Current research on preventing Alzheimer's disease

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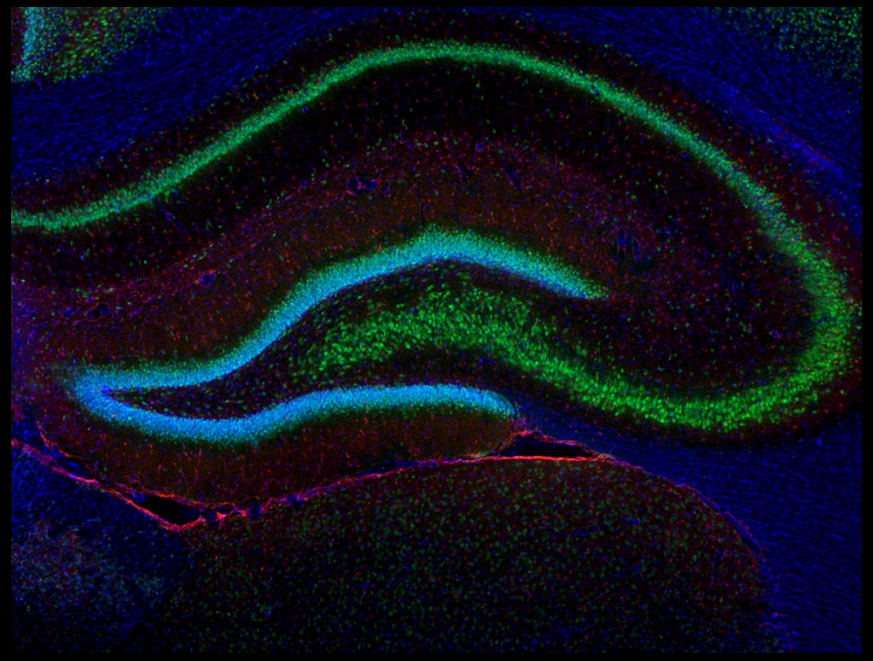

Bottom Lines

The number of people with dementia is increasing globally

Be ambitious about prevention

Treat cognitive symptoms

Care for family care providers

Plan for future

What is dementia?

Dementia is not a disease, but a general term to describe symptoms of severe cognitive impairment, such as impaired memory, communication, and thinking, so severe that daily life functioning is affected.

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Dementia & AD

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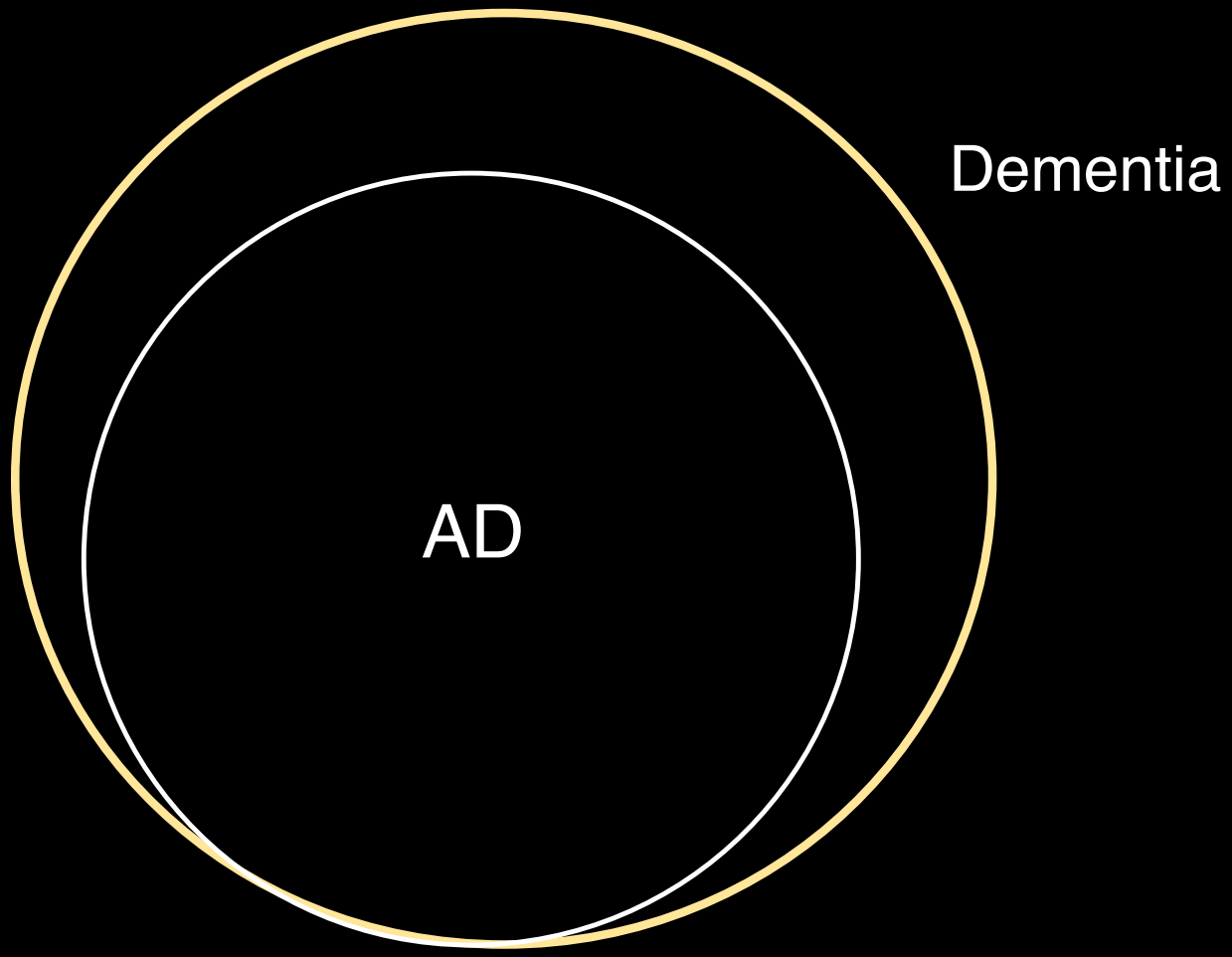


The number of people with dementia is increasing globally

Age-related dementia cases will double in 20 years, costs will triple.

Now more costly than heart disease and cancer combined.

Emerging as the leading cause of death in many Western countries

Alzheimer's disease (AD)

Two types:

1) In **familial Alzheimer's disease (FAD)**, genes directly cause the disease. These cases are relatively rare.
2) In **sporadic Alzheimer's disease (SAD)**, genes influence the risk of developing the disease. It is less predictable, with many risk factors, and typically in fewer family members. This is far and away the more common form of the disease (~95%)

- Both involve the same amyloid-β plaques and tau tangles with neurodegeneration

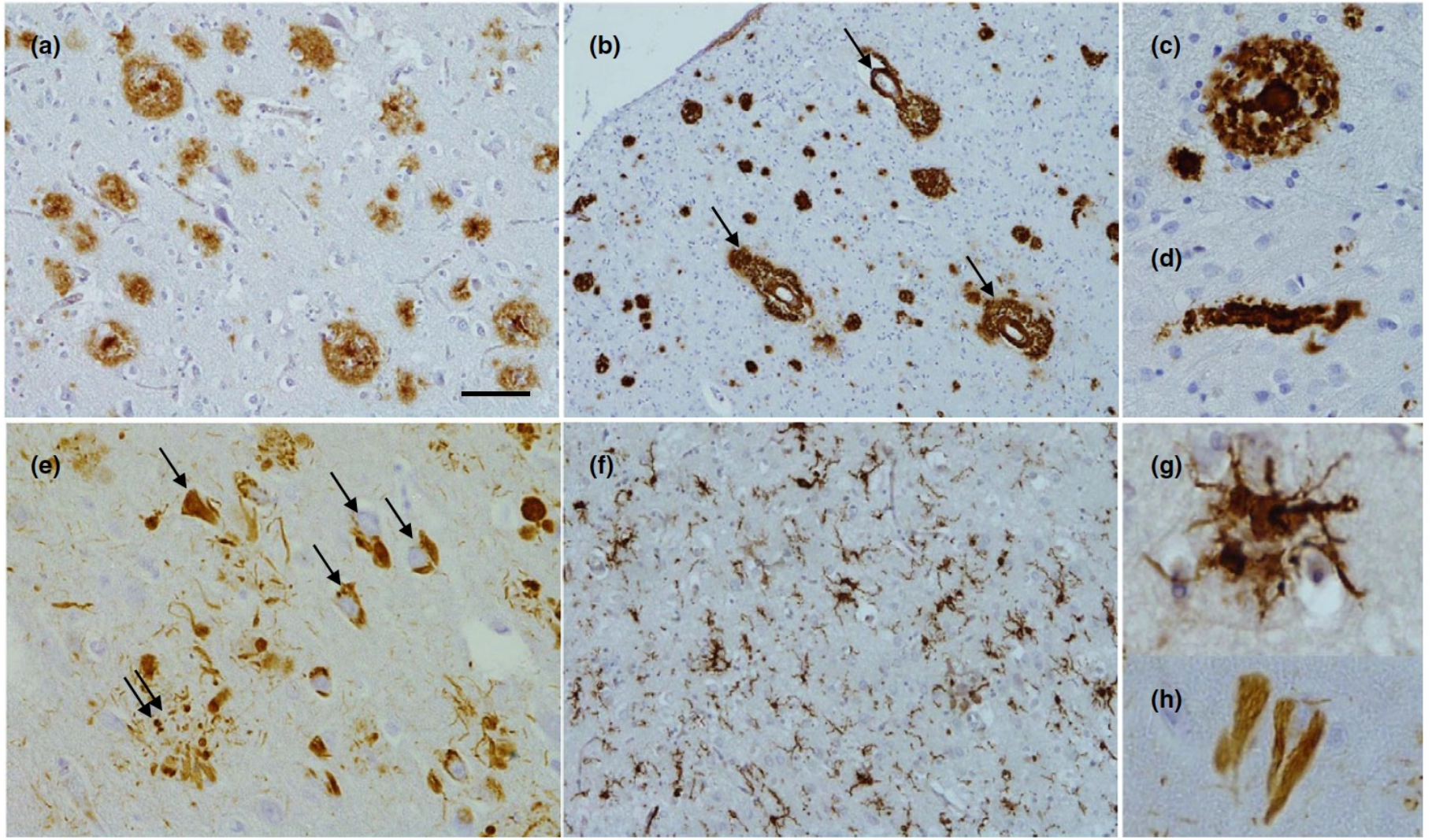
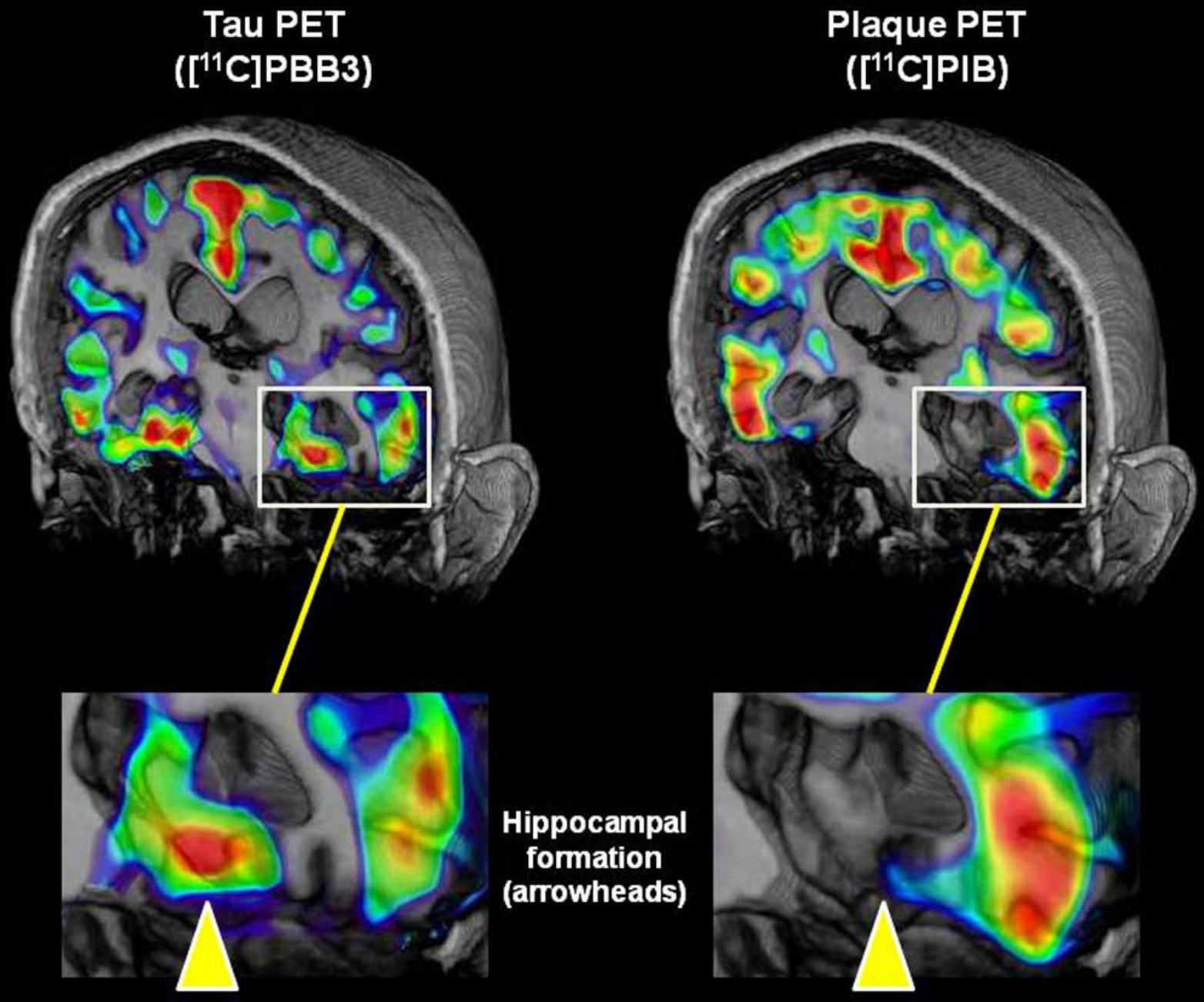


Figure 2 Pathology of Alzheimer's disease. Aβ immunohistochemistry highlights the plaques in the frontal cortex (a) and cerebral amyloid angiopathy (CAA) where Aβ accumulates within blood vessel (b, arrows). An Aβ cored plaque is shown at higher magnification in (c) showing a central core. In severe CAA Aβ accumulates within capillaries (d). Tau immunohistochemistry demonstrates both neurofibrillary tangles (e, arrows; h at higher magnification) and neuritic plaques (e, double arrow). Neuroinflammation is a prominent feature in Alzheimer's disease and this is evident by the number of reactive microglia (f; g at higher magnification). The bar represents 50 μm in a and f; 100 μm in b; 25 μm in c and e; 15 μm in d, g and h. Figure courtesy of Dr Tammaryn Lashley, Queen Square Brain Bank.

Tau lesions and senile plaques in Alzheimer's disease



Alzheimer's disease (AD)

Familial Alzheimer's disease (FAD)

Three known gene mutations of 3 genes: Presenilins, and amyloid precursor protein gene. If you inherit one of the mutation, you will have AD by about age 50.

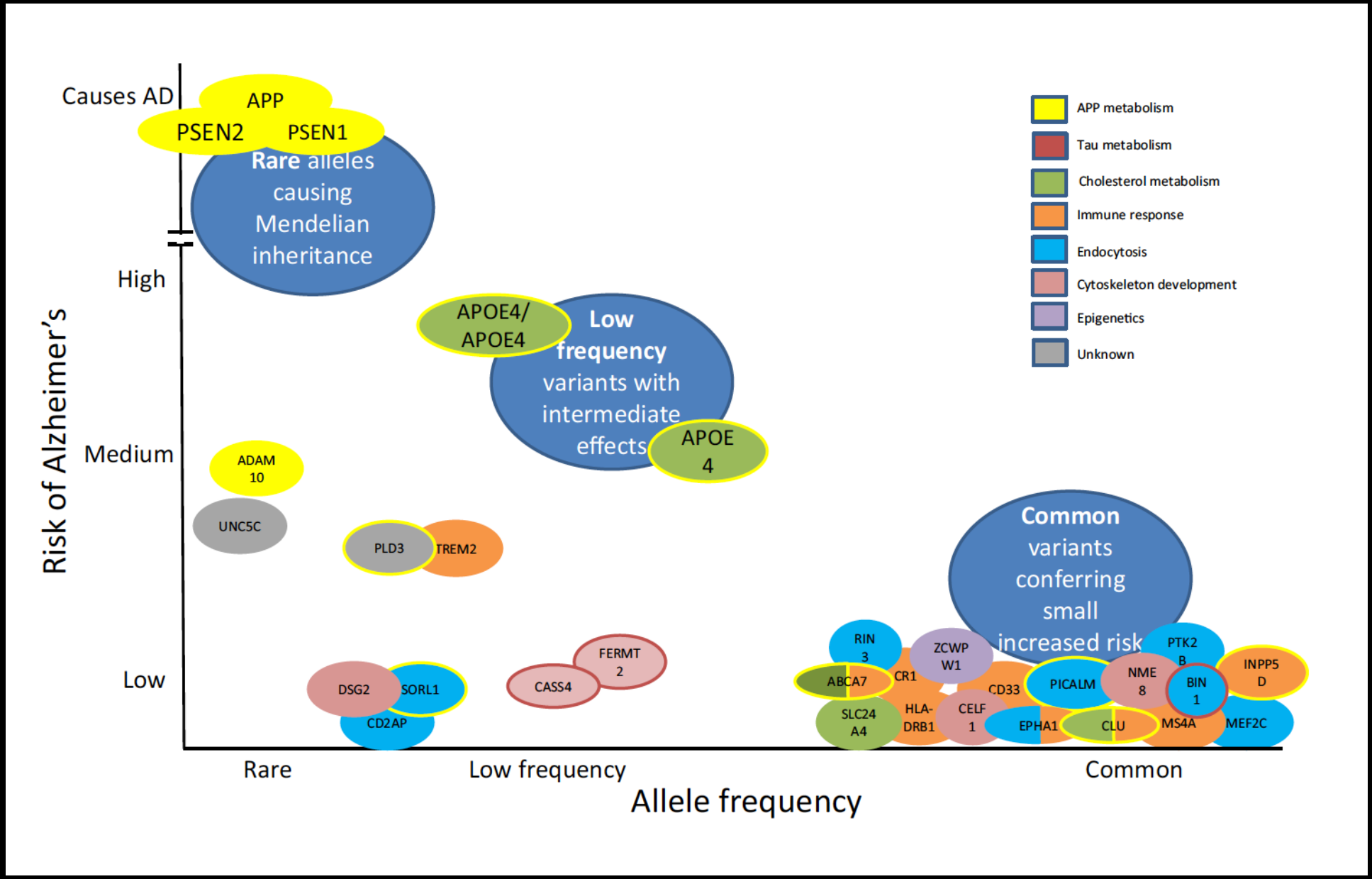
Polygenic risk in SAD

Variation in about 30 genes accounts for most of the risk in SAD. Higher the load, higher the risk.

Three clusters:
In addition to Aβ and Tau variants

1. Innate immune system processes
2. Clearing out debris, damaged membranes
3. Inflammation

Variation in about 30 genes predicts AD risk

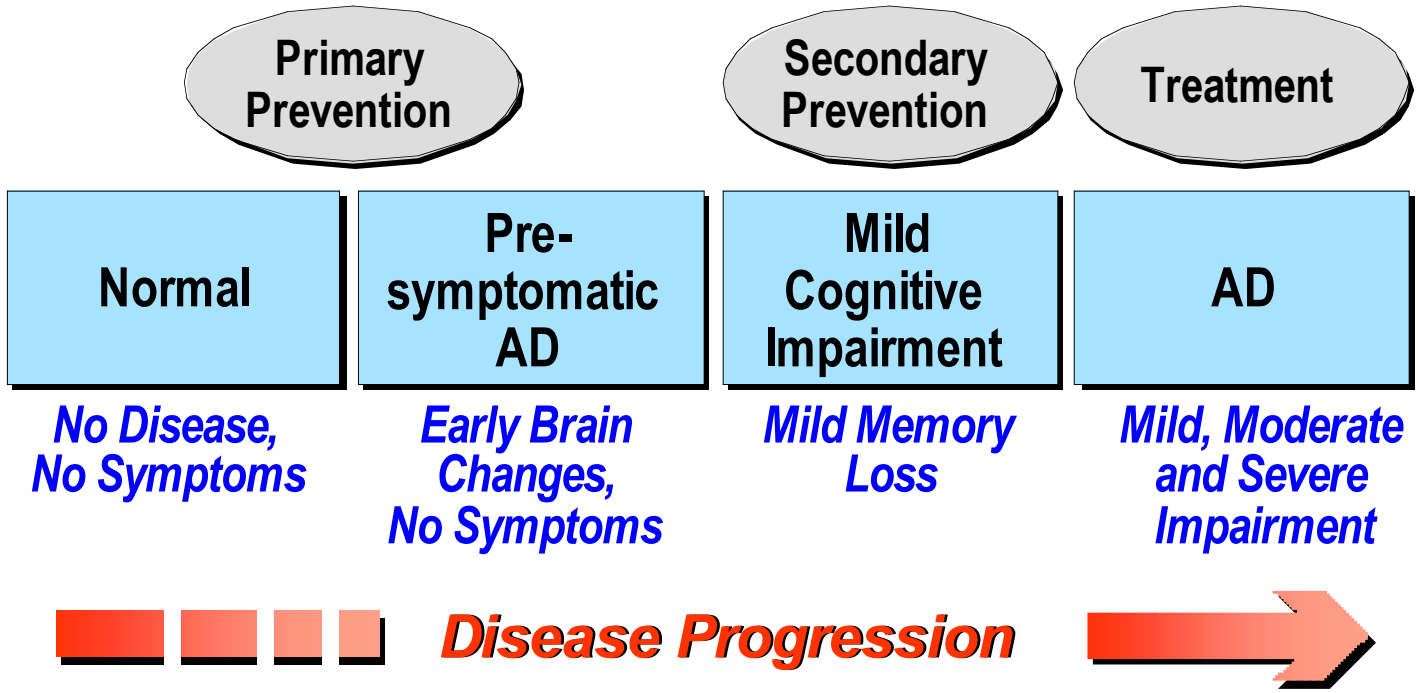


Modifiable risk in SAD

Despite polygenic risk factors, modifiable risks are significant.

Based on current knowledge we can prevent more than one in three AD cases.

Alzheimer's Disease Prevention Initiative



Likely sequence in SAD

Events trigger accumulation of Amyloid-β (pre-symptomatic)

Aβ causes inflammation, membrane breakdown, tau tangles

Aβ, tau and neuron loss gradually interfere with functioning neuron networks in a progressive manner

Amyloid "trigger"

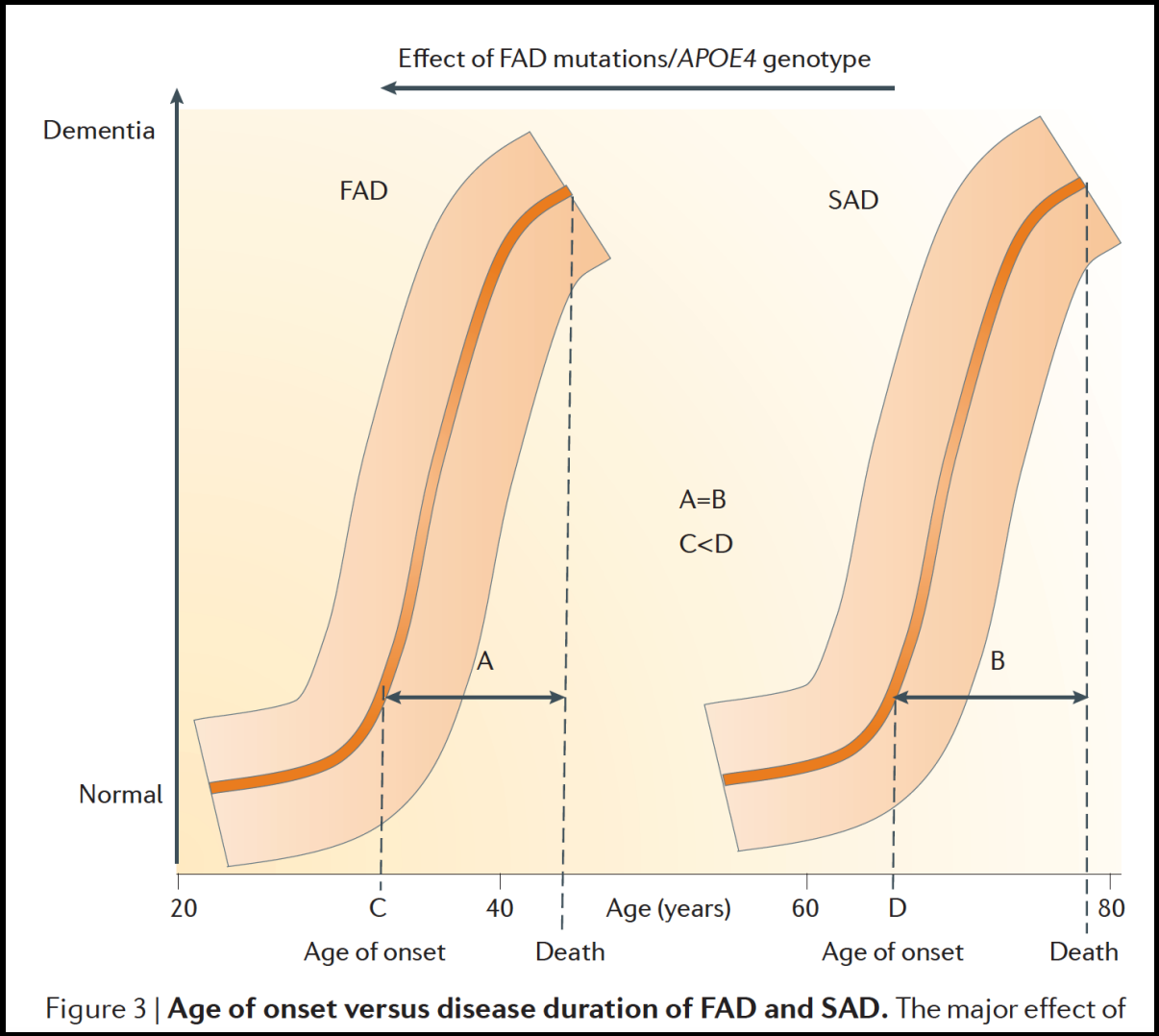


Figure 3 | **Age of onset versus disease duration of FAD and SAD.** The major effect of

Tau tangling is the "bullet"?

What triggers Aβ in SAD?

Hypoxia/ischemia

Brain injury

Pathogens (viruses, bacteria, fungus)

Sporadic AD

Most important risk factor is age

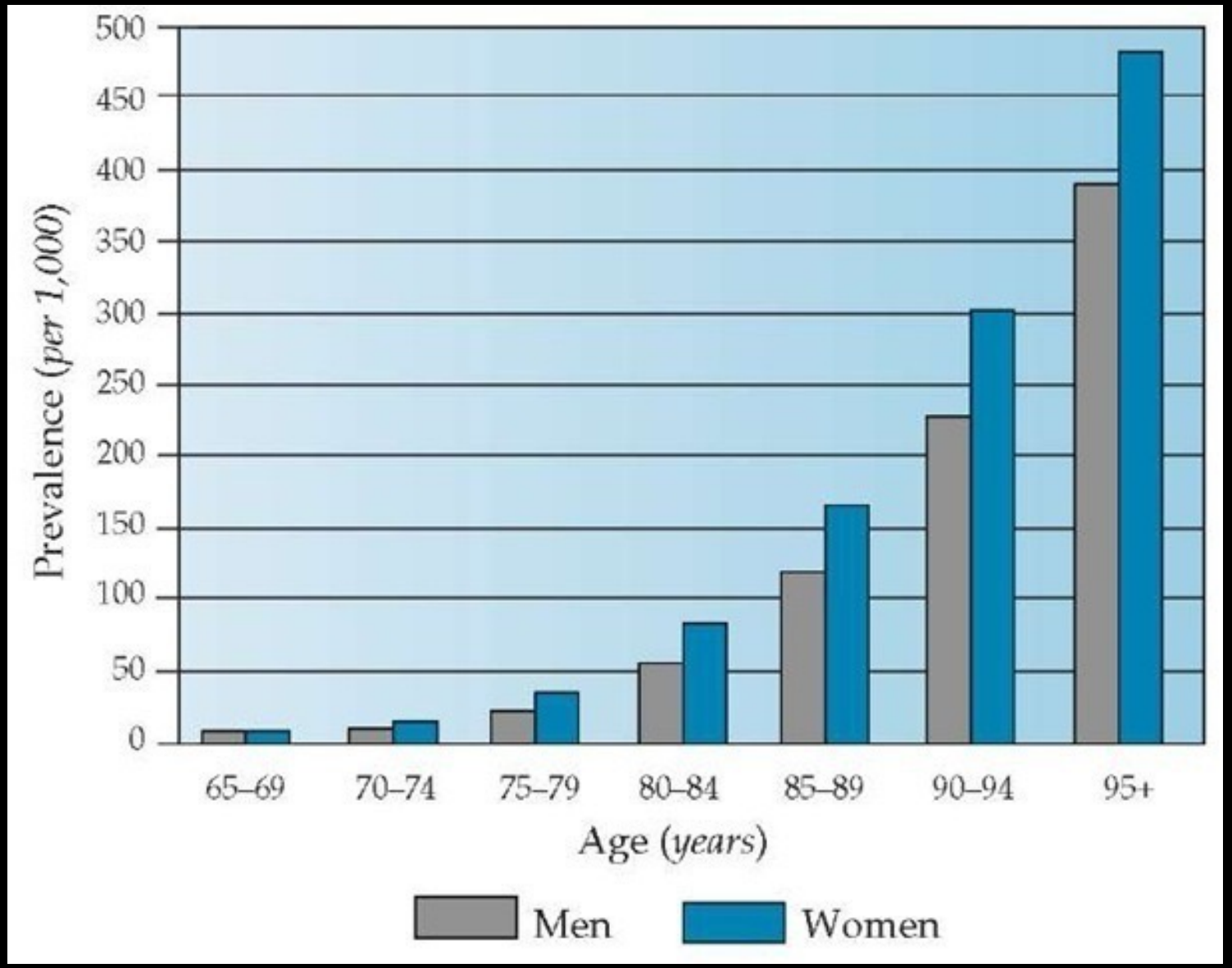
Major Risk Factors

Hearing problems
Hypertension
Smoking
Diabetes
Lack of activity

Other Risk Factors

Head injury
Heavy drinking
Migraine
Pathogens

Age is the biggest risk in SAD



Be ambitious about prevention

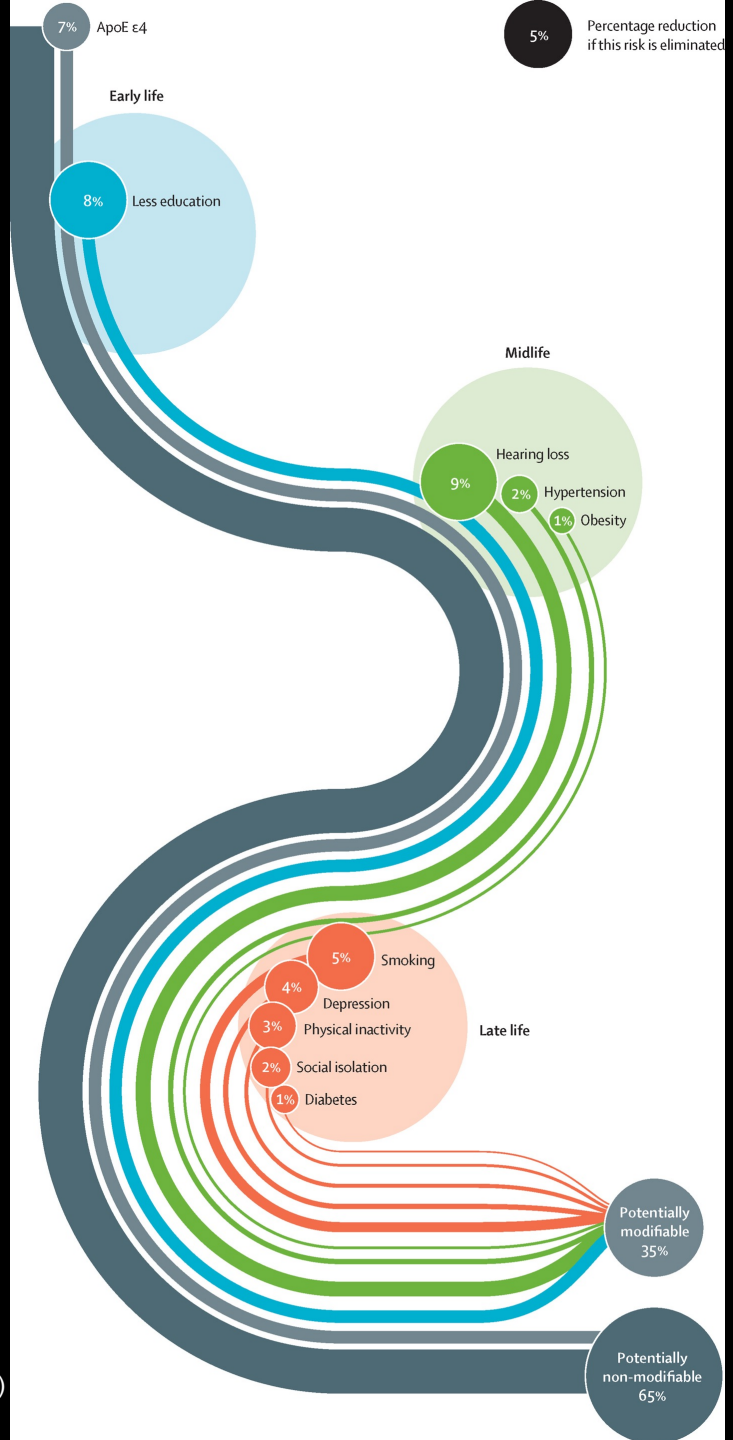
In Western countries rate of dementia is declining.

Factors

*College ↑ Less than high school ↓

* BP & smoking ↓

- Lipid and BP drugs ↑
- Obesity, HDL, Type 2 diabetes ↑
- CV disease – little change



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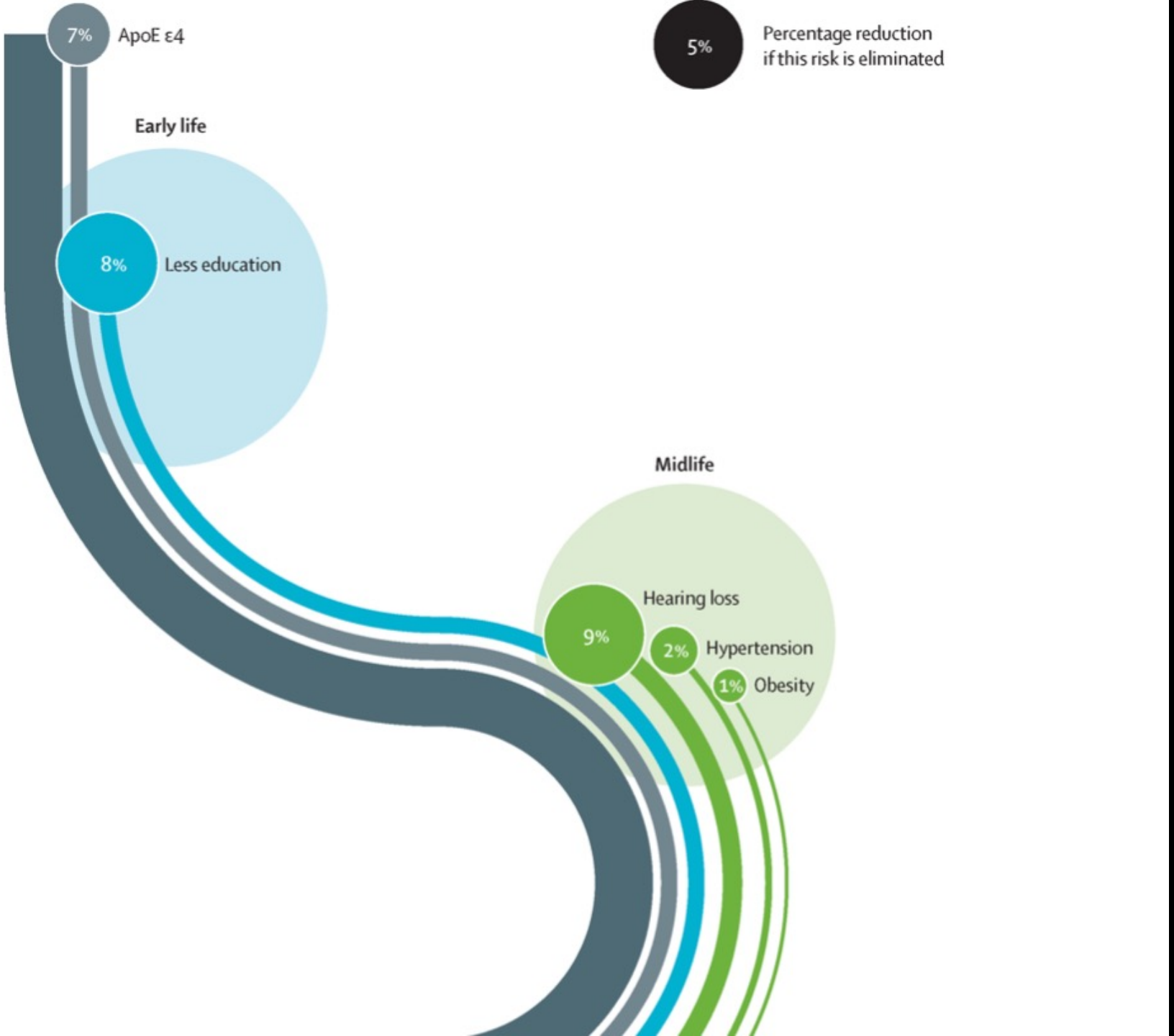
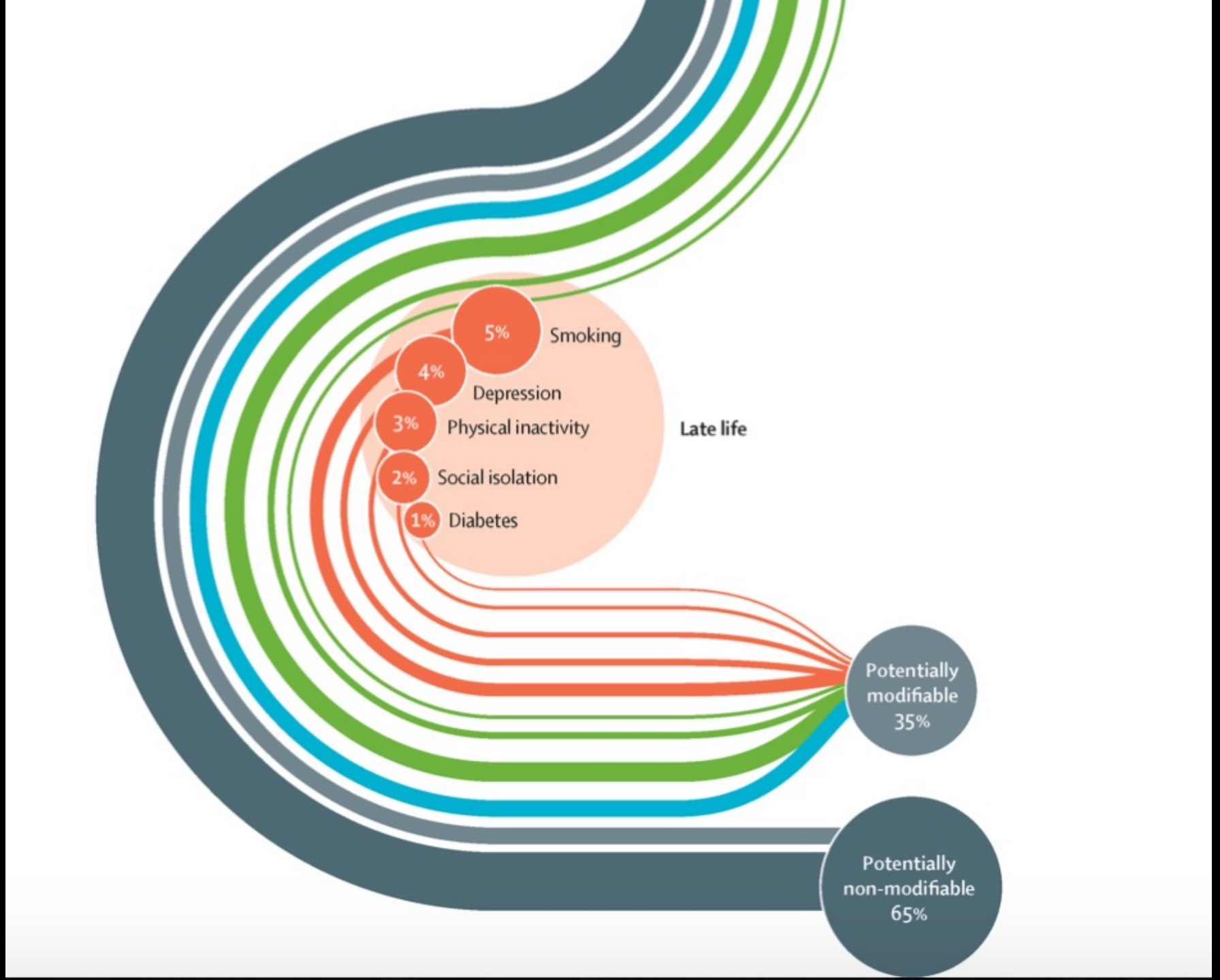

7% ApoE ε4
5% Percentage reduction if this risk is eliminated
Early life
8% Less education
Midlife
9% Hearing loss
2% Hypertension
1% Obesity


5%
Smoking
4%
Depression
3%
Physical inactivity
2%
Social isolation
1%
Diabetes
Late life
Potentially modifiable 35%
Potentially non-modifiable 65%

Primary prevention in AD

Early in life

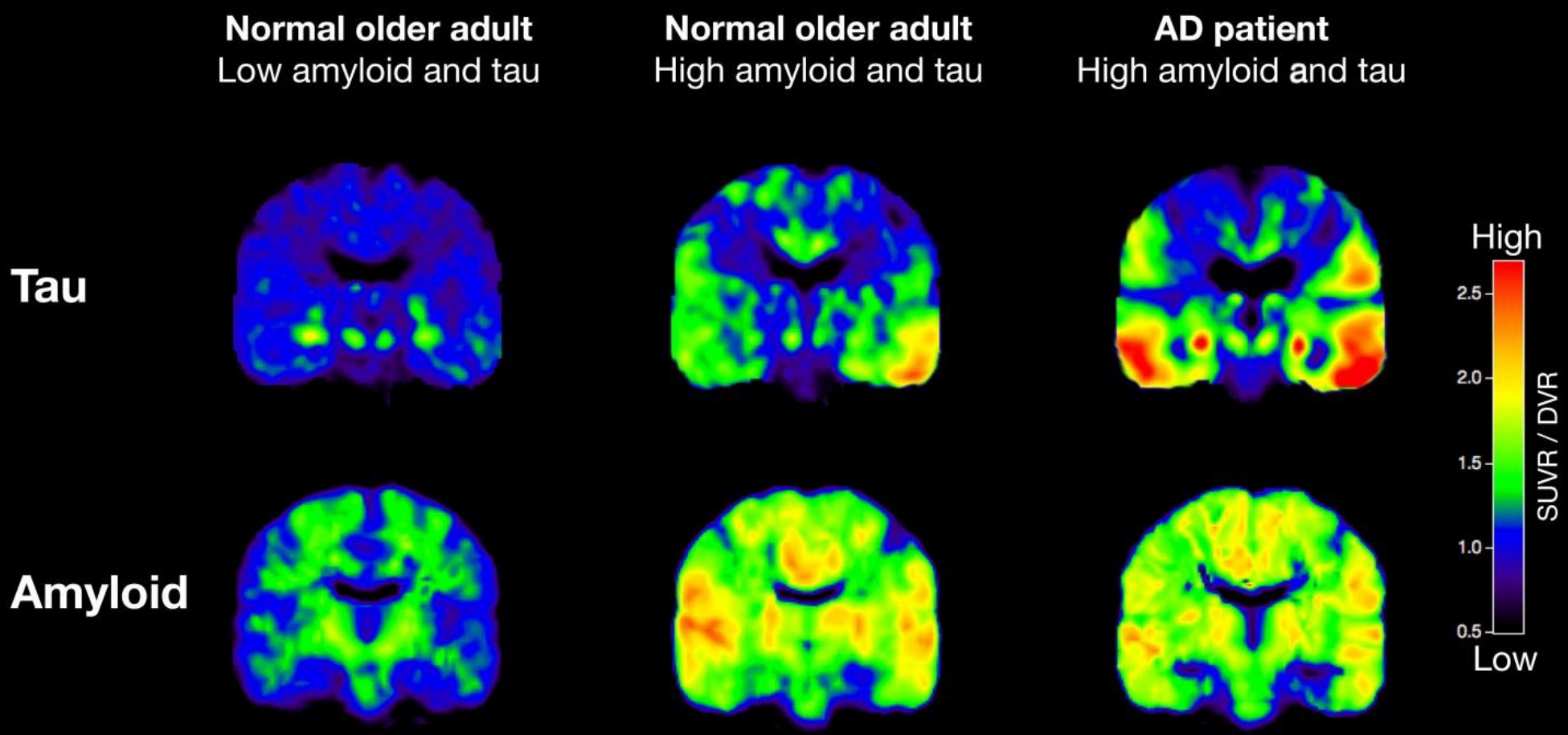
Create cognitive/brain reserve (resilience)

- education, bilingualism
- Physical activity

Prevent brain injury/concussion

Vaccinations

Cognitive reserve is protective



Primary prevention in AD

Midlife

Correct hearing loss
Treat hypertension (sartans*)
Mediterranean diet
Sleep hygiene

Prevent brain injury/concussion
(Avoid high alcohol intake, Anti-inflammatory drugs, Cognitive activity)

Diet and AD

The MIND diet focuses on plant-based foods linked to dementia prevention. It encourages eating from 10 healthy food groups:

- Leafy green vegetables, at least 6 servings/week
- Other vegetables, at least 1 serving/day
- Berries, at least 2 servings/week
- Whole grains, at least 3 servings/day
- Fish, 1 serving/week
- Poultry, 2 servings/week
- Beans, 3 servings/week
- Nuts, 5 servings/week
- Wine, 1 glass/day*
- Olive oil

The MIND diet limits servings of red meat, sweets, cheese, butter/margarine and fast/fried food.

Early diagnosis of AD?

Potential for secondary prevention delaying conversion from MCI through to moderate AD

Improve possibility of aging in place

Lengthening reasonable quality of life

Primary and secondary prevention in AD

Late life

Eliminate smoking
Exercise
Socialize
Control diabetes
Treat depression
Donepezil
Memantine
Sleep
Sartans

Prevent brain injury/concussion

Slowing AD

Mild AD

Acetylcholinesterase inhibitors
(donepezil, galantamine, rivastigmine)
Aβ antibodies* (aducanumab and lecanemab)

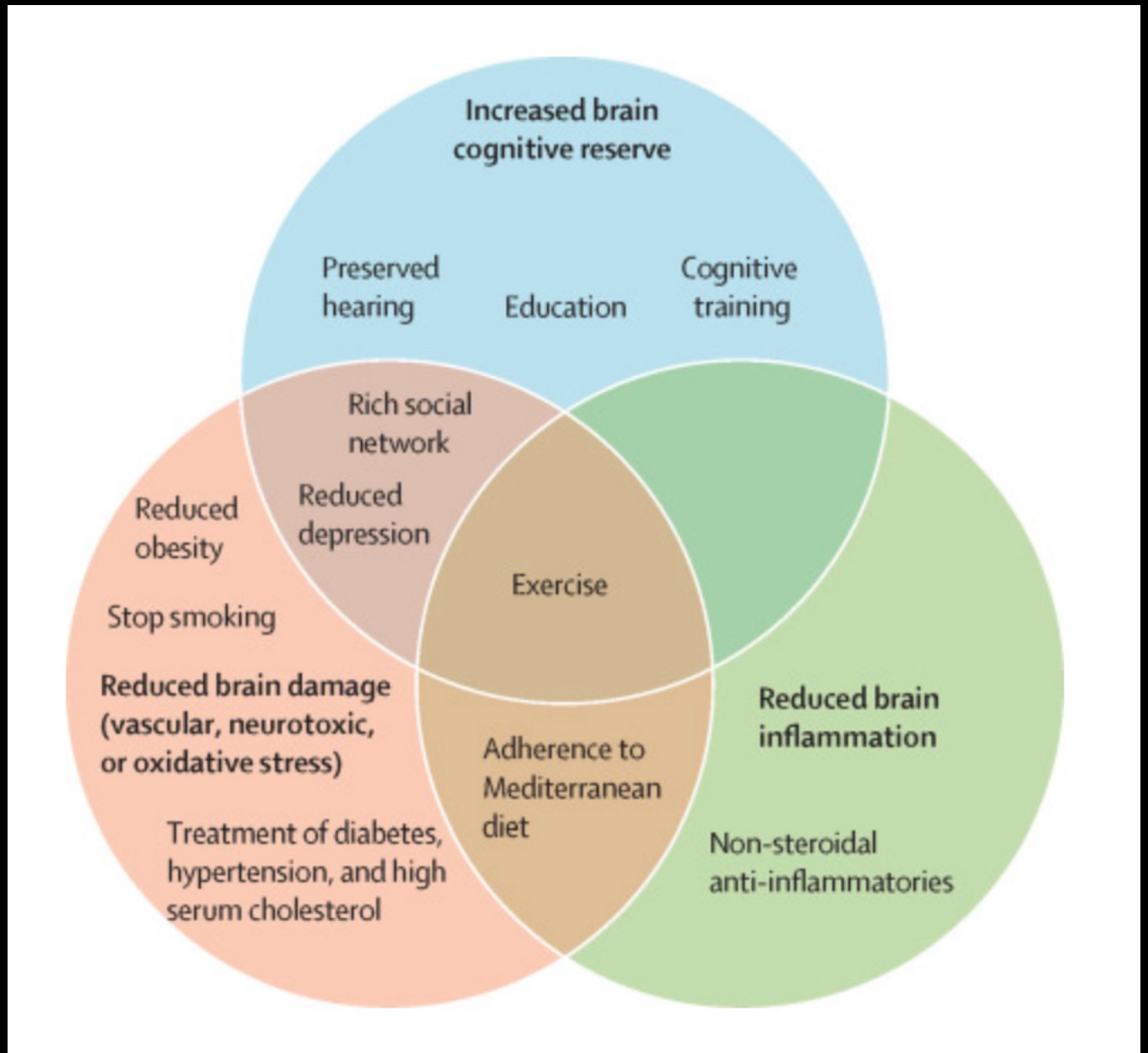
Moderate-Severe AD

Acetylcholinesterase inhibitors
+ Memantine

Experimental

Sartans, accelerate Aβ clearance
BIIB080 tau gene silencing

Reducing risk of SAD



Acknowledgements

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Thank you

Questions?