Vascular medical treatment influences the association between vascular burden and amyloid pathology

- in middle-to-late-aged cognitively normal individuals at risk for Alzheimer's disease -

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BACKGROUND

- 1/3 of late-onset Alzheimer's disease (AD) cases are attributed to modifiable risk factors[1]
- Vascular dysregulation has been suggested to proceed amyloid-ß (Aß) and *tau* pathology[2]
- However, it is still a matter of debate whether vascular risk factors (VRF) act through AD-related neuropathological pathways (Aß and tau) on disease expression, or if this is merely mediated through other cerebrovascular changes[3]

AIM: to examine the associations of lipids, blood pressure and combined VRF scores with Aß and *tau* pathology (measured in PET and CSF) in the preclinical disease stage, considering the moderating impact of vascular drug treatment

METHODS

Participants

Cognitively-normal adults with **family history of AD**

PET n=120 – 63% non-treated
CSF n=162 – 70% non-treated

- 63 ± 4.8 years old
- 75% female
- 41% APOE ε4 carrier

VRF

Plasma lipids
total Cholesterol, HDL & LDL cholesterol
Blood pressure (BP)
systolic & diastolic BP, pulse pressure (systolic – diastolic BP)
Combined vascular risk scores
CAIDE, FCRP, FHS-CVD

PET

^{18}F-NAV4694: Aβ SUVR
in AD-typical ROI[4] (Ref: cerebellar ctx)
^{18}F-AV1451: *Tau* SUVR
in entorhinal ctx (Ref: inferior cerebellar ctx)
extracted from FreeSurfer Desikan atlas cortical regions

CSF

$Aß_{1-42}$ and **p-*tau*** *(ELISA, INNOTEST; Fujirebio)*

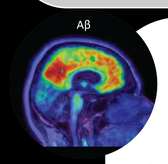
Statistics

Univariate linear **regression analyses**

Interaction models with vascular medication **for dyslipidemia and/or hypertension (0/1)**

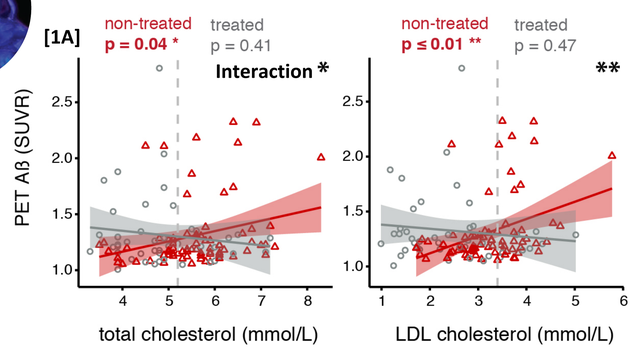
Adjustment for age, sex and time difference between measurement time points (and APOE ε4 status)

RESULTS

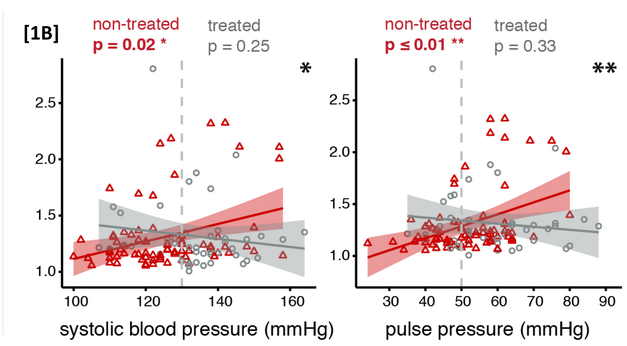


PET

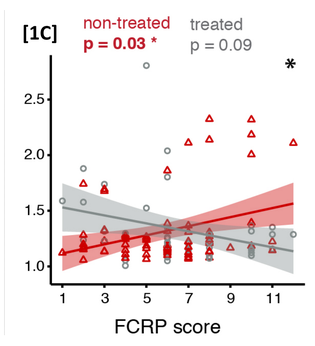
Lipid measures



Blood pressure measures



Combined vascular risk scores



Interaction effects between vascular risk factors (VRF) and vascular medical treatment are indicated within the graphs (** ≤ 0.001, * ≤ 0.05, † ≤ 0.1). Shaded areas represent 95% confidence intervals for regression lines' slopes.

We found **no main effect** of vascular risk factors **on cerebral Aß** within the **whole study sample** (p>0.05)

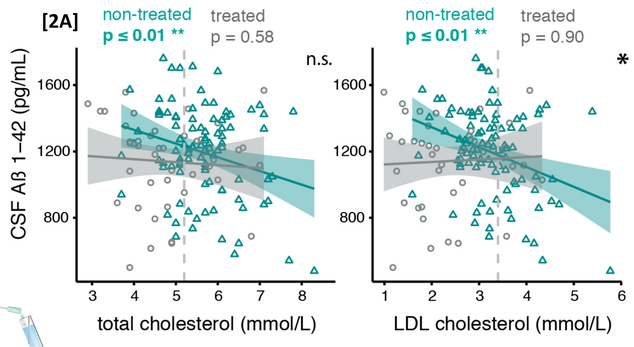
Interaction effects:
between vascular medical treatment and total cholesterol, LDL cholesterol, systolic blood pressure, pulse pressure, CAIDE (marginally), as well as FCRP, and FHS-CVD (marginally) scores on global cerebral Aß (all p≤0.022, marginal effects p≤0.072)

Post-hoc regression analyses:
positive associations between total cholesterol as well as LDL cholesterol (p=0.042/ p=0.004), systolic blood pressure as well as pulse pressure (p=0.023/ p=0.002), FCRP, CAIDE as well as FHS-CVD scores (p=0.032/ p=0.001/ p=0.027) and cerebral Aß in non-treated participants (***Figure 1A-C***)

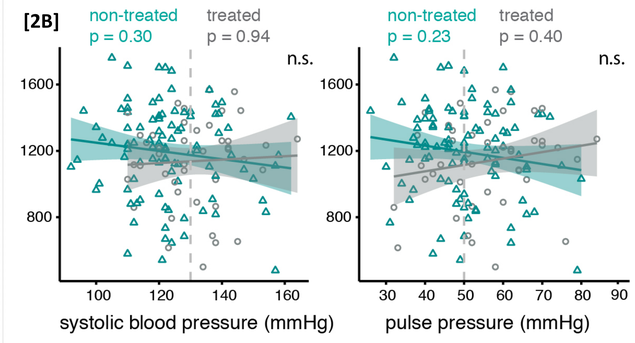
Results remained **unchanged** when **APOE ε4 status** was added as an additional covariate

CSF

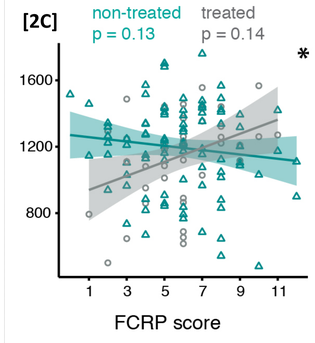
Lipid measures



Blood pressure measures



Combined vascular risk scores

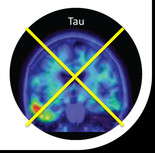


Interaction effects between vascular risk factors (VRF) and vascular medical treatment are indicated within the graphs (** ≤ 0.001, * ≤ 0.05, † ≤ 0.1). Shaded areas represent 95% confidence intervals for regression lines' slopes.

Complementary CSF analyses:
similar **interaction effects** between vascular medical treatment and LDL cholesterol, FCRP as well as FHS-CVD score (marginally) on **$Aß_{1-42}$** (all p≤0.042, marginal effect p=0.088, ***Figure 2A-C***), but not for blood pressure measures and the CAIDE score

Post-hoc regression analyses:
positive associations between total cholesterol as well as LDL cholesterol and $Aß_{1-42}$ (p=0.001/ p=0.001; see ***Figure 2A & 2B***), and between CAIDE score and $Aß_{1-42}$ (p=0.021), in non-treated participants

No interaction effects were found between VRF and vascular medical treatment on ***tau* pathology** and neither when the analyses are restricted to non-treated participants (p>0.05)



SUMMARY

- Our findings underline the importance of **participant stratification** with regard to **medical treatment for dyslipidemia and/or hypertension**, while studying the relationship between VRF and AD pathology
- Higher levels of **lipids** and **blood pressure** were **associated** with **higher Aß**, but not *tau* pathology, **only in participants that were non-treated** for dyslipidemia and/or hypertension, **independent** of **age, sex and APOE ε4 status**
- Disruption of the blood-brain-barrier, promoting the internalization of apoB-containing LDL cholesterol that may enhance the amyloidogenic process, and impaired cerebral perfusion might be underlying mechanisms that link higher VRF to higher Aß burden[3,5,6]
- Overall, a **better understanding of those modifiable disease pathways** could have a major **impact on** the development of AD **prevention** and **intervention** strategies

Literature:
[1]Norton S et al. 2014, *Lancet Neurol.*; [2]Iturria-Medina Y et al. 2016, *Nat Commun.*; [3]Zlokovic BV et al. 2011, *Nat Rev Neurosci.*; [4]Villeneuve S et al. 2015, *Brain*; [5]Chen X et al. 2014, *J Neurol Neurophysiol.*; [6]Weller RO et al. 2009, *Acta Neuropathol.*

Abbreviations:
CAIDE: cardiovascular risk factors, aging, and dementia risk score;
FCRP: Framingham Coronary Risk Profile; FHS-CVD: Framingham general CVD risk score

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