# Alzheimer’s disease background

## Risk factors for AD

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

Eisai hhc human health care

# Non-modifiable risk factors: age

**Age is the most important risk factor for AD**; the vast majority of individuals with AD are ≥65 years

The percentage of individuals with dementia **increases markedly after age 65**: 5% for patients aged 65–74 years, 13.1% for 75–84 years, and 33.3% for 85 years and older

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

AD, Alzheimer's disease

1. 2023 Alzheimer's disease facts and figures. Alzheimers Dement. 2023;19(4):1598–1695

# Non-modifiable risk factors: sex (1/2)

While the difference in AD incidence between sexes is unclear, the prevalence of AD is higher in women than in men, and lifetime risk of developing AD dementia is about double for women than men in the USA;[1]* possible reasons for this include:

## Increased life expectancy in women

- On average, women live longer than men; this increases their risk of AD because age is an important risk factor[2]

## Decreased cardiovascular disease risk in men >65

- It is thought that men who live longer than 65 years may have a healthier cardiovascular risk profile than women of the same age; this may decrease the risk of AD for men over 65[1]

## Increased vulnerability to tau aggregation in women

- At equal levels of amyloid beta (Aβ) cognitively normal, elderly women have more tangles in the entorhinal cortex than cognitively normal, elderly men[3]
- Tau aggregation is greater in women with MCI than men with MCI, possibly due to structural and functional differences between male and female brain regions[4]
- Female ApoE ε4 carriers have stronger associations between Aβ and tau biomarkers than male carriers, indicating a greater vulnerability to tau accumuation[5]

*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; ApoE ε4, apolipoprotein E ε4; MCI, mild cognitive impairment

1. Chêne G, et al. Alzheimers Dement 2015;11:310–320 2. 2021 Alzheimer's disease facts and figures. Alzheimers Dement. 2023;19(4):1598–1695; 3. Buckley R, et al. JAMA Neurol 2019;76:542–551; 4. Banks SJ, et al. Neurobiol Aging 2021;107:70-77; 5. Buckley RF, et al. Neurobiol Aging 2019;78:178–185;

# Non-modifiable risk factors: sex (2/2)

**Decreased brain volume in women (on average)**

- There is evidence that men suffer slower or less structural neuronal loss compared to women[1,2]
- In AD, the rate of neurodegeneration may be higher in women than in men[2]

**Differing hormonal compositions**

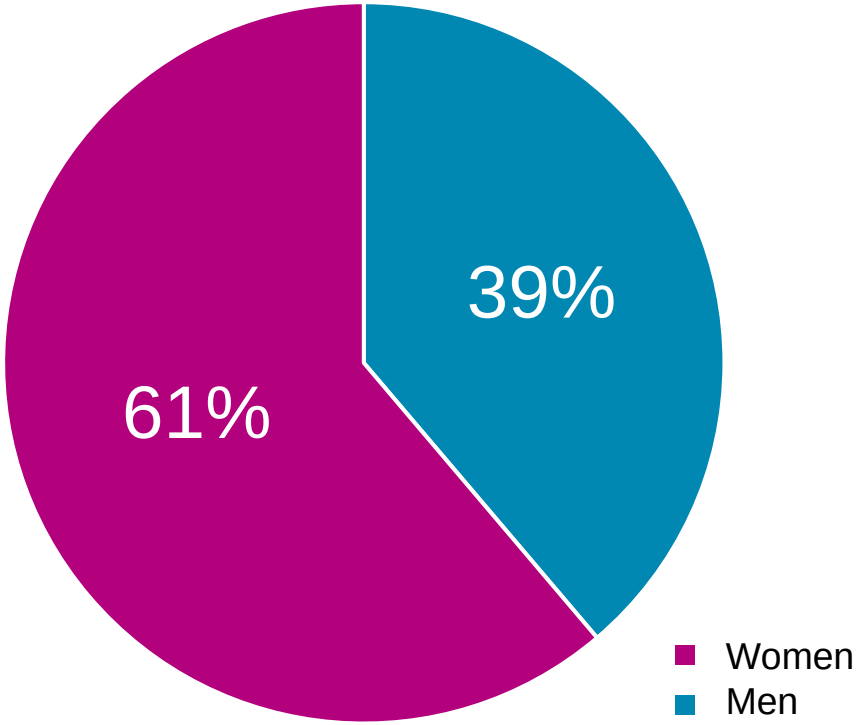
- Estrogen 17β-estradiol, which is associated with female reproductive development and function, has been shown to regulate synaptic plasticity, promote neural survival, and mediate sex-specific behaviors[3]
- The depletion of estrogen in women during menopause has been described as a trigger for brain aging and AD development[4,5]
- ERT has been shown to be neuroprotective in the perimenopause but not in the post-menopause period[4]

AD, Alzheimer's disease; ERT, estrogen replacement therapy

1. Zhu D, et al. Cell Mol Life Sci 2021;78:4907–4920; 2. Koran ME, et al. Brain Imaging Behav 2017;11:205–213; 3. Cui J, et al. Trends Mol Med 2013;19:197–209; 4. Zandi PP, et al. JAMA 2002;288:2123–2129; 5. Mosconi L, et al. Sci Rep 2021;11:10867

# More women than men have a diagnosis of AD

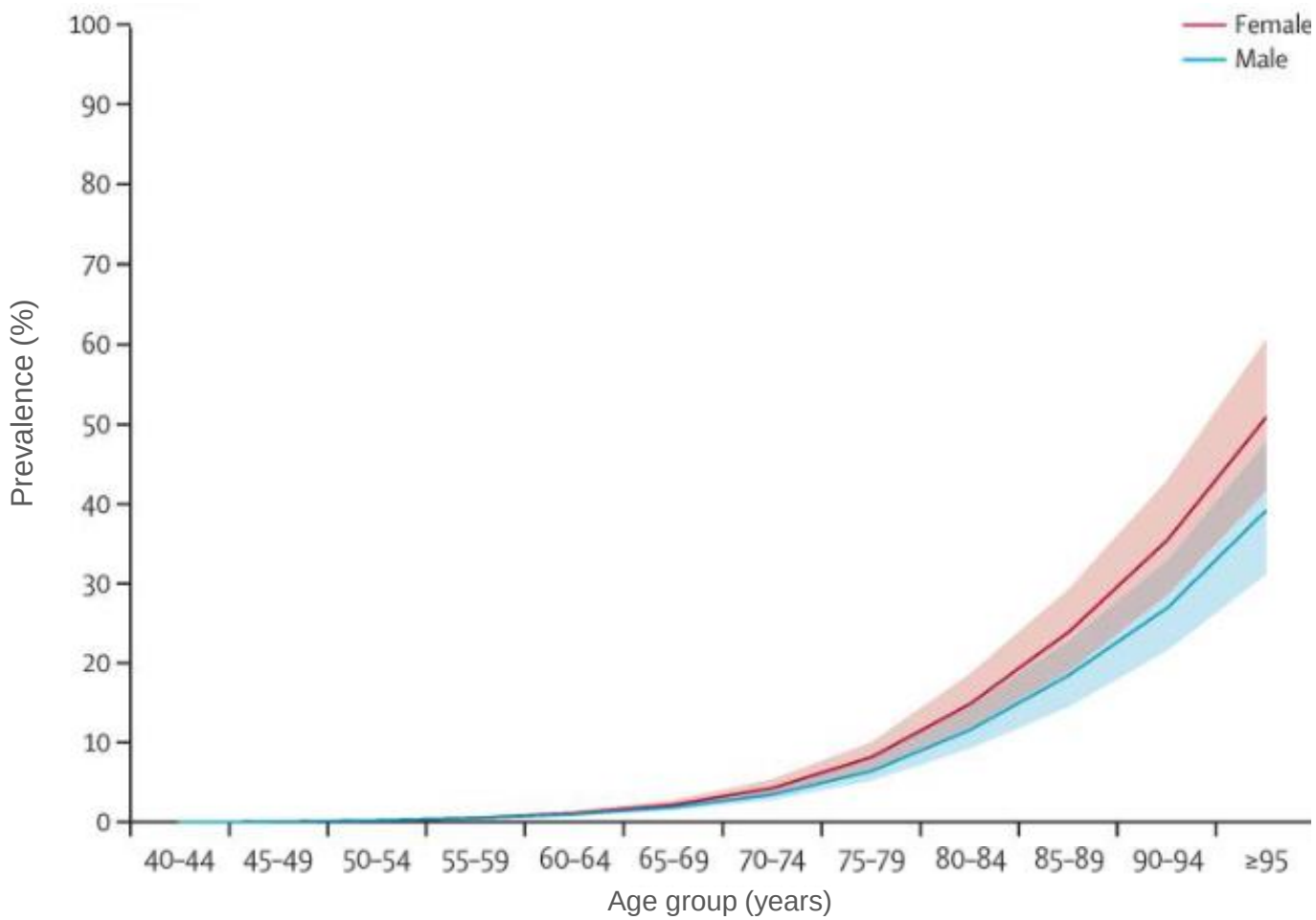
Adults ≥65 years of age with AD by sex, 2023 in the USA




Of the 6.7 million people ≥65 years of age with a clinical diagnosis of AD in the USA almost **two-thirds** are women (4.1 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
1. 2023 Alzheimer's disease facts and figures. Alzheimers Dement 2023;19(4):1598–1695.

# Global age-standardized prevalence of AD and other dementias



# Non-modifiable risk factors: genetic factors (1/2)

A family history of AD is not necessary for an individual to develop the disease[1]

However, individuals who have a close relative (eg parent, sibling) with dementia are up to two times more likely to develop the disease[2]

AD likely arises from a complex interplay between genetic susceptibility, interacting molecular mechanisms, and environmental factors[3,4]

Dominantly inherited AD is associated with rare mutations in the APP, PSEN1, and PSEN2 genes;[5] mutations in these genes disrupt pathways that are directly involved in amyloid processing[3]

Sporadic AD also has a strong genetic component[3] – the allele ε4 of APOE represents one gene associated with increased AD risk[3]

AD, Alzheimer's disease; ApoE ε4, apolipoprotein E ε4; APP, amyloid beta precursor protein; PSEN, presenilin

1. Alzheimers Dement. 2023;19(4):1598–1695; 2. Loy CT, et al. Lancet 2014;383:828–840; 3. Karch CM, Goate AM. Biol Psychiatry 2015;77:43–51; 4. Livingston G, et al. Lancet 2020;396:413–446; 5. Pilotto A et al. Biomed Res Int 2013;2013:689591

# Non-modifiable risk factors: genetic factors (2/2)

## Genes associated with Alzheimer's disease risk

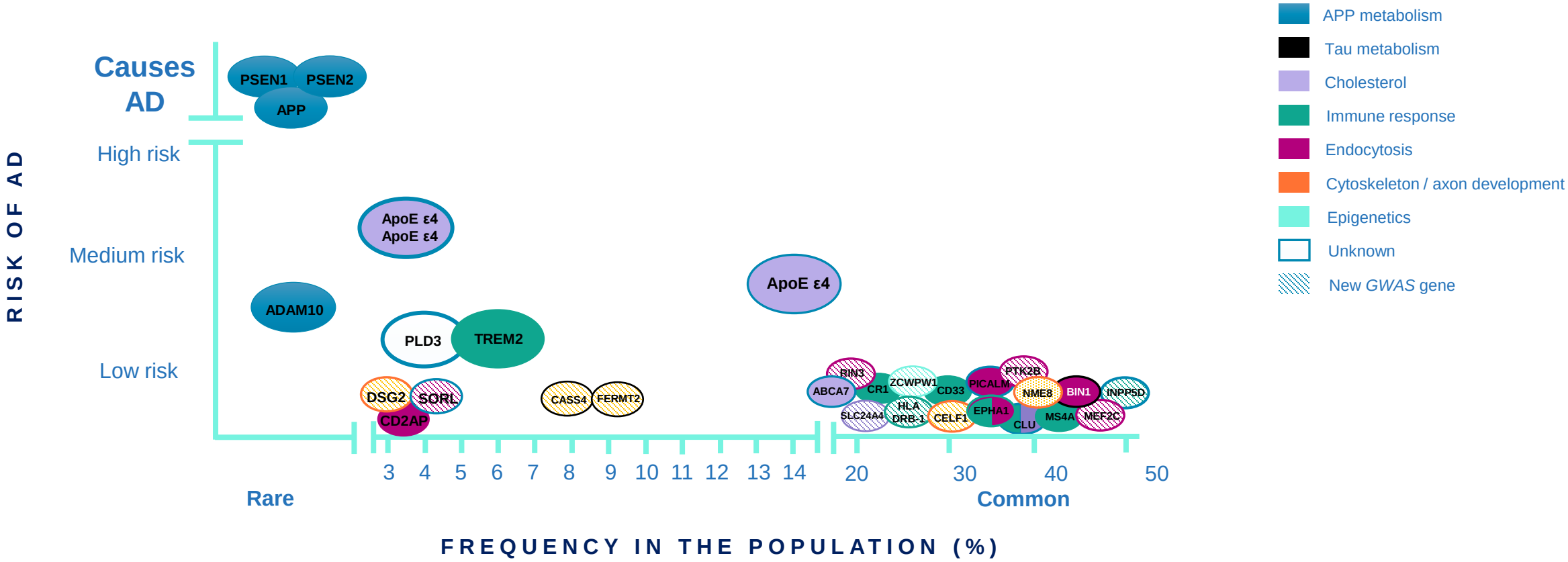



Figure adapted with permission from Karch CM, Goate AM. Biol Psychiatry 2015;77:43–51

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

# Non-modifiable risk factors: APOE genetic variance

**APOE, the dominant cholesterol and lipid carrier in the brain, is critical for Aβ catabolism[1]**

The human APOE gene has three major allelic variants, which differ by a single nitrogenous base:[2]

- ε2 offers protective effects against AD (112 Cys, 158 Cys)
- ε3 is the most common isoform (112 Cys, 158 Arg)
- ε4 increases the risk of developing AD (112 Arg, 158 Arg)

The presence of the *APOE ε4* allele may affect many components of AD pathogenesis, including amyloid deposition, neurodegeneration and blood-brain barrier dysfunction[2–5]

The number of copies of the *APOE ε4* allele a person carries impacts AD risk and age of onset, with homozygous ε4 carriers having the greatest AD risk and lowest average age of onset:

| | Heterozygous ε4 carriers | Homozygous ε4 carriers |
|---|---|---|
| AD risk increase[2]* | 3.7-fold | Up to 12-fold |
| Average age of clinical symptom onset[5] | 76 years | 68 years |

*Relative to the most common APOE ε3/ε3 genotype

Aβ, amyloid beta; AD, Alzheimer's disease; ApoE ε4, apolipoprotein E ε4; Arg, arginine; Cys, cysteine

1. Sadigh-Eteghad S, et al. Med Princ Pract 2015;24:1–10; 2. Serrano-Pozo A, et al. Lancet Neurol 2021;20:68–80; 3. Montagne A, et al. Nature 2020;581:71–76; 4. Chen XR, et al. J Alzheimers Dis 2021;82:921–937; 5. Liu CC, et al. Nat Rev Neurol 2013;9:106–118

# Non-modifiable risk factors: race-specific APOE genetic variance

**Pooled allele frequency data** show that the APOE ε4 allele is most common in Black populations and least common in West Asian populations

| Allele | Race* | | | | |
|---|---|---|---|---|---|
| | Black | White | Eastern Asian | Central/Southern Asian and Northern African | Other |
| APOE ε4 | 38.30% | 35.77% | 22.61% | 21.98% | 27.13% |
| APOE ε2 | 5.94% | 3.97% | 5.44% | 4.75% | 3.68% |

**The increased risk of developing AD in APOE ε4+** individuals differed among races; a larger risk was associated with White, Central/Southern Asian and Northern African populations

**The protective effects observed in APOE ε2+** individuals were strongest in White populations

**Race-specific environmental** factors, such as socioeconomic status and educational attainment, may influence the ApoE-related risk variability

*The Stoddard race map was used to categorize race in this study. Available from: https://commons.wikimedia.org/wiki/File:Stoddard_race_map_1920.jpg
AD, Alzheimer's disease; APOE ε4, apolipoprotein E ε4
Qin W, et al. J Alzheimers Dis 2021;83:897–906

# Non-modifiable risk factors: Down syndrome

Individuals with Down syndrome are typically born with three copies of chromosome 21 (trisomy 21) and **carry three copies of the APP gene**[1]

Neuritic Aβ plaques and other AD pathologies are an almost certain finding in adults with Down syndrome. However, predictions regarding timing of the onset of dementia are less certain[2]

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

| | 50 years old | 55 years old | 65 years or older |
|---|---|---|---|
| Dementia risk | **23%** | **45%** | **88%** |

Aβ, amyloid beta; AD, Alzheimer's disease; APP, amyloid beta precursor protein
mage from: UW Health Sciences/UW Medicine. Available from: https://www.washington.edu/news/2012/11/08/extra-chromosome-21-removed-from-down-syndrome-cell-line/ (Accessed May 27, 2020)
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;61:843–852

# Modifiable risk factors

**Education:** low number of years of education[1]

**Sleep:** disturbance in sleep pattern[1]

**Cardiovascular risk factors:** hypertension, diabetes mellitus, hypercholesterolemia, obesity, smoking[1]

**Lifestyle factors:** physical activity, social and cognitive engagement, diet[1]

**Traumatic brain injury**[1]

**Neuropsychiatric conditions:** anxiety, apathy, and depression[2]

1. Alzheimer's Association. Alzheimers Dement. 2023;19(4):1598–1695; 2. Roberts R, Knopman DS. Clin Geriatr Med 2013;29:10

# Potential modifiable risk factors that contribute to the incidence of dementia

| | RR for dementia (95% CI) | Prevalence, % | Communality,* % | PAF,† % | Weighted PAF,‡ % |
|---|---|---|---|---|---|
| **Early life (age <45 years)** | | | | | |
| Less education | 1.6 (1.3–2.0) | 40.0 | 61.2 | 19.4 | 7.1 |
| **Mid-life (age 45–65 years)** | | | | | |
| Hearing loss | 1.9 (1.4–2.7) | 31.7 | 45.6 | 22.2 | 8.2 |
| Traumatic brain injury | 1.8 (1.5–2.2) | 12.1 | 55.2 | 9.2 | 3.4 |
| Hypertension | 1.6 (1.2–2.2) | 8.9 | 68.3 | 5.1 | 1.9 |
| Alcohol (>21 units/week) | 1.2 (1.1–1.3) | 11.8 | 73.3 | 2.1 | 0.8 |
| Obesity (body-mass index ≥30) | 1.6 (1.3–1.9) | 3.4 | 58.5 | 2.0 | 0.7 |
| **Later life (age >65 years)** | | | | | |
| Smoking | 1.6 (1.2–2.2) | 27.4 | 62.3 | 14.1 | 5.2 |
| Depression | 1.9 (1.6–2.3) | 13.2 | 69.8 | 10.6 | 3.9 |
| Social isolation | 1.6 (1.3–1.9) | 11.0 | 28.1 | 4.2 | 3.5 |
| Physical inactivity | 1.4 (1.2–1.7) | 17.7 | 55.2 | 9.6 | 1.6 |
| Diabetes | 1.5 (1.3–1.8) | 6.4 | 71.4 | 3.1 | 1.1 |
| Air pollution | 1.1 (1.1–1.1) | 75.0 | 13.3 | 6.3 | 2.3 |

*Communality is the common variance shared by factors with given variables; †PAF is the proportional reduction in population disease or mortality that would occur if exposure to a risk factor were reduced to an alternative ideal exposure scenario;
‡Weighted PAF is the relative contribution of each risk factor to the overall PAF when adjusted for communality (35.0%)
CI, confidence interval; PAF, population attributable fraction; RR, relative risk
Table adapted with permission from Livingston G, et al. Lancet 2020;396:413–446

# Modifiable risk factors: education

People with more years of formal education, including ApoE ε4 carriers,[1] have been found to be at lower risk of AD dementia than those with fewer years of formal education[2]

A possible mechanism for this is the development of greater **cognitive reserve**[1] – the brain's ability to make flexible and efficient use of cognitive networks (networks of neuron-to-neuron connections), allowing a person to continue to carry out cognitive tasks despite brain changes[2]

High cognitive reserve has been associated with a **reduced relative risk** of MCI or dementia[3]

## Other considerations:

- **Having fewer years of** education is associated with **lower socioeconomic status**,[4] which has been associated with increased risk of cardiovascular disease and poor nutritional habits, which may contribute to increased risk of developing AD[2]
- **Mental stimulation** at work[5] and **sex differences**[6] have been shown to be potential moderating factors of cognitive reserve in AD
- **Women born** in the first half of the 20th century typically have lower education and increased unemployment than men, which may contribute to increased risk of AD. Additional elevated risk factors for women include increased rates of depression, stress, and sleep disorders[7]

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

1. Dekhtyar S, et al. Ann Neurol 2019;86:68–78; 2. Alzheimer's Association. Alzheimers Dement. 2023;19(4):1598–1695; 3. Nelson ME, et al. Neuropsychol Rev 2021;31:233–250; 4. McDowell I, et al. J Clin Exp Neuropsychol 2007;29:127–141; 5. Pool LR, et al. Neurology 2016;86:1386–1392; 6. Ewers M. Curr Opin Psychiatry 2020;33:178–184; 7. Zhu D, et al. Cell Mol Life Sci 2021;78:4907–4920

# CV risk factors associated with Alzheimer's disease (1/2)

## Hypertension and arterial stiffness

- Correlations have been found between hypertension and white matter lesions[1], reduced brain reserve[2], neuritic plaques and NFTs[3] associated with AD
- **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]
- **High blood pressure variability** can cause high flow pulsatility and arterial stiffness, which may lead to damage within the microvascular system of the brain causing **impaired Aβ clearance** and **cognitive decline**[5]

## Glucose metabolism and diabetes mellitus

- Insulin resistance in T2DM leads to higher circulating blood glucose levels, which in turn leads to **microvascular damage,**[6] **protein glycation,**[6] **and oxidative stress**[7]
- T2DM is directly related to AD via **neurotoxicity** mediated by increased glucose and insulin levels[6]
- Higher levels of insulin can also **disrupt Aβ clearance** leading to increased Aβ burden[8]

## Hypercholesterolemia

- Hypercholesterolemia is an **emerging CV risk factor** for AD, but studies have produced conflicting results[6]
- **High cholesterol in mid-life** may be a risk factor for AD, whereas low cholesterol levels in later life may reflect preclinical disease, as lifestyle and dietary habits change in individuals with subclinical AD[6]

Aβ, amyloid beta; AD, Alzheimer's disease; ApoE ε4, apolipoprotein E ε4; CV, cardiovascular; NFT, neurofibrillary tangle; T2DM, type 2 diabetes mellitus

1. Van Dijk EJ, et al. Hypertension 2004;44:625–630; 2. Jeon SY, et al. Neurobiol Aging 2019;75:62–70; 3. Petrovich H, et al. Neurobiol Aging 2000;21:57–62; 4. Lennon MJ, et al. J Alzheimers Dis. 2019;71(1):307-316; 5. de Heus RAA, et al. Hypertension 2019;74:1172–1180; 6. de Bruijn RFAG, Ikram MA. BMC Med 2014;12:130; 7. Biessels GJ, et al. Lancet Neurol 2006;5:64–74; 8. Gasparini L, Xu H. Trends Neurosci 2003;26:404–406

# CV risk factors associated with Alzheimer’s disease (2/2)

## Smoking

- A meta-analysis of 19 prospective studies found that current smokers had a RR of 1.79 (95% CI 1.43, 2.23) for AD compared with non-smokers at baseline[1]
- Current smokers have been found to have significantly increased risk of AD, independent of the ApoE ε4 carrier status (HR 1.95, 95% CI 1.29, 2.95)[2]
- The Honolulu-Asia Aging Study found that number of pack-years was related to AD risk in a dose-response manner[3]
- The exact mechanisms underlying the relationship between smoking and AD require further investigation[4]

## Obesity

- Obesity in mid-life is associated with an increased risk of AD[4]
- Mid-life high BMI has been associated with dementia independently of lifespan vascular diseases, suggesting the involvement of non-vascular pathways[5]
- Obesity and higher BMI over the life course are associated with cognitive decline, cognitive deficit, and an increased risk of developing dementia[6]

Aβ, amyloid beta; AD, Alzheimer's disease; ApoE ε4, apolipoprotein E ε4; BMI, body mass index; CI, confidence interval; HR, hazard ratio; RR, relative risk

1. Anstey KJ, et al. Am J Epidemiol 2007;166:367–378; 2. Reitz C, et al. Neurology 2007;69:998–1005; 3. Tyas SL, et al. Neurobiol Aging 2003;24:589–596; 4. de Bruijn RFAG, Ikram MA. BMC Med 2014;12:130; 5. Xu WL, et al. Neurology 2011;76:1568–1574; 6. Elias MF, et al. J Alzheimers Dis 2012;30:S113–S125

# Modifiable risk factors: traumatic brain injury (TBI)

TBI is the disruption of normal brain function caused by a blow or jolt to the head or penetration of the skull by a foreign object, and is **thought to increase the risk of dementia**[1,2]

The **frequency and severity** of TBI required to increase dementia risk **decrease with age**; it has been shown that a **single, mild TBI** may be sufficient to increase dementia risk in those aged ≥65 years[4]

Even **mild TBI** – defined as loss of consciousness or post-traumatic amnesia lasting 30 minutes or less – has been associated with a **two-fold increase in risk of dementia**[3]

TBI has been linked with **accelerated tau pathology**,[5,6] as well as increased **amyloid plaques**[7] – two hallmarks of AD; however, some studies have failed to find links between TBI and AD pathology[8,9]

Risk of dementia has been shown to **increase with the number of TBIs sustained**[2]

A further consideration is that **CTE** – a non-AD-related neuropathological diagnosis associated with repeated blows to the head – is also characterized by **abnormal tau accumulation**[1]

AD, Alzheimer's disease; CTE, chronic traumatic encephalopathy

1. Alzheimer's Association. Alzheimers Dement 2021;17:327–406; 2. Fann JR, et al. Lancet Psychiatry 2018;5(5):424–31; 3. Barnes DE, et al. JAMA Neurol 2018;75(9):1055–61; 4. Johnson VE, Stewart W. Nat Rev Neurol 2015;11:128–130; 5. Edwards GA 3rd, et al. J Neurotrauma 2020;37:80–92; 6. Risacher SL, et al. Alzheimers Dement (Amst) 2021;13:e12230; 7. Johnson VE, et al. Nat Rev Neurosci 2010;11(5):361–370; 8. Huang CH, et al. BMC Neurol 2018;18:184; 9. Robinson AC, et al. Int J Geriatr Psychiatry 2019;34:1262–1266

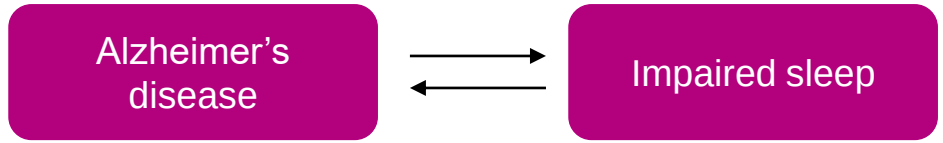
# Modifiable risk factors: sleep

There is a **bidirectional relationship** between AD and impaired sleep:[1]

- Impaired sleep is a consequence of AD pathology, affecting brain regions regulating the sleep-wake or circadian rhythm
- Impaired sleep is also a modifiable risk factor for initiation and progression of AD

Sleep problems/disorders are associated with significant increases in the risk ratio for cognitive impairment, preclinical AD and AD diagnosis, including:[2]

- Short or long sleep duration
- Poor sleep quality, eg difficulty falling asleep, increased intermittent nocturnal arousal
- Circadian rhythm abnormality
- Insomnia
- Obstructive sleep apnea




- **One night of sleep deprivation** has been shown to result in:
  - Increased Aβ burden measured by amyloid PET[3]
  - Elevated $A\beta_{40}$ and $A\beta_{42}$ production[4] and elevated CSF tau[5]
- Evidence suggests that slow-wave sleep is the most important stage of sleep for amyloid clearance[6]

Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid

1. Minakawa EN, et al. Int J Mol Sci 2019;20:pii: E803; 2. Bubu OM, et al. Sleep 2017;40; 3. Shokri-Kojori E, et al. Proc Natl Acad Sci USA 2018;115:4483–4488; 4. Lucey BP, et al. Ann Neurol 2018;83:197–204; 5. Holth JK, et al. Science 2019;363:880–884; 6. Boespflug EL, Iliff JJ. Biol Psychiatry 2018;83:328–336

Eisai hhc human health care

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