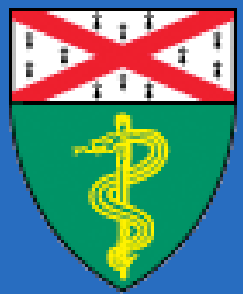


Reproductive lifespan and hormonal therapy in relation to later-life neurovascular health in community-dwelling older women

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Background

Endogenous exposure (reproductive span):

Longer span → potentially protective
Shorter span ↑dementia risk ¹

Exogenous exposure (hormonal therapies):

Mixed evidence for menopausal hormone therapy (MHT)²
Limited research on oral contraceptives (OC)²
No prior studies on combined OC+MHT effect

Aims

Examine associations between **endogenous** and **exogenous** estrogen on **cerebrovascular** and **neurodegenerative** markers of dementia, as well as potential combined OC + MHT effects and modification by APOE-ε4.

Methods

Study Population

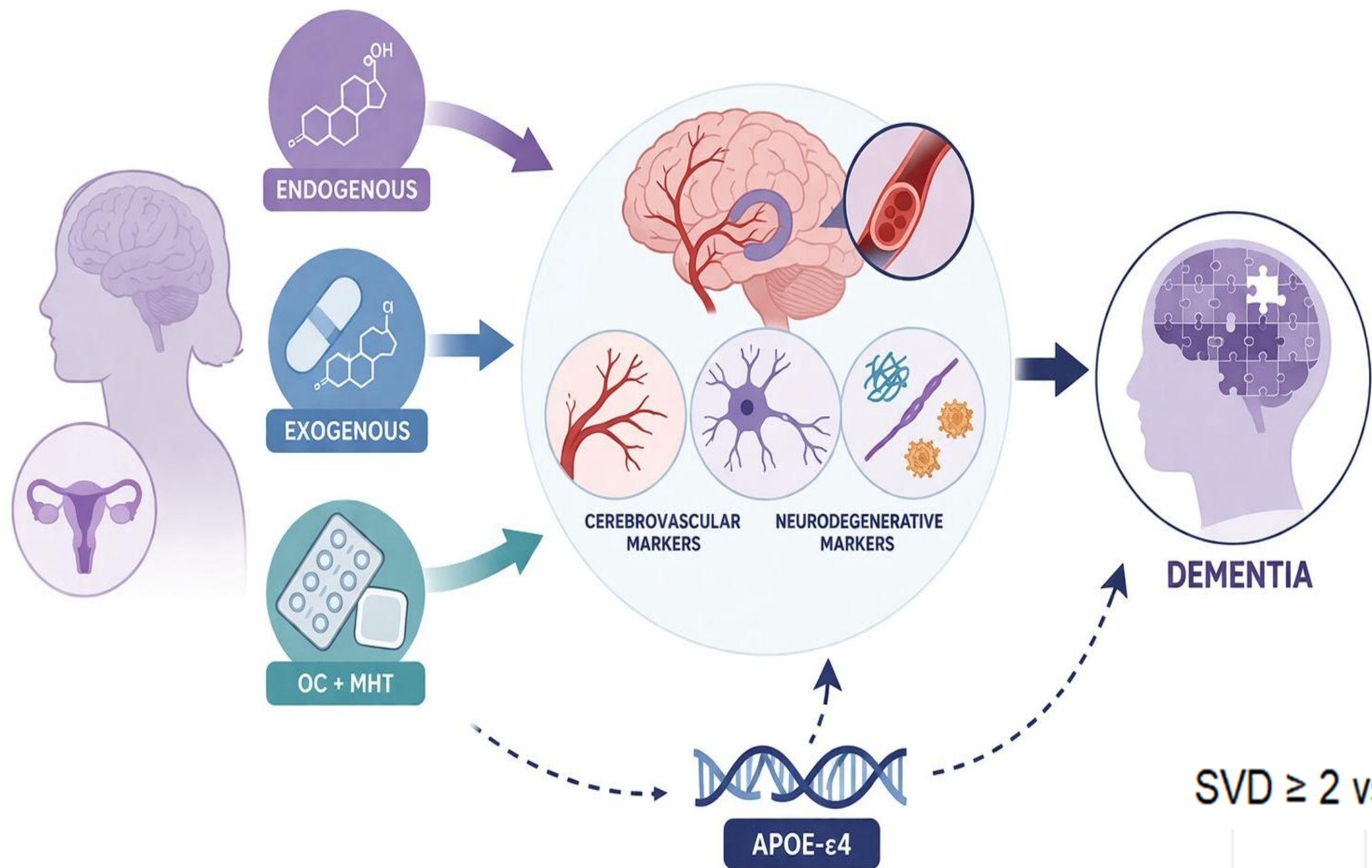
Gothenburg H70 Birth Cohort (Sweden)
N = 352 women (age 70) at baseline
205 with MRI at 5 years
No neurological disorders

Endogenous estrogen

Reproductive lifespan: age at menopause – age at menarche, incl. surgical (bilateral oophorectomy)

Exogenous estrogen

Oral contraceptives (OC)
Menopausal hormone therapy (MHT)



- **Vascular brain injury (SVD)** from Staals score: White matter hyperintensities (WMH), Lacunes, Microbleeds, Perivascular spaces
- **White matter integrity (FA)** from DTI
- **AD signature cortical thickness**
- **CSF** (β-amyloid 42, phosphorylated tau 181, neurofilament light, CSF/serum albumin ratio)

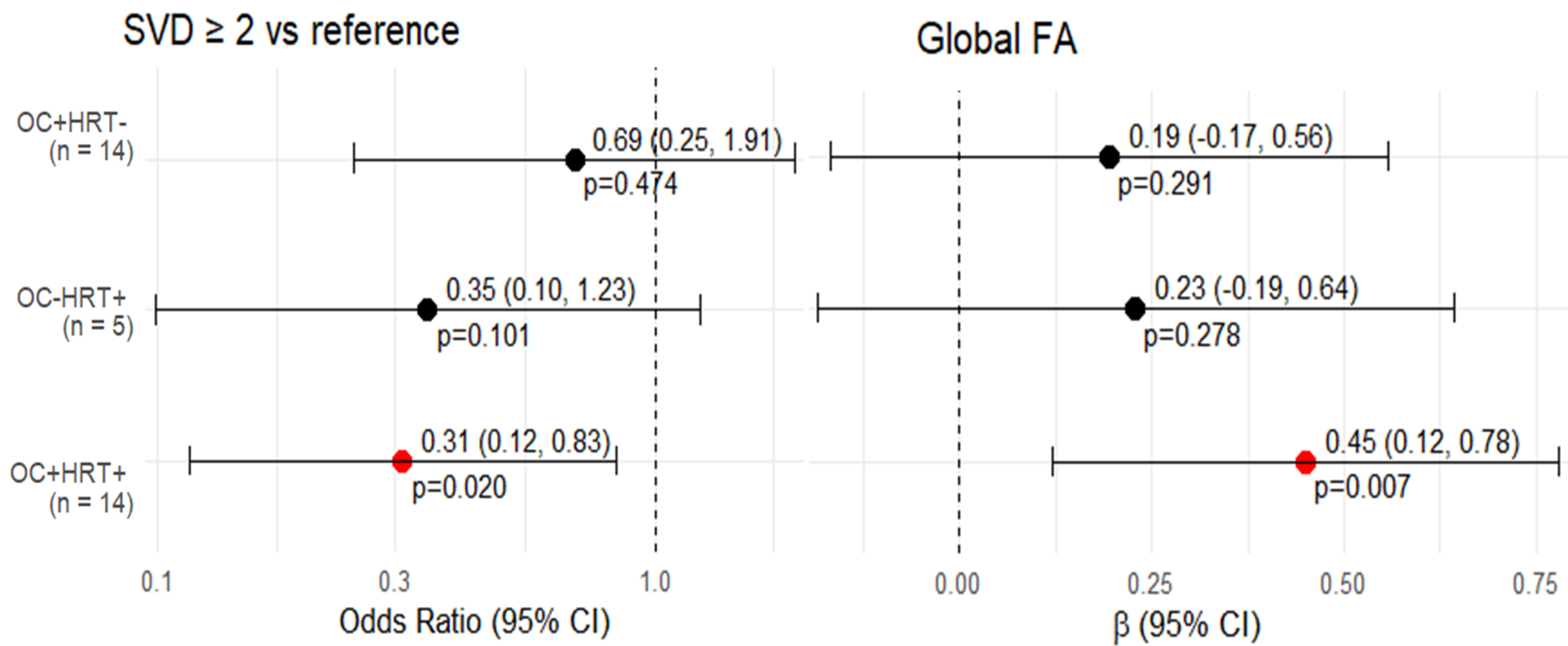
Statistical analyses

- Simple linear regression for AD thickness, FA
- Multinomial / logistic regression for SVD outcomes
- Joint exposure model: No hormones / OC only / MHT only / Both
- Linear mixed-effects models for longitudinal analyses
- Stratified analyses by APOE-ε4

Results

- **Longer reproductive span** (esp. later menopause) → lower SVD≥2 (OR=0.92[0.86–0.99], p=0.031)
- **OC** → higher FA (β=0.25, p=0.047)
- **MHT** → lower SVD≥2 (OR=0.41[0.20–0.81], p=0.011) – esp. perivascular spaces and microbleeds – and higher FA (β=0.28, p=0.012)
- **Combined OC + MHT Effects**

No significant interaction but joint users → lower SVD burden and higher FA:



- Significant interaction: **MHT × APOE-ε4** (p = 0.037)

Among ε4 carriers only MHT → greater AD cortical thickness (β = 0.38, p = 0.045)

While SVD and FA associations seem stronger in non-carriers

- No associations between estrogen and AD biomarkers
- No longitudinal differences, but trend MHT → less WMH

Strengths

- Population-based
- Age-homogeneous cohort
- Detailed reproductive history
- MRI + longitudinal data

Limitations

- Self-report
- No info on MHT timing/dose/formulation
- Limited power for CSF, high SVD burden
- Healthy sample → limited generalizability

Conclusions

- Estrogen exposure (endogenous + exogenous) likely supports brain health via **vascular** mechanisms, less AD-specific
- **MHT** may support cerebrovascular + potential **cumulative benefit** with OC (lifecourse perspective)
- Potential **mechanisms**: vascular integrity, anti-inflammatory, glymphatic function
- **APOEε4** modulation suggests **dual pathway**:
 - greater MHT benefits on AD neurodegeneration (ε4 carriers) → more responsive³ or antagonistic pleiotropy⁴
 - BUT greater MHT benefits on cerebrovascular health (non-carriers)⁵

References

- ¹ Han et al. BMC Med 2023. PMID: 37996855.
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