tools in dementia research are the frailty index and frailty phenotype. Another frailty tool used widely for clinical purposes is the Clinical Frailty Scale.63

In 2016, a meta-analysis of seven longitudinal studies concluded that frailty (as measured by either the frailty index [n = 2], or frailty phenotype [n = 5]) was a significant predictor of incident AD (four studies: pooled HR = 1.28 [1.00–1.63]), VaD (two studies: pooled HR = 2.70 [1.40–5.23]), and all dementia (three studies: pooled HR = 1.33 [1.07–1.67]).64 Another meta-analysis, published in February 2019, included six longitudinal studies and concluded that frailty (as measured by the frailty phenotype) was significantly associated with an increased risk of geriatric cognitive disorders (pooled odds ratio [OR] = 1.80 [1.11–2.92]).55 A more recent meta-analysis published in September 2019 focused on the co-occurrence of frailty and cognitive impairment in both dementia (CIND).66 They identified five longitudinal studies (all of which used modified versions of the frailty phenotype) that showed that in comparison to people without frailty and CIND, frailty (pooled HR = 1.47 [0.89–2.40]) and co-occurrence of frailty with CIND (pooled HR = 5.36 [3.26–8.81]) was associated with incident dementia.

Our search strategy identified 11 longitudinal studies—most of these were included in the meta-analyses described above. Please see the supporting information for details on our search strategy. The sample size of these studies ranged from 252 to 8722 with only two studies including <1000 people.17,67 The oldest study was published in 2007.67 The follow up period ranged from 3 to 10 years. Frailty was measured using the frailty phenotype (N = 8)14,17,67–72 and the frailty index (N = 3).14,17,58,67,69,68 One study used self-report to identify dementia73 whereas the rest used established diagnostic
criteria: Diagnostic and Statistical Manual of Mental Disorders-3 Revised (DSM-3R), DSM-4, DSM-5, National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN), National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA), Clinical Dementia Rating (CDR), and the International Statistical Classification of Diseases 10th revision (ICD-10). The participants of eight of the included studies had no cognitive impairment at baseline,14,58,67–70,72,73 whereas three studies included people either with or without cognitive impairment.17,71,74 Among the included 11 studies, 9 studies reported frailty as a significant predictor of dementia.14,58,67–71,73,74

*Recommendation 5*. We recommend that frailty is assessed as a marker of future dementia in primary care and memory clinics. 1B.

*Recommendation 6*. We recommend that frailty is included/or adjusted in prediction models of dementia, for clinician researcher settings. 1B.

2.3 Behavioral markers for late-onset dementia

Behavioral change is an important non-cognitive marker associated with cognitive decline and dementia risk. However, inclusion of behavioral changes as a marker for dementia has not fully penetrated into primary clinical care, in part due to limited access for general clinicians, and to a lack of operationalized guidelines on the application of these markers in clinical practice. If early dementia detection is to occur in settings outside specialty clinics, prior to cognitive decline, exploration of additional at-risk markers will be required.

Identifying emergent neuropsychiatric symptoms (NPS) may provide a simple and efficient method to identify a high-risk population for dementia.75,76 NPS are traditionally conceptualized as non-cognitive symptoms including impairments of mood, anxiety, drive, sleep, appetite and behavioral disturbances such as agitation and personality changes.77 They are included in the 2011 National Institute on Aging-Alzheimer’s Association (NIA-AA) consensus recommendations for diagnosis of all cause dementia core criteria.78 However, NPS are common in MCI,79 where they are associated with poorer cognition and psychosocial function within MCI cohorts.80 Population-based81,82 and clinic-based cohort studies83 provide consistent evidence that NPS in MCI are associated with higher risk for conversion to dementia, with an estimated annual dementia incidence rate of 25% for MCI plus NPS83 in contrast to the overall rate for MCI of 10% to 15%.84

Similarly, NPS in older adults with normal cognition confers a higher likelihood of incident cognitive decline or progression to MCI and dementia, as shown in the Alzheimer’s Disease Cooperative Study,85 one Alzheimer’s Disease Research Center,86 the Cache County Study,87 the Danish Psychiatric and Somatic Health Register,88 the Mayo Clinic Study of Aging,89 the Medical Research Council Cognitive Function and Ageing Study,90 the National Alzheimer’s Coordinating Center database,7,91–93 and the U.K. PROTECT study.94

Disentangling NPS symptoms as prodromal to dementia from primary late life psychiatric conditions has resulted in challenges in interpreting this literature. While the links between chronic psychiatric conditions and incident dementia are not fully clear,95 the links between later life NPS and incident cognitive decline are clearer.96 At least three large long-term observational cohort studies have determined a link between later life onset of the first episode of psychiatric symptoms and dementia diagnosis 5 to 11 years later, all suggesting these psychiatric symptoms may indeed be manifestations of prodromal dementia.97–99 DSM based nosology and cross-sectional assessments of psychiatric symptoms using conventional rating scales may not distinguish between new onset and emerging symptoms, as natural history and age of onset of symptoms are not considered. A study comparing people with late life psychiatric disorders to those with new onset psychiatric symptoms (classified as mild behavioral impairment [MBI]) demonstrated a significantly greater dementia conversion rate at 5 years in MBI, reinforcing the importance of assessing age of onset and natural history of psychiatric and behavioral symptoms.100

Mild behavioral impairment is a recently validated neuro-behavioral syndrome, characterized by later life onset of sustained NPS as an at-risk state for incident cognitive decline and all-cause dementia, and the index manifestation of dementia for some.100–105 MBI criteria stipulate the emergence of new NPS in later life, that are persistent for at least 6 months, and can manifest in any of the following five domains: (1) impaired drive and motivation (apathy), (2) emotional dysregulation (mood and anxiety symptoms), (3) impulse dyscontrol (agitation, aggression, impulsivity, abnormal reinforcement and reward), (4) social inappropriateness (impaired social cognition), and (5) abnormal thoughts and perception (ie, psychotic symptoms—delusions and hallucinations).101 MBI is associated with cognitive decline,94 faster progression to dementia,100,102 a complementary association with subjective cognitive decline for incident cognitive decline and dementia7 and utility in machine learning models of dementia prediction.103 MBI is represented in stage 2 of the NIA-AA research framework for AD108 and has demonstrated an association with known AD genetic loci,109,110 greater axonal loss measured by neurofilament light accumulation,111 and amyloid burden in patients with normal cognition112 and tau in MCI.113 The case ascertainment instrument for MBI was developed specifically for functionally intact community dwelling older adults, and has also been validated.94,114–119 With this increasing body of evidence on the association of later life onset NPS with incident cognitive decline and dementia, we recommend the following.

*Recommendation 7*. Older adults presenting with neuropsychiatric symptoms (NPS) should be assessed with respect to the natural history of symptoms. Those with first episode psychiatric symptoms in later life should be assessed for a psychiatric condition, but with a high index of suspicion for a neurocognitive disorder. 1B.

*Recommendation 8*. Corroborative information from a reliable informant, if available, is recommended. Using a validated informant-rated scale like the Neuropsychiatric Inventory (NPI-Q) or Mild
2.4 | Sleep markers for late-onset of dementia

Abnormalities of sleep and circadian rhythms are common in older adults with dementia and may precede the onset of cognitive symptoms by years. It is hypothesized that in some cases, these sleep and circadian rhythm abnormalities may reflect the accumulation of dementia-related neuropathologies in sleep-regulatory brain regions. A careful sleep history, including assessment of sleep time, insomnia, excessive daytime sleepiness, napping, and rapid eye movement (REM) sleep behavior disorder, may facilitate identification of individuals with pre-clinical dementia, or at high risk of developing dementia.

2.4.1 | REM sleep behavior disorder

In normal REM sleep, there is strong inhibition of motor neurons by glycnergic inputs, resulting in paralysis. When these mechanisms are disrupted, REM sleep behavior disorder (RBD) ensues, in which patients “act out their dreams.” The association between RBD and subsequent development of a synucleinopathy is well established. Seventy percent to 80% or more of patients with idiopathic RBD subsequently develop a neurodegenerative syndrome, the vast majority of which are synucleinopathies. For instance, in 101 older adults with a family history of AD from the Wisconsin registry (mean age 63), excessive daytime sleepiness was associated with lower cerebral spinal fluid (CSF) amyloid beta (Aβ1-42/Aβ40 ratio, and higher t-tau/Aβ42, and phosphor-tau/Aβ42 ratios. In a subset of participants from the same cohort with positron emission tomography (PET) imaging, there was also an association between excessive somnolence and greater Pittsburgh compound B (PIB)-PET binding in the angular gyrus, medial orbitofrontal cortex, cingulate, and precuneus.

2.4.2 | Long sleep, excessive daytime sleepiness, and napping

Long sleep need, and excessive daytime sleepiness, can be markers of nocturnal sleep disruption, or of impairment of wake promoting brain circuits. Cohort studies in the United States, Italy, and UK including more than 6000 older adults have found that excessive daytime sleepiness predicts future cognitive decline and dementia. In a large cohort of 4894 French adults without dementia in their mid 70s, baseline excessive daytime sleepiness predicted subsequent change in the Mini-Mental State Examination (MMSE; OR 1.39; 95% confidence interval [CI]: 1.00-1.97). In 2751 older men participating in the MrOS study, objective napping quantified by actigraphy was associated with a subsequent higher risk of MCI (OR 1.66; 95% CI: 1.09-2.54). As with excessive daytime sleepiness, numerous cohort studies have found that long sleep need also predicts future cognitive decline and dementia in older adults. Lengthening of sleep over time is also associated with a higher risk of incident dementia. In 7422 older Japanese adults, lengthening of sleep duration by 1 hour between the ages of 65 and 75 predicted incident dementia (HR 1.31, 95% CI: 1.07-1.60). Similarly, in the Whitehall study of more than 5000 adults aged 45 to 69, an increase in sleep above 7 or 8 hours predicted lower cognitive function (−1.73 points on the MMSE compared to reference group). Some cross-sectional observational studies have found associations between excessive daytime sleepiness and AD biomarkers. For instance, in 1407 Finns from the CAIDE (Cardiovascular Risk Factors, Aging, and Dementia) study, mid-life insomnia (mean age 50) was associated with a higher risk of late-life dementia (HR 1.24; 95% CI: 1.02-1.50). A single cross-sectional study examined self-reported insomnia in relation to CSF AD biomarkers. In 23 individuals with insomnia and 23 matched controls, participants with insomnia had higher CSF Aβ42. The causal direction of the above associations remains ambiguous and there are no trials thus far that have demonstrated an impact of pharmacologic or psychotherapeutic approaches to managing insomnia, on the subsequent risk of cognitive impairment.

2.4.4 | Sleep fragmentation

Sleep fragmentation, the interruption of sleep by repeated awakenings, is a common complaint in older adults. Longitudinal cohort studies have found associations between sleep fragmentation in older adults and future cognitive decline and dementia. Among 732 older adults without dementia participating in the Rush Memory and Aging...
Project, increased sleep fragmentation, measured by actigraphy, was associated with an elevated risk of incident AD, and more rapid cognitive decline, over a follow-up period of up to 6 years (HR 1.22 95% CI 1.03-1.44 per 1SD difference in sleep fragmentation). Moreover, higher sleep fragmentation accentuated the negative impact of apolipoprotein E (APOE) genotype on incident dementia risk and cognitive decline, while low sleep fragmentation attenuated the negative effect of APOE genotype such that APOE ε4+ individuals with low sleep fragmentation had an AD risk similar to APOE ε4− individuals. In 759 participants in the National Social Life, Health, and Aging Project, higher actigraphic sleep fragmentation (measured by wake time after sleep onset, duration of wake bouts, or sleep efficiency) was associated with more rapid 5-year cognitive decline measured by the Montreal Cognitive Assessment survey adaptation (MoCA-SA; OR 4.62; 95% CI 1.04-1.98 for WASO). In 2822 older men with actigraphy (mean age 76) in the MrOS cohort, higher wake time after sleep onset, lower sleep efficiency, and longer wake episodes were associated with a higher likelihood of cognitive decline over a mean follow-up of 3.4 years (eg, OR 1.47; 95% CI 1.09−1.98 for wakefulness after sleep onset [WASO]). In the same cohort, 2601 men had home polysomnography (PSG). In this subset, a greater proportion stage N1 sleep, an electroencephalography (EEG) marker of sleep fragmentation, was associated with faster decline in Trail-Making Test B and in a modified MMSE after a mean of 3.4 years (~0.22% vs −0.49% change per year). In 1245 older women from the study of osteoporotic fractures (mean age 82.6 at baseline), lower actigraphic sleep efficiency was associated with a higher odds of subsequently developing MCI or dementia (OR 1.53; 95% CI: 1.07-2.19).

Cross-sectional studies have also found associations between objectively quantified sleep fragmentation and markers of dementia pathology. For instance, in 17 cognitively normal adults recorded with actigraphy followed by AM assessment of CSF Aβ and tau, lower actigraphic sleep efficiency was associated with higher CSF tau. Moreover, in 145 cognitively normal individuals, lower CSF Aβ42 is associated with lower actigraphic sleep efficiency (ie, higher sleep fragmentation). In a post mortem study of 201 older adults in the Rush Memory and Aging Project, ante mortem sleep fragmentation was associated with a higher density of neurofibrillary tangles in APOE ε4 carriers. However, the same investigators showed that sleep fragmentation is also associated with other dementia-associated pathologies including arteriolosclerosis and subcortical infarcts, Lewy Body pathology, and microglial aging and activation.

2.4.5 | NREM slow wave activity

Aging is accompanied by a decrease in non-REM (NREM) sleep EEG slow-wave power and decreases in the proportion of time spent in slow-wave sleep. In small cross-sectional studies of older adults, these changes have been associated with biomarkers of AD pathology. For instance, in 36 older adults without cognitive impairment who underwent PSG, lower slow wave sleep duration and total frontal slow wave activity was associated with greater CSF Aβ42. In 26 older adults without cognitive impairment, lower prefrontal cortex slow wave activity correlated with higher cortical amyloid measured by PIB-PET. Meanwhile, in 119 older adults who underwent single-channel EEG and PET, lower NREM slow-wave activity was associated with higher AV1451-Tau binding and higher CSF tau/Aβ42 ratio. It remains uncertain how specific these findings are—that is, whether similar associations will be seen with other pathologies (eg, Lewy body pathology, microglial activation, TDP-43 pathology, small vessel disease), and as of now they have not been widely replicated.

2.4.6 | Sleep spindles

Sleep spindles are characteristic thalamo-cortical rhythms of NREM sleep. Aging is accompanied by a decline in spindle density, amplitude, and duration and spindle density in turn predicts next morning cognitive performance.

A small number of small observational studies support an association between spindle characteristics and change in cognition and/or AD biomarkers. For instance, in 29 older French adults with MCI (mean age 71), lower spindle amplitude predicted cognition 1 year later. Moreover, in 50 older adults without cognitive impairment studied with PSG and CSF, higher NREM spindle density was associated with lower CSF phopho-tau and tau.

2.4.7 | REM sleep

Rapid eye movement sleep is one of the cardinal sleep stages. The amount of REM sleep diminishes with age. A couple of observational cohort studies suggest that less REM sleep may be associated with future cognitive decline. For instance, in 321 older adults (mean age 67) participating in the Sleep Heart Health study, a lower percentage of REM sleep and a longer REM latency was associated with a higher risk of incident MCI 12 years later. Moreover, in 2601 older men in the MrOS cohort who underwent home PSG, those with less REM sleep had a greater decline in a modified MMSE after a mean follow-up of 3.4 years.

"Recommendation 10", A careful sleep history, including assessment of sleep time, insomnia, daytime sleepiness, napping, and REM sleep behavior disorder, may facilitate identification of pre-clinical dementia, or high risk of developing dementia, and should be included in assessments in both the primary care and specialized memory clinic settings. 1A.

“Recommendation 11”, Objective assessment of sleep using actigraphy or polysomnography may facilitate identification of individuals at high risk of developing dementia. Individuals in whom a careful sleep history, taken in the context of a work-up for cognitive impairment or dementia, suggests the possibility of a sleep abnormality, should be referred to a specialized sleep clinic for further assessment. 1C.
Sensory status as a marker of dementia

There is a substantial body of evidence showing consistent associations between sensory impairment and loss and reduced cognitive function.4 Of all sensory systems, olfaction, audition, and vision are the domains receiving the most examination, with the earliest association between olfactory impairment and dementia reported almost 40 years ago.162 The recent Lancet Commission163 reviewed the evidence for nine potentially modifiable risk factors for all-cause dementia, citing midlife hearing loss as having the highest weighted population attributable fraction (PAF), ranking above hypertension, obesity, smoking, depression, etc. Both hearing and vision have been linked with cognitive performance in non-clinical samples,164 supporting epidemiological evidence of increased risk for incident dementia with one sensory impairment and further risk with dual sensory impairment.165 At present, there are few published high-quality randomized controlled trials showing that correction for sensory impairments (eg, hearing aid use) significantly reduces risk of dementia; thus, the current evidence is primarily in the form of prospective or retrospective longitudinal studies. For details pertaining to our search strategy, please see the supplementary materials.

2.5.1 Audition

Age-related hearing loss (ARHL; 17.5% in ages 45–54, 25% in ages 65–74, increasing to 37% in ages 85+) are both highly prevalent in the Canadian adult population. Moreover, these conditions are highly comorbid.167

There is now a substantial body of evidence showing consistent associations between sensory loss and lower cognitive function. The recent Lancet Commission163 reviewed the evidence for nine potentially modifiable risk factors for all-cause dementia. Based on the three high quality studies available at the time, they identified hearing loss as having the highest weighted PAF. This was based on the high pooled risk ratio of hearing loss for dementia (pooled risk ratio [RR] 1.94; which was higher than the other individual modifiable risk factors considered) and its high prevalence (32% of persons aged 55+).168 The authors reported the results of a recent meta-analysis of nine prospective cohort studies. They found that hearing loss was associated with a higher risk for cognitive impairment (OR, 1.22; 95% CI: 1.09–1.36) and significant association for dementia (OR, 1.28; 95% CI: 1.02–1.59) but not for AD specifically (OR, 1.69; 95% CI: 0.72–4.00).169 The authors also reported on the results of a meta-analysis examining the association between HL and MCI (four studies) or dementia (seven studies). The meta-analysis was based on a total of 15,521 subjects with follow-up periods between 2 and 16.8 years. All but one study used a standardized hearing assessment. Compared to normal hearing participants, HL was associated with a greater risk of MCI (RR = 1.30, 95% CI: 1.12–1.51) and dementia (RR = 2.39, 95% CI: 1.58, 3.61). Some studies demonstrated linear associations between hearing impairment and dementia, suggesting that there is no specific degree or threshold of hearing impairment associated with significantly increased dementia risk. Finally, in a meta-analysis of studies examining HL and dementia, 12 studies were prospective cohort studies with dementia as outcome. All studies found that HL was associated with either cognitive decline or dementia, with hazard ratios ranging between 1.24 and 1.55.170

**Recommendation 12.** There is enough observational evidence that hearing impairment is associated with the development of dementia. We recommend assessing and recording hearing impairment in primary clinics as a dementia risk factor. 1B.

2.5.2 Vision

Incident dementia or AD as outcome

Five prospective cohort studies were found171–175 with enrollment of non-demented participants at baseline and multiple follow-ups ranging from 8.5 to 11 years. Of these, three studies were judged strong in design and sample size with clinical diagnoses of dementia as the outcome. In one,175 the OR of MCI or dementia diagnosis was 2.16 (95% CI: 1.58–2.96) for those in the lowest quartile of contrast sensitivity. A similar HR result (2.05; 95% CI: 1.24–3.38) was reported for contrast sensitivity when outcome was either diagnosis of dementia or MMSE score <24.173 Third, individuals rating their vision as “moderate” at baseline, showed 2x greater odds (95% CI: 1.4–3.1) of receiving a dementia diagnosis, while those rating vision impairment as “severe” showed 4x odds (95% CI: 2.6–6.1) of a dementia diagnosis.174 A similar relationship (relative risk ratio = 1.52) was reported in a smaller study (n = 625) using self-reported vision.171

Cognitive score as outcome

Two large prospective cohort studies were found176,177 associating contrast sensitivity and/or far-visual acuity with cognitive performance scores but not clinically defined cognitive status. Notably, one study176 combined data from three large longitudinal studies (ELSA, HRS, SHARE) with an overall sample size totaling more than 45,000. Across each data set, associations were consistently found between self-reported vision quality and episodic memory (word recall) scores. Similarly, using Health ABC data177 individuals with visual acuity impairment (HR: 1.55; 95% CI: 1.12–2.14) and contrast sensitivity impairment (HR: 1.33; 95% CI: 1.13–1.55) were at greater risk of incident cognitive impairment relative to those without vision impairments, as defined by 3MS score < 80 or declining by > 5 points over 3 years, suggesting consistent evidence of an association between vision and cognitive status in the absence of clinical diagnosis.

Diseases of the eye

Three population-based studies178–180 address the longitudinal association between age-related diseases of the eye (ie, macular degeneration, glaucoma) and cognitive status using retrospective follow-up designs. In one study (n = 65,894) patients with a diagnosis of macular degeneration were followed over 12 years, the rate ratios for dementia diagnosis were non-significant suggesting that age-related macular degeneration (AMD) is not strongly associated with the development
of dementia. Conversely, two studies (n = 19,895179; n = 66,80180) consider the association between glaucoma and dementia.179,180 In one,179 individuals who received a recent diagnosis of glaucoma had an incidence rate of 2.85 (95% CI: 2.19–3.70) for AD compared to those without glaucoma (IR: 1.98, 95% CI: 1.68–2.31). In the second study, for patients with a recent AD diagnosis, the adjusted odds ratio for glaucoma diagnosis was 1.5 (95% CI: 1.19–1.89).180 To summarize the vision-cognition evidence, a minority of studies produced strong evidence linking visual impairment (including diseases of the eye) and increased risk of dementia. Although very few studies indicated a non-significant relationship, the present evidence indicates a moderate predictive relationship at best. Notably comorbid visual and hearing impairments increase the risk of incident dementia.165,176 Vision screening is recommended based upon the low burden and high potential benefit of treatment for general cognitive functioning.

**Recommendation 13**: There is insufficient evidence to support assessment of vision impairment for dementia risk. However, vision assessment and correction outweigh burden and vision correction could improve cognitive functioning. 1C.

### 2.5.3 Olfaction

**Incident MCI, dementia, or AD as outcome**

Five prospective cohort studies were found173,181–184 with enrollment of non-demented and non-MCI participants at baseline and multiple follow-ups ranging from 3.5 to 12 years. All were judged to be strong in design and sample size. Outcomes were either clinical diagnoses of MCI or dementia or cognitive impairment defined by MMSE score. Two studies demonstrated that odor identification deficits were associated with an increased risk of incident MCI (HRs: 1.12 and 1.15, respectively)181,183; or dementia/cognitive impairment (HRs ranging from 1.15 to 3.92).173,182,184 Of note, Fischer compared the risk of hearing, visual, and olfactory impairments and showed that each were independently associated with cognitive impairment risk, with olfaction having the largest HR (3.92) followed by vision (2.05), and then hearing (1.90).

Three studies evaluated the risk of olfactory identification deficits for decline from MCI to dementia/AD using prospective cohorts.185–187 Here, sample sizes tended to be smaller (<130 participants) but designs were of good quality. Follow-up ranged from 2 to 4.9 years on average. Devanand et al.185 found that, in 77 MCI participants, those with low olfaction and poor subjective awareness of their smell problems were more likely to develop AD (relative risk = 10.8, 95% CI = 1.1–105.0, P < .05; controlling age, sex, years of education, and baseline MMSE). Tahmasebi et al.187 found that baseline olfactory identification differed between converters and non-converters, with low sensitivity of AD prediction (46.2%) but high specificity (81.9%). Comparing MCI participants who differed in their dementia outcome after an average of 4.9 years, one study found that MCI-DLB converters had lower olfactory scores than MCI-AD converters or MCI-stable participants.186

**Association with AD pathology**

Although outside our specific purview, we evaluated studies that tested the association between olfaction and AD pathology or neuroimaging markers. Two studies188,189 found that poorer olfactory performance was associated with smaller hippocampal volumes and one181 with greater with amyloid plaques and neurofibrillary tangles.

**Suggestion**: There is moderate to strong evidence to support assessment of olfaction for dementia risk. 1B.

*This item is a Suggestion and not a Recommendation because it was not able to be submitted for voting.*

### 3 IMPLICATIONS FOR PRACTICE AND RESEARCH

While non-cognitive markers for dementia are an emerging area of investigation, enough data have accrued to incorporate their use in clinical practice. Future work should continue to examine their clinical utility in diverse populations and practice settings. In particular, application to different at-risk setting (ie, post-stroke, PD) requires further elaboration. Additional operationalization and establishment of sensitivity, specificity, and predictive values based on appropriate thresholds should further enhance the utility of these markers. Examining longitudinal changes and the impact of interventions, which improve these features, are important. Future studies are required to understand the basis for and neural impact of each of the non-cognitive markers examined. Other non-motor markers with potential relevance to public health and medical practice, such as orthostatic hypotension, as an example, may emerge, but further studies are required.190,191

Motor function decline affecting gait, balance, and motor composite measures were associated with an increased risk of incident dementia syndromes in non-PD populations. In a clinical setting these motor markers are accessible with minimal cost and time, do not require specialized equipment or extensive training, and can help to detect individuals at risk of cognitive decline and dementia syndromes among older adults.192 From a practical diagnostic perspective, the results suggest that the prediction of dementia can be augmented by adding simple motor assessments, particularly gait velocity tests, in primary care and memory clinics. Motor decline is amenable to improvement through exercise and other interventions to enhance activity. Motor decline is a key component of frailty which itself requires further parsing to understand what aspects of frailty impact cognitive risk. It is clear that frailty is associated with adverse outcomes including cognitive decline, but the impact and approaches to reversing frailty are not clear.

Behavior disturbances have long been categorized and recognized, but recognized them as a prodromal state has only more recently been operationalized. Given the availability of practical tools, including informant-administered instruments (like the MBI-C) opens the door to examination of the impact of treatment of these disturbances at an early stage. Their recognition and treatment may improve both dementia risk and potential affect quality of life.

Sleep disorders are associated with higher risk of developing dementia. The impact of intensive assessment and treatment of sleep...
disorders in older people requires further investigation. As important is the development of new treatments. Incorporation of expertise and facilities for the assessment and treatment of diverse sleep disorders has implications for training priorities, which might have profound impacts on public health.

Sensory changes, particularly visual and auditory declines, are amenable to treatment and prevention. A key area from the public health perspective is the impact of interventions on cognitive outcomes and their impact on overall health-care cost. Auditory decline has been recognized as a risk factor for dementia, and audiological rehabilitation, which may include assistive devices and/or behavioral techniques, can improve quality of life, regardless of its impact on dementia risk. While we did not show that visual impairment was associated with cognitive decline, visual impairment is associated with reduced quality of life and increased falls and should be treated. Olfactory dysfunction is also an emerging marker and its loss is linked to cholinergic integrity. Sense of smell is modulated by cholinergic neurons in the brain stem and may signal early stages of neurodegenerative processes in the brain moving from lower to higher brain regions.\(^{19,194}\) In addition to its strong association with general dementia risk, the nature of olfactory impairment may improve prediction of specific dementia subtypes (ie, Lewy body subtypes). Safety may be impacted by poor olfaction. Although olfactory dysfunction is difficult to treat, its presence may have an impact on appetite via its effects on taste.

In summary, attention to non-cognitive markers of risk for cognitive decline and dementia may have a profound impact in detecting older adults at risk of progressing to dementia. Additional development of clinical practice guidelines will be needed to establish the logistics of how to incorporate these concepts in to routine health care and to understand their bases. Existing consensus guidelines may help in clinical implementation of these tests in practice.\(^{7,26}\)

**CONFLICTS OF INTEREST**

The authors have no conflicts of interest to disclose.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

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