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HUMAN DEVELOPMENT, BIRTH TO DEATH

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Concept Paper Form

Provisional Paper Title: Midlife-onset alcohol dependence: Testing early-life predictors and adult correlates in a five-decade longitudinal cohort study
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P.I. Sponsor: Terrie Moffitt, Avshalom Caspi (if the proposing author is a student or colleague of an original PI)
Today's Date: 10/8/2021 Additional variables requested 10/27/2021, prior to receipt of dataset and start of data analysis

Objective of the study:

Prior work has revealed that alcohol dependence tends to increase in adolescence and early adulthood, then declines sharply in the late 20s. This decline has been attributed to role transitions, including marriage and childbearing. However, not all individuals follow this developmental trajectory[1]. Indeed, some studies have identified a group of individuals who first develop alcohol dependence in middle adulthood[2,3]. Middle age also involves a variety of role transitions, including preparations for the health, financial, and social demands that accompany older age[4], making it a developmentally-salient period for understanding alcohol dependence.

The existing literature on midlife-onset alcohol dependence is limited by three factors. First, most research has relied on retrospective recall for assessing age-of-onset[5], which entails sources of invalidity and can underestimate prevalence rates for alcohol dependence[6]. Second, studies have largely employed selected samples (e.g., all-male veterans[5,7] and older patients[8]). Third, studies have failed to consider early-life predictors of midlife-onset alcohol dependence and have considered only a limited range of psychosocial and diagnostic correlates. It therefore remains unclear (a) what the prevalence of midlife-onset alcohol dependence is, when assessed prospectively; (b) which early-life and adult factors characterize individuals with midlife-onset alcohol dependence; and (c) whether these factors differ from those that characterize alcohol dependence with an earlier onset. Our study aims to address these gaps by providing a comprehensive analysis of the developmental epidemiology of midlife-onset alcohol dependence, within a five-decade longitudinal cohort study. We consider a broad range of theoretically- and empirically-driven predictors and correlates, and focus on factors that are relevant to the midlife transition period. In particular, extending prior work on midlife aging[4,9], we investigate how fast individuals with midlife-onset alcohol dependence are aging biologically, and how well they are preparing for later-life demands.

We have four primary aims:

Aim 1: To document the prevalence of new-onset alcohol dependence at midlife.

Aim 2: To identify prospective predictors that characterize individuals with midlife-onset alcohol dependence. We will consider measures in the following domains:

- Family psychiatric history
- Early-life mental health and substance use
- Personality traits
- [Secondary]: Socioeconomic status and IQ

Aim 3: To identify adult correlates that characterize individuals with midlife-onset alcohol dependence. We will consider measures in the following domains:

- Pace-of-aging and aging preparedness
- Mental health
- Life functioning
- Life events and stressors

Aim 4: To compare the predictors and correlates of midlife-onset alcohol dependence against those of early-onset alcohol dependence.

Data analysis methods:

Data preparation.

Group definitions.

The *midlife-onset alcohol dependence* group will be defined as individuals who first met criteria for DSM-IV alcohol dependence at age 38 or 45 years.

The *early-onset alcohol dependence* group will be defined as individuals who first met criteria for DSM-IV alcohol dependence at age 18 or 21 years.

The *never-dependent* group will be defined as individuals who never met criteria for DSM-IV alcohol dependence at any assessment wave between age 18 and 45 years.

All other individuals will comprise a fourth group: *other onset patterns*. This group is not of primary interest for analyses.

**Note:* To be included in analyses, we will require that individuals (a) have alcohol-dependence data available for at least three of the six assessment waves between age 18 and 45 years, and (b) have alcohol-dependence data available at age 18 or 21 years, to ensure that individuals are not misclassified as midlife-onset cases due to missing information about their symptoms at earlier assessments.

Predictors and correlates.

All continuous explanatory variables will be standardized prior to conducting regression analyses.

Aim 1: What is the prevalence of new-onset alcohol dependence at midlife?
We will calculate the proportion of cohort members who are in the midlife-onset alcohol dependence group.

To provide greater insight into the midlife-onset group's alcohol-dependence symptomatology, we will also calculate the endorsement rate for each alcohol-dependence symptom.

Aim 2: What prospective predictors characterize individuals with midlife-onset alcohol dependence?
Logistic regression models will be used to identify prospective predictors that differentiate the midlife-onset from the never-diagnosed group. All predictors will be treated as independent, and a binary variable indicating alcohol-dependence group membership will be treated as the outcome.

Aim 3: What adult correlates characterize individuals with midlife-onset alcohol dependence?
Logistic regression models will be used to identify adult correlates that differentiate the midlife-onset from the never-diagnosed group. All correlates will be treated as independent predictors, and a binary variable indicating alcohol-dependence group membership will be treated as the outcome.

Aim 4: Do the predictors and correlates of midlife-onset alcohol dependence differ from those of early-onset alcohol dependence?
Logistic regression models will be used to test whether the prospective predictors and adult correlates considered in Aims 2 and 3 differentiate (a) the early-onset group from the never-diagnosed group, and (b) the midlife-onset group from the early-onset group. All predictors and correlates will be treated as independent, and a binary variable indicating alcohol-dependence group membership will be treated as the outcome.

**Note:* Analyses for Aims 2 through 4 will control for sex.

Supplemental analysis:
To determine whether individuals in the midlife-onset group were close to meeting diagnostic criteria for alcohol dependence (were sub-threshold) at earlier ages, we will evaluate their levels of alcohol-dependence symptom endorsement at prior assessment waves. We will also consider informant reports of alcohol problems at prior waves.

Variables needed at which ages:
**Variable names are provided for measures currently listed on the data dictionary.*

Background and control variables
Participant ID number (SNUM)
Participant sex (SEX)

DSM-IV alcohol dependence across waves
Alcohol dependence diagnosis, DSM-IV, past-year, phase 45 (DXAL45D4)
Alcohol dependence diagnosis, DSM-IV, past-year, phase 38 (DXAL38D4)

Alcohol dependence diagnosis, DSM-IV, past-year, phase 32 (DXAL32D4)
Alcohol dependence diagnosis, DSM-IV, past-year, phase 26 (DXAL26D4)
Alcohol dependence diagnosis, DSM-IV, past-year, phase 21 (DXAL21D4)
Alcohol dependence diagnosis, DSM-IV, past-year, phase 18 (DXAL18D4)
Specific alcohol dependence symptoms (each individual symptom), phases 38 and 45

Prospective predictors

Primary

Proportion of first-degree relatives with alcohol dependence (PRALC1)
Proportion of first-degree relatives with substance dependence (PRSUB1)
Proportion of first-degree relatives with any anxiety disorder (PRANX1)
Proportion of first-degree relatives with major depressive episode (PRMDE1)

Low childhood self-control (LSCUW311)
Any mental-health diagnosis by age 15 (ANYDX1115)
Early exposure to any substances between ages 13--15 (EARLYUSE_2)

Past-year frequency of marijuana use, age 18 (MARJTRUNC18)
Past-year frequency of hard drug use, age 18 (DRGFRQ18)

MPQ Constraint scale, age 18 (back-filled with age 26 data) (ZMPQCON18i)
MPQ Negative Emotionality scale, age 18 (back-filled with age 26 data) (ZMPQNEM18i)
MPQ Positive Emotionality scale, age 18 (back-filled with age 26 data) (ZMPQPEM18i)

Secondary

Childhood IQ (WFSIQ711STD)
Childhood SES (SESAV115)

Any mental-health diagnosis by age 15 (see above), broken down by contributing diagnoses:

- ADHD (ADDLIFTM)
- Conduct disorder (CD1115)
- Anxiety (ANX1115)
- Depression (DEP1115)

Adult correlates

Pace-of-aging and aging preparedness

Pace-of-aging, phase 45 (PACEOFAGINGP45)
Facial age, phase 45 (ZFACIALAGE45)
Health preparedness PC, Richmond-Rakerd et al., PNAS 2021 (HLTH_FACTOR_IMP)[a]
Financial preparedness PC, Richmond-Rakerd et al., PNAS 2021 (FIN_FACTOR_IMP)[a]
Social preparedness PC, Richmond-Rakerd et al., PNAS 2021 (SOC_FACTOR_IMP)[a]
[a]These principal components were computed on the analytic sample for Richmond-Rakerd et al., PNAS 2021, and used mean-imputation based on that analytic sample. We may re-construct these PCs (using the same approach) on our analytic sample.

Mental health

Major depressive episode, DSM-5, past-year, phase 45 (DXMDE45)
Generalized anxiety disorder, DSM-5, past-year, phase 45 (DXGAD45)

Drug dependence (or on methadone maintenance), DSM-IV, past-year, phase 45 (DXDRG45M)
Nicotine dependence, DSM-IV, past-year, phase 45 (DXTOB45)
Ever attempted suicide in lifetime, through phase 45 (EVERATTSUIC45)
Informant-reported alcohol use problems, mean of raters, phase 45
Self-reported impairment/interference from alcohol dependence, phase 45
EHC, any treatment for emotional problems, phase 20 to 45 (EHCHELP2045)

Life functioning
Any adult conviction by phase 45 (ADLTCN45B)
LHC, months of unemployment from ages 26 to 45 (DURUNEM2645)
Social-welfare benefit days, 21 to 46 (BLENGTH_PRE2146)

Life events and stressors
LHC, count of stressful life events experienced between phases 38 and 45 (from Bourassa, Rasmussen, et al., 2021)

LHC, living with parents between phases 38 and 45
LHC, living with parents between phases 32 and 38
LHC, number of children (biological and non-biological) living in the home between phases 38 and 45
LHC, number of children (biological and non-biological) living in the home between phases 32 and 38
**We will use the four variables above to construct a measure indicating whether there has been a change in intergenerational household structure since the prior phase.*

Supplemental analysis
Alcohol dependence symptom count, DSM-IV, phase 18 (AD4count_18)
Alcohol dependence symptom count, DSM-IV, phase 21 (AD4count_21)

Informant-reported alcohol problems, phase 18 (INALC18)
Informant-reported alcohol problems, phase 21 (INALC21)

**Note:* Described above are the pre-planned analyses. Additional analyses may be added as suggested through internal and external peer review and will be identified as secondary in the manuscript.

Significance of the Study (for theory, research methods, or clinical practice):
There has been a call to improve understanding of the etiological factors involved in midlife alcohol dependence[10]. This is particularly important as middle age involves a variety of role transitions and is a critical period of preparing for the demands of older age[4]. To our knowledge, however, no prospective studies have considered the developmental origins of midlife-onset alcohol dependence, and there is a dearth of research on the relation between alcohol dependence in midlife and other key aspects of adult functioning. The present study will address these literature gaps. Results of this study could inform life-course epidemiologic models of alcohol dependence and improve early identification and prevention of alcohol-related problems in middle adulthood.

References cited:

[1]Vergés A, Haeny AM, Jackson KM, et al. Refining the notion of maturing out: Results from the national epidemiologic survey on alcohol and related conditions. *Am J Public Health*. 2013;103:e67-73.

[2]Moss HB, Chen CM, Yi H. Subtypes of alcohol dependence in a nationally representative sample. Drug Alcohol Depend. 2007;91:149-158.

[3]Moss HB, Chen CM, Yi H-Y. Prospective follow-up of empirically derived alcohol dependence subtypes in Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC): Recovery status, alcohol use disorders and diagnostic criteria, alcohol consumption behavior, health status, and treatment seeking. Alcohol Clin Exp Res. 2010;34:1073-1083.

[4]Richmond-Rakerd LS, Caspi A, Ambler A, et al. Childhood self-control forecasts the pace of midlife aging and preparedness for old age. Proc Natl Acad Sci U S A. 2021;118:e2010211118.

[5]Jacob T, Koenig LB, Howell DN, Wood PK, Haber JR. Drinking trajectories from adolescence to the fifties among alcohol-dependent men. J Stud Alcohol Drugs. 2009;70:859-869.

[6]Moffitt TE, Caspi A, Taylor A, et al. How common are common mental disorders? Evidence that lifetime prevalence rates are doubled by prospective versus retrospective ascertainment. Psychol Med. 2010;40:899-909.

[7]Jacob T, Bucholz KK, Sartor CE, Howell DN, Wood PK. Drinking trajectories from adolescence to the mid-forties among alcohol dependent males. J Stud Alcohol Drugs. 2005;66:745-755.

[8]Kist N, Sandjojo J, Kok RM, van den Berg JF. Cognitive functioning in older adults with early, late, and very late onset alcohol dependence. Int Psychoger. 2014;26:1863-1869.

[9]Wertz J, Caspi A, Ambler A, et al. Association of history of psychopathology with accelerated aging at midlife. JAMA Psychiatry. 2021;78:530-539.

[10]Chassin L, Sher KJ, Hussong A, Curran P. The developmental psychopathology of alcohol use and alcohol disorders: Research achievements and future directions. Dev Psychopathol. 2013;25:1567-1584.

Data Security Agreement

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Today's Date: 10/8/2021

☒	I am current on Human Subjects Training (CITI (www.citiprogram.org) or equivalent)
☒	My project is covered by the Duke ethics committee OR I have /will obtain ethical approval from my home institution.
☒	I will treat all data as "restricted" and store in a secure fashion. My computer or laptop is: a) encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines) b) password-protected c) configured to lock-out after 15 minutes of inactivity AND d) has an antivirus client installed as well as being patched regularly.
☒	I will not "sync" the data to a mobile device.
☒	In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact Moffitt or Caspi.
☒	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
☒	I will not post data online or submit the data file to a journal for them to post. *Some journals are now requesting the data file as part of the manuscript submission process. Study participants have not given informed consent for unrestricted open access, so we have a managed-access process. Speak to Temi or Avshalom for strategies for achieving compliance with data-sharing policies of journals.*
☒	I will delete all data files from my computer after the project is complete. Collaborators and trainees may not take a data file away from the office. This data remains the property of the Study and cannot be used for further analyses without an approved concept paper for new analyses.
☒	I have read the Data Use Guidelines and agree to follow the instructions.

Signature: Lara Khalifeh