Alzheimer’s Disease Background

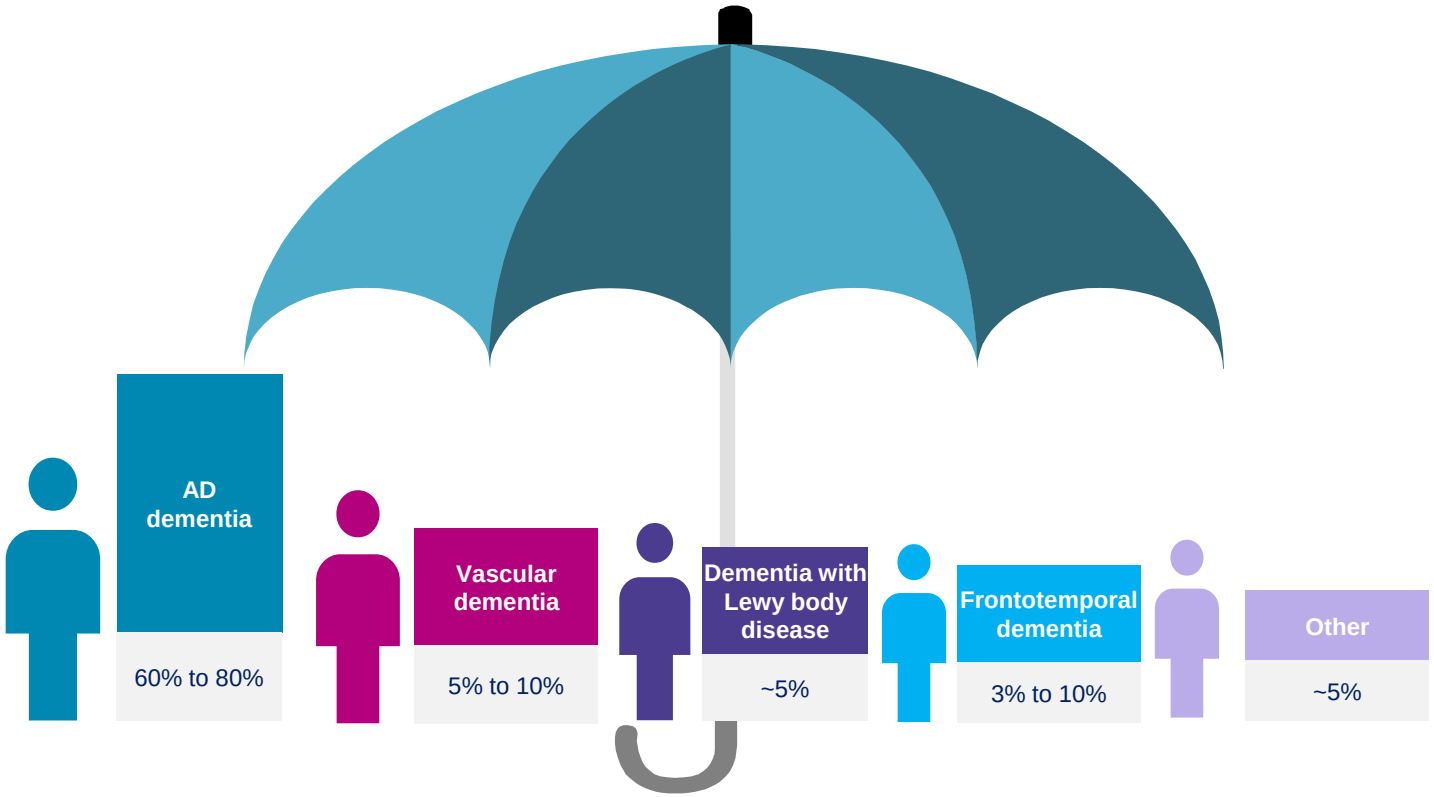
Risk Factors

This content is intended for US health care professionals only for educational and informational purposes and does not substitute for sound medical judgment or clinical decision-making in the context of medical treatment

AD-M2417
May 2025

Alzheimer's Disease Is One Cause of Dementia

Dementia is a **clinical syndrome** – a group of symptoms – that has several causes



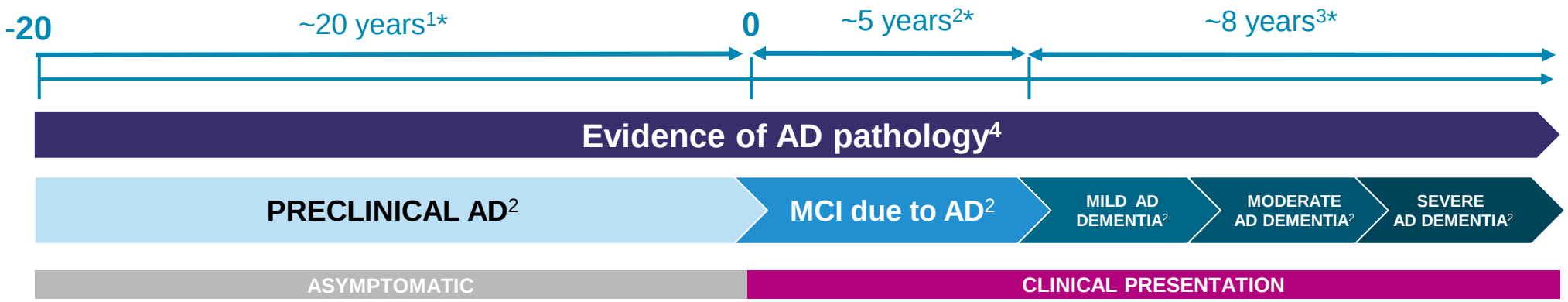
AD is the **most common** primary cause of dementia, although most patients with AD have **co-pathologies**

DEMENTIA is an "umbrella" term for decline in memory and thinking severe enough to interfere with activities of daily life

AD, Alzheimer's disease.

2024 Alzheimer's disease facts and figures. Alzheimers Dement. 2024;20(5):3708–3821.

AD Progression Is a Continuum: Preclinical AD, MCI Due to AD, and AD Dementia



* Depending on age of onset – timing in each stage of disease is highly variable.

AD, Alzheimer's disease; MCI, mild cognitive impairment.

1. Betthauser TJ, et al. Brain 2022;145(11):4065-4079; 2. Alzheimer's Association. Special Report on MCI. 2022. Available from: https://www.alz.org/alzheimers-dementia/what-is-dementia/related_conditions/mild-cognitive-impairment (Accessed May 2025); 3. Alzheimer's Society. The progression and stages of dementia. October 2020. Available from: https://www.alzheimers.org.uk/sites/default/files/pdf/factsheet_the_progression_of_alzheimers_disease_and_other_dementias.pdf (Accessed May 2025); 4. Aisen PS, et al. Alzheimers Res Ther. 2017;9(1):60.

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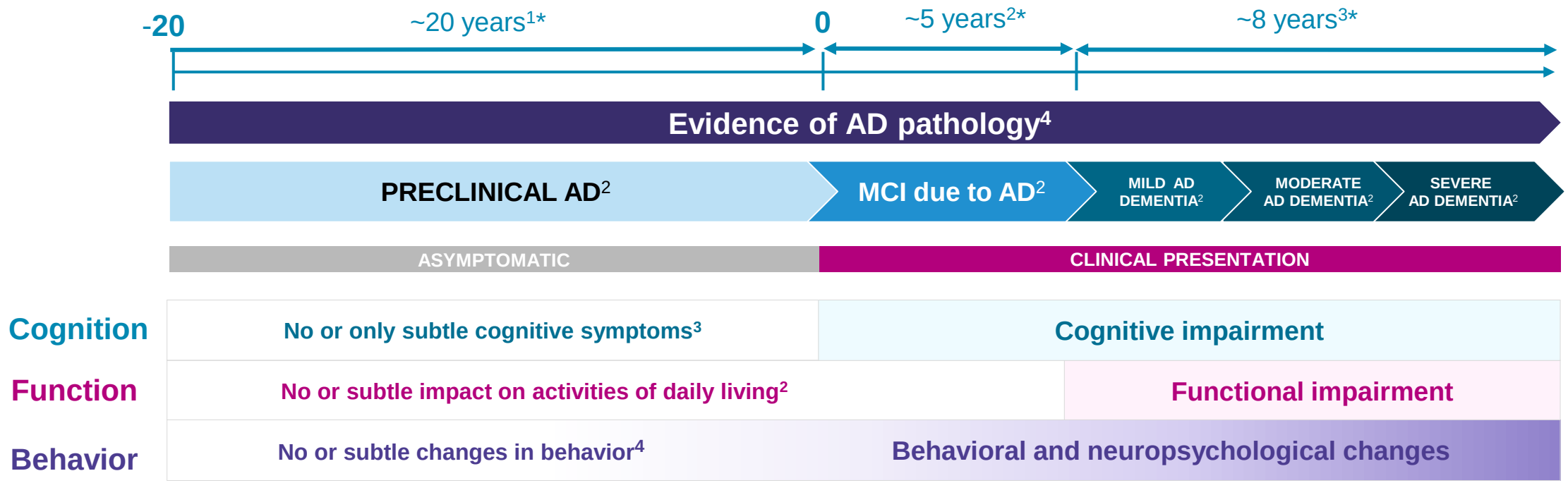

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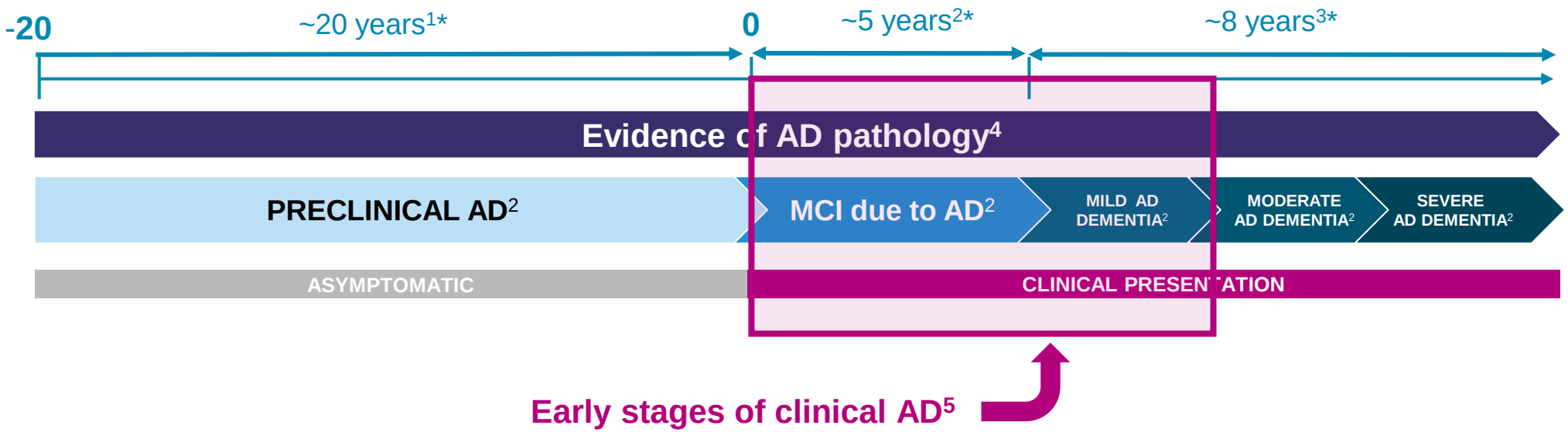
AD, Alzheimer's disease; MCI, mild cognitive impairment.

1. Betthauser TJ, et al. Brain 2022;145(11):4065-4079; 2. Alzheimer's Association. Special Report on MCI. 2022. Available from: https://www.alz.org/alzheimers-dementia/what-is-dementia/related_conditions/mild-cognitive-impairment (Accessed May 2025); 3. Alzheimer's Society. The progression and stages of dementia. October 2020. Available from: https://www.alzheimers.org.uk/sites/default/files/pdf/factsheet_the_progression_of_alzheimers_disease_and_other_dementias.pdf (Accessed May 2025); 4. Aisen PS, et al. Alzheimers Res Ther. 2017;9(1):60.

Early Stages of Clinical AD Include a Period of Mild Cognitive Changes



Approximately 1/3 of individuals with MCI due to AD will develop dementia within the next 5 years[6]

* Depending on age of onset – timing in each stage of disease is highly variable.

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1. Betthauser TJ, et al. Brain 2022;145(11):4065-4079; 2. Alzheimer's Association. Special Report on MCI. 2022. Available from: https://www.alz.org/alzheimers-dementia/what-is-dementia/related_conditions/mild-cognitive-impairment (Accessed May 2025); 3. Alzheimer's Society. The progression and stages of dementia. October 2020. Available from: https://www.alzheimers.org.uk/sites/default/files/pdf/factsheet_the_progression_of_alzheimers_disease_and_other_dementias.pdf (Accessed May 2025); 4. Aisen PS, et al. Alzheimers Res Ther. 2017;9(1):60; 5. Porsteinsson AP, et al. J Prev Alzheimers Dis. 2021;8(3):371–386; 6. 2024 Alzheimer's disease facts and figures. Alzheimers Dement. 2024;20(5):3708–3821.

There Are Modifiable and Non-Modifiable Risk Factors for AD

Non-Modifiable Risk Factors

- Age[1]
- Sex[1,2]
- Genetics and family history[3]

Potentially Modifiable Risk Factors

- Cardiovascular comorbidities[4]
- Traumatic brain injury[4]
- Sleep disturbances[1,4]
- Hearing loss[4]
- Vision loss[4]
- Social isolation[4]
- Air pollution[4]
- Less education[4]
- Smoking
- Consuming >12 US units of alcohol per week
- Obesity and physical inactivity[4]
- Neuropsychiatric conditions[4,5] (Eg, anxiety, apathy, depression)

Addressing modifiable risk factors may prevent or delay nearly half of dementia cases[4]

AD, Alzheimer's disease.

1. 2024 Alzheimer's disease facts and figures. Alzheimers Dement. 2024;20(5):3708–3821; 2. Chêne G, et al. Alzheimers Dement. 2015;11(3):310–320; 3. Pilotto A, et al. Biomed Res Int. 2013;2013:689591; 4. Livingston J, et al. Lancet 2024;404(10452):572–628; 5. Roberts R, Knopman DS. Clin Geriatr Med. 2013;29(4):753–772.

Around 45% of Worldwide Dementia Incidence Could Be Prevented or Delayed With Risk Factor Modification[1]

Potential Protective Factors for Brain Health[2]

Exercise

Healthy diet

Social engagement

Medical health

Regular sleep

Mental stimulation

Adapting healthy lifestyle habits at any age can be beneficial in reducing the risk of dementia

1. Livingston G, et al. Lancet 2024;404(10452):572–628; 2. Cleveland Clinic. Healthy Brains – 6 Pillars of Brain Health. Available from: https://shorturl.at/d6Tvm (Accessed May 2025).

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There Are Key Non-Modifiable Risk Factors for AD

Age

Older age is the most **prominent risk factor**

Family History

Having a **parent or sibling** with the disease increases the likelihood of developing AD

Genetics

Researchers have identified **many genes** that increase or decrease the risk of AD dementia

Sex

AD is **more prevalent among women** than men

Race and Ethnicity

In the USA, **non-Hispanic black and Hispanic older adults** are more likely than white older adults to have AD or other dementias

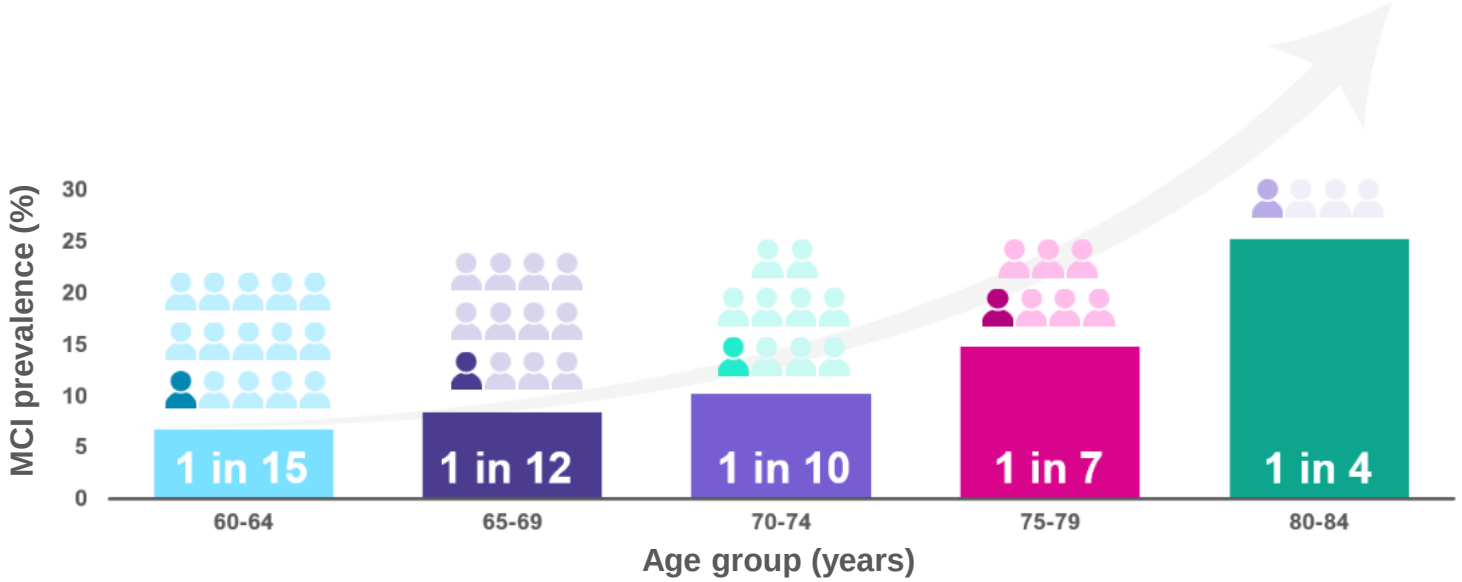
AD, Alzheimer's disease.

2024 Alzheimer's disease facts and figures. Alzheimers Dement. 2024;20(5):3708–3821.

Age Is a Prominent Non-modifiable Risk Factor for AD

- The vast majority of individuals with AD are >65[1]
- The percentage of individuals with dementia **increases markedly after age 65 years**:[1]
  - 5% for patients aged 65–74 years
  - 13% for 75–84 years
  - 33% for ≥85 years

Association of MCI Prevalence With Age[2]



AD dementia is not a normal part of aging, and older age alone is not sufficient to cause AD dementia

AD, Alzheimer's disease; MCI, mild cognitive impairment.

1. 2024 Alzheimer's disease facts and figures. Alzheimers Dement. 2024;20(5):3708–3821; 2. Petersen RC, et al. Neurology 2018;90(3):126–135.

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Many Genes Affect the Risk of Developing AD Dementia

Of all the genes that increase the risk of late-onset AD dementia, *APOE ε4* has the strongest impact[1]

APOE ε4

3–4x

increased risk of AD with **1** copy

12x

Increased risk of AD with **2** copies

Relative to the most common ***APOE ε3* allele**[2]

≤1% of AD dementia cases are caused by rare mutations that disrupt pathways that are directly involved in amyloid processing[1,3]

PSEN1 ***APP*** ***PSEN2***

- In patients with these mutations, symptoms tend to develop before 65 years of age[1]
- People with Down syndrome also have an increased risk of AD dementia; this is thought to be related to carrying **3 copies of chromosome 21**, which encodes the ***APP* gene**[1]

AD, Alzheimer's disease; APOE, apolipoprotein E; APP, amyloid precursor protein; PSEN, presenilin.

1. 2024 Alzheimer's disease facts and figures. Alzheimers Dement. 2024;20(5):3708-3821; 2. Serrano-Pozo A, et al. Lancet Neurol. 2021;20(1):68–80; 3. Karch CM, Goate AM. Biol Psychiatry 2015;77(1):43–51.

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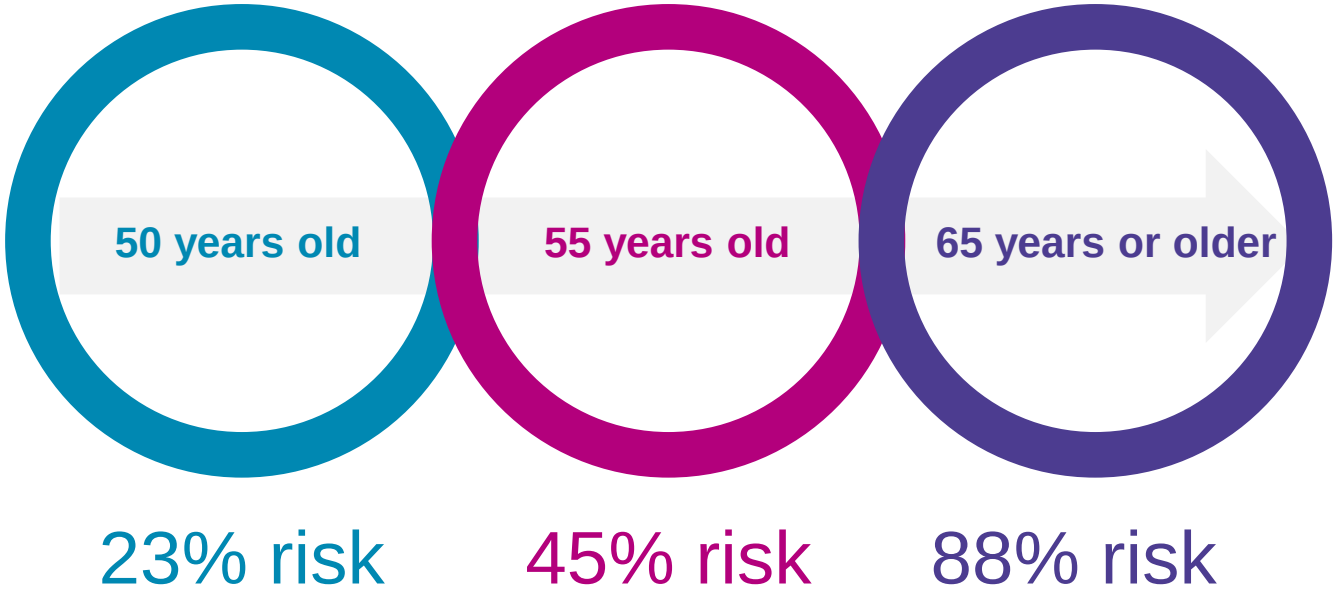
There Is a Strong Genetic Risk of AD in Individuals With Down Syndrome

- Individuals with Down syndrome are typically born with 3 copies of chromosome 21 (trisomy 21) and **carry 3 copies of the *APP* gene**[1]
- Neuritic Aβ plaques and other AD pathologies are an almost certain finding in adults with Down syndrome[2]

In a 20-year longitudinal study of a female Down syndrome population, **97% developed dementia**[3]



Aβ, amyloid beta; AD, Alzheimer's disease; APP, amyloid beta precursor protein.

1. Zigman WB, et al. Int Rev Res Ment Retard. 2008;36:103–145; 2. Wilcock DM, Griffin WS. J Neuroinflammation 2013;10:84; 3. McCarron M, et al. J Intellect Disabil Res. 2017;61(9):843–852.

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The Genes That Affect the Risk of Developing AD Dementia Vary in Frequency in the Population

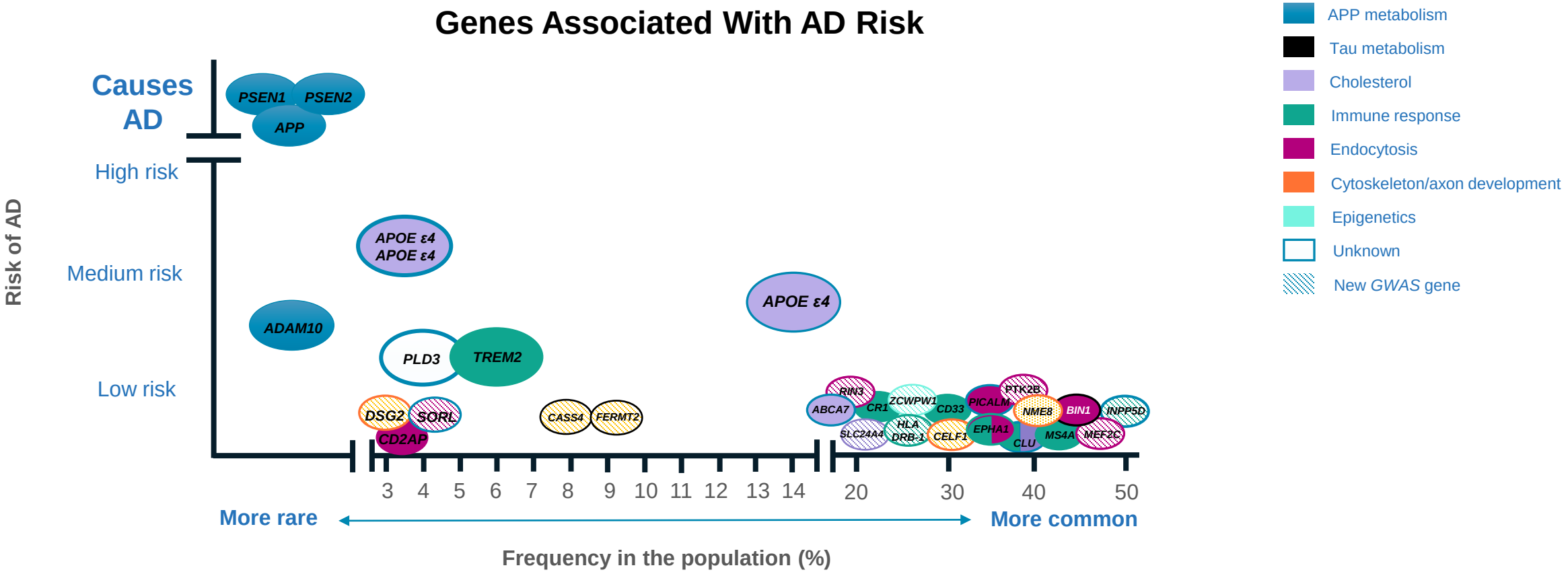
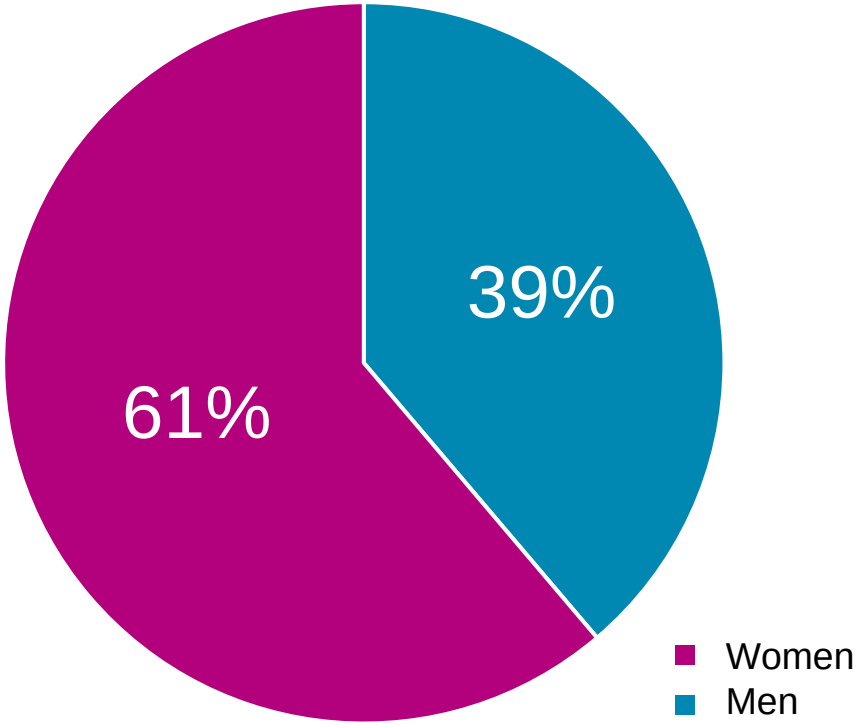


Figure adapted with permission from Karch CM, Goate AM. Biol Psychiatry 2015;77(1):43–51.

AD, Alzheimer's disease; APOE ε4, apolipoprotein E ε4; APP, amyloid beta precursor protein; GWAS, Genome-Wide Association Study; PSEN, presenilin.

More Women Than Men Have a Diagnosis of AD

Adults ≥65 Years of Age With AD by Sex, 2024 in the USA



*Of the 6.7 million people ≥65 years of age with a clinical diagnosis of AD in the USA, almost **two-thirds** are women (4.2 million)*

* Estimates from the Chicago Health and Aging Project incidence rates converted to prevalence estimates and applied to 2011 US Census Bureau estimates of the population ≥65 years of age.

AD, Alzheimer's disease.

2024 Alzheimer's disease facts and figures. Alzheimers Dement. 2024;20(5):3708–3821.

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Women’s Global Prevalence of AD and Other Dementias Doubles About Every 5 Years Until Age 85

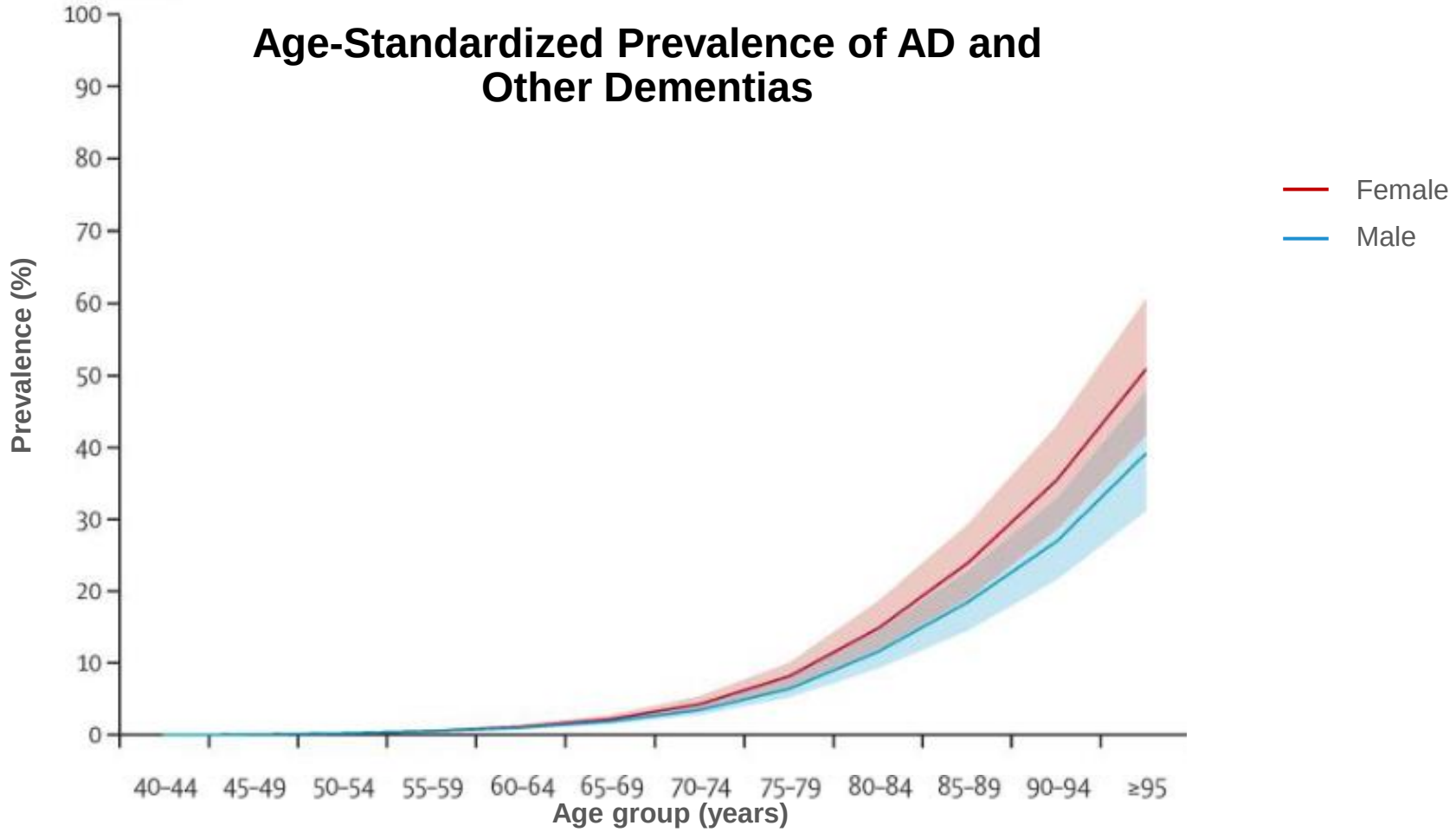


Figure used with permission from GBD 2019 Dementa Forecasting Collaborators. Lancet Public Health 2022;7:e105-e125 (CC-BY 4.0, https://creativecommons.org/licenses/by/4.0/).
AD, Alzheimer’s disease.

While the Prevalence of AD Is Higher in Women Than in Men, the Reason(s) for This Difference Is Unclear

Lifetime risk of developing AD dementia is about double for women than men in the USA;[1]* possible reasons for this include:

Life expectancy	On average, women live longer than men; this increases their lifetime risk of AD because age is an important risk factor[2]
Cardiovascular risks	Men who live longer than 65 years may have a healthier cardiovascular risk profile than women of the same age, suggesting the relationship to AD may be due to survival bias[1]
Tau aggregation	In women and men with equal levels of Aβ, a greater and more aggressive tau burden has been observed in women[3–5]
Brain volume	In AD, the rate of neurodegeneration may be higher in women than in men, resulting in decreased brain volume[6]
Hormonal changes	Menopause leads to a significant drop in estrogen levels, which are known to regulate synaptic plasticity and promote neural survival[7–9]

* In an analysis of data from the Framington Heart Study, lifetime risk at age 45 years was estimated as 20% for women and 10% for men.

Aβ, amyloid beta; AD, Alzheimer's disease.

1. Chêne G, et al. Alzheimers Dement. 2015;11(3):310–320; 2. 2024 Alzheimer's disease facts and figures. Alzheimers Dement. 2024;20(5):3708–3821; 3. Buckley R, et al. JAMA Neurol. 2019;76(5):542–551; 4. Buckley RF, et al. Neurobiol Aging 2019;78:178–185; 5. Coughlan GT, et al. JAMA Neurol. 2025;82(4):364–375; 6. Koran ME, et al. Brain Imaging Behav. 2017;11(1):205–213; 7. Cui J, et al. Trends Mol Med. 2013;19(3):197–209; 8. Zandi PP, et al. JAMA. 2002;288(17):2123–2129; 9. Mosconi L, et al. Sci Rep. 2021;11(1):10867.

Dementia Risk May Be Reduced by Addressing Modifiable Risk Factors

Education

Higher educational attainment and cognitive stimulation at work are associated with reduced risk of dementia[1]

CV Risk Factors

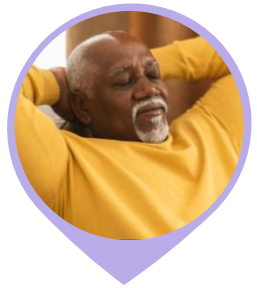
Reduced CV risk factors are associated with lower dementia risk[1]

TBI

TBI increases dementia risk[1]

Lifestyle Factors

A healthy lifestyle – with regular physical activity, healthy weight, not smoking, and avoiding excess alcohol – lowers dementia risk[1]



Sleep

Impaired sleep may increase the risk of cognitive impairment and AD[2,3]

Medical Health

Managing hypertension, type 2 diabetes, and depression can reduce dementia risk[1]

AD, Alzheimer's disease; TBI, traumatic brain injury.

1. 2024 Alzheimer's disease facts and figures. Alzheimers Dement. 2024;20(5):3708–3821; 2. Minakawa EN, et al. Int J Mol Sci. 2019;20(4):803; 3. Bubu OM, et al. Sleep 2017;40(1):zsw032.

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Incidence of Dementia Has Been Associated With Key Modifiable Risk Factors

	RR for Dementia (95% CI)	Prevalence, %	Communality,* %	Unweighted PAF, %	Weighted PAF %
Early life (age <45 years)					
Less education	1.6 (1.3–2.0)	23.2	0.608	12.2	4.5
Mid-life (age 45–65 years)					
Hearing loss	1.4 (1.0–1.9)*	59.0	0.609	19.1	7.0
High LDL cholesterol	1.3 (1.3–1.4)	76.5†	0.469	18.7	6.9
Depression	2.2 (1.7–3.0)*	7.2	0.452	8.3	3.0
Traumatic brain injury	1.7 (1.4–1.9)	12.1	0.423	7.8	2.9
Physical inactivity	1.2 (1.2–1.3)	27.5	0.567	6.4	2.4
Smoking	1.3 (1.2–1.4)	22.3	0.650	6.3	2.3
Hypertension	1.2 (1.1–1.4)	31.1	0.595	5.9	2.2
Obesity (body mass index ≥30)	1.3 (1.0–1.7)	13.0	0.622	3.8	1.4
Alcohol (>12 US units/week)	1.2 (1.0–1.5)	13.3	0.772	2.6	1.0
Later life (age >65 years)					
Social isolation	1.6 (1.3–1.8)	24.0	0.408	12.6	4.6
Air pollution	1.1 (1.1–1.1)	75.0	0.341	7.0	2.6
Untreated vision loss	1.5 (1.4–1.6)	12.7	0.553	6.0	2.2

Table adapted with permission from Livingston G, et al. Lancet 2024;404(10452):572–628.

* Calculated by authors in this Commission; † Prevalence derived from 37,000 participants aged ≥45 years from the Norwegian HUNT study.

CI, confidence interval; LDL, low density lipoprotein; PAF, population attributable fraction; RR, relative risk.

Individuals With More Formal Education Have a Lower Risk of AD Dementia[1,2]

More years of education may contribute to **greater cognitive reserve** – the brain's ability to make flexible and efficient use of cognitive networks[1–3]

Considerations:

Socioeconomic status

Having fewer years of education is associated with lower socioeconomic status, which has been associated with increased risk of cardiovascular disease and AD[2,4]

Mental stimulation at work

Mental stimulation at work may contribute to cognitive reserve in late life[2]

Sex differences

Unequal work and education opportunities for women (born in the 20th century) may contribute to increased risk of AD[5,6]

AD, Alzheimer's disease.

1. Dekhtyar S, et al. Ann Neurol. 2019;86(1):68–78; 2. 2024 Alzheimer's disease facts and figures. Alzheimers Dement. 2024;20(5):3708–3821; 3. Nelson ME, et al. Neuropsychol Rev. 2021;31(2):233–250; 4. McDowell I, et al. J Clin Exp Neuropsychol. 2007;29(2):127–141; 5. Ewers M. Curr Opin Psychiatry 2020;33(2):178–184; 6. Zhu D, et al. Cell Mol Life Sci. 2021;78(11):4907–4920.

Hypertension Increases the Risk of AD Dementia

Hypertension

- Correlations have been found between hypertension and **white matter lesions**, **reduced brain reserve**, **neuritic plaques** and **NFTs** associated with AD[1–3]
- **Mid-life systolic hypertension** has been associated with **increased risk of AD by up to 25%**[4]
- In *APOE ε4* carriers, hypertension is associated with **elevated Aβ deposition**[2]

Aβ, amyloid beta; AD, Alzheimer's disease; APOE ε4, apolipoprotein E ε4; NFT, neurofibrillary tangle.

1. Van Dijk EJ, et al. Hypertension 2004;44(5):625–630; 2. Jeon SY, et al. Neurobiol Aging 2019;75:62–70; 3. Petrovich H, et al. Neurobiol Aging 2000;21(1):57–62; 4. Lennon MJ, et al. J Alzheimers Dis. 2019;71(1):307–316.

Smoking and Obesity Increase the Risk of AD Dementia

Smoking

- A meta-analysis of 19 prospective studies found that current smokers had a RR of 1.79 for AD dementia compared with non-smokers at baseline[1]
- Current smokers have been found to have significantly increased risk of AD dementia, independent of the *APOE ε4* carrier status (HR 1.95)[2]

Obesity

- Obesity and higher BMI over the lifespan are associated with increased cognitive decline and risk of dementia[3]
- Higher BMI in mid-life has been associated with dementia independently of vascular diseases over the lifespan, suggesting the involvement of non-vascular pathways[4]

Aβ, amyloid beta; AD, Alzheimer's disease; APOE ε4, apolipoprotein E ε4; BMI, body mass index; HR, hazard ratio; RR, relative risk.

1. Anstey KJ, et al. Am J Epidemiol. 2007;166(4):367–378; 2. Reitz C, et al. Neurology 2007;69(10):998–1005; 3. Elias MF, et al. J Alzheimers Dis. 2012;30(Suppl 2):S113–S125; 4. Xu WL, et al. Neurology 2011;76(18):1568–1574.

Diabetes Increases the Risk of AD Dementia

Glucose Metabolism and Diabetes Mellitus

- Insulin resistance in T2DM leads to higher circulating blood glucose levels, which in turn leads to **microvascular damage, protein glycation, and oxidative stress – neurotoxicity in the brain**[1,2]
- Higher levels of insulin can also **disrupt Aβ clearance** leading to increased Aβ burden[3]

Aβ, amyloid beta; AD, Alzheimer's disease; T2DM, type 2 diabetes meillitus.

1. de Bruijn RFAG, Ikram MA. BMC Med. 2014;12:130; 2. Biessels GJ, et al. Lancet Neurol. 2006;5(1):64–74; 3. Gasparini L, Xu H. Trends Neurosci. 2003;26(8):404–406.

Traumatic Brain Injury (TBI) Can Increase the Risk of Dementia[1–3]

TBI is commonly caused by falls, violence, or contact sports[1]

Mild TBI*

- Two-fold increased risk of dementia has been associated with mild TBI[4]
- Risk of dementia increases with the number of TBIs sustained[3]
- With age, the frequency and severity of TBI required to increase dementia risk decreases; mild TBI is sufficient to increase risk in the elderly[5]

AD pathology

TBI has been linked with the 2 hallmarks of AD (amyloid and tau); however, some studies do not support this link[6–10]

Chronic traumatic encephalopathy

Although CTE is not related to AD, it is characterized by abnormal accumulation of tau (a hallmark of AD) and is associated with repeated blows to the head[2]

* Defined as loss of consciousness or post-traumatic amnesia (≤30 minutes).

AD, Alzheimer's disease; CTE, chronic traumatic encephalopathy; TBI, traumatic brain injury.

1. Livingston G, et al. Lancet 2024;404(10452):572–628; 2. 2024 Alzheimer's disease facts and figures. Alzheimers Dement. 2024;20(5):3708–3821; 3. Fann JR, et al. Lancet Psychiatry 2018;5(5):424–431; 4. Barnes DE, et al. JAMA Neurol. 2018;75(9):1055–1061; 5. Johnson VE, Stewart W. Nat Rev Neurol. 2015;11(3):128–130; 6. Edwards GA 3rd, et al. J Neurotrauma 2020;37(1):80–92; 7. Risacher SL, et al. Alzheimers Dement (Amst). 2021;13(1):e12230; 8. Johnson VE, et al. Nat Rev Neurosci. 2010;11(5):361–370; 9. Huang CH, et al. BMC Neurol. 2018;18(1):184; 10. Robinson AC, et al. Int J Geriatr Psychiatry 2019;34(8):1262–1266.

Impaired Sleep May Increase Risk of AD

Impaired Sleep

- Sleep problems/disorders are associated with significant increases in the risk ratio for cognitive impairment and AD diagnosis[1,2]
- **Sleep disorders include:[1]**
  - Short or long sleep duration
  - Poor sleep quality
  - Insomnia
  - Sleep apnea
- Increased Aβ burden has been found in individuals who suffer from sleep deprivation[3–5]

Aβ, amyloid beta; AD, Alzheimer's disease.

1. Minakawa EN, et al. Int J Mol Sci. 2019;20(4):803; 2. Bubu OM, et al. Sleep 2017;40(1):zsw032; 3. Shokri-Kojori E, et al. Proc Natl Acad Sci U S A. 2018;115(17):4483–4488; 4. Holth JK, et al. Science 2019;363(6429):880–884; 5. Boespflug EL, Iliff JJ. Biol Psychiatry 2018;83(4):328–336.

Summary

While the risk of AD increases with age and is impacted by genetics, it can be reduced through lifestyle changes

Dementia prevention requires both governmental policy changes and individually tailored interventions

As risks tend to cluster in individuals, interventions should be multicomponent

Actions to decrease dementia risk should begin early and continue through life

Specific recommendations to reduce dementia risk include, but are not limited to:

- Engaging in cognitively stimulating activities in midlife
- Addressing hearing loss and protecting from harmful noise exposure
- Treating vision loss
- Reducing risk of TBI, eg, through protective headwear and preventing falls
- Taking regular physical activity
- Avoiding cigarettes and excessive alcohol
- Preventing or reducing hypertension
- Maintaining a healthy weight and addressing obesity early

AD, Alzheimer's disease; TBI, traumatic brain injury.

Livingston G, et al. Lancet 2024;404(10452):572–628.

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