ARIC Manuscript Proposal #4096

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1.a. Full Title:
Dissertation Project: Liver integrity over the adult lifespan and the risk of Alzheimer's disease and related dementias, dementia-related pathology, and cognitive function

b. Abbreviated Title (Length 26 characters): liver and brain health

2. Writing Group:
Writing group members: James Pike, Ron Hoogeveen, Keenan Walker, Laura Raffield, Elizabeth Selvin, Christy Avery, Stephanie M. Engel, Michelle M. Mielke

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __YL___ **[please confirm with your initials electronically or in writing]**

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3. Timeline: This proposal is part of the dissertation project and is being submitted in conjunction with another part of the dissertation proposal entitled 'Plasma proteomic markers of liver integrity and the risk of Alzheimer's disease and related dementias, dementia-related pathology, and cognitive function'. All proposed work is expected to be completed within 12 months.

4. Rationale:
Alzheimer's disease (AD) and related dementias affect more than 50 million people worldwide,[1-3] and in the U.S., disproportionally burdens racial/ethnic minority groups, including Black and Hispanic adults.[3, 4] No therapeutic options of proven efficacy are currently available to treat the symptoms nor underlying causes of dementia, highlighting a critical need to identify upstream predictors to prevent dementia and preserve cognitive function. AD pathology can be present in 60-80% of dementia cases.[3] In the most common form, mixed dementia, the abnormal protein deposits associated with AD coexist with cerebrovascular disease sequelae that is often linked to vascular dementia.

Although mounting evidence recognizes dementia as a systemic metabolic disorder,[5-7] most attention has focused on brain metabolism without consideration of systemic metabolomics in peripheral samples. While emerging evidence in animal studies highlights extensive links between the liver and brain function, the human evidence is suggestive but limited,[8] and a comprehensive investigation into liver integrity and subsequent AD neuropathological and cerebral vascular alterations is lacking. Moreover, liver function intersects with other components of metabolic dysregulation such as adiposity, diabetes, hypertension, and dyslipidemia,[9] all recognized risk factors of late-onset dementia.[10-12] Whether impaired liver structure and associated functional changes directly influence the risk of dementia independent of other cardiometabolic conditions, a question of considerable potential impact, is not known.

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease type among adults, and is recognized as having a high prevalence of 20-35% among US population and prolonged subclinical stages.[13] NAFLD is characterized by the accumulation of fat in the liver, with insidious progression to liver cell damage and dysfunction. Based on disease progression and severity, NAFLD is further categorized into a spectrum from simple steatosis to steatohepatitis, fibrosis, and to cirrhosis.[9] Although associations of NAFLD and liver fibrosis with impaired cognitive function and dementia have been investigated, the results are not consistent and are subject to many limitations, such as cross-sectional study design, and a lack of assessment of NAFLD across the full spectrum and at multiple time points.[14-24] In addition, while an increased risk of dementia associated with low levels of liver aminotransaminases was recently reported by the Alzheimer's Disease Neuroimaging Initiative (ADNI) investigators[14] and by our group,[25] a pathological explanation underlying this relation is unclear.

We thus propose to quantify liver integrity on the NAFLD-liver fibrosis spectrum (assessed by fatty liver index (FLI) and FIB-4) and aminotransferase levels in Black and White participants enrolled in the community-based cohort of the Atherosclerosis Risk in Communities (ARIC) Study, and prospectively assess their associations with incident dementia over 30 years follow up. Further, we will draw on (i) plasma assays of amyloid-β40 (Aβ40), Aβ42, phosphorylated-tau181 (p-tau181), neurofilament light (NfL) and plasma glial fibrillary acidic protein (GFAP),[26-29] and (ii) brain morphology on magnetic resonance imaging (MRI) to explore the contributions of impaired liver integrity to AD neuropathology and cerebrovascular pathology, the two most common pathways to dementia.[3, 30] This study will add new information on the systemic pathogenesis of dementia over the adult life span, as influenced by a highly prevalent hepatic disease, with the goal of identifying modifiable targets for intervention.[31]

Remodeling of hepatic architecture and dysregulation in hepatocellular function plausibly induce peripheral promoters of neurodegeneration and may expose a large segment of the population to increased risk of AD and related dementias.[8] The proposed research, based on an innovative study question and conducted in a well-characterized, population-based prospective cohort will contribute new information of potential high impact on brain health in relation to liver integrity.

5. Main Hypothesis/Study Questions:

Aim 1: Quantify liver integrity on the i) NAFLD-fibrosis spectrum and ii) aminotransferase level over the adult life course, and estimate the associated risk of dementia over 30 years of follow-up.

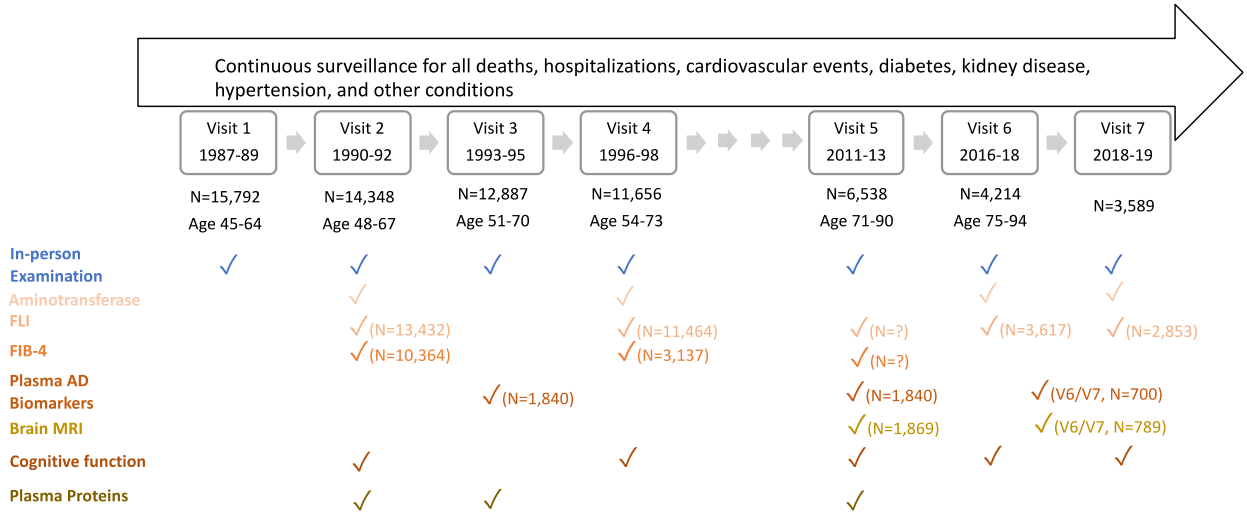
Aim 2: Estimate the association of liver integrity on the i) NAFLD-fibrosis spectrum and ii) aminotransferase level over the adult life course with dementia-related pathological change.

Aim 2a. Assess the association with plasma biomarkers of AD neuropathology (Aβ40, Aβ42, p-tau181), neurodegeneration (NfL), and reactive astrocytosis (GFAP) in mid- and late

adulthood.
<u>Aim 2b.</u> Assess the association with dementia-related cerebral MRI markers, and markers of cerebral vascular sequelae in later adulthood.

Aim 3: Estimate the association of liver integrity on the i) NAFLD-fibrosis spectrum and ii) aminotransferase level over the adult life course with cognitive function.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).



Using the longitudinal ARIC study cohort we propose to estimate prospective associations of liver integrity with the risk of dementia, with intermediate markers of AD neuropathologic and brain morphologic change related to dementia, and with cognitive function. The 1990-92 examination of the ARIC cohort will serve as the baseline, with cohort follow-up through 2020. Participants who self-identified as Black or White (Black participants from Minneapolis and Washington County will be excluded due to the small numbers), without a diagnosis of stroke, dementia and clinical manifestations of liver disease (identified by hospital discharge diagnoses, International Classification of Diseases, Tenth Revision Clinical Modification [ICD-10-CM] codes K70-K77), lack of significant alcohol consumption (defined as current alcohol consumption of >21 standard drinks/week for men and >14 standard drinks/week for women), and AST:ALT ratio <2 (indicative of alcoholic fatty liver disease) at baseline constitute the study population. The analysis will include the entire cohort (N= ~12,000) for the risk assessment of dementia. For dementia-related pathological change, the analyses will include a stratified random sample of ARIC participants with brain MRI scans in 2011-2013 (N= ~1,500). Plasma markers of AD pathology also were assayed on this sample of the cohort.

Liver integrity

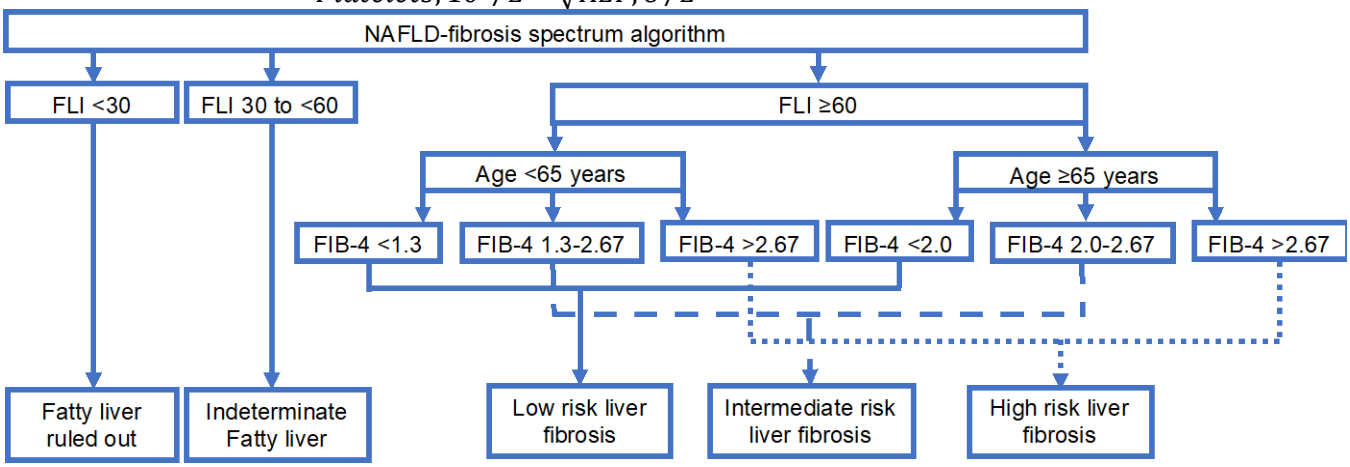
(1) Assessment of the NAFLD-fibrosis spectrum:

The NAFLD-fibrosis spectrum will be estimated by combining the fatty liver assessment model of FLI and liver fibrosis assessment model of FIB-4,[31-33] following the equation and algorithm shown as below.

$$Fatty\ liver\ index\ (FLI) = \frac{e^{y}}{e^{y}+1} * 100$$

$$where\ y = 0.953 * ln(triglycerides, mg/dL) + 0.139 * BMI, kg/m^2 + 0.718 * ln(GGT, U/L) + 0.053 * waist\ circumference, cm - 15.745$$

$$FIB-4\ score = \frac{Age, year * AST, U/L}{Platelets, 10^9/L * \sqrt{ALT, U/L}}$$



(2) Aminotransferase measurements

Plasma ALT, AST were measured at visits 6 and 7, and by two ancillary studies, namely AS2009.16 (PI: Selvin) and AS2014.13 (PI: Selvin) at visits 2, 4, and 5. Recalibration was conducted to harmonize the assay methodologies across study visits.[34] We will classify low aminotransferase as being below the 10th percentile, a category for which previous evidence suggests a high risk of all-cause dementia.[25]

Incident dementia

The ARIC study administered 3 cognitive tests at visits 2 and 4, and a comprehensive in-person neuropsychological battery was implemented at ARIC-NCS visits 5, 6, 7, and 8. Visit 8 also administrated a phone-based neuropsychological assessment due to COVID-19. Three dementia variables have been defined. Level 1 dementia was defined for cohort participants who completed in-person neuropsychological assessments at ARIC-NCS visits 5, 6, 7, or 8, or completed the phone-based assessments at visit 8 and had 1) a low Mini-Mental State Examination (MMSE) score (<21 for whites or <19 for blacks) or 2) Functional Activities Questionnaire (FAQ) >5 or Clinical Dementia Rating (CDR) sum of boxes >3, at least two cognitive domain Z score ≤-1.5, and a decline rate in general cognitive performance score >0.055/year. Dementia cases ascertained from phone-based assessments are carried forward unless a subsequent in-person assessment renders a different diagnosis. Inconsistent diagnosis or probable cases were adjudicated by an expert panel.[35, 36] Among participants who did not complete an in-person visit examination, level 2 dementia was determined by using the education-adjusted Telephone Interview for Cognitive Status–Modified (TICSm), a combination of the CDR and FAQ from an informant interview, or the Eight-item Dementia Screening Interview (AD8) or Six-Item Screener (SIS). Level 3 dementia included all level 1 and level 2 dementia diagnoses plus dementia cases for participants who had no neuropsychological assessments, informant interviews, TICS, AD8, or SIS assessments, identified from surveillance data, including dementia codes from discharge hospitalization records and death certificates.[36] Each participant was followed up for incident dementia up to 2020. Level 1 represents the

highest degree of confidence in a diagnosis but has the most missing data; level 3 has the least missing data because it is derived using all available sources of information. We will use level 3 dementia for the primary analyses, and perform a sensitivity analysis using level 1 dementia to confirm the robustness of our results.

Cognitive function

Cognitive performance was tested by the delayed word recall test, digit symbol substitution test, and word fluency test through visits 2-4. A comprehensive neuropsychological battery was implemented at ARIC-NCS/visit 5-8 and examined cognitive function in 3 domains: (1) memory (delayed word recall, logical memory, and incidental learning); (2) executive function (trail making tests parts A and B, and digit symbol substitution); and (3) language (word fluency, and Boston naming test). A longitudinal categorical confirmatory factor analysis model was utilized to generate factor scores for each domain. In addition, a global cognition factor score was computed utilizing the nine tests from the three domains and the digit span backwards. The recently developed V2_V8_CNF factor scores will be used.

Plasma-based biomarkers of AD pathology

The N4PE single-molecule array (Simoa™) of Aβ40, Aβ42, p-tau181, NfL, and GFAP are available on all cohort members who received brain MRI scans, both on visit 3 and visit 5, and a subsample who had a repeat MRI scan at visit 6/visit 7. (AS2020.27, PI: Palta)

Markers of cerebrovascular pathology

Brain morphology was measured with 3 Tesla MRI in 2011-13 and 2016-19 at the time of re-examination, and quantified at a central image processing center at the Mayo Clinic. Cerebrovascular lesions included brain infarcts (cortical, subcortical, and lacunar infarcts [lacunes<20mm]) and cerebral microhemorrhages (lobar and subcortical microhemorrhages). Cerebrovascular lesion markers will be analyzed as present/absent. White matter hyperintensity (WMH) was summed over the frontal, parietal, temporal, and occipital lobe volumes. WMH volume will be log transformed due to highly right skewed distribution. Diffusion tensor imaging (DTI) was used to assess WM microstructural integrity by estimating fractional anisotropy (FA) and mean diffusivity (MD). FA measures the directional constraint of water diffusion and ranges from 0 to 1. MD measures how quickly water molecules diffuse. Higher MD and lower FA usually indicate impaired WM microstructural integrity.[37] The brain volume and cortical thickness were quantified for the temporal lobe meta regions of interest (ROI) and the temporal-parietal lobe meta-ROI, regions considered susceptible to age-related neurodegenerative disease. The temporal lobe meta-ROI included the following brain regions: entorhinal cortex, fusiform gyri, inferior temporal lobe, middle temporal lobe, hippocampus, and amygdala. The temporal-parietal lobe meta-ROI included entorhinal, fusiform, inferior temporal, middle temporal, hippocampus, amygdala, and precuneus. To be noted, the hippocampus and amygdala regions were evaluated volumetrically and therefore only included in the brain volume quantification, but not in the cortical thickness quantification.[38, 39] Since only derived variables but not cerebrovascular lesions (identified and counted by radiologists) were reanalyzed in 2020 to produce harmonized measures to reconcile inconsistent trends over time, only longitudinal progression in derived variables will be included in the analysis related to the liver integrity.

Demographic, behavior, and cardiometabolic factors

Information about date of birth, sex, race-center, and education was collected at visit 1 by interview. Apolipoprotein E (APOE) ε4 was genotyped using the TaqMan assay (Applied Biosystems, Foster City, CA).[40] Participants' behavioral and clinical characteristics were ascertained at each exam visit using standardized protocols. Smoking and habitual alcohol use

were self-reported. Standardized anthropomorphic measurements of weight, height, and waist circumference were obtained at all exam visits. Body mass index was calculated using weight in kilograms divided by the square of height in meters. Sitting arm blood pressures were measured after a 5-minute rest using a standardized sphygmomanometer.[41] Three measures were taken for each individual and the average of the last two readings was calculated. Total and high-density lipoprotein cholesterols were measured using automated enzymatic methods.[42, 43] Estimated glomerular filtration rate was calculated using the CKD-EPI creatinine equation.[44] Matrix metalloproteinase 7 (MMP7) was assayed at visit 5.[45] Glucose was measured by a hexokinase/glucose-6-phosphate dehydrogenase method on a Coulter DACOS device (Beckman Coulter, Fullerton, CA).[46] Diabetes was defined as fasting glucose ≥126 mg/dL, non-fasting glucose ≥200 mg/dL, self-reported diagnosis of diabetes by a physician, or using antidiabetic medications. Use of medications for hypertension, dyslipidemia, and diabetes in the previous two weeks was self-reported by the participants and validated by medication containers brought to the ARIC clinic.

Statistical evaluation

[Aim 1] Liver integrity and risk of dementia over 30 years of follow up.

NAFLD-fibrosis spectrum and dementia

Multivariable Cox proportional hazards regression will be used to quantify the prospective association of NAFLD-fibrosis spectrum measured at midlife (visit 2) and late-life (visit 5) with incident dementia. Individuals without fatty liver (ruled out by FLI) will serve as the referent group. Within a subpopulation with NAFLD-fibrosis assessed at both visit 2 and visit 5, we will further quantify the association of NAFLD progression with incident dementia. The shift in categories of NAFLD-fibrosis from visit 2 to visit 5 (~20 years apart) will be characterized. Compared to the people who remained free of NAFLD (will combine fatty liver ruled out group and indeterminate fatty liver group due to small sample size), the risk of incident dementia associated with consistent low, intermediate, and high risk of liver fibrosis, and the progression from lower to higher risk of liver fibrosis will be quantified using multivariable Cox proportional hazards regression.

Midlife aminotransferase and dementia

ALT and AST at baseline will be categorized as quintiles. The first quintile will be subdivided into a <10th percentile and a 10th-20th percentiles to allow for observed non-linearity of associations at low plasma aminotransferase levels. We will estimate age, sex, race-center adjusted incidence rates of dementia over plasma aminotransferases using Poisson regression with robust standard errors. ALT and AST will be modeled as continuous variables with linear splines at 10th, 20th, 40th, and 60th percentiles (with a linear association at higher levels). Multivariable Cox proportional hazards regression will be used to quantify the prospective association of midlife plasma aminotransferases with incident dementia. ALT and AST will be examined individually according to the aforementioned categories, with the second quintile serving as the distribution-based referent.

Longitudinal change in aminotransferase across adult lifespan and dementia

Association of dementia risk with longitudinal change in aminotransferase level from visit 2 to visit 7 will be estimated using joint modeling, of a longitudinal model for aminotransferase level, and a Cox proportional hazards model for incident dementia, linked through either a latent growth trajectory or shared random effects.[47-49] This shared-parameter modeling will provide a flexible framework to account for the cohort attrition.[50] A latent growth trajectory model

identifying subpopulations based on their probability of sharing a similar aminotransferase change trajectory will be implemented following Andruff et al.[51] Alternatively, we will use a generalized linear mixed effects regression model accounting for the correlations of repeated aminotransferase measures at different time points. Random slopes and intercepts will be used to estimate inter-individual differences. For both modeling strategies, time on study will be modeled with a 2-piece linear spline with a knot at year 10, and a quadratic and/or a cubic term to account for the nonlinearity. Models will be compared and selected based on the Bayesian Information Criterion.

All of aforementioned Cox models will employ Efron's approximation to handle ties. Since many dementia cases were diagnosed at an ARIC visit, we will perform a sensitivity analysis using complementary log-log to handle interval censoring to evaluate the robustness of the results. We will repeat aforementioned analyses using level 1 dementia as the outcome. In this analysis, cohort attrition due to death and non-death drop-out associated with impaired integrity and cognitive function will be addressed analytically using stabilized inverse probability weighting. Logistic regression will be used to estimate the probability of death and non-death drop-out separately, with covariates selected per a priori knowledge, including all variables mentioned above plus dementia status, a composite factor score of global cognition,[52] comorbidities associated with attrition (coronary heart disease, heart failure, stroke), health information collected through annual follow-up interviews (an indicator of a report by proxy, self-reported poor health, number of hospitalizations), and interactions between variables.

[Aim 2] Liver integrity and dementia-related pathological change.

NAFLD-fibrosis spectrum and plasma AD biomarkers

The prospective associations of midlife NAFLD-fibrosis spectrum at visit 2 and AD biomarkers measured in midlife (visit 3), or later life (visit 5) will be assessed separately using linear regression models. The cross-sectional association of late-life NAFLD-fibrosis spectrum with AD biomarkers measured at visit 5 will also be assessed using linear regression model. To identify the trajectory of each AD biomarker from middle to later life across NAFLD-fibrosis spectrum measured at visit 2, we will fit linear mixed effects regression models which account for the correlations of AD biomarkers measured at different time points within the same individual. Random slope and intercept will be employed to account for individual differences. Applying the same approach to the brain imaging subcohort with available NAFLD-fibrosis assessment at both visit 2 and 5, AD biomarker trajectories associated with the shift in categories of NAFLD-fibrosis from visit 2 to visit 5 will be estimated.

NAFLD-fibrosis spectrum and brain MRI morphological markers

Prospective associations of midlife NAFLD-fibrosis spectrum at visit 2 and cross-sectional association of late-life NAFLD-fibrosis spectrum at visit 5 with brain MRI morphological markers measured at visit 5 will be quantified using linear regression models for continuous dependent variables, and logistic regression for binary dependent variables. Analyses of MRI brain markers will include sampling weights to account for the ARIC brain MRI sampling strategy. Total intracranial will be included as a covariate to adjust for differences caused by head size for volumetric brain MRI measures. For the longitudinal assessment of brain MRI morphological progression, to account for the potential bias caused by informative attrition of brain imaging subcohort, we will firstly apply multiple imputation by chained equations (MICE) to impute the missing values. Then the brain morphological progression will be quantified by subtracting measures at visit 5 from measures at visit 6/visit 7, and their associations with midlife or late-life NAFLD-fibrosis spectrum will be quantified using linear regression model. The value of the MRI measures at the visit 5 and the time between assessments will be included as covariates. Applying the same approach to the brain imaging subcohort with available NAFLD-fibrosis

assessment at visit 2 and 5, brain MRI morphological markers measured at visit 5 and progression associated with the shift in categories of NAFLD-fibrosis from visit 2 to visit 5 will also be estimated.

Aminotransferase and plasma AD biomarkers

As aforementioned in section ***Midlife aminotransferase and dementia***, midlife aminotransferase measured at visit 2 will be grouped into six categories. And longitudinal change in aminotransferase will be grouped by its latent class membership identified in section ***Longitudinal change in aminotransferase across adult lifespan and dementia***. The associations of midlife aminotransferase at visit 2 and AD biomarkers measured in midlife (visit 3), or later life (visit 5) will be assessed separately using linear regression models. To identify the trajectory of each AD biomarker from middle to later life across categories of midlife aminotransferase and its change, we will fit linear mixed effects regression models which account for the correlations of AD biomarkers measured at different time points within the same individual. Random slope and intercept will be employed to account for individual differences.

Aminotransferase and brain MRI morphological markers

Associations of midlife aminotransferase and its change with brain MRI morphological markers measured at visit 5 will be quantified using linear regression models for continuous dependent variables, and logistic regression for binary dependent variables. Analyses of MRI brain markers will include sampling weights to account for the ARIC brain MRI sampling strategy. Again, within a subsample of ~700 participants with brain MRI re-scanned at visit 6/visit 7, the association of midlife aminotransferase and its change with the brain morphological progression will be quantified using linear regression model.

If power allows, we will further use the method proposed by *Lange et al.* to estimate the proportion of additional dementia cases due to impaired liver integrity that can be attributed to, mediated by, the AD pathology or brain morphology changes.[53] The analysis will also consider an interaction between liver integrity with other metabolic risk factors and behavioral risk factors. Briefly, in step 1, we will fit generalized linear regression for markers of early AD pathology or cerebral vascular changes, one for each mediator, regressing on liver function and integrity and conditioning on a confounder set. In step 2, we will use the Aalen additive hazard model for dementia risk regressing on liver function and integrity, mediators, liver function and integrity-metabolic risk factor interactions, liver function and integrity-behavior factor interactions, and confounders. The natural direct (NDE) and indirect effects (NIE) will then be obtained using the coefficients from the aforementioned models, with confounders set at the mean levels. The percentage of additional risk due to mediators will be calculated as the ratio of (HR_{NDE}*HR_{NIE}-HR_{NDE}) over (HR_{NDE}*HR_{NIE}-1). Confidence intervals will be estimated using bootstrapping incorporating the correlations among direct, indirect, and total effects.

[Aim 3] Liver integrity and cognitive function.

NAFLD-fibrosis spectrum and cognitive function

The associations of midlife NAFLD-fibrosis spectrum at visit 2 and cognitive function measured in midlife (visit 2, cross-sectional), or later life (visit 5, prospective association) will be assessed separately using linear regression models. Cross-sectional association of late-life NAFLD-fibrosis spectrum and cognitive function at visit 5 will also be assessed. To identify the trajectory of cognitive function from mid- to later life across NAFLD-fibrosis spectrum measured at visit 2, we will fit linear mixed effects regression models which account for the correlations of cognitive function measured at different time points within the same individual. Random slope and intercept will be employed to account for individual differences. Applying the same approach to

a subpopulation with available NAFLD-fibrosis assessment at visit 2 and 5, cognitive function trajectories associated with the shift in categories of NAFLD-fibrosis from visit 2 to visit 5 will also be estimated.

Aminotransferase and cognitive function

As aforementioned in section ***Midlife aminotransferase and dementia***, midlife aminotransferase measured at visit 2 will be grouped into six categories. Longitudinal change in aminotransferase will be grouped by its latent class membership identified in section ***Longitudinal change in aminotransferase across adult lifespan and dementia***. The associations of midlife aminotransferase at visit 2 and cognitive function measured in midlife (visit 2, cross-sectional), or later life (visit 5, prospective association) will be assessed separately using linear regression models. To identify the trajectory of cognitive function from mid- to later life across categories of midlife aminotransferase and its change, we will fit linear mixed effects regression models which account for the correlations of cognitive function measured at different time points within the same individual. Random slope and intercept will be employed to account for individual differences.

Progressive adjusted models will be used. Model 1 is crude model. Model 2 will adjust for age, sex, race-center, education, and APOE ε4 genotype. Model 3 will additionally adjust for alcohol use and kidney function. In Model 4, we will further include other metabolic disorders of obesity, diabetes, hypertension, and dyslipidemia to assess the independent association. Model 3 will be used as the primary model.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes __X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.
ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/aricproposals/dtSearch.html

__X___ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?
ARIC MP #3487

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No

11.b. If yes, is the proposal

_X__ A. primarily the result of an ancillary study (list number* _____)
___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __ AS2009.16 (PI: Selvin), AS2014.13 (PI: Selvin), and AS2020.27 (PI: Palta) __**)**

*ancillary studies are listed by number https://sites.cscc.unc.edu/aric/approved-ancillary-studies

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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