# Supplemental data

Increased midlife triglycerides predict brain amyloid  and tau pathology

20 years later

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# e-Methods

The following covariates were derived from the self-administered questionnaire at the baseline examination1, 2. Smoking habits were stated as one of the following alternatives; 1 = Yes, I smoke regularly, 2 = Yes, I smoke occasionally, 3 = No, I have stopped smoking, or 4 = No, I have never smoked. We then categorized smoking as ever smoker (alternative 1 through 3) or never smoker (alternative 4). Regarding cardiovascular diseases, participants responded to the following questions; “Have you ever been treated for heart attack (infarction)?”, “Have you ever been treated for stroke?” and “Have you ever been treated for claudication in the legs?” as yes/no. We then categorized cardiovascular disease as present if any of these three questions were answered with yes, thus defining cardiovascular disease as self-reported myocardial infarction, stroke and/or claudication in the legs.Physical activity score was entered as a numeric variable constructed of self-reported minutes of physical activity in leisure time, multiplied with an activity specific factor representing the intensity of each reported activity3, 4.

Since midlife lipids were the covariates of primary focus in this study, we included lipid-lowering medication at follow-up in the analyses (the only covariate not collected at baseline) in order to explore if lipid levels were associated with the outcome, regardless of potential treatment effects later on. Data on medication use was gathered at both MDCS baseline and MDCS re-examination using self-administered questionnaires. The questions regarding medication did not differ between the questionnaire forms. Participants stated use of medication in response to the questions: “What medical prescription drugs do you use regularly?” and “What medical drugs

(incl vitamins etc) that you have bought without a prescription do you use regularly?” Drugs were then classified according to the international Anatomical Therapeutic Chemical Classification (ACT) and all drugs from group C10 (lipid modifying agents) were categorized as lipid lowering medication.

A variable list covering the baseline questionnaire as a whole is enclosed as an appendix (appendix e-1).

# e-Results

## Sensitivity analyses

Substituting systolic blood pressure with diastolic blood pressure and pulse pressure respectively, did not alter the associations between triglycerides and A-pathology in the multivariable regression models. Neither did analyses where lipid-lowering medication at follow-up was substituted with lipid-lowering medication at baseline, alter the results (no individuals in the PET group used lipid-lowering medication at baseline). Further, the results were not altered when we substituted BMI with weight reduction between baseline and follow-up.

When logistic regression models were performed without any variable elimination, all the presented significant associations between triglycerides and brain Aβ remained robust (p<0.05).

### APOE ε4

Presence of *APOE* ε4 was strongly associated with abnormal CSF Aβ42 (OR 7.96, 95% CI 4.4114.4, *p*<0.0001), abnormal Aβ42/P-tau ratio (OR 7.32, 95% CI 3.71-14.5; *p*<0.0001), and abnormal Aβ PET (OR 7.85, 95% CI 2.72-22.6; *p*<0.0001) in multivariable logistic regression models adjusting for age, gender, education, triglycerides, IMT, systolic blood pressure, fbglucose, BMI, cardiovascular disease, smoking, physical activity and lipid-lowering medication (at follow-up). We found no statistical interactions between triglyceride level and APOE ε4 (p>0.05) when simultaneously entering triglycerides, APOE ε4 and a variable consisting of their product (triglycerides × APOE ε4) in regression models.

# e-References

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4. Taylor HL, Jacobs DR, Jr., Schucker B, Knudsen J, Leon AS, Debacker G. A questionnaire for the assessment of leisure time physical activities. J Chronic Dis 1978;31:741-755.