# Cross-sectional & longitudinal associations between visceral adipose tissue, brain aging, and cognition – a sex differences perspective

**Charlotte R. Koch** *[1,2], **Livia Ruehr** *[2,3,4], Daria E. A. Jensen[2,4], Laurenz Lammer [2,3], Steffi G. Riedel-Heller[5], Ronny Baber[6,7], Samira Zeynalova[8,9], Arno Villringer[2,3,4], Julia Sacher✣[1,2,3,4,10], Frauke Beyer✣ [2,4,11], & A. Veronica Witte✣[2,3,4]

koch@cbs.mpg.de
ruehr@cbs.mpg.de

MAX PLANCK INSTITUTE FOR HUMAN COGNITIVE AND BRAIN SCIENCES
MAX PLANCK SCHOOL of cognition
UNIVERSITÄT LEIPZIG
Universitätsklinikum Leipzig – Medizin ist unsere Berufung.
LIFE Leipziger Forschungszentrum für Zivilisationserkrankungen
UNIVERSITÄT LEIPZIG
LeiCeM

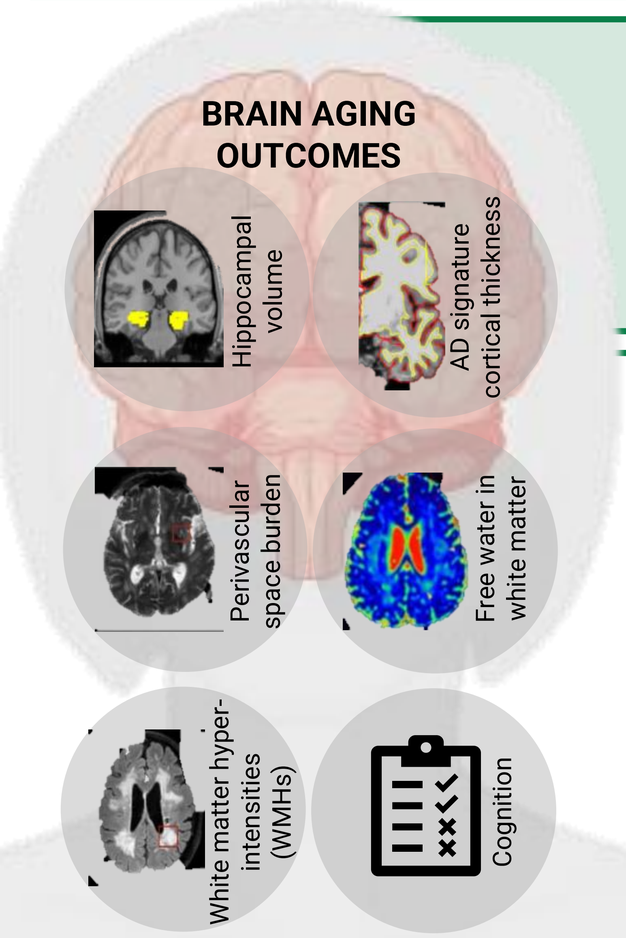
* equally contributing first authors
✣ equally contributing last authors

## AIMS & BACKGROUND

Obesity, particularly excess **visceral adipose tissue (VAT)**, is a risk factor for cognitive decline and neurodegeneration.[1,2]
Yet, **longitudinal** evidence and studies on its **interplay with individual factors** such as sex or genetics remain scarce.
This study aimed to investigate:

1) Both **cross-sectional and longitudinal associations between VAT and brain aging**.
2) The **role of biological sex** (given that females and males differ in both brain aging and VAT accumulation rates [3,4]).
3) Further modification by **genetic risk (APOE ε4)**.

## STUDY DESIGN




### Sample

*N* ~ 1,000 LIFE participants (population-based cohort study)

Baseline & follow-up (after 4-7 years)

Mean (baseline) ~ 51 – 58 y.
Range: 19 – 80 y. (40 – 80 y. for WMH and Free Water analyses)

~ 50% female

~ 23% APOE ε4 carriers (≥ 1 allele)

### Data acquisition

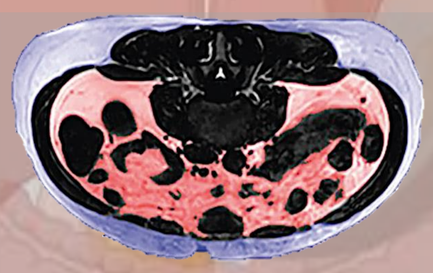
MRI outcomes (3T Siemens VERIO):

- **Hippocampal volume** and **cortical thickness** via MPRAGE, Freesurfer samseg and cortical parcellation
- **White matter hyperintensities** via FLAIR and SPM lesion segmentation
- **Perivascular space burden** via MPRAGE and FLAIR, using a 3D convolutional network
- **Free water** via DWI, using a two-compartment model

Cognitive outcome:
Global cognitive function composite score from CERAD (incl. S-words) and TMT

MRI predictors:
Abdominal MRI scan with subsequent abdominal fat tissue segmentation (visceral vs. subcutaneous) and volumetric quantification

### PREDICTOR: Visceral Adipose Tissue



*Abdominal MRI scan with cross-sectional view of the fat tissue, with visceral adipose tissue (VAT) in red, and subcutaneous adipose tissue (SAT) in blue.*

### Statistical models

**Cross-sectional associations via linear regression models:**

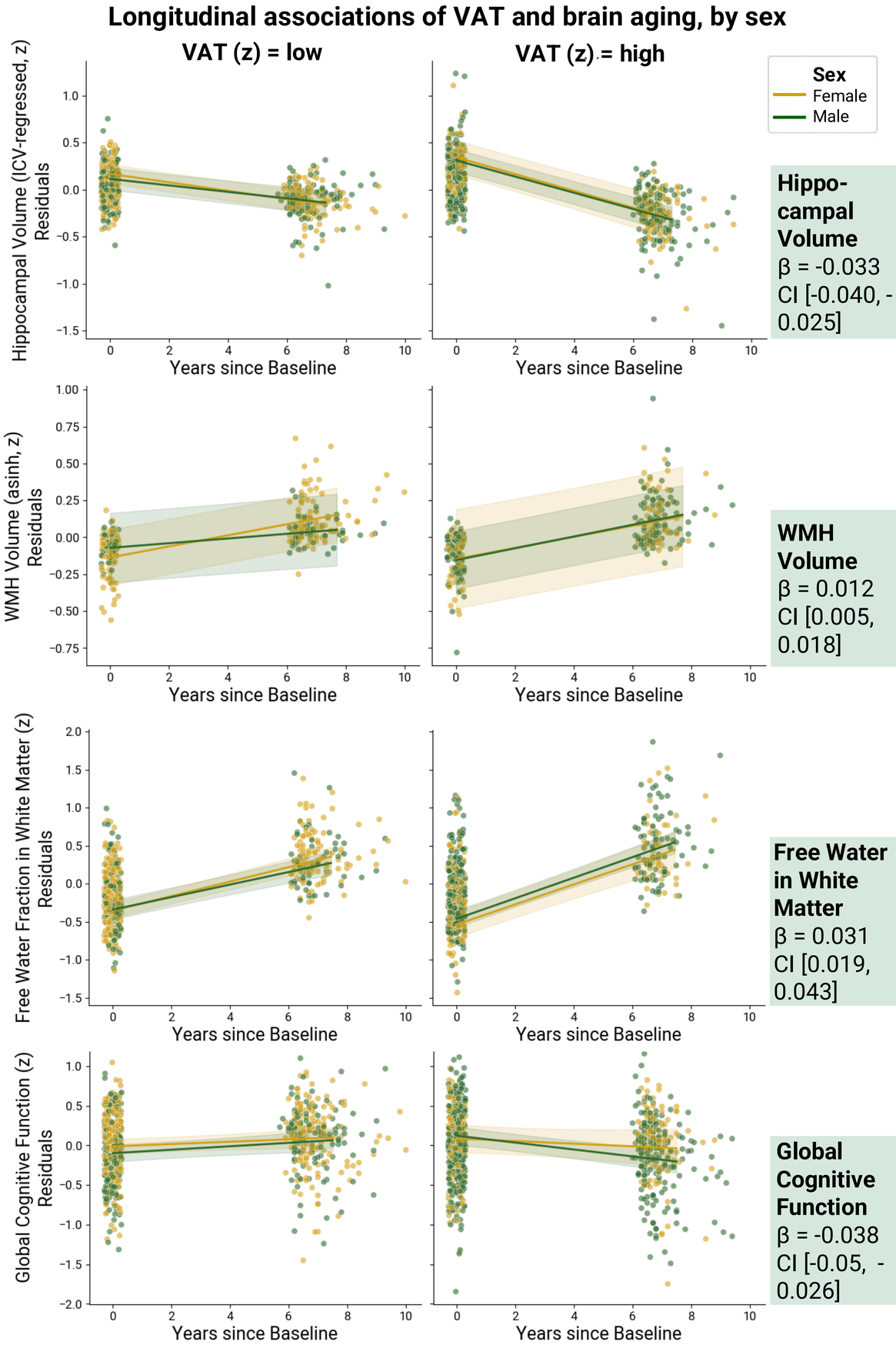
Outcome ~
VAT * sex (* APOE ε4)
+ age_baseline
(+ ICV)

**Longitudinal associations via linear mixed-effects models:**

Outcome ~
age_change * VAT * sex (* APOE ε4)
+ age_baseline
(+ ICV)
+ (1 | subject)

## RESULTS

### Longitudinal associations of VAT and brain aging, by sex




**Hippocampal Volume**
β = -0.033
CI [-0.040, -0.025]

**WMH Volume**
β = 0.012
CI [0.005, 0.018]

**Free Water in White Matter**
β = 0.031
CI [0.019, 0.043]

**Global Cognitive Function**
β = -0.038
CI [-0.05, -0.026]

*Plotted are outcomes (confounder-adjusted) vs. follow-up period per VAT median and sex. Points: outcome after removing basline age (and intracranial volume); Lines: model-predicted trajectories; Bands: 95% CI.*

## KEY MESSAGES

1. Higher VAT is a robust predictor of **accelerated future brain aging** across multiple MRI markers and global cognition, with no effects present in cross-sectional analyses. Effects also apparent for **subcutaneous fat** (except for white matter hyperintensity burden), indicating a general role of abdominal fat in brain aging.[5]
2. We did **not find evidence for sex differences, or exacerbating effects of APOE ε4** in our interaction analyses.

## LIMITATIONS & OUTLOOK

- Limited power for VAT X Sex interaction analyses; lack of information on longitudinal VAT trajectory or its secretatory profile; missing information on sex-specific lifespan contributions (e.g., perimenopause).[6,7]
- Future studies should incorporate more granular measures of individual susceptibility such as **reproductive stage**, **metabolic and endocrine profiles**, as well as **systemic inflammatory markers**, to identify biological factors underlying brain aging and support more targeted interventions.

**Abbreviations**
AD = Alzheimer's Disease
APOE = Apolipoprotein E
CERAD = Consortium to Establish a Registry for Alzheimer's Disease
FLAIR = Fluid-attenuated inversion recovery sequence
ICV = Intra-cranial Volume
LIFE = Leipziger Forschungszentrum für Zivilisationserkrankungen
MPRAGE = Magnetization-prepared rapid gradient echo sequence
MRI = Magnetic Resonance Imaging
SAT = Subcutaneous Adipose Tissue
TMT = Trail Making Test
VAT = Visceral Adipose Tissue
WMHs = White Matter Hyperintensities

**References**
1 Livingston et al., 2024. In: *The Lancet.* doi: 10.1016/S0140-6736(24)01296-0
2 Pachter et al., 2026. In: *Nature Communications.* doi: 10.1038/s41467-026-71141-4
3 Zsido et al., 2019. In: *JAMA Network Open*. doi:
4 Armstrong et al., 2022. In: *Neurobiology of Aging.* doi: 10.1016/jneurobiolaging.2019.05.020
5 Boccara et al., 2023. In: *Frontiers in Medicine.* doi: 10.3389/fmed.2023.1160426
6 Maeyens et al., 2026. In: *Nature Aging*, doi: 10.1038/s43587-026-01076-4
7 Lovejoy et al., 2009. In: *Internation Journal of Obesity.* doi: 10.1038/ijo.2008.25

**Figures**
Gatz et al. (*Archives General Psychiatry*, 2006); Huang et al. (*Translational Stroke Research*, 2022); Ke et al. (*Brain Sciences*, 2022); Zhou et al. (*BMC Psychiatry*, 2016); Zsido et al. (*JAMA Network Open*, 2019). All other figures were created by the authors (left figure: BioRender).

**Preregistration**
This work is currently in prep. for submission. It was preregistered at Open Science Framework (OSF), see https://osf.io/8qvsb/.

**Funding**
This work was supported by the Max Planck School of Cognition (LR), the MPG Brain HATCH Project (Human Cognition Hormones; LR, JS), the LeiCeM Project (Nr.: EXC-3105/1 – 533765739; JS, AVW) and University Medical Center Leipzig (JS. AVW).

**Affiliations**
[1] Medical Faculty, University of Leipzig, Leipzig, Germany
[2] Neurology Department, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[3] Max Planck School of Cognition, Leipzig, Germany
[4] Cognitive Neurology, University of Leipzig Medical Center, Leipzig, Germany
[5] Institute of Social Medicine, Occupational Health & Public Health (ISAP), Medical Faculty, University of Leipzig, Leipzig, Germany
[6] Institute of Laboratory Medicine, Clinical Chemistry, and Molecular Diagnostic, University of Leipzig Medical Center, Leipzig, Germany
[7] Leipzig Medical Biobank, University of Leipzig, Leipzig, Germany
[8] LIFE - Leipzig Research Centre for Civilization Diseases, University of Leipzig, Leipzig, Germany
[9] Institute for Medical Informatics, Statistics, and Epidemiology, University of Leipzig, Leipzig, Germany
[10] Medical Department III – Endocrinology, Nephrology, Rheumatology, Leipzig University, Leipzig, Germany
[11] Bordeaux Population Health Research Center, University of Bordeaux, Bordeaux, France