Alzheimer disease

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BOX 1. Criteria for major neurocognitive disorders

The DSM-5 criteria for major neurocognitive disorders include the following[10]:

- ☐ Evidence from the history and a clinical assessment that indicates significant cognitive impairment in at least one of the following cognitive domains:
  1. Learning and memory;
  2. Language;
  3. Complex attention;
  4. Perceptual-motor function;
  5. Social cognition.
- ☐ The impairment must be acquired and represent a significant decline from a previous level of functioning.
- ☐ The cognitive deficits must interfere with independence in everyday activities.
- ☐ In the case of neurodegenerative dementia such as Alzheimer's disease, the disturbances are of insidious onset and are progressive, based on evidence from the history or serial mental status examinations.
- ☐ The disturbances are not occurring exclusively during the course of delirium.

Abbreviation: DSM-5 = The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders

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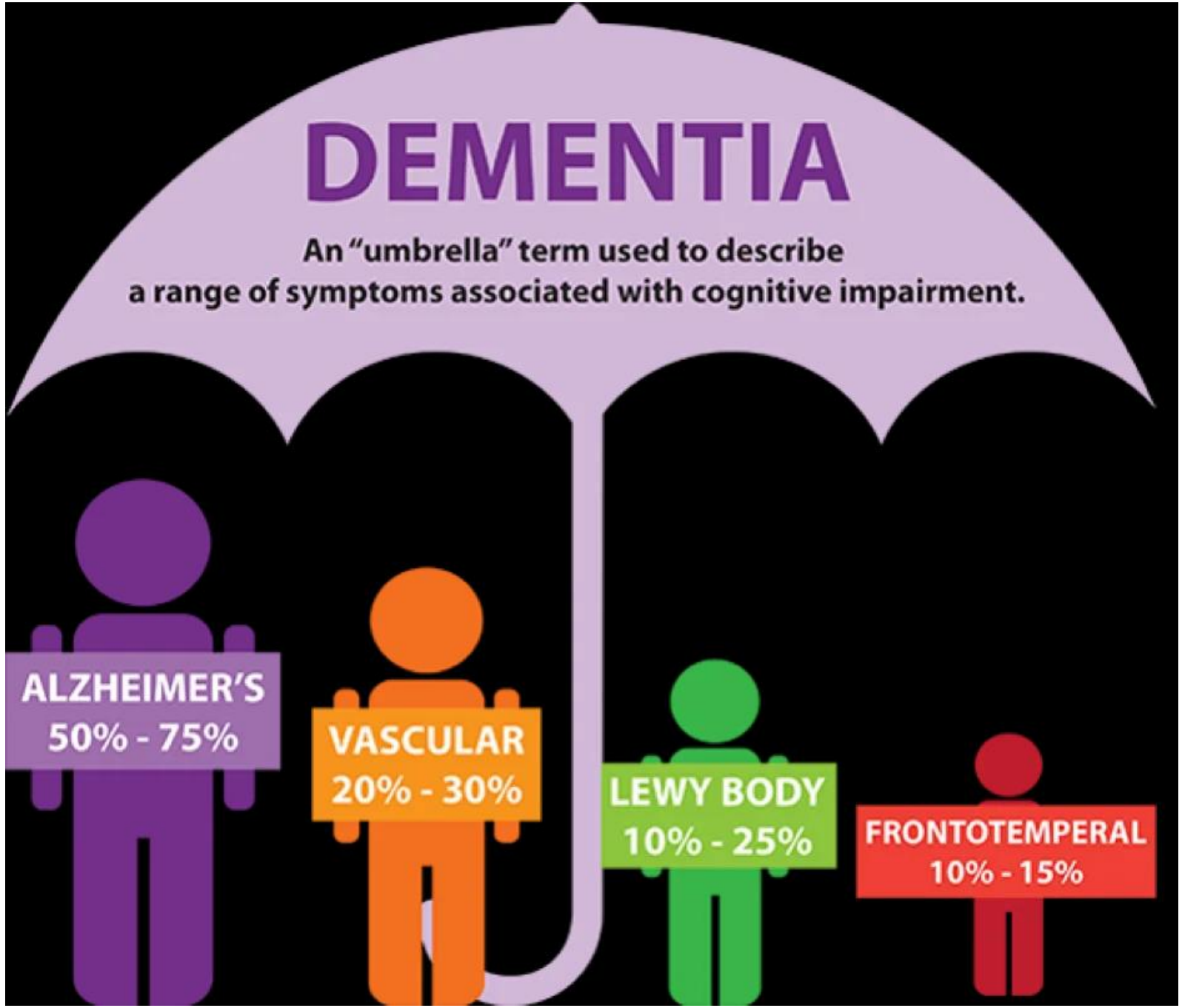


Dementia-like symptoms from the following causes may be reversible.

HEAD INJURIES
See a health care provider for scans and other tests after any type of head injury to see if there is bleeding or other damage.

DRUG & ALCOHOL ABUSE
Cessation of drug and alcohol consumption may result in change in symptoms.

VITAMIN & MINERAL DEFICIENCIES
A blood test can determine if there is a B12 deficiency, and supplements are widely available as needed.

MEDICATION SIDE EFFECTS
Talk to a health care provider about medication interaction or side effect interactions, and ask for alternatives as needed.

THYROID ISSUES
Medication can typically stabilize thyroid issues after a diagnosis.

HEART DISEASE
Have a health care provider do tests for any blockages and prescribe treatment to improve oxygen flow to the brain.

DEPRESSION
Share symptoms with a health care provider for a correct diagnosis and follow prescribed treatment which may include antidepressants, exercise, and support groups.

Symptoms of the conditions listed above may include:

MEMORY LAPSES • CONFUSION
IRRITABILITY • LACK OF CONCENTRATION

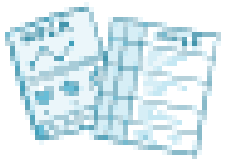
DEMENTIA

DECLINE in ≥ 1 COGNITIVE FUNCTION → IMPAIRMENT of DAILY FUNCTIONING

REVERSIBLE CAUSES:
- ALCOHOL DEPENDENCE
- HYPOTHYROIDISM
- VITAMIN B12 DEFICIENCY
- NEUROSYPHILIS
- NORMAL PRESSURE HYDROCEPHALUS
- DEPRESSION

IRREVERSIBLE CAUSES:
- ALZHEIMER
- VASCULAR DEMENTIA
- FRONTOTEMPORAL DEMENTIA
- LEWY BODY DEMENTIA
- PARKINSON
- HUNTINGTON
- CREUTZFELDT-JAKOB

DIAGNOSTIC TESTS
- MONTREAL COGNITIVE ASSESSMENT (MOCA)
- MINI-MENTAL STATUS EXAMINATION (MMSE)



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Introduction

- AzD dementia is a chronic condition that develops silently for well over 10 years before the appearance of symptoms.
- Burden of AD on individuals & society increase in longevity of humans
- The leading neurodegenerative cause of dementia
- Incidence of 0.4% in 65 to 74 years → 7.6% in 85 years and older
- Will double in the next 30 years
- Decreased in the past 2 decaded due to educational attainments and improved cardiovascular risk control
- Double in women

- AD remains the most likely cause for a dementia before 65
- Relative proportion of non-AD causes, particularly FTD, increases in < 65 and comorbid pathologies such as α-synuclein, tdp-43 and vascular lesions frequently comorbid
- Substantially higher rates of abnormal amyloid biomarkers for non-AD dementias from the sixth to ninth decades and in cognitively normal individuals.

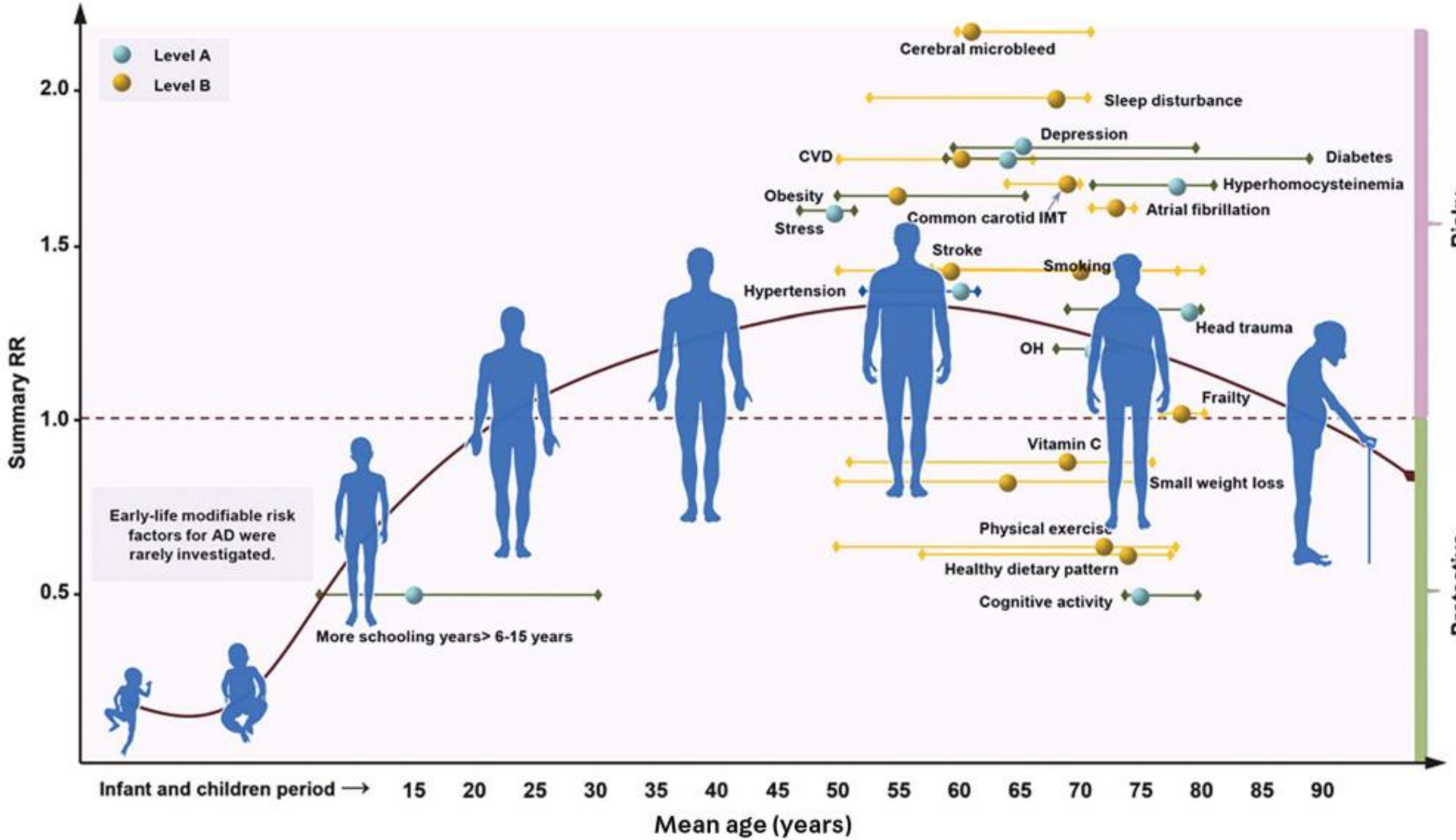
❑The older an individual is, the less likely a positive biomarker for AD is to represent the sole cause of the dementia syndrome, but negative AD biomarkers strongly suggest a non-AD dementia syndrome.

Risk Factors: Non-modifiable

- Age is the strongest risk factor for AD.
- Beyond age, approximately 80% of the variance of AD risk is attributed to genetic factors, with the APOE ε4 allele by far the strongest. Heterozygotes → 2 to 3 times greater lifetime and ε4 homozygotes have greater than 10 times the risk relative to APOE ε3/ε3 Homozygotes (the most common APOE allele).
- APOE ε2 carriers have a substantially lower lifetime risk of developing AD.
- In less than 1%, dominantly inherited mutations of APP gene, PSEN1 gene, or PSEN2 gene result in **early-onset AD**.
- In the vast majority of **late-onset AD**, the genetic contribution to AD is likely multifactorial as more than 30 genetic loci have currently been identified (eg, cholesterol metabolism, lysosomal and endocytosis, immune pathways).
- In the future, a polygenic risk score or hazard risk score could be used to identify an individual's risk

Risk Factors: Modifiable

- Length of childhood education
- Higher body mass index in older adults
- Participation in cognitively active activities.
- Eight factors were found to have the **strongest negative effects**: DM, OH, HTN in midlife, HT, stress, depression, midlife obesity, and CABG surgery.
- Midlife exercise decrease the risk in a dose-dependent manner
- In those older than 65 suggest that exercise may decrease the likelihood of dementia.
- Hyperhomocysteinemia may increase the risk of late-life dementia
- Treatment with folic acid and vitamins B6 and B12 may decrease the risk


Level A
Level B
Summary RR
2.0
1.5
1.0
0.5
Cerebral microbleed
Sleep disturbance
Depression
CVD
Diabetes
Hyperhomocysteinemia
Obesity
Common carotid IMT
Atrial fibrillation
Stress
Stroke
Smoking
Hypertension
Head trauma
OH
Frailty
Vitamin C
Small weight loss
Physical exercise
Healthy dietary pattern
Cognitive activity
Risky
Protective
Early-life modifiable risk factors for AD were rarely investigated.
More schooling years> 6-15 years
Infant and children period ⟶
15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90
Mean age (years)

Diagnosis

- Key to an accurate diagnosis is access to an informant who knows the patient well and can provide observations of the temporal course of symptom development and the degree of functional impairment
- AAN guidelines for the diagnosis of dementia recommend a cognitive screen, structural brain imaging (MRI or CT), screening for depression, and assessment of serum TSH and vitamin B12 levels
- Medications, potential toxic exposures (eg, excessive alcohol, occupational exposure), and modifiable factors
- A thorough review of the family history, particularly of first-degree relatives

Clinical Approach

- Because the process of neurodegeneration evolves over many years of synaptic and neuronal loss, the symptomatic phase represents the end stage of a 1- to 2-decade process that once fully established is inexorably progressive.
- Once symptoms appear, time to death is most commonly in range of 7 to 10 years.
- At an individual level, the expression of the disease vary significantly
- Patterns of cognitive Decline in AD, this is typically visual and verbal memory.
- Progression of AD is also associated with noncognitive symptoms (eg, mood disorders, motor changes, circadian rhythm alterations)

Prodromal/Early Alzheimer/ MCI

- Terms are used for the earliest detectable stages of cognitive decline
- The earliest stages of AD, before significant functional impairment (ie, impairment of instrumental ADL ; eventually loss of independence),
- Subtle cognitive changes often be detected by patients or their collateral source.
- MCI is a transitional state between the normal function and dementia
- Risk of progression from MCI to dementia over 2 years is 14.9%
- A chance of reversion to normal is 14% to 39%

- With positive amyloid-β (Aβ) biomarker (amyloid PET), the risk in 2 years is likely between 22% and 50%
- Primary goal after diagnosis of MCI → 1- Assess for reversible causes of cognitive changes 2-identify a neurodegenerative source
- If access to specific CSF- or PET-based biomarkers is limited, the use of MRI has so many limitation
- When AD is the probable cause of MCI, the most frequently reported symptoms are related to changes in episodic memory, both verbal and nonverbal : In addition to asking about specific examples (eg, misplacing items, forgetting appointments, repeating questions, getting lost, forgetting to pay bills), it can be helpful to inquire about autobiographical events from the past 1 to 4 weeks, corroborated by an informant.

- Basic cognitive screening assessments (eg, MMSE, MoCA) may be normal but in the case of early AD will typically demonstrate some difficulties with memory.
- Then, dysexecutive problems are commonly reported in early stages of AD (eg, poor decisions while operating a motor vehicle or in managing complex financial decisions).
- The MoCA (with a cutoff of 24 or 25) is likely more sensitive and specific in detecting the earliest stages of cognitive impairment than the MMSE.
- In the case of very mild symptoms, a comprehensive neuropsychological assessment, if available, can be helpful in confirming and quantifying the level of impairment.
- Screening for a mood disorder, such as depression, anxiety, or apathy, can provide information supportive of underlying dementia

Mild to moderate symptoms

- As AD progresses to the mild to moderate stages, the overall clinical picture remains primarily a cognitive-predominant syndrome (worsening memory, increasing language problems, and greater visuospatial decline).

❑A pattern of early and progressive episodic memory remains the most common core symptom in typical AD.

- The appearance of significant movement disorders, behavioral changes, pronounced hallucinations, or severe hypersomnia, even at the moderate stage, should prompt consideration of another diagnosis or at least pronounced copathology.
- However, mild motor symptoms, mood disorders (primarily affective disorders), and circadian rhythm changes emerge during the moderate stages of AD dementia

Moderate stages

- Judgment and decision-making abilities may begin to be significantly affected, resulting in a decline in independent function (eg, driving, managing financial decisions, shopping and cooking unaided, difficulty with using appliances/television/computer/mobile phone).
- Therefore → safety is important during each assessment.
- It is the loss of independent function that typically marks the transition to the moderate stages of AD.

- The loss of independence in basic activities of daily living (eg, dressing, personal hygiene, preparation of simple meals) that results in a major increase in burden for those caring for patients with AD typically begins during the moderate stages of the disease (MMSE <18).

Behavioral and noncognitive symptoms

- In moderate AD, the frequency of noncognitive symptoms increases significantly. Although the transition is fluid.
- The presence of noncognitive problems characteristic of the moderate to severe stages in patients with only mild cognitive symptoms should raise concern for an alternative diagnosis.
- During the stage of mild to moderate disease, problems with incontinence may begin to develop and continue to worsen into the more severe stages.

PSYCHIATRIC SYMPTOMS.

- Mild irritability and mood changes are common during the initial stages of AD
- The frequency and magnitude of these increases during the moderate stages.
- Agitation, depressive symptoms, and anxiety are more common and may impact patient safety.
- With progression, particularly MMSE scores below 20, the frequency of psychotic symptoms, primarily delusions (eg, paranoia, accusations of infidelity of spouses, misidentification of familiar individuals or environments) but also hallucinations (eg, simple visual hallucinations of objects or people), increase significantly and may reach as high as 50% .
- From a prognostic standpoint, the presence of psychotic symptoms → with a more rapid progression and higher rate of entering an institutional setting

NONCOGNITIVE SYMPTOMS.

- Like psychiatric and behavioral symptoms, they increases significantly during the moderate to severe stages of disease.
- These symptoms can be classified as motor or nonmotor.
- In moderate AD during the stage of significant functional impairment, extrapyramidal symptoms, mild tremor, and myoclonus develop in 30% to 50%, and clinical seizures range from 2% to 15%.
- Relative to non-AD and non–Lewy body dementias, myoclonus and seizures are likely less common in vascular and frontotemporal dementia, which can be used as a clinical symptom to help differentiate AD from non-AD dementias

DISORDERS OF HOMEOSTASIS/ HYPOTHALAMIC FUNCTION

- Both circadian rhythm disorders (particularly insomnia and increased sleep fragmentation) and weight loss tend to increase as AD progresses → reflect degeneration of the hypothalamus.
- Patterns of circadian disruption help distinguish between the different disorders. For example, DLB is commonly associated with sleep disorders, but greater EDS (more than 2 hours) and more frequent fluctuations of arousal and orientation are seen DLB> AD
- RBD→ alpha synucleinopathies

Mild

Cognitive symptoms

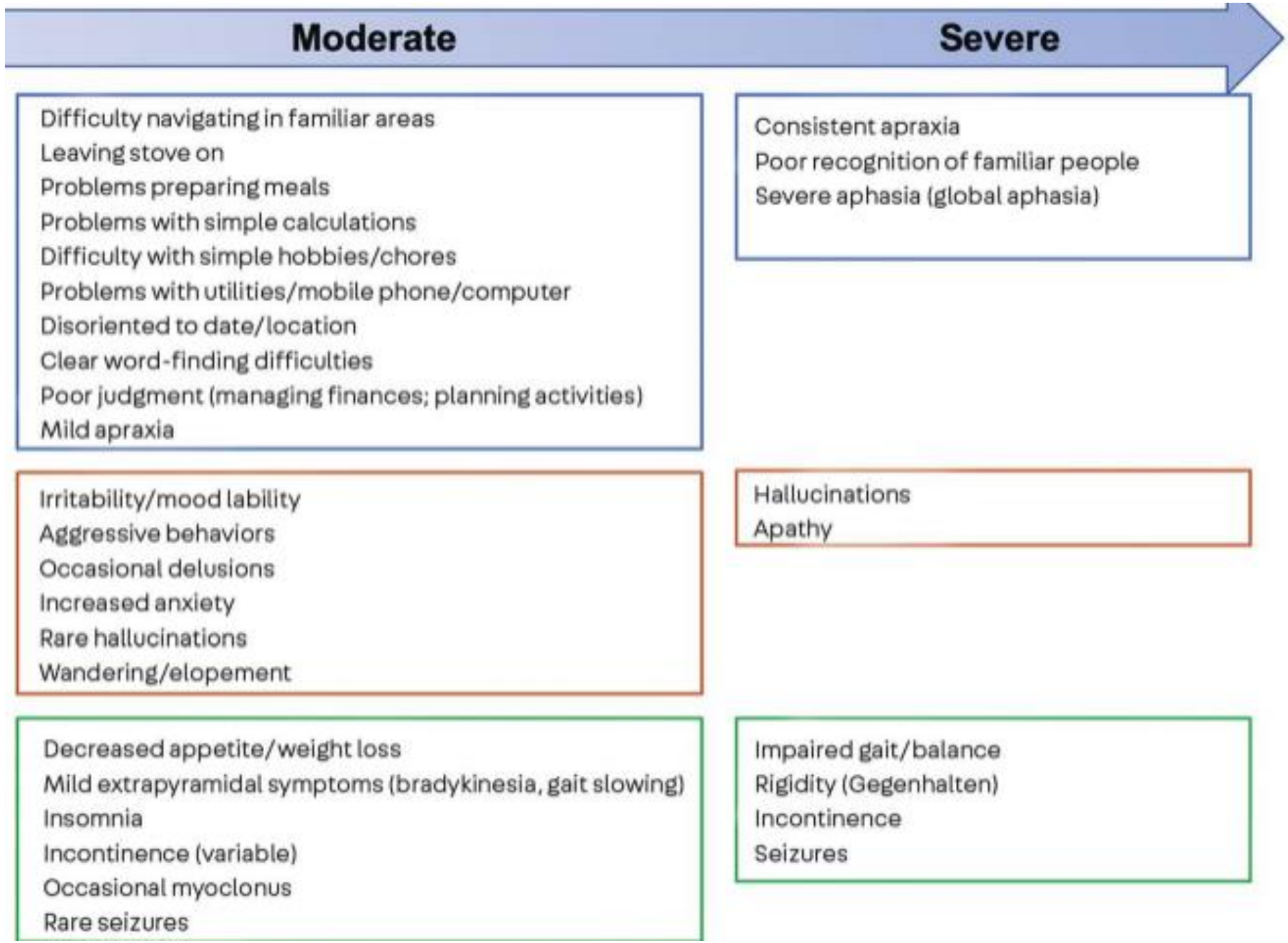
- Misplacing items
- Forgetting appointments
- Forgetting bills/medications
- Occasional word-finding problems
- Difficulty navigating in unfamiliar areas
- More challenging hobbies/tasks abandoned

Psychiatric symptoms

- Mild anxiety
- Mild depression
- Mild social withdrawal
- Mild irritability

Non-Neuropsychiatric

- Sleep maintenance problems


Moderate
Severe
Difficulty navigating in familiar areas
Leaving stove on
Problems preparing meals
Problems with simple calculations
Difficulty with simple hobbies/chores
Problems with utilities/mobile phone/computer
Disoriented to date/location
Clear word-finding difficulties
Poor judgment (managing finances; planning activities)
Mild apraxia
Consistent apraxia
Poor recognition of familiar people
Severe aphasia (global aphasia)
Irritability/mood lability
Aggressive behaviors
Occasional delusions
Increased anxiety
Rare hallucinations
Wandering/elopement
Hallucinations
Apathy
Decreased appetite/weight loss
Mild extrapyramidal symptoms (bradykinesia, gait slowing)
Insomnia
Incontinence (variable)
Occasional myoclonus
Rare seizures
Impaired gait/balance
Rigidity (Gegenhalten)
Incontinence
Seizures

Neuropsychological and functional evaluation

Cognitive domain	Test
VMCI-Tuscany neuropsychological battery	
Global mental functioning	Mini-Mental State Examination
	Montreal Cognitive Assessment
Memory	Rey Auditory Verbal Learning Test (immediate and delayed recall)
	Short story
	Rey-Osterrieth Complex Figure (recall)
Attention/executive function	Trail Making Test, parts A and B
	Visual search
	Symbol Digit Modalities Test Stroop Color-Word Test
Language	Phonemic verbal fluency
	Semantic verbal fluency
Visuoconstructional abilities	Rey-Osterrieth Complex Figure (copy)
Functional evaluation	Activities of Daily Living scale
	Instrumental Activities of Daily Living scale

Age of Onset in Alzheimer Disease

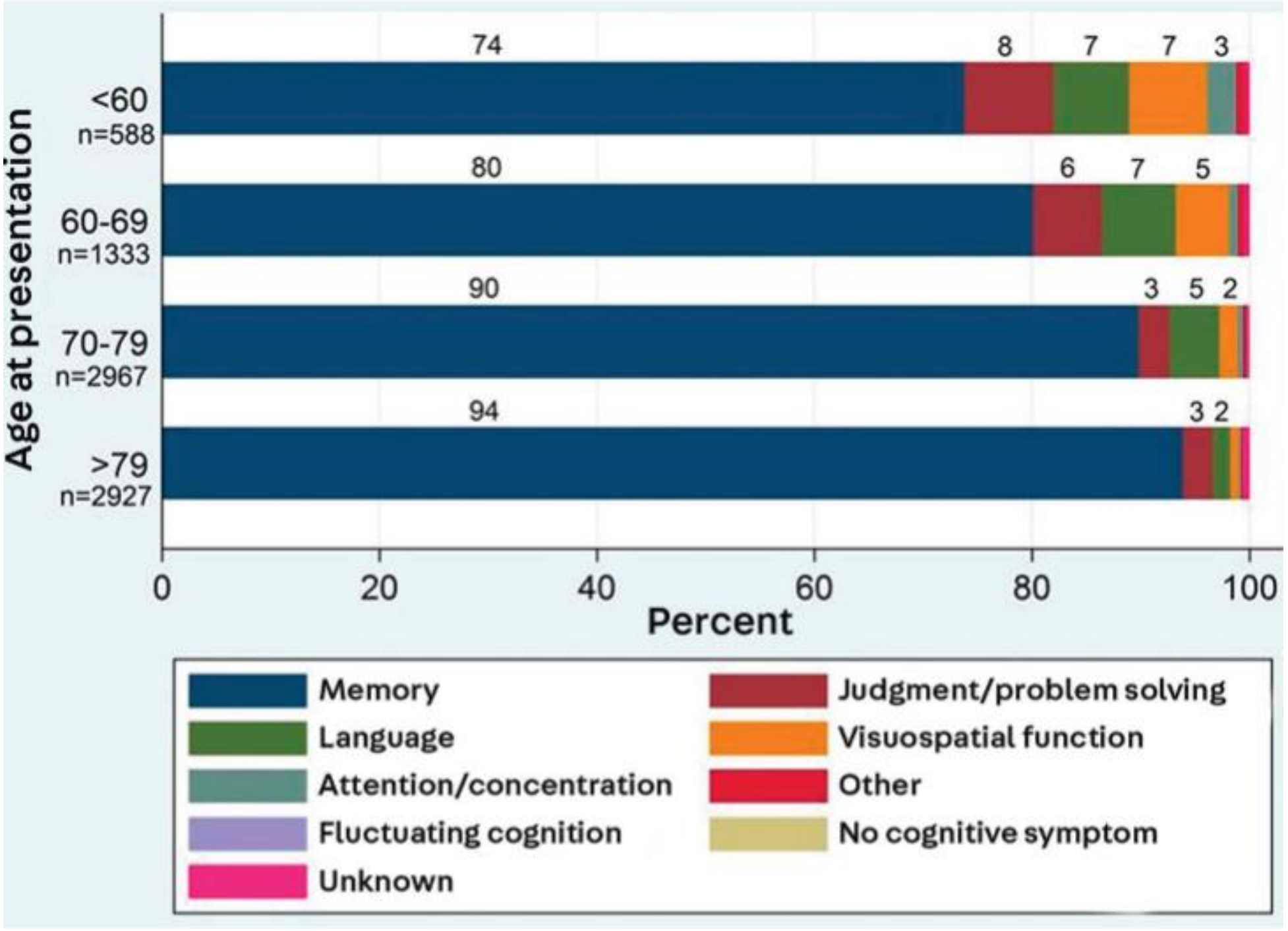
- Incidence begins to increase substantially in the eighth decade
- Also is the most common cause of dementia with onset in the fifth to seventh decades of life.

❑Some important points in those younger than 65 :

- First, a nonamnestic (focal variant) presentation is more common in early-onset AD, often leading to an initial misdiagnosis (eg, anxiety disorder, adult attention-deficit disorder).
- The focal variants of AD typically fall into three broad categories: a visuospatial variant, a language variant, and a frontal- executive /behavioral variant. However, in the majority of cases, cognitive assessments still identify a clear amnestic pattern

- Second, the rate of progression in patients with early onset may be more rapid than the typical amnestic-predominant pattern most common in later ages of onset.
- However, postmortem studies suggest that rather than the age of onset, it more likely the pattern of regional neurofibrillary tau pathology burden that determines the rate of progression : tau pathology outside of the temporal lobes to that in the hippocampus (hippocampal sparing) had evidence of a significantly faster rate of progression than those with neurofibrillary tau pathology limited to the hippocampus
- In the clinical setting, this may be approximated with cognitive testing demonstrating a greater ratio of nonmemory test impairment to memory impairment and MRI patterns of atrophy demonstrating greater cortical-to-hippocampal atrophy

- Finally, in those with a younger age of onset, AD biomarkers can be particularly helpful in confirming a diagnosis of AD over a non-AD cause.
- With increasing age, the probability of having evidence of AD-related neuropathologic changes, particularly Aβ plaques, in the absence of clinical symptoms increases, particularly in the eighth to tenth decades of life.


Age at presentation
<60
n=588
60-69
n=1333
70-79
n=2967
>79
n=2927
74
8
7
7
3
80
6
7
5
90
3
5
2
94
3
2
0
20
40
60
80
100
Percent
Memory
Judgment/problem solving
Language
Visuospatial function
Attention/concentration
Other
Fluctuating cognition
No cognitive symptom
Unknown

PATHOLOGY AND PATHOLOGY-RELATED BIOMARKERS

- The core pathologies of AD are extracellular aggregated Aβ plaques and intracellular neurofibrillary tau tangles.
- Postmortem tissue → microstructural pattern of tau pathology in AD relative to non-AD tauopathies → individual differences in the rate of progression of AD might relate to distinct differences in the structure of both Aβ plaques and NFTS
- Tau → differences in thephosphorylation patterns between individuals → account for differences in the rate of progression

Pathology-related Biomarkers

- Recently, major advances have been made in the development of imaging and fluid biomarkers that represent different components of amyloid and tau-related pathologic changes, which allow for an increase in the accuracy of diagnosis
- A recent biomarker-based classification scheme was proposed to identify AD-related pathophysiologic profiles, called the A/T/N (for amyloid, tau, and neurodegeneration) criteria

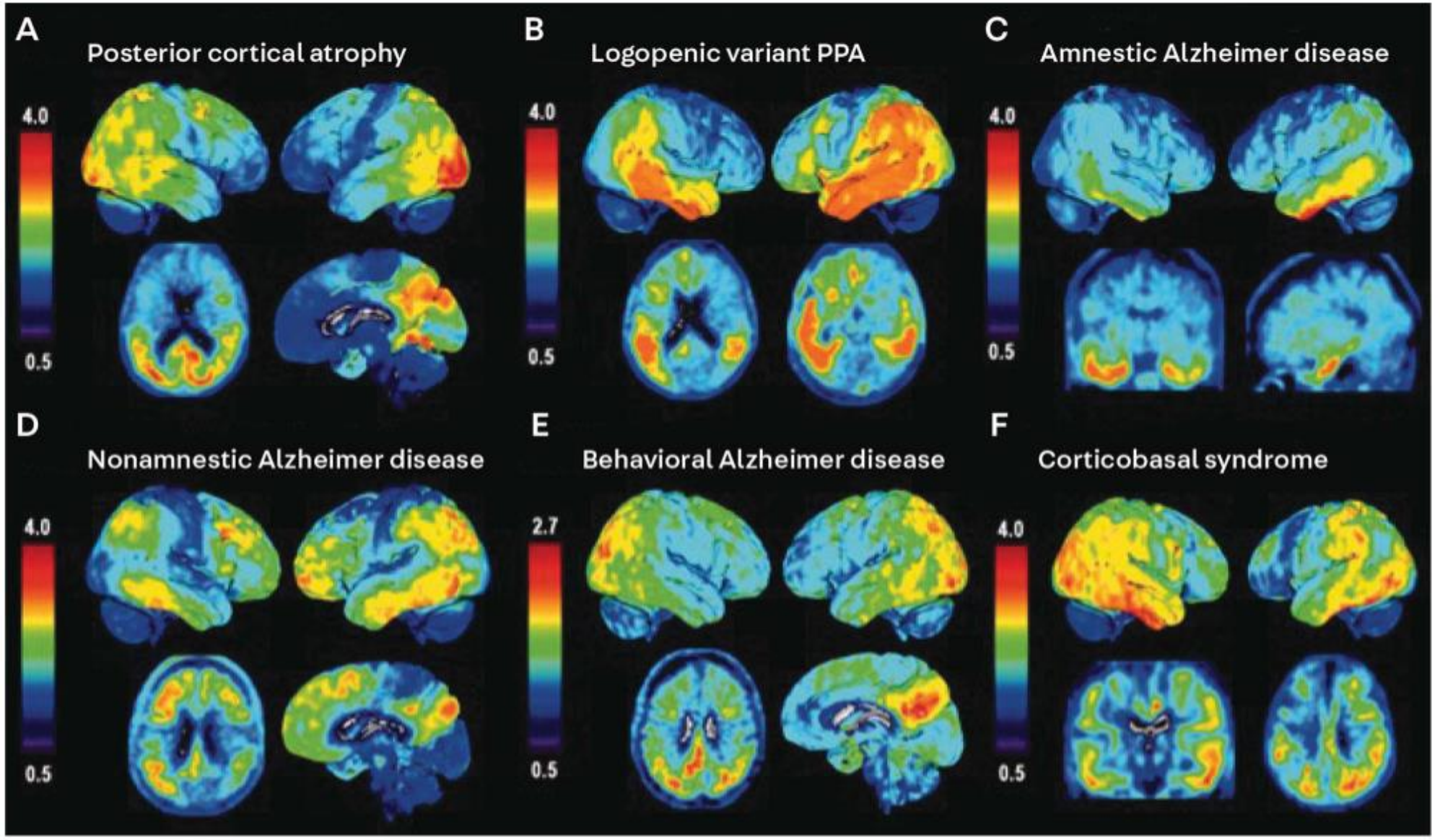
Pathologic process	Fluid biomarker	Brain imaging biomarker
Amyloid-β (Aβ) plaques	CSF Aβ40 and 42; plasma Aβ42/Aβ40 ratio	Amyloid PET[a]
Tau	CSF phosphorylated tau (p-tau); plasma p-tau	Tau PET[b]
Neurodegeneration	CSF total tau; CSF neurofilament light chain (NfL); plasma NfL	FDG-PET hypometabolism characteristic of Alzheimer disease; MRI (volumetric changes) characteristic of Alzheimer disease

- Within this classification system, the use of AD-specific and nonspecific biomarkers are dichotomized as normal or abnormal to provide eight possible combinations
- A-/T-/N- suggesting very low probability of AD-related biomarker changes and A+/T+/N+ suggesting a high probability of AD-related biomarker changes and different combinations between of various levels of uncertainty.

Positron Emission Tomography–based Biomarkers

- Currently four tracers for Aβ plaques and neurofibrillary tau have been approved FDA.
- Both are considered valid markers for AD-related Aβ plaque and neurofibrillary tau changes in those with symptoms of dementia.
- Tau PET tracer retention correlates broadly with different clinical phenotypes of AD.
- However, current tau PET tracers do not accurately identify non-AD–related tau aggregates, and are more specific to AD-related tau pathology.

Tau PET


A
Posterior cortical atrophy
4.0
0.5
B
Logopenic variant PPA
4.0
0.5
C
Amnestic Alzheimer disease
4.0
0.5
D
Nonamnestic Alzheimer disease
4.0
0.5
E
Behavioral Alzheimer disease
2.7
0.5
F
Corticobasal syndrome
4.0
0.5

Fluid-based Biomarkers

- The most well-established fluid biomarkers are from the CSF: Aβ42 and Aβ40 peptides, total tau, and p-tau.
- The typical pattern is low Aβ42 levels (which are proposed to occur as soluble Aβ42 is sequestered into Aβ plaques) and elevated p-tau and total tau (which are proposed to represent the changes in tau metabolism and release from neurons in response to Aβ plaques).
- Recent development → blood-based biomarkers of both Aβ and AD-related tau changes. They may become an important tool for diagnosing AD should current findings from the research cohort translate to clinic- and community-based populations.

- Blood-based biomarkers specific to AD-related changes are likely to improve the diagnostic and prognostic capabilities of neurologists in the near future
  - Neurofilament light chains [Nfl])
  - CNS immune function (glial fibrillary acidic protein [GFAP])

THANKS FOR YOUR ATTENTION