The interplay of multi-ancestry polygenic risk scores with vascular and menopause-related factors in Alzheimer's disease and cognitive decline

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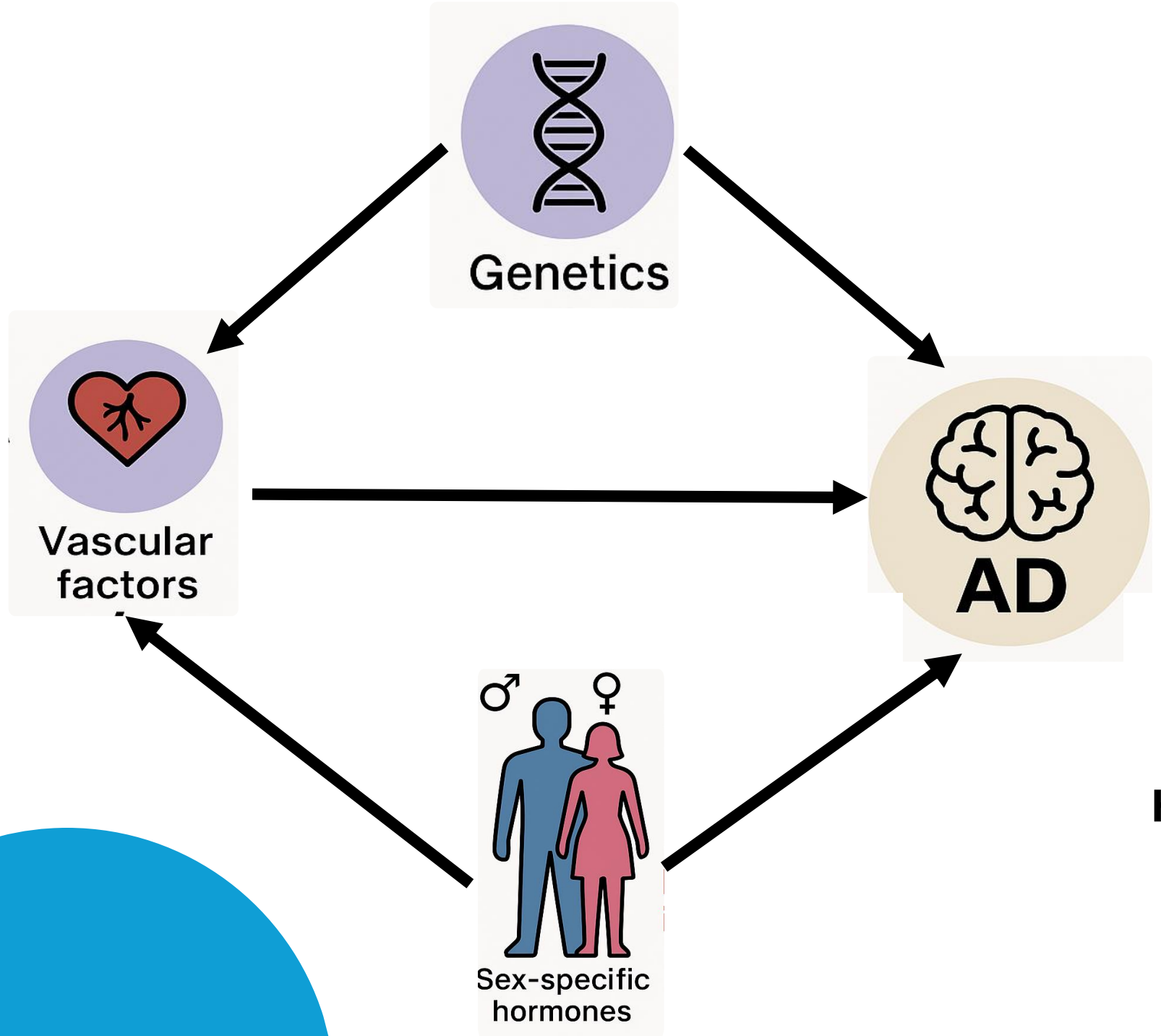
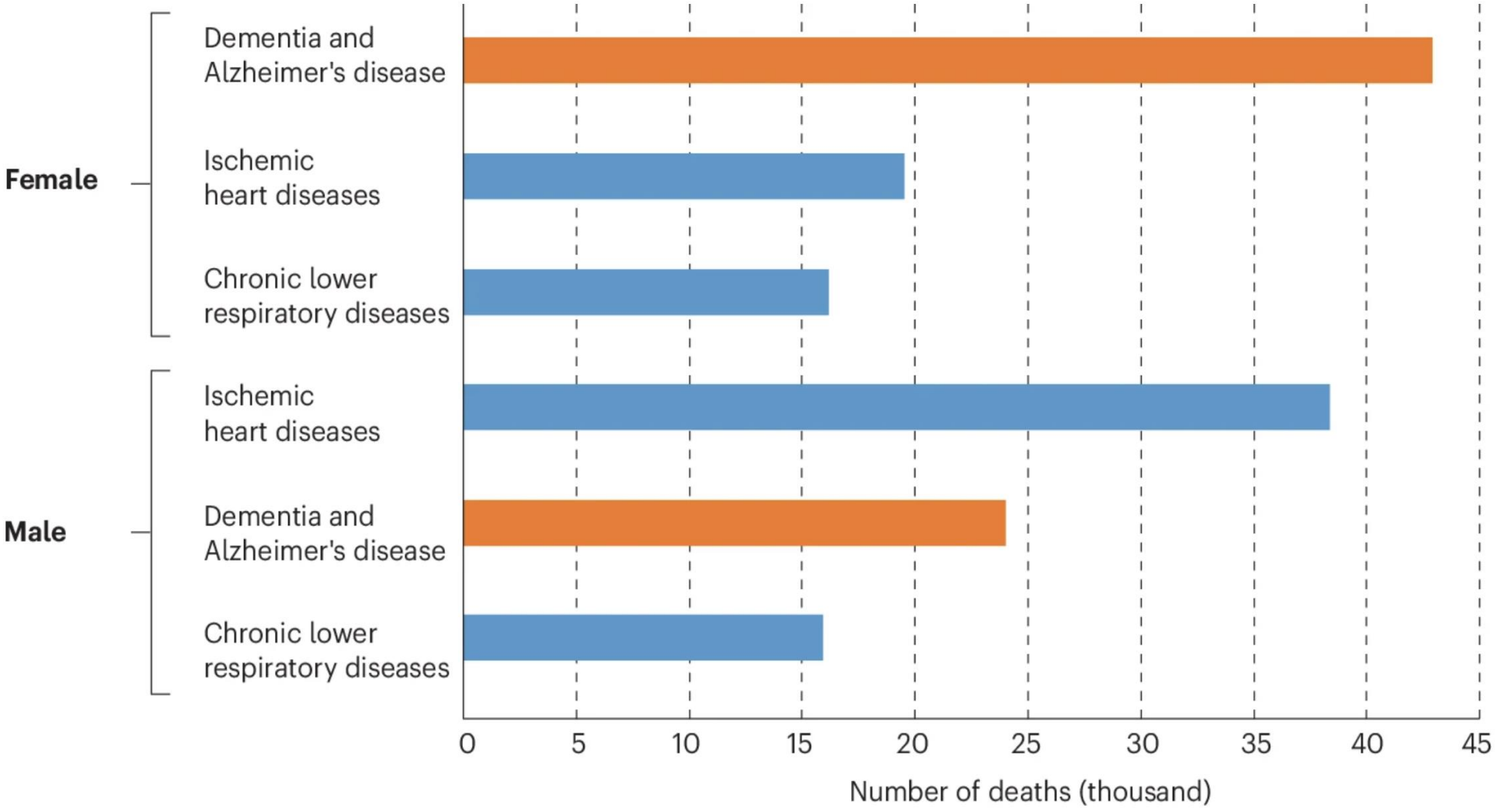
Background



Higher risk in women!

Background



Moutinho, S. Women twice as likely to develop Alzheimer's disease as men — but scientists do not know why. *Nat Med* **31**, 704–707 (2025)

Dementia and Alzheimer's disease have collectively been the number one cause of death for women in the UK since 2011. Data shown are for England and Wales in 2023. Source: Office for National Statistics, UK.

Hypothesis

“***We hypothesize that genetic predisposition, hormonal changes, vascular health, and environmental exposures interact to drive ancestry- and sex-specific differences in Alzheimer's disease risk and progression.***”

Specific aims

1

Develop novel **sex-specific, multi-ancestry PRS** for Alzheimer's disease.

2

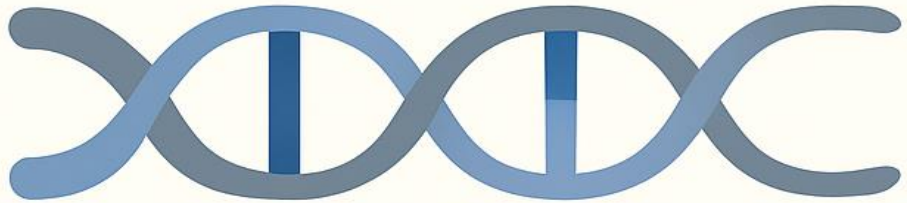
Assess **menopause-related factors** (age at menopause, HRT, contraception) in AD risk.

3

Determine the extent to which AD shares **environmental exposures, genetic architecture, and causal pathways** with vascular health, and assess the long-term impact of vascular risk factors on AD risk.

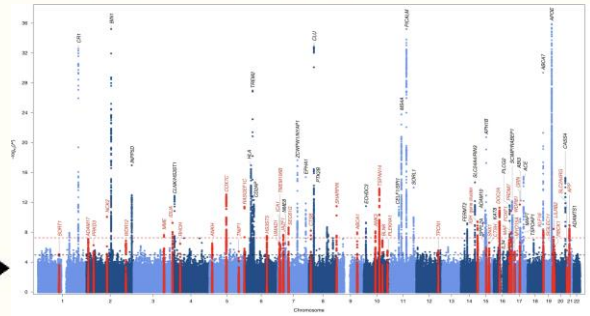
Polygenic risk score (PRS)

A PRS is a single-value estimate of an individual's genetic liability to a trait or disease.



sum their genome-wide genotypes

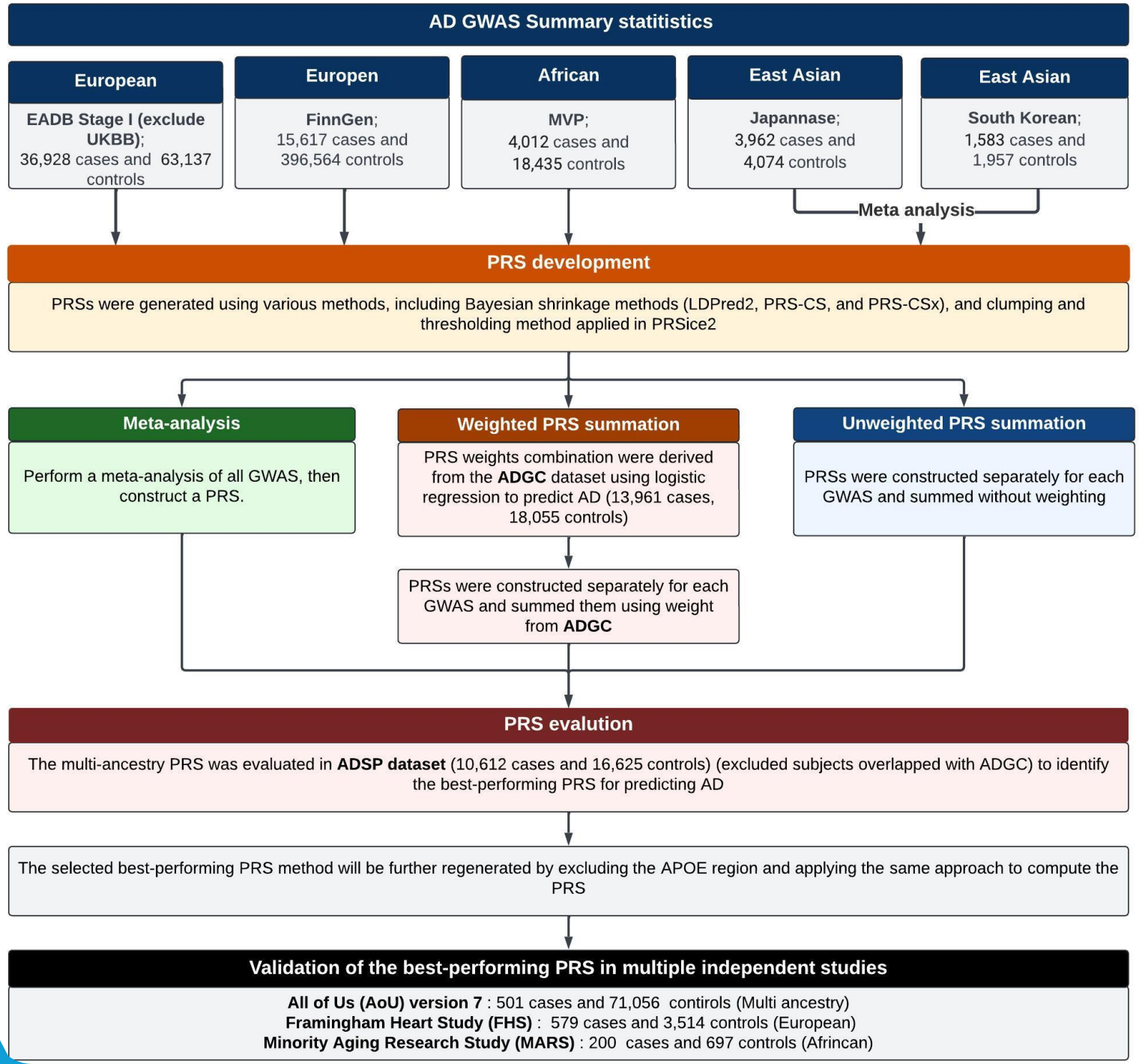
weighted by effect sizes from GWAS summary statistics



PRS

PRS method comparison

Method	Key Features	Multi-ancestry strategy	Strengths	Limitations
Clumping + Thresholding (PRSice2)	Selects SNPs by p-value and LD-based clumping	• Meta-analysis GWAS, then construct PRS • Unweighted PRS summation • Weighted PRS summation	Simple and fast; Widely used; Low computational burden	Arbitrary threshold selection; Ignores ancestry-specific LD structure; Can lose genetic information
LDpred2	Adjusts SNP effects using LD structure (Bayesian method; uses individual-level or reference LD matrices)	• Meta-analysis GWAS, then construct PRS • Unweighted PRS summation • Weighted PRS summation	Considers LD structure; Good prediction accuracy within ancestry groups; Flexible tuning parameters	Requires precise LD estimation; Reference LD panels needed; Moderate computational complexity
PRS-CS	Bayesian approach applying continuous shrinkage priors	• Unweighted PRS summation • Weighted PRS summation	Robust PRS estimation; Accounts for LD structure effectively; Performs well in single ancestry datasets	Less optimal in admixed or diverse ancestry samples compared to
PRS-CSx	Extended PRS-CS by Integrates GWAS summary stats from multiple ancestries	• Unweighted PRS summation • Weighted PRS summation • Meta PRS (meta-analysis the PRS score)	Optimal for multi-ancestry datasets; Better predictive performance across diverse groups; Addresses cross-population LD differences	Needs high-quality GWAS from multiple ancestries; Computationally demanding

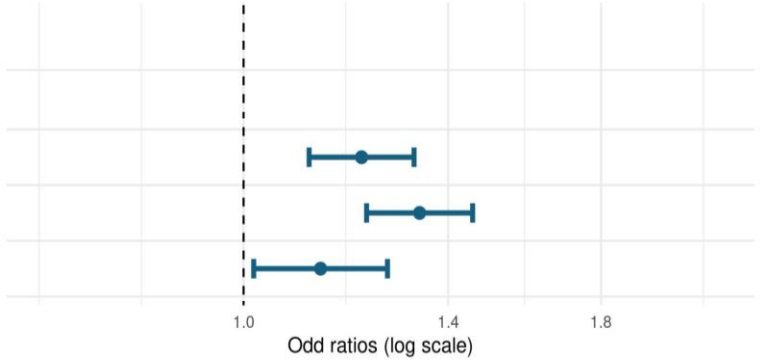


The overview **Current PRS development**

Comparison of the multi-ancestry approach PRS with European - based PRS in ADSP

Multi-ancestry PRS-CS (Weighted PRS summation): Current works

	case	control	OR [95% CI]	P	AUC
ADSP					
African	1883	3373	1.21 [1.11;1.32]	1.04e-05	0.70
Caribbean Hispanic	1696	2302	1.34 [1.22;1.46]	7.69e-11	0.69
Native American Hispanic	705	3282	1.14 [1.02;1.27]	2.40e-02	0.69

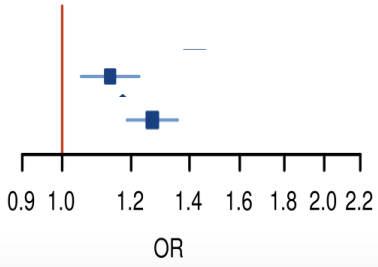


$$PRS = wPRS_{EADB} + wPRS_{FinnGen} + wPRS_{MVP} + wPRS_{EAS}$$

Vs.

European - based PRS

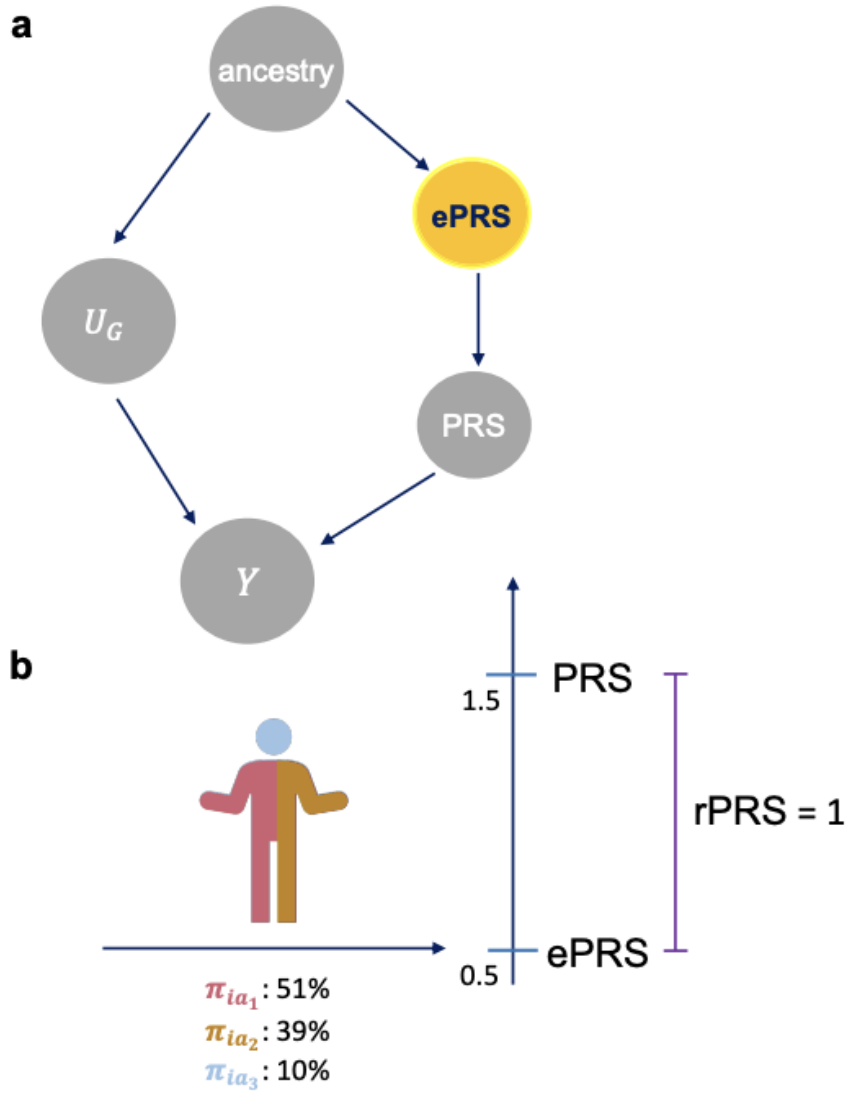
Country	Ncases	Ncontrols	OR	95% CI	P-value	HetIsq	HetPVal
African American ADSP	1,108	2,325	1.14	[1.05-1.23]	1.23e-03		
US LA Ancestry ADSP	1,629	2,456	1.27	[1.19-1.36]	3.31e-12		



$$PRS_{EA} = \sum_{i=1}^{n} (\beta_i * genotype_{i,\,sample})$$

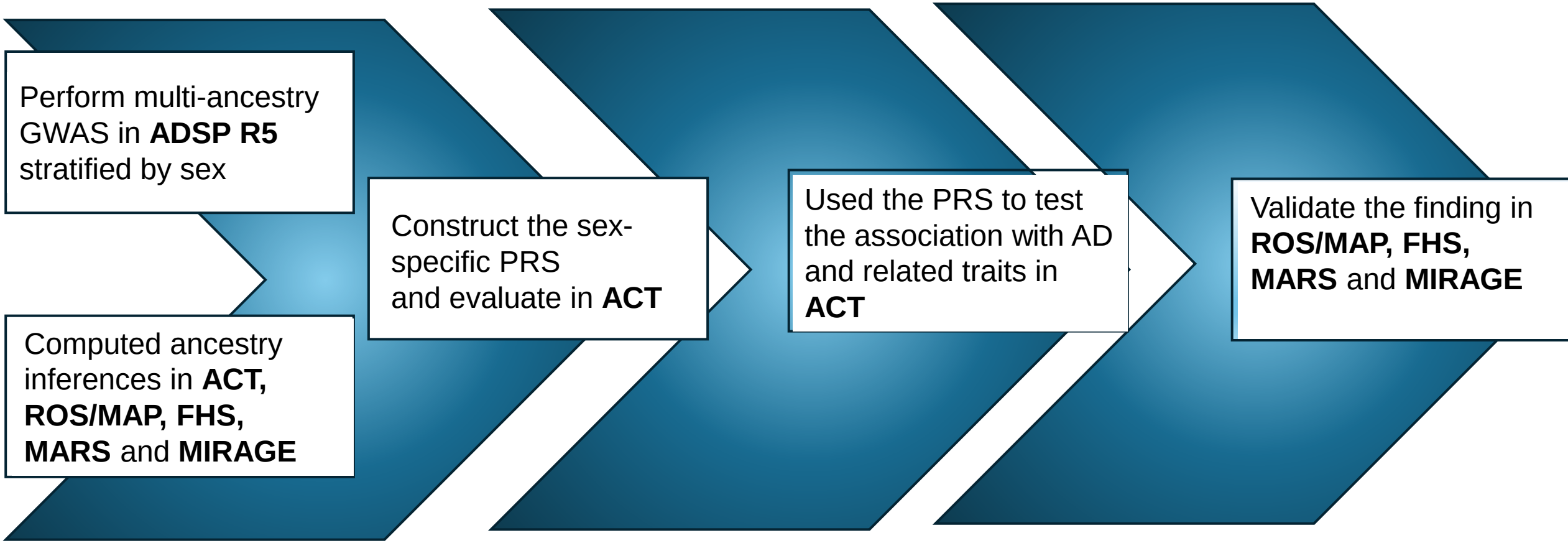
Nicolas. A & Lambert, JC. *Transferability of European-derived Alzheimer's Disease Polygenic Risk Scores across Multi-Ancestry Populations*. medRxiv (2024)

Aim 1: Developing a multi ancestry PRS



Huang, J.H, **Kurniansyah. N**, et al. The expected polygenic risk score (ePRS) framework: an equitable metric for quantifying polygenetic risk via modeling of ancestral makeup. medRxiv (2024)

Aim 1: PRS overview:

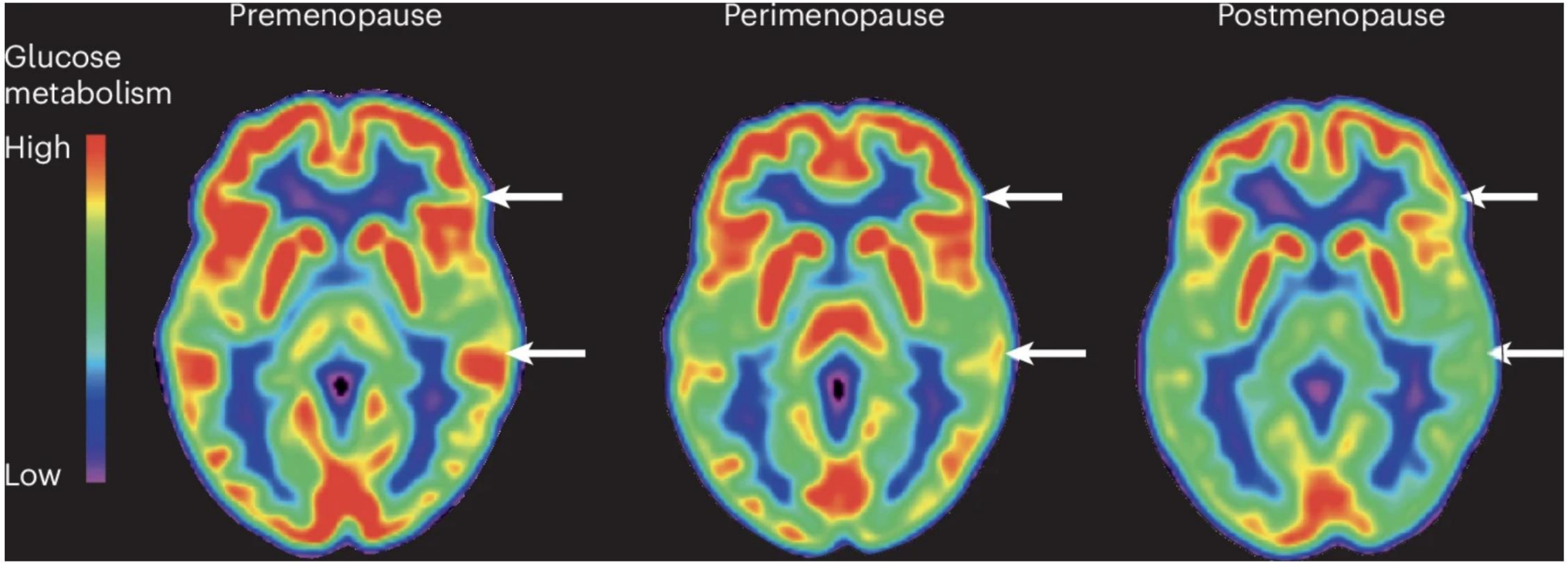


Aim 2: Role of menopause-related factors

Earlier age at menopause, whether natural or surgical, is associated with increased risk of Alzheimer's disease and cognitive decline.

Growing evidence suggests that hormone replacement therapy (HRT) may help mitigate this risk, particularly when initiated near the time of menopause.

Alzheimer’s begins in midlife—brain changes appear decades before symptoms

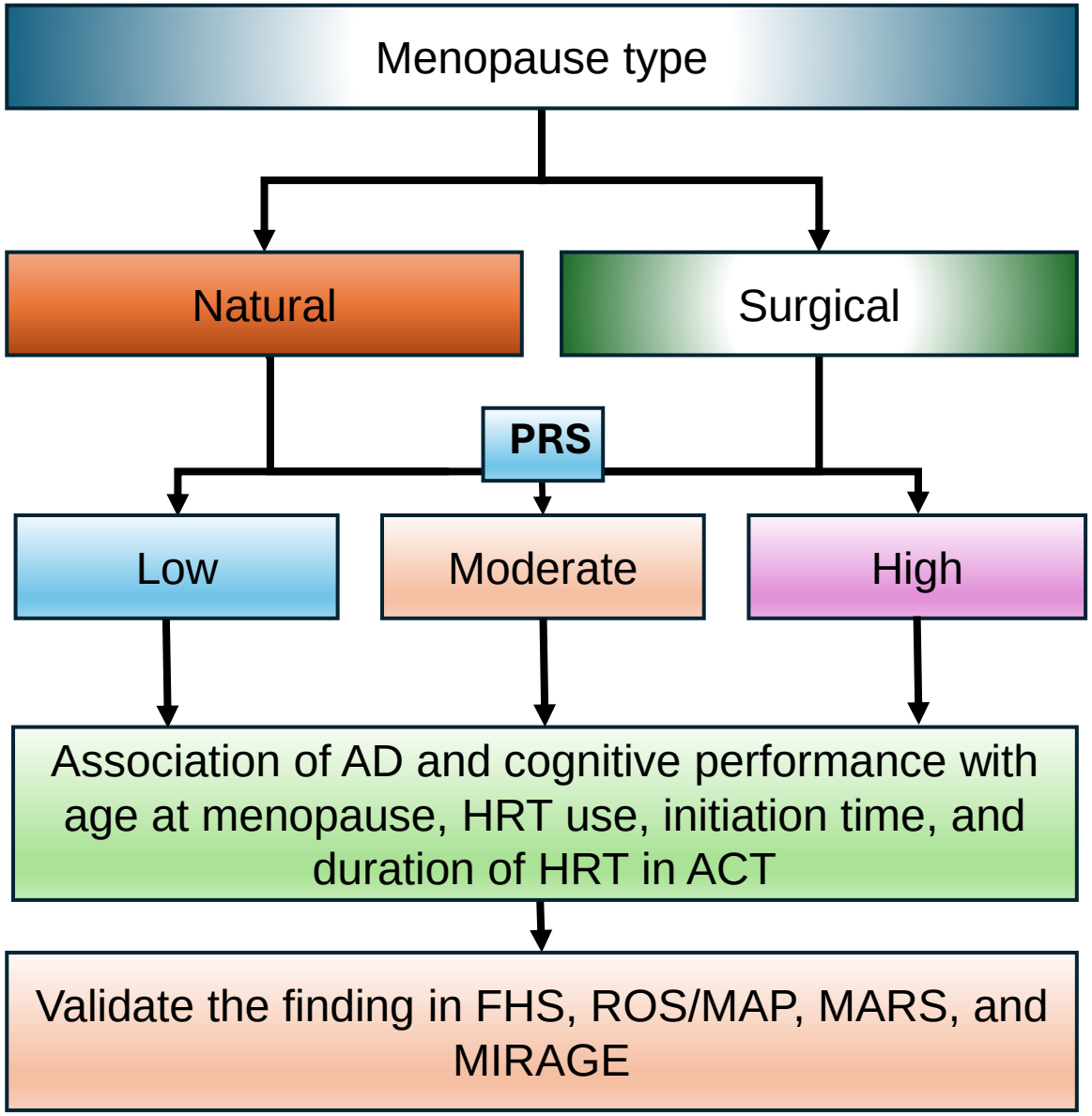


Lisa Mosconi/Weill Cornell Medicine.

Images of the brains of three 50-year-old women, each at different stages of menopause, show higher energy levels in the premenopausal brain than in the perimenopausal or postmenopausal brain.

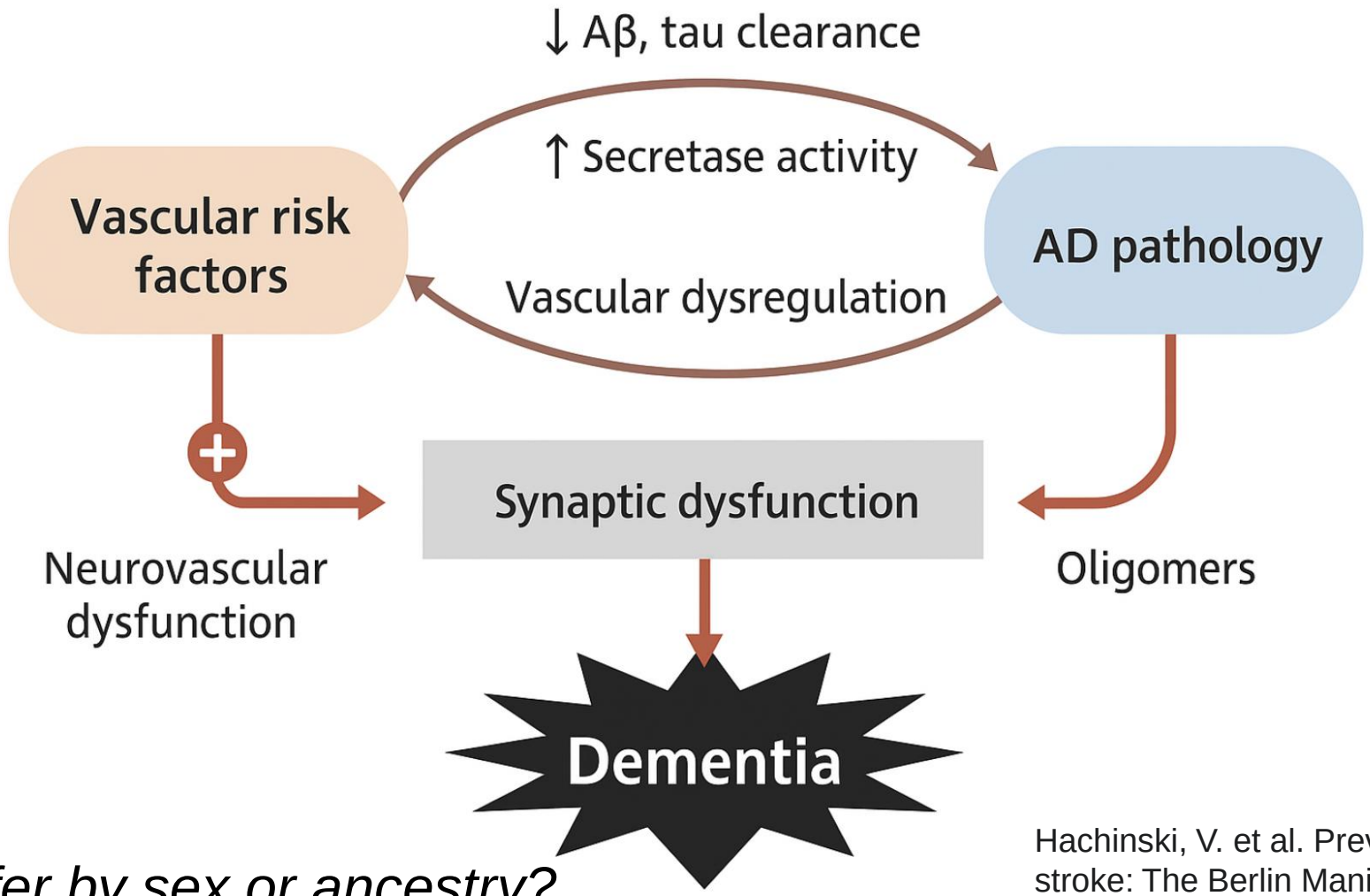
Moutinho, S. Women twice as likely to develop Alzheimer’s disease as men — but scientists do not know why. *Nat Med* **31**, 704–707 (2025)

Aim 2: Role of menopause-related factors



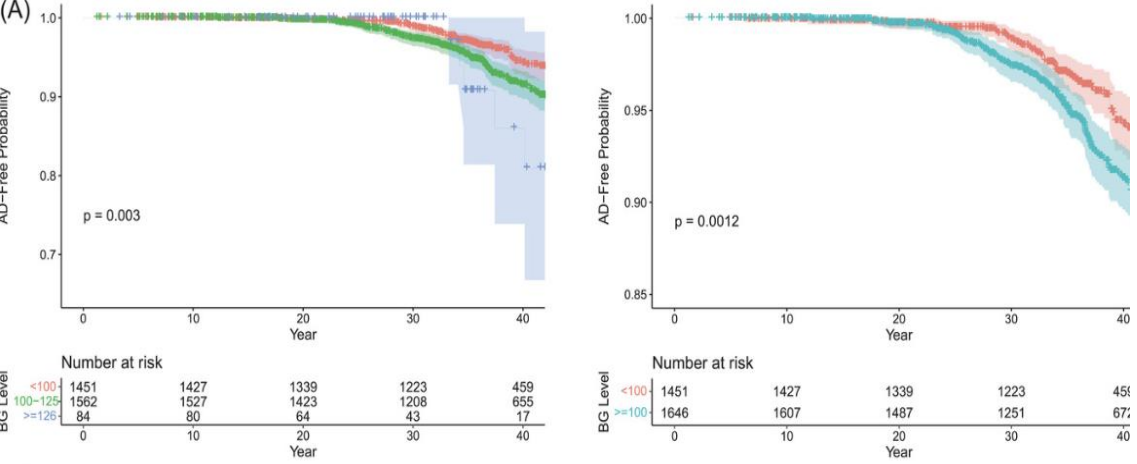
Aim 3: Role of vascular risk factors in AD

Obesity
Hypertension
Heart diseases
Hyperlipidemia
Diabetes

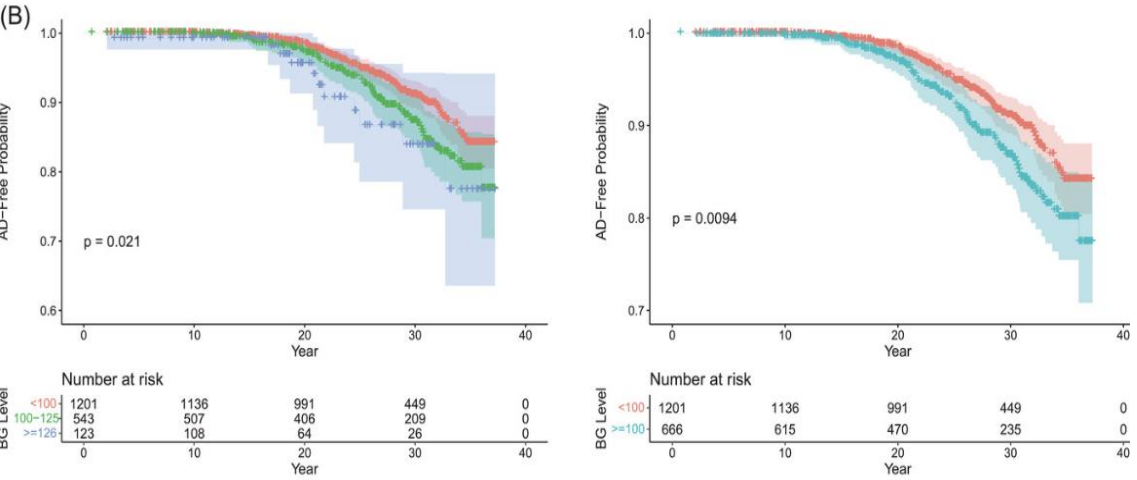


Does this differ by sex or ancestry?

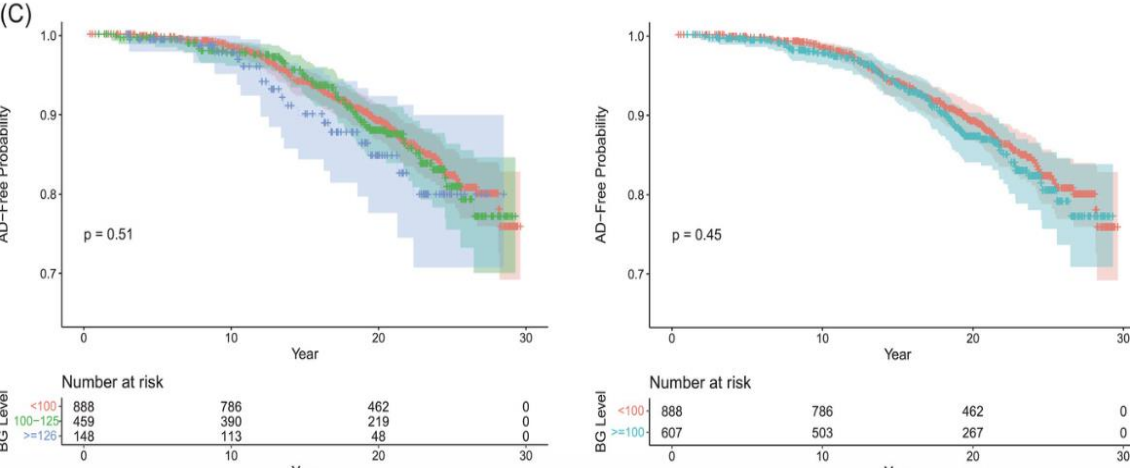
Hachinski, V. et al. Preventing dementia by preventing stroke: The Berlin Manifesto. *Alzheimer's Dement*. 2019; 15: 961-984.



Early



Middle



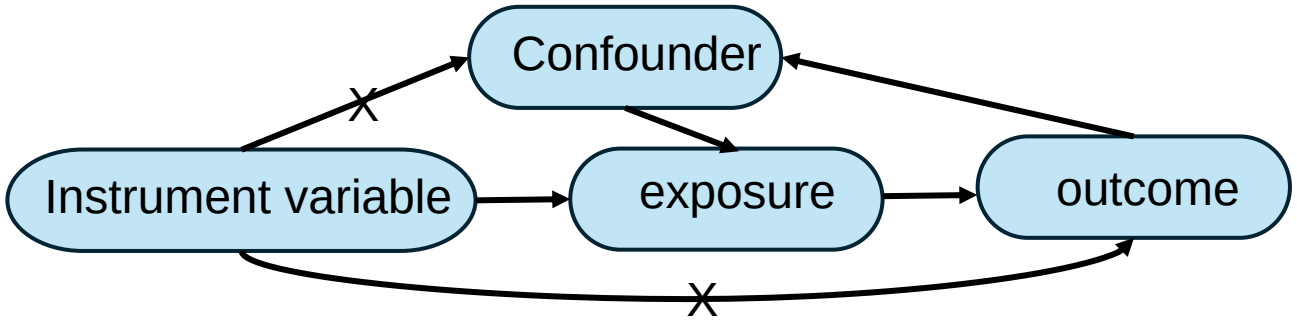
Late

Higher blood glucose in early and middle adulthood was associated with earlier and increased risk of AD.

Zhang. X, et al. Midlife lipid and glucose levels are associated with Alzheimer's disease. *Alzheimer's Dement*. 2023; 19: 181–193.

Aim 3: Role of vascular risk factors in AD

1. Construct the various risk factors PRS
2. Test the bidirectional association between AD and vascular risk factors using PRS
   - Vascular trait PRS with AD
   - AD PRS with vascular trait
3. Test causality association using MR



4. Assess long-term effects of vascular on AD risk using longitudinal data (ACT & FHS), stratified by PRS distribution

Analytical Goals of the Project

- **Demonstrated the utility of an ancestry-aware, sex-specific PRS** to improve understanding of Alzheimer's disease risk across diverse populations.
- **Clarified the role of menopause-related and sex-specific factors** in shaping AD vulnerability in diverse populations, informing prevention strategies.
- **Explored the directionality between AD and vascular factors**, highlighting shared pathways and potential reverse causality across the ancestry and sex
- Provide a comprehensive understanding of how vascular factors genetically contribute to AD risk, enabling better stratification and potential identification of intervention targets for AD prevention.

Thank you

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