Sex differences in the associations between visceral adipose tissue, brain aging, and cognition

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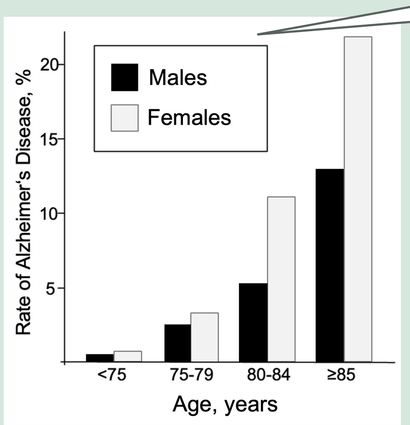
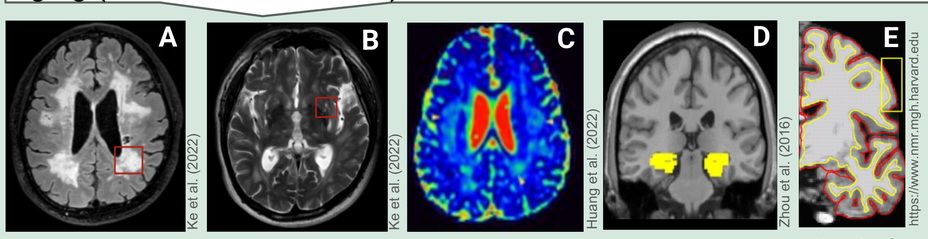
Introduction

Two thirds of patients with Alzheimer's disease (AD) are female. [1,2]



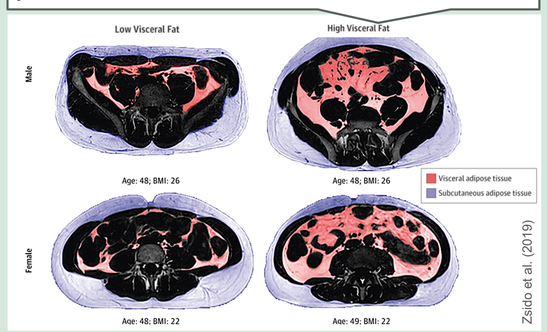
Gatz et al. (2006)

Cerebral small vessel disease (cSVD) typically features changes in white matter (A, B, and C), and is associated with AD and brain aging (reductions in D and E). [3,4]



White matter hyperintensities (WMHs) | **Perivascular space (PVS) burden** | **Free water (FW) in white matter** | **Hippocampal gray matter volume (GMV)** | **Cortical thickness (CT)**

Visceral adipose tissue (VAT) is linked to cognitive decline [5]. In females, loss of estradiol (E2)[5] with menopause[6], parallels increases in VAT. [7]

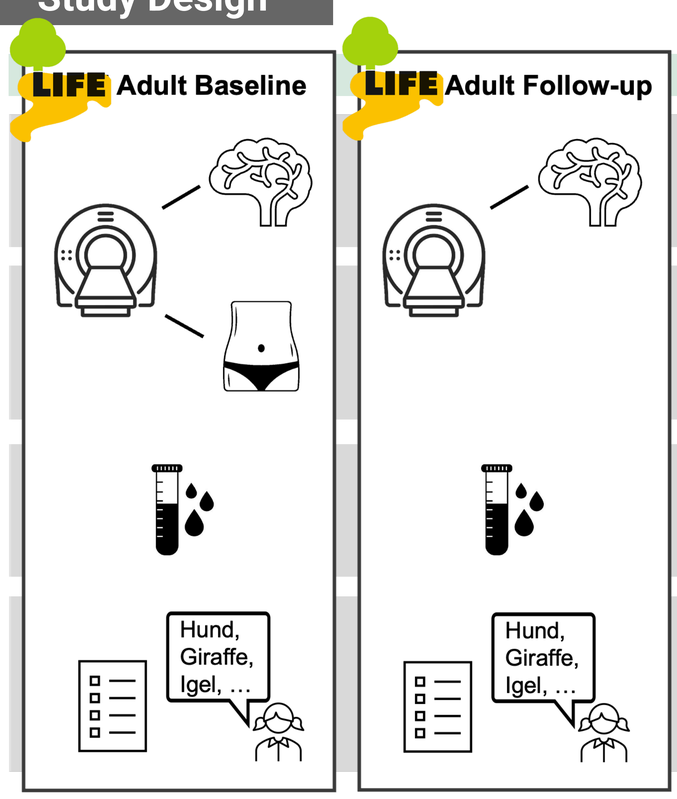


Research questions

1. Is VAT volume associated with brain aging and cSVD, and predictive for progression of these parameters?
2. Do these effects differ between sexes?
3. Are APOE4 carriers more susceptible to negative effects of VAT, and does this depend on sex?
4. Is E2 protective in this framework?

Methods

Study Design



Brain MRI measures
- cSVD markers: **WMHs**, **PVS burden**, **FW**
- brain aging markers: **hippocampal GMV**, **CT** in AD regions

Abdominal measures
- MRI: VAT volume (corrected for height)
- complementary: waist-to-hip ratio (WHR), or waist-to-height ratio (WHtR)

Biomarker
- serum E2: from liquid chromatography mass-spectrometry
- APOE4 status (0 vs. 1/2 alleles): from serum genotyping

Behavioral measures/ questionnaires
- **cognitive performance**: CERAD score
- lifetime endogenous estrogen exposure (age at first menses to age of last menses)

Preregistration
https://osf.io/8qvsb/

Sample

Participants of the Leipzig Research Center for Civilization Diseases (LIFE) Adult cohort

- baseline age ≥ 18 y. for analyses of **hippocampal GMV**, **CT**, and **cognitive performance**
- baseline age ≥ 40 y. for analyses of **WMHs**, **PVS**, and **FW**
- baseline brain MRI and abdominal MRI scans (or WHR/WHtR) in n~1000
- subsample with follow-up brain MRI scans in n~800

Exclusion criteria
- history of stroke
- self-reported dementia
- intake of centrally active medications
- Mini Mental State Examination score < 24
- MRIs with exclusion due to motion/ quality assessment

Hypotheses & analysis plan

H1 | Cross-sectional (**C**) & longitudinal (**L**) effects of VAT, sex, and their interactions on brain aging, cSVD & cognitive performance
H2 | Cross-sectional (**C**) & longitudinal (**L**) effects of H1, stratified for APOE4 status (0 vs. 1/2 alleles)
\+ **exploratory analyses** of role of serum E2 and lifetime endogenous estrogen exposure in female participants
→ Linear (mixed effects) regression models per **outcome variable** and hypothesis

H1-C | brain ~ abdomen × ♀♂

$\text{outcome}_{baseline} \sim \beta0 + \beta1 \cdot (\text{VAT}_{baseline} \times \text{sex}) + \beta2 \cdot \text{VAT}_{baseline} + \beta3 \cdot \text{age}_{baseline} + \beta4 \cdot \text{sex} + \varepsilon$

H2-C | brain ~ abdomen × ♀♂ × APOE4 vs.

$\text{outcome}_{baseline} \sim \beta0 + \beta1 \cdot (\text{VAT}_{baseline} \times \text{sex} \times \text{APOE4}) + \beta2 \cdot \text{VAT}_{baseline} + \beta3 \cdot \text{age}_{baseline} + \beta4 \cdot \text{sex} + \beta5 \cdot \text{APOE4} + \varepsilon$

H1-L | brain ~ abdomen × ♀♂ × age_{change}

$\text{outcome}_{change} \sim \beta0 + \beta1 \cdot (\text{VAT}_{baseline} \times \text{age}_{change} \times \text{sex}) + \beta2 \cdot \text{VAT}_{baseline} + \beta3 \cdot \text{age}_{baseline} + \beta4 \cdot \text{age}_{change} + \beta5 \cdot \text{sex} + (1|\text{subject}) + \varepsilon$

H2-L | brain ~ abdomen × ♀♂ × APOE4 vs. × age_{change}

$\text{outcome}_{change} \sim \beta0 + \beta1 \cdot (\text{VAT}_{baseline} \times \text{age}_{change} \times \text{sex} \times \text{APOE4}) + \beta2 \cdot \text{VAT}_{baseline} + \beta3 \cdot \text{age}_{baseline} + \beta4 \cdot \text{age}_{change} + \beta5 \cdot \text{sex} + \beta6 \cdot \text{APOE4} + (1|\text{subject}) + \varepsilon$

Exploratory analyses
- absolute E2 levels at baseline
- postmenopausal females: lifetime endogenous estrogen exposure (reproductive span in years)

Outlook

This works aims to support…
… multimodal frameworks of research on brain aging and AD, integrating insights from neuroimaging, metabolism, and endocrinology
… ongoing research on early interventions for pathological brain aging trajectories, focusing on modifiable risk factors such as metabolic health
… acknowledging biological sex as a relevant variable in basic and clinical research, fostering a deeper understanding of sex-specific plasticity vs. susceptibility
… moving towards a personalized medicine approach based on the identification of individual risk profiles, enabling tailored prevention and therapeutic strategies

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