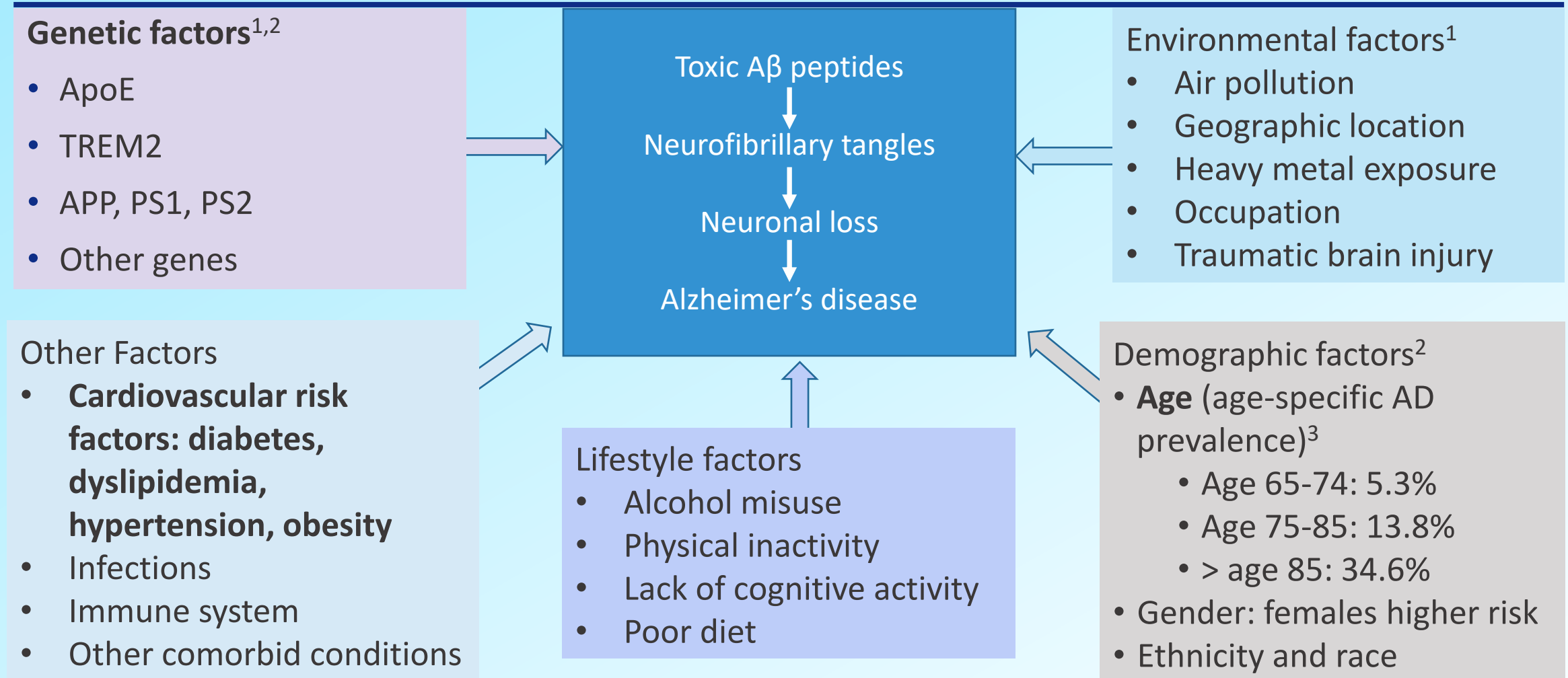


Alzheimer's Disease Risk Is Multifactorial



ApoE, apolipoprotein E; TREM2, triggering receptor expressed on myeloid cells 2; APP, amyloid precursor protein; PS1, presenilin 1; PS2, presenilin 2.

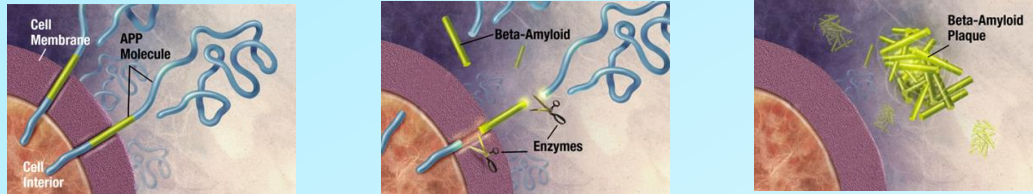
1. Armstrong R. *Folia Neuropathol.* 2019;57:87-105; 2. Kamboh MI. *Neurotherapeutics.* 2022;19:152-172;

3. 2021 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2021;17:327-406.

Alzheimer's Disease Has a High Heritability Caused by a Combination of Genes

Disease-causing gene

- A single mutation causes the disease
- Deterministic genes, autosomal dominant
- APP, PS1, and PS2 cause early-onset Alzheimer's disease (EOAD, disease before age 60 to 65)



Images: National Institute on Aging, public domain

Mutations in APP or gamma-secretase complex (PS1 or PS2) increase amyloid production

- 1st-degree relatives have a 50% risk
- Predictive testing offered to relatives of affected people

Disease-association gene

- Three common variants/alleles of the ApoE gene:
 - **ApoE2**: reduces risk
 - **ApoE3**: most common, used for comparison
 - **ApoE4**: increases risk
- More than 80 AD-associated genes have been identified in non-Hispanic White populations^{1,2}
- Late-onset Alzheimer's disease heritability is high and is estimated to be between 58%-79%, depending on the age of onset³
- Susceptibility testing

APP, amyloid precursor protein; EOAD, early-onset Alzheimer's disease; PS1, presenilin 1; PS2, presenilin 2.

1. Reitz C et al. *Nat Rev Neurol*. 2023;19:261-277; 2. Bellenguez C et al. *Nat Genet*. 2022;54:412-436; 3. Gatz M et al. *Arch Gen Psychiatry*. 2006;63:168-174.

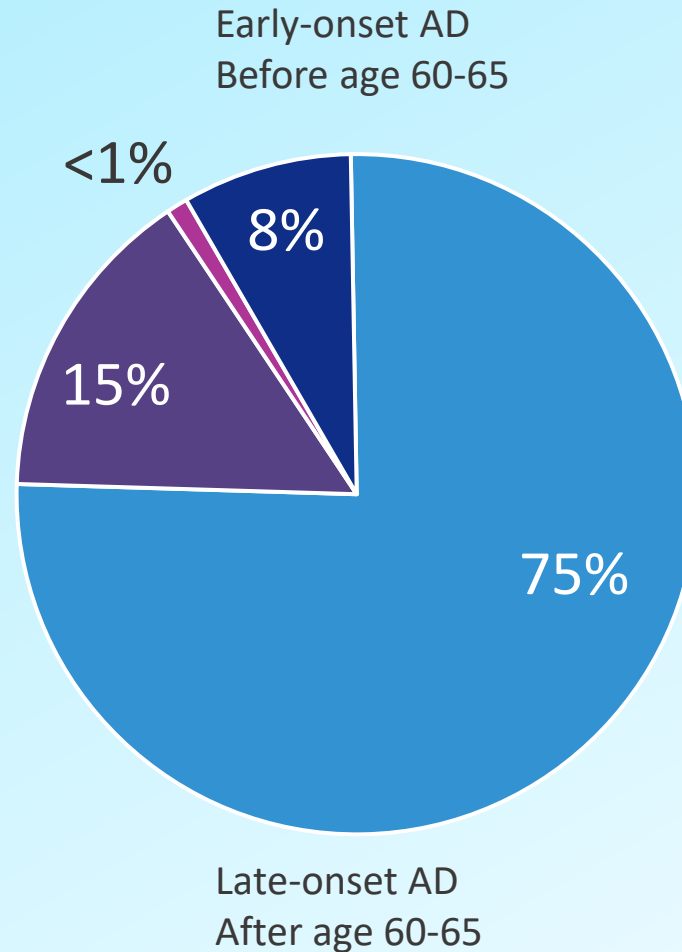
Genetic Variants Contribute to Both Early-Onset and Late-Onset Alzheimer's Disease

Early-onset familial AD (<1%)

- Autosomal dominant
- Deterministic genes
- APP, PS1, or PS2

Late-onset familial AD (15%)

- 2 or more cases in a family
- Multiple susceptibility genes



Early-onset AD (8%)

- Familial (recessive genes) or sporadic

Sporadic late-onset AD (75%)

- Multiple susceptibility genes

APP, amyloid precursor protein; PS1, presenilin 1; PS2, presenilin 2.

Bird TD. Alzheimer disease overview. 1998 Oct 23 [Updated 2018 Dec 20]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1161/>