



Long-term associations of cigarette smoking in early mid-life with predicted brain aging from mid- to late life

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Abstract

Background and aims: Smoking is associated with increased risk for brain aging/atrophy and dementia. Few studies have examined early associations with brain aging. This study aimed to measure whether adult men with a history of heavier smoking in early mid-life would have older than predicted brain age 16–28 years later.

Design: Prospective cohort observational study, utilizing smoking pack years data from average age 40 (early mid-life) predicting predicted brain age difference scores (PBAD) at average ages 56, 62 (later mid-life) and 68 years (early old age). Early mid-life alcohol use was also evaluated.

Setting: Population-based United States sample.

Participants/cases: Participants were male twins of predominantly European ancestry who served in the United States military between 1965 and 1975. Structural magnetic

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resonance imaging (MRI) began at average age 56. Subsequent study waves included most baseline participants; attrition replacement subjects were added at later waves.

Measurements: Self-reported smoking information was used to calculate pack years smoked at ages 40, 56, 62, and 68. MRIs were processed with the Brain-Age Regression Analysis and Computation Utility software (BARACUS) program to create PBAD scores (chronological age—predicted brain age) acquired at average ages 56 ($n = 493$; 2002–08), 62 ($n = 408$; 2009–14) and 68 ($n = 499$; 2016–19).

Findings: In structural equation modeling, age 40 pack years predicted more advanced age 56 PBAD [$\beta = -0.144$, $P = 0.012$, 95% confidence interval (CI) = -0.257 , -0.032]. Age 40 pack years did not additionally predict PBAD at later ages. Age 40 alcohol consumption, but not a smoking \times alcohol interaction, predicted more advanced PBAD at age 56 ($\beta = -0.166$, $P = 0.001$, 95% CI = -0.261 , -0.070) with additional influences at age 62 ($\beta = -0.115$, $P = 0.005$, 95% CI = -0.195 , -0.036). Age 40 alcohol did not predict age 68 PBAD. Within-twin-pair analyses suggested some genetic mechanism partially underlying effects of alcohol, but not smoking, on PBAD.

Conclusions: Heavier smoking and alcohol consumption by age 40 appears to predict advanced brain aging by age 56 in men.

KEYWORDS

Aging, alcohol, imaging, longitudinal, PBAD, smoking

INTRODUCTION

According to a World Health Organization 2020 report, more than 1.3 billion people currently smoke cigarettes world-wide, with an estimated 8 million people dying from smoking-related illness each year [1]. Smoking is a global health risk, associated with higher morbidity and mortality and increased risk for cognitive impairment and Alzheimer's disease (AD) [2,3]. Neuroimaging studies of cigarette smoking and brain regions of interest (ROIs) consistently show that higher levels of cigarette smoking are related to thinner cortex and smaller subcortical volumes [4–9]. A UK Biobank study comprising approximately 20 000 participants reported smaller total gray matter volume in long-term smokers [10]. Smokers seeking treatment for tobacco use have shown smaller cerebellar volumes relative to non-smokers [11]. Associations between smoking, the entorhinal cortex, fusiform gyrus and inferior temporal lobe provide additional evidence of links between smoking behaviors and pathological brain aging [6]. A study of middle-aged adults found that individuals who had ever smoked had brain signatures more similar to adults with AD than non-smokers [12]. Currently there are gaps in the literature as to whether smoking earlier in adulthood is related to later brain aging or how early in the life-course those associations manifest, and whether the degree of brain aging continues to advance with continued aging.

Machine learning algorithms applied to magnetic resonance imaging (MRI) data have been developed to create neuroimaging-derived biomarkers of estimated 'brain age' that can be used to predict a person's age based on the morphometry of their brain relative to chronological age or the brain of one's peers [13–16]. In contrast to approaches focused on specific ROIs, the brain age approach

contextualizes a person's brain age by their chronological age group, thereby summarizing a large amount of complex information into a single metric—the difference between one's chronological age and estimated brain age. This allows for inferences about advanced brain aging and global brain integrity for one's age. This approach comprises a powerful tool for identifying associations between premature/advanced brain aging and potential contributing factors or clinically relevant consequences. In predominantly cross-sectional studies, older brain age relative to chronological age is significantly associated with neurodegenerative diseases such as AD [13,17–19], poorer cognitive performance [15,20–22], health, life-style factors and stress [13,23–26]. Smoking has been associated with an older predicted brain age [21,24,25,27]. Brains of individuals who smoked or consumed alcohol frequently appear to exhibit older predicted brain age compared to those of their peers [24]. Some researchers have also proposed synergistic effects between smoking and alcohol [8,11]. Importantly, the majority of studies have been cross-sectional or only included a single time-point for brain imaging indices and had limited covariates.

In the present study we expand upon the existing literature on relationships between smoking and brain aging by (a) isolating cigarette smoking history (e.g. smoking pack years) at age 40 and (b) incorporating longitudinal MRI data. Smoking data were available at average ages 40, 56, 62 and 68 years. We created estimates of brain age at ages 56, 62 and 68 based on the MRI data. We predicted that a history of heavier smoking by early mid-life would be associated with more advanced brain aging later in life. Secondly, because some previous studies report co-occurrence of smoking and alcohol consumption, we conducted sensitivity analyses by additionally

examining early mid-life alcohol consumption and the interaction between smoking and alcohol consumption.

METHODS

Participants

We recruited the original Vietnam Era Twin Study of Aging (VETSA) 1 (age 56; 2002–08) participants [28] from the Vietnam Era Twin Registry (VETR) members who participated in the Harvard Twin Study of Substance Abuse (HTSSA) [29]. All VETR members were eligible to participate in the HTSSA and were not selected for any disorder or substance use. The VETR is a large nationally distributed registry of male–male twin pairs who served in the United States military at some point between 1965 and 1975 [30,31]; most (80%) did not experience combat. VETSA 1 MRI (2004–08) sub-study eligibility requirements included enrolling in the VETSA parent study starting in 2004, being between the ages of 51 and 59 at enrollment, both members of a twin pair agreeing to participate and passing the MRI safety screen ($n = 493$). There were no significant differences between participants who had an MRI and those who did not. VETSA 2 (age 62; 2009–14) and VETSA 3 (age 68; 2016–19) data collections included the majority of the original participants as well as attrition replacement participants recruited from the same VETR cohort (Figure 1 shows the enrollment in the MRI study over time). The time between VETSA 1 and 2 was approximately 5.6 years, and 5.7 years between VETSA 2 and 3. Details of the sample ascertainment and data collections are described elsewhere [28,32,33].

The majority of participants (90.8%) were non-Hispanic white, with average life-time education of 13.88 years. On average,

participants were age 56 at VETSA 1 [mean = 56.2, standard deviation (SD) = 2.6, range = 51–60], age 62 at VETSA 2 (mean = 61.8, SD = 2.6, range = 56–66) and age 68 at VETSA 3 (mean = 67.5, SD = 2.6, range = 66–73) (see Table 1 for descriptive statistics). Participants had comparable health and life-style characteristics to American men in their age range [34]. We excluded participants if they had a history of seizures, multiple sclerosis, HIV/AIDS or schizophrenia.

Procedures

VETSA in-person assessments involved questionnaires, medical history interviews, neuropsychological testing and structural MRI of the brain. Assessments occurred at two sites [University of California, San Diego and Boston University (with MRIs at Massachusetts General Hospital)], but MRIs were conducted only in San Diego in VETSA 3. In addition, we accessed previously collected data from the VETR archive for these participants. First, from mean age 20 (SD = 1.31, range = 17–26), we used a cognitive assessment participants completed at their induction into the military as a measure of early adult general cognitive ability (GCA). Secondly, we utilized data from a mailed health survey conducted when participants were, on average, aged 40 years (SD = 2.7, range = 33–44; 1990) [30,31] which asked about cigarette smoking, alcohol consumption, health problems and demographics. Approximately 16 years elapsed between the first assessment of smoking at age 40 and the first MRI at age 56. Measures assessed at each wave of data collection are depicted in Table 2.

The studies were approved by local institutional review boards at the participating institutions and participants provided written informed consent. From this point forward we refer to data collections by the mean participant age at time of assessment: 20, 40, 56, 62 and 68 years.

MRI Participants ($n=712$)

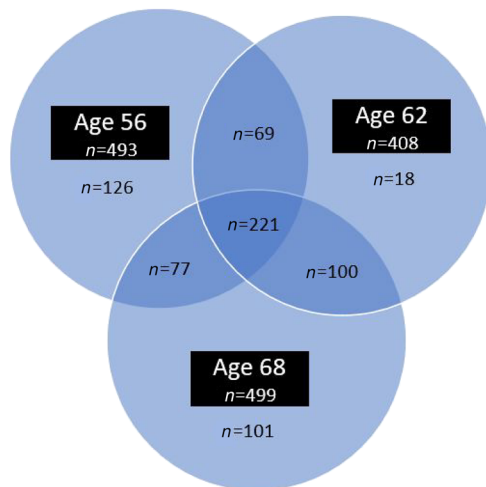


FIGURE 1 Enrollment in the Vietnam Era Twin Study of Aging (VETSA) magnetic resonance imaging (MRI) study at different waves and overlap over time

Measures

Smoking pack years

At ages 40, 56 and 68, participants responded to the same questions evaluating start- and end-dates of smoking and number of cigarettes smoked, if they had smoked more than 100 cigarettes in their life-time. By age 40, 39% of participants had never smoked and 29% currently smoked (Table 1). At age 62, participants were asked whether their smoking habits had changed since the last data collection. If they smoked and indicated no change, the values for number of cigarettes smoked and initiation data at age 56 were used; if they indicated a change they reported their current smoking information.

Pack years is a standard measure of exposure risk which combines duration plus intensity of cigarette smoking. The pack years a person had smoked at each time-point were calculated by multiplying the number of packs (no. of cigarettes/20) smoked per day by the number of years the person smoked). Pack years were highly correlated over time, from $r = 0.96$ (age 40 with age 68) to $r = 0.99$

TABLE 1 Descriptive information on the VETSA participants with magnetic resonance imaging (MRI)

	Age 40	Age 56	Age 62	Age 68	c ²	F-value	P-value
Participants with MRI (n)		493	408	499			
Age (years)	40.03 (2.69)	56.20 (2.62)	61.82 (2.62)	67.53 (2.61)			
Age change (years)							
Age 40 to MRI		16.17	21.79	27.5			
Education (years completed)	13.88 (2.09)	13.82 (2.12)	13.74 (2.03)	13.98 (2.07)		1.108	0.344
Ethnicity					2.030		0.512
White non-Hispanic	90.76%	89.86%	88.24%	88.58%			
Other	9.24%	10.14%	11.76%	11.42%			
Pack years (if smoker)	20.29 (14.94)	27.20 (21.25)	28.78 (22.84)	28.57 (23.51)		13.030	< 0.001
Smoking status					56.828		< 0.001
Current	29.48%	23.12%	18.63%	13.45%			
Former	31.79%	40.77%	43.38%	48.39%			
Never	38.73%	36.11%	37.99%	38.15%			
Alcohol (drinks/14 days)	12.14 (21.73)	10.91 (20.09)	12.39 (22.09)	11.37 (20.95)		0.498	0.684
Alcohol status					2.282		0.892
None	35.30%	35.50%	34.31%	37.95%			
Light	50.86%	52.33%	51.72%	50.20%			
Heavy	13.84%	12.17%	13.97%	11.85%			
Body mass index (BMI)	25.61 (3.19)	28.72 (4.15)	28.89 (4.25)	29.24 (4.25)		108.900	< 0.001
Health issues (% with condition)							
Stroke	0.31%	1.42%	1.72%	4.61%	2038.900		< 0.001
Hypertension	15.99%	55.17%	61.03%	70.14%	400.360		< 0.001
Diabetes	1.39%	9.53%	14.46%	24.05%	147.770		< 0.001

Abbreviations: BMI, body mass index; VETSA, Vietnam Era Twin Study of Aging.

TABLE 2 Assessment time-line of key variables

Average age at assessment					
20	40	56	62	68	
Regular variables					
General cognitive ability	Smoking consumption		PBAD	PBAD	PBAD
	Alcohol consumption		Age		
	BMI		Ethnicity		
	Cardiovascular health problems		Education		
	Hypertension				
	Depression				
	Respiratory health problems				
Change scores					
	Change in alcohol consumption (56–40)				
	Change in smoking consumption (56–40)				
			Age change (62–56)		
			Age change (68–56)		

Abbreviations: BMI, body mass index; PBAD, predicted brain age difference score.

(age 62 with age 68). Change in smoking was calculated by subtracting pack years at age 40 from pack years at age 56, where values of the change score represent gain in pack years.

Due to non-normal distributions both pack years at age 40 and the pack years change score were subsequently square root-transformed.

MRI acquisition and predicted brain age

Structural MRIs of the brain were acquired at age 56 ($n = 493$) using 1.5-tesla (1.5 T) MRI scanners, and at ages 62 ($n = 408$) and 68 ($n = 499$) using 3-tesla (3 T) MRI scanners; 221 participants were scanned at all three times (Figure 1). Full MRI methods are provided in Supporting information, S1 [35,36]. We used Brain-Age Regression Analysis and Computation Utility software (BARACUS) version 0.9.4 [15,26] linear support vector regression models derived from each individual's cortical thickness, cortical surface area and subcortical volume data to create the composite predicted brain age score. Predicted brain age is subtracted from chronological age creating the predicted brain age difference score (PBAD) [26]. A negative PBAD indicates brain age that is estimated to be older than one's chronological age. We then used residualized PBAD scores that were adjusted for scanner.

Covariates

Covariates included age, race/ethnicity, education, GCA assessed at age 20 and alcohol consumption, cardiovascular health, respiratory health, hypertension, body mass index (BMI) and depression at age 40. Participants completed the age 20 GCA measure: the Armed Forces qualification test (AFQT). The AFQT is a 100-item multiple-choice test [37,38] that is highly correlated with other tests of GCA, such as the Wechsler Adult Intelligence Scale ($r = 0.84$); the average intelligence of the VETSA sample is estimated at 105 [39].

Health variables at age 40 were self-reported. Alcohol consumption was based on consumption of wine, beer and/or hard liquor during the past 14 days (total of number of days drank \times number of drinks per day). We computed a change in alcohol consumption score by calculating the difference in drinks per 14 days at age 56 minus age 40. Due to a non-normal distribution, alcohol consumption at age 40 was square root-transformed, while the alcohol consumption change score was left in its original units. BMI was calculated as $[\text{weight (lbs)}/\text{height (inches)}^2] \times 703$; hypertension was self-reported (yes/no). The cardiovascular disease (CVD) index composite included heart attack, angina, heart failure, rheumatic heart disease, mitral valve prolapse, stroke, heart surgery, peripheral vascular disease, atrial fibrillation and diabetes. Respiratory health was a composite of history of asthma, chronic bronchitis, chronic obstructive pulmonary disease and emphysema. At age 40, approximately 3.9% of participants had any CVD, 5.4% reported respiratory issues and 7.8% said a doctor had ever told them they had depression.

We were primarily interested in modeling how smoking history at age 40 smoking predicts later PBAD, but this could be affected by change in several measures from age 40. We therefore included several change variables as covariates in various statistical models. Change scores simply subtract a participant's smoking pack years, alcohol consumption or age between respective assessments. Change in smoking pack years age range from 0 to a positive value; alcohol

change could be positive or negative. Age change variables were the elapsed number of years between assessments. Note that ages 56, 62 and 68 are averages, so the actual number of elapsed years varies across individuals. We included both education and age 20 GCA in order to adjust for social class/opportunity (e.g. education) and early adult cognitive ability, both of which may play a role in smoking initiation and continuity.

Data analyses

Descriptive statistics tested for participant differences at assessment waves by using analysis of variance (ANOVA) or χ^2 tests (Table 1). Structural equation modeling (SEM) used full information maximum likelihood (FIML) with robust standard errors (MLR) because twin data were nested in families in these non-twin analyses.

We used MPlus version 8.4 (Muthen & Muthen, 2019) to construct three SEM models: (1) model 1 is the base—most simple—model where smoking pack years and change in smoking pack years predicted PBAD at ages 56, 62, and 68, and included demographic covariates and age 20 GCA; (2) model 2 added age 40 alcohol consumption and change in alcohol consumption predicting PBAD at ages 56, 62 and 68, plus age 40 health covariates to model 1; and (3) model 3 added the smoking \times alcohol consumption interaction to model 2.

Models controlled for a variety of covariates directly on age 56 PBAD and indirectly on ages 62 and 68 PBAD, which include education, race/ethnicity, age, age changes (between VETSAs 1 and 2 and between VETSAs 2 and 3), age 40 health covariates and age 20 GCA. Key predictors that directly predicted ages 56, 62 and 68 PBAD included smoking pack years at age 40, alcohol consumption at age 40, age tested at the age 56 assessment and the change in smoking pack years between age 40 and age 56 assessments, and change in alcohol consumption between age 40 and age 56 assessments. Additionally, elapsed age in years between age 56 and age 62 assessments (AgeChange_{56-62}) and between the ages 56 and 68 assessments (AgeChange_{56-68}) predicted ages 56 and 68 PBAD, respectively. All three models adjusted for family, as these are non-twin analyses.

From a data visualization perspective, in Figure 2 we show simplified models, using blue paths to display correlations and orange paths to display predictor variables. In this figure, we also divided variables into how they were modeled. These included covariates (correlated with other variables and only predict age 56 PBAD), key predictors (correlated with other variables and predict ages 56, 62, and 68 PBAD) and age change variables (correlated with other variables, but only predict ages 62 or 68 PBAD). Age change scores account for amount of elapsed time between assessments.

We applied a FIML approach where we added all covariates, key predictors and age change variables as stand-alone variables in the models, estimating their individual variances. FIML allows for all available data to be used and produces unbiased parameters assuming data are missing at random with variables relevant to missingness included [40]. Models were adjusted for chronological age to control for effects of regression dilution bias in the PBAD measures [41]. FIML raw

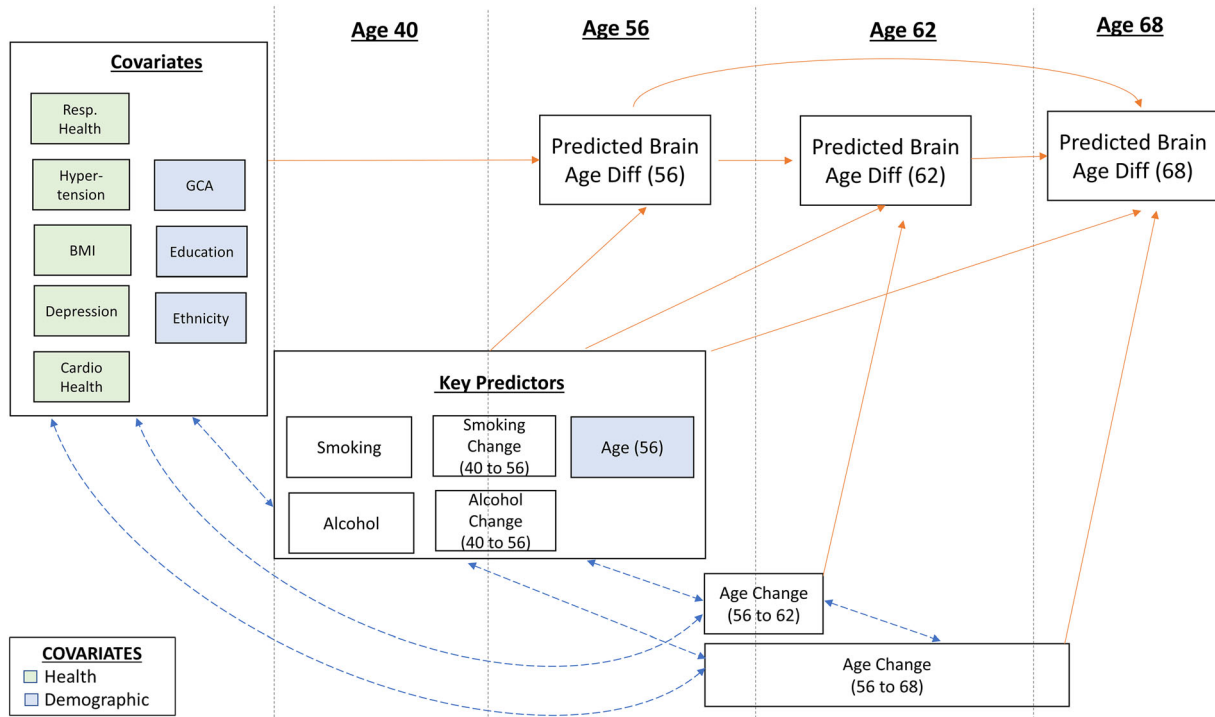


FIGURE 2 Measures in model 2: smoking and alcohol predicting PBAD, with covariates. GCA = general cognitive ability; Resp = respiratory; BMI = body mass index; Diff = difference; PBAD = predicted brain age difference. GCA, education, ethnicity, respiratory health, hypertension, BMI, cardiovascular health and depression were correlated with each other. Key predictors [smoking, smoking change (age 40–56), alcohol consumption and alcohol consumption change (age 40–56)] were correlated with each other. Age change at 56–62 and 56–68 were correlated with each other. Then, covariates, key predictors and age change intercorrelations were modeled. Age 56 PBAD was regressed onto covariates. All three PBAD scores were regressed onto key predictors. Age 62 PBAD was regressed onto age change (56–62) and age 68 PBAD was regressed onto age change (56–68). Age 68 PBAD was regressed onto both age 56 PBAD and age 62 PBAD and age 62 PBAD was regressed onto age 56 PBAD

continuous data methods used here are very robust to data missing at random (MAR). In contrast, if data are missing not at random, then missing values of a given variable may be related to the values of the variable itself. For example, subjects who report higher substance use or show signs of advanced brain aging may experience poorer health preventing study participation, which results in non-random attrition. Capitalizing on this being a twin sample, for each of the six variables of interest (smoking pack years, pack years change, alcohol consumption and PBAD at waves 1–3), we tested for distributional differences between complete and incomplete twin pair data using tests of mean and variance homogeneity [42]. To the extent that higher substance use or advanced brain aging is (a) familial and (b) predicts subject attrition, then data from twin singletons (whose co-twin did not participate) would reveal different response distributions when compared to data from complete twin pairs. After false discovery rate (FDR) correction for multiple testing [43], we found no significant differences (see Supporting information, Table S4-1). Thus, there does not appear to be non-random attrition related to our variables of interest.

We report standardized beta estimates. Significance levels are two-tailed. Age change covariates were considered as control variables of no interest. The analysis was not pre-registered.

In secondary analyses that further capitalized on this being a twin sample, we compared within-twin-pair differences in monozygotic

(MZ) and dizygotic (DZ) pairs—a type of co-twin-control analysis—to assess whether effects of pack years or alcohol on PBAD were due to environmental influences or due to genetic confounding [44,45]. Detailed methods of this approach are provided in Supporting information, S3. Briefly, because MZ twins are genetically identical, only environmental factors can make them different [45]. Thus, smaller within-pair differences in MZs compared with DZs would suggest that some genetic influences are at work. A lack of within-pair difference between MZ and DZ pairs would suggest environmental influences. A table of results for these analyses is provided in Supporting information, S3.

Goodness-of-fit analyses

Multiple measures were used to assess fit [46,47]: Tucker–Lewis index (TLI) [48]; comparative fit index (CFI) [49]; root-mean square of approximation (RMSEA); and χ^2 statistic [50], where significance suggests lack of fit. Because these models are nested, χ^2 tests were adjusted with a scaling factor [51]. Good RMSEA values are typically < 0.06; good-fitting CFI and TLI values are typically > 0.95 [52]. Finally, the Akaike information criterion (AIC) is used to compare two models, where lower values indicate better fit [53]. See Supporting information, Table S2-3 for goodness-of-fit results.

RESULTS

Preliminary analyses

Correlations among key measures are provided in Supporting information, Table S2-1. Smoking pack years by age 40 were negatively correlated with PBAD at ages 56, 62 and 68 ($r = -0.12$, $P = 0.005$; $r = -0.09$, $P = 0.06$; $r = -0.15$, $P = 0.001$, respectively). Alcohol consumption at age 40 was also negatively correlated with PBAD at ages 56, 62 and 68 ($r = -0.18$, $P < 0.001$; $r = -0.22$, $P < 0.001$, $r = -0.22$, $P < 0.001$, respectively). Thus, participants who smoked or drank more heavily had older than expected brains for their age, indicating more advanced brain aging. PBAD scores correlated highly across the 12 years of assessment ($r_s = 0.75-0.79$, $P_s < 0.001$). At age 40, heavier smokers consumed higher amounts of alcohol ($r = 0.25$, $P < 0.001$).

SEM

We focus here on the results for the main effects of age 40 smoking pack years and alcohol consumption and their interaction. Full results for all the variables in the models with confidence intervals are shown in Supporting information, Table S2-2.

Model 1 (base model)

Age 40 pack years were associated with age 56 PBAD ($\beta = -0.165$, $P = 0.004$, 95% CI = 0.276, -0.053), indicating that heavier smoking was associated with older brain age than expected (see Table 3). Age 40 pack years were not associated with PBAD at age 62 ($\beta = 0.010$, $P = 0.839$, 95% CI = -0.090, 0.111) or age 68 PBAD ($\beta = -0.041$, $P = 0.297$, 95% CI = -0.117, 0.036). Age 56 PBAD was significantly associated with ages 62 and 68 PBAD ($\beta = 0.736$, $P = 0.000$, 95% CI = 0.673, 0.798; $\beta = 0.363$, $P = 0.000$, 95% CI = 0.244, 0.482,

respectively) and age 62 PBAD was significantly associated with age 68 PBAD ($\beta = 0.503$, $P = 0.000$, 95% CI = 0.385, 0.621). Neither age 20 GCA, education or change in smoking from ages 40 to 56 was associated with age 56 PBAD. Model 1 demonstrated a good fit compared to a saturated model (see Supporting information, Table S2-3).

Model 2

Model 2 added age 40 alcohol consumption measures and health covariates to model 1. Age 40 pack years were associated with age 56 PBAD ($\beta = -0.144$, $P = 0.012$, 95% CI = -0.257, -0.032; see Table 3 and Figure 3), but not with ages 62 or 68 PBAD. Age 40 alcohol consumption was associated with both ages 56 PBAD ($\beta = -0.166$, $P = 0.001$, 95% CI = -0.261, -0.070) and age 62 PBAD ($\beta = -0.115$, $P = 0.005$, 95% CI = -0.195, -0.036), but not with age 68 PBAD ($\beta = -0.028$, $P = 0.471$, 95% CI = -0.105, 0.048). Thus, heavier smoking and alcohol consumption at age 40 were independently associated with having an older than predicted brain at age 56 and, for alcohol, also at age 62. Neither change in smoking nor change in alcohol consumption contributed significantly to model 2. The model demonstrated a good fit compared to a saturated model (see Supporting information, Table S2-3). Of the age 40 covariate health measures, only hypertension was associated with age 56 PBAD ($\beta = -0.125$, SE = 0.036, $P < 0.0001$), indicating that early hypertension was independently associated with having an older than expected brain age at age 56.

Model 3

Model 3 added the age 40 smoking \times alcohol consumption interaction to model 2. Neither age 40 smoking ($\beta = -0.102$, $P = 0.122$, 95% CI = -0.231, 0.027), alcohol ($\beta = -0.095$, $P = 0.23$, 95% CI = -0.249, 0.06) or their interaction ($\beta = -0.11$, $P = 0.222$, 95% CI = -0.286, 0.066) were significantly associated with age 56 PBAD; nor were

TABLE 3 Structural equation model results for key measures from best-fitting model (model 2)

	PBAD age 56 Standardized estimate (SE) P-value	PBAD age 62 Standardized estimate (SE) P-value	PBAD age 68 Standardized estimate (SE) P-value
Smoking pack years age 40	-0.144 (0.06) P = 0.012	0.030 (0.05) P = 0.563	-0.043 (0.04) P = 0.286
Change in smoking	0.130 (0.07) P = 0.059	-0.020 (0.06) P = 0.723	-0.014 (0.05) P = 0.775
Alcohol consumption age 40	-0.166 (0.06) P = 0.001	-0.115 (0.04) P = 0.005	-0.028 (0.04) P = 0.471
Change in alcohol	-0.042 (0.05) P = 0.359	-0.009 (0.04) P = 0.806	0.018 (0.03) P = 0.534
PBAD age 56		0.721 (0.03) P < 0.0001	0.361 (0.06) P < 0.0001
PBAD age 62			0.499 (0.06) P < 0.0001

Note: Bold type indicates significant results.

Abbreviations: BMI, body mass index; PBAD, predicted brain age difference; SE, standard error. Model 2 variables include: smoking pack years at age 40, average drinks of alcohol in past 14 days at age 40, demographics (age, ethnicity, education), age 20 general cognitive ability, age 40 BMI, hypertension, cardiovascular disease index, respiratory index, depression (yes/no), changes in age (56-62; 56-68), changes in smoking (from 40 to 56), changes in alcohol consumption (40-56) (full models including confidence intervals are provided in Supporting information, Table S2-2).

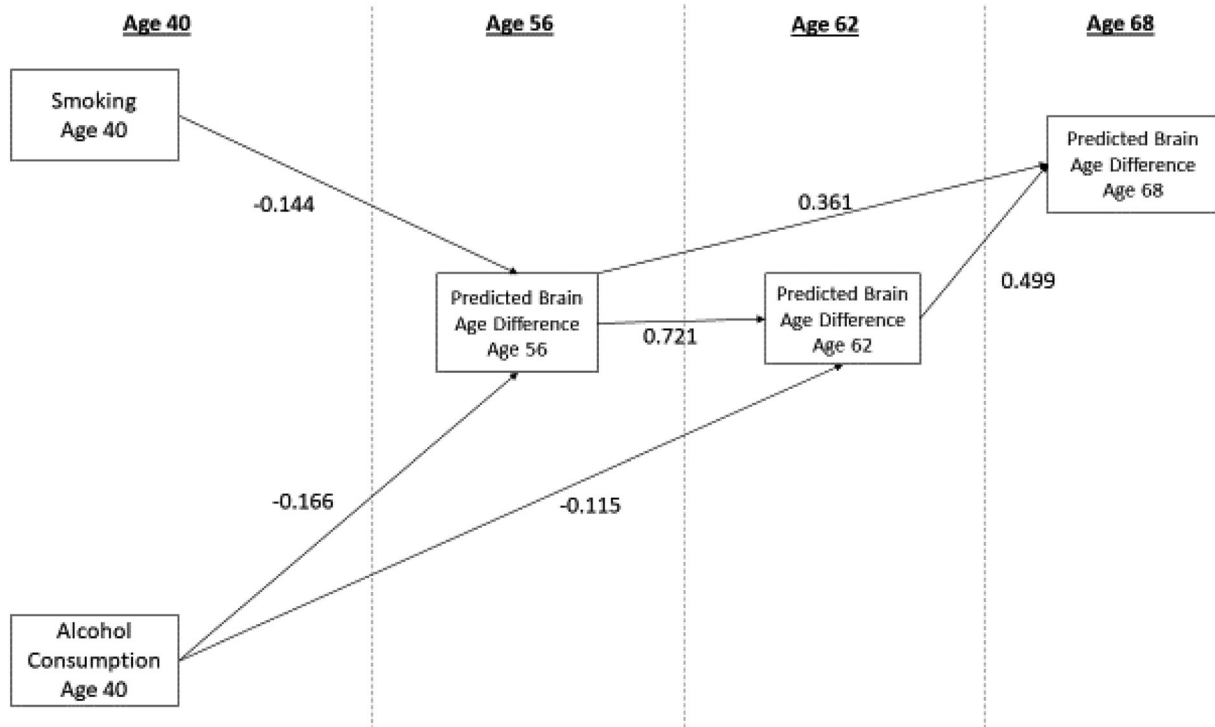


FIGURE 3 Significant main effects of age 40 smoking pack years and alcohol consumption on predicted brain age difference (PBAD) for the best-fitting model (model 2). Model 2 adjusts for all covariates as indicated in Figure 2 except the smoking \times alcohol interaction. Shown are standardized parameter estimates for significant paths (see Supporting information, Table S2-2 for full results, including the confidence intervals). We constrained paths with the interaction term in model 3 to zero and the model 2 Akaike's information criterion (AIC) was then compared to model 3. Model 3's AIC was higher than the constrained model (37 797.452 versus 37 793.782), indicating that the more parsimonious model 2, without the interaction, is a better-fitting model

they associated with ages 62 or 68 PBAD (see Supporting information, Table S2-2). Although model 3 demonstrated a good fit ($\chi^2_{(20)} = 21.48$, $P = 0.3694$, RMSEA = 0.010, CFI = 0.998, TLI = 0.995), comparisons of model 3 with model 2 by constraining paths with the interaction term in model 3 to zero showed that model 3's AIC was higher than the constrained model (37 797.452 versus 37 793.782). Thus, the more parsimonious model 2—without the interaction—is a better-fitting model.

Co-twin control analyses

We compared within-twin pair differences in MZ and DZ pairs—a type of co-twin control analysis—to assess whether effects of pack years or alcohol on PBAD were due to environmental influences or to genetic confounding. A lack of MZ–DZ pair differences indicated that smoking effects on PBAD were due to environmental exposure. Because MZ twins are genetically identical, only environmental factors can make them different (see Supporting information, S3 for detailed methods and Table S3-1 for results). Although underpowered for a definitive conclusion, the lower MZ than DZ between-pair difference suggested some genetic confounding of alcohol consumption effects on PBAD.

DISCUSSION

Our major finding was that smoking history at age 40 was associated with more advanced predicted brain age 16 years later at age 56 and that alcohol consumption independently contributed to advanced predicted brain age at both ages 56 and 62. Individuals with lower cognitive ability in young adulthood and fewer years of education were more likely to have higher pack years and higher alcohol consumption, but age 20 GCA and education were not directly associated with predicted brain age after accounting for their associations with alcohol consumption and smoking history at age 40. Hypertension was the only early mid-life health factor that was associated with PBAD. Consistent with prior cross-sectional results, high blood pressure was associated with worse predicted brain age; however, our results were across a 16-year period [54]. Studies of much older adults have reported associations between smoking and alcohol consumption and associations of advanced predicted brain age with mild cognitive impairment (MCI) and dementia [6,17,18,27,55]. Our finding that age 40 smoking and alcohol consumption independently predicted PBAD as early as age 56 suggests that their associations with brain aging begin earlier than previously identified.

There are a number of distinguishing features of the present study. First, we had information on history of smoking and alcohol

consumption at age 40, 16 years before the brain age measures, and we had access to a broad array of risk/protective factors. It is a particular strength of the study that we are able to adjust for age 20 GCA, as higher GCA is typically associated with having a larger and healthier brain as well as with less smoking and alcohol consumption [12,22]. Previous findings about education are probably confounded with GCA and measures of pre-morbid GCA are seldom available in studies of older adults. With the data back to age 20 and use of SEM, we were able to adjust for inter-relationships among these measures over a long period of time. The PBAD measure is also a strength of the study. In contrast to ROI-based measures, the brain-age approach contextualizes a person's overall brain morphometry by their age group. This creates a single metric that summarizes a large amount of complex information across the brain, thus allowing for inferences about advanced brain aging and global brain morphometry. Having multiple measures of PBAD from ages 56 to 68 as well as smoking history assessed at multiple time-points allowed us to examine the timing of the effects of smoking on brain aging. We were surprised, however, that with the exception of age 40 hypertension, age 40 health problems—including the cardiovascular disease index—were not associated with this metric of brain aging. Lane *et al.*, [56] for instance, reported that higher Framingham cardiovascular risk scores at ages 36, 53 and 69 were associated with smaller whole brain volume at age 69. It may be that the low prevalence of diseases at age 40 in our sample or the reliance upon self-report reduced our ability to find these associations. However, while the original Framingham index may pick up on aggregated risk factors prior to disease onset, it may also obscure the relative contribution of separate risk factors at different times, as smoking is one component of the Framingham index.

Smoking and alcohol consumption are presumed to affect brain health through multiple pathways involving cardiovascular risk and neurotoxic effects [11,57–60]. In addition, smoking and alcohol consumption in early mid-life could increase risk for dementia through their effects on brain aging [27]. Smoking and alcohol consumption as environmental exposure effects on brain aging are intuitive. Interestingly, however, our within-twin-pair analyses also suggested some genetic effects underlying the association of alcohol consumption and PBAD. Whether these genetic effects are related to genes that influence susceptibility to or amount of alcohol consumption or genes that influence how the brain responds to alcohol remains to be determined. In any case, the results suggests that a partial mechanism underlying this effect is genetic differences. Further follow-up will also be needed to determine the extent to which earlier smoking, alcohol consumption and PBAD modulate risk for AD or MCI.

Limitations

The study has limited generalizability to women and ethnic minorities. Ample data on the deleterious effects of smoking and alcohol are suggestive of causality, but without age 40 MRI data definitive causal inferences cannot be made from our observational study. Although smoking pack years is an imperfect measure, it provides perspective

on life-time risk and exposure [61]. Thus, smoking pack years at age 40 helps to anchor risk in early mid-life. Also, due to a change in smoking questions only at age 62, the age 62 report of smoking required that the participant be able to compare their current smoking with smoking at age 56. This may introduce some bias due to recall at age 62 for those who were still smoking. The original BARACUS formulas were developed with data from 3 T scanners, but our age 56 data were from 1.5 T scanners [15]. However, the high intercorrelations among the PBAD measures across the three waves support the validity of the age 56 measure. Finally, genetic influences underlie both smoking behavior and brain aging. Our results suggest the interesting conclusion that alcohol's effect on brain aging is partially genetic, but due to insufficient power that conclusion must be considered preliminary.

CONCLUSIONS

Meta-analyses suggest that a brain health risk reduction agenda could be effective in reducing risk for dementia, and smoking and alcohol consumption are among the top modifiable risk factors for dementia [3,62,63]. The 2020 Lancet Dementia Prevention, Intervention and Care Commission reported that ~40% of dementia incidence can be attributed to modifiable risk factors [2], although this remains to be fully supported by clinical trials [64]. The suggestion of genetic confounding for the effects of alcohol indicates that risk assessment and optimal intervention strategies regarding alcohol might differ for different genetic subgroups. The Lancet Commission life-course model recommended targeting alcohol consumption during middle age and smoking in old age. Our findings regarding age 40 smoking and alcohol consumption extend life-course research in this area and suggest that harm associated with these modifiable life-style behaviors was evident as early as mid-life in men.

DECLARATION OF INTERESTS

No competing interests to declare.

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AUTHOR CONTRIBUTIONS

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SUPPORTING INFORMATION

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