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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• 1/3 of late-onset Alzheimer’s disease (AD) cases are attributed to modifiable risk factors1
• Vascular dysregulation has been suggested to proceed amyloid-β (Aβ) and tau pathology2
• However, it is still a matter of debate whether vascular risk factors (VRF) act through AD-related neuropathological pathways (Aβ and tau) on disease expression, or if this is merely mediated through other cerebrovascular changes3

AIM: to examine the associations of lipids, blood pressure and combined VRF scores with Aβ 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
1fF-NAV4694; Aβ SUVr in AD-typical ROIs (Ref: cerebellar ctx)
1fF-AV1451; Tau SUVr in entorhinal ctx (Ref: inferior cerebellar ctx)
extracted from FreeSurfer Desikan atlas cortical regions

CSF
AB1-42 and p-tau (ELISA, INNOTEST, Fujirebio)

RESULTS

Lipid measures

Blood pressure measures

Combined vascular risk scores

We found no main effect of vascular risk factors on cerebral AB 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 Aβ (all p≤0.022, marginal effects p≤0.017)

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 Aβ in non-treated participants (Figure 1A-C)

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

Complementary CSF analyses:
similar interaction effects between vascular medical treatment and LDL cholesterol, FCRP as well as FHS-CVD score (marginally) on Aβ1-42 (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 Aβ1-42 (p=0.001/ p=0.001, see Figure 2A & 2B), and between CAIDE score and Aβ1-42 (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 Aβ, 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 Aβ burden
• Overall, a better understanding of those modifiable disease pathways could have a major impact on the development of AD prevention and intervention strategies

REFERENCES

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

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)

Literature:
• Norton S et al. 2014, Lancet Neurol;
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