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Impact of lifestyle dimensions on brain pathology and cognition

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ABSTRACT

Single lifestyle factors affect brain biomarkers and cognition. Here, we addressed the covariance of various lifestyle elements and investigated their impact on positron emission tomography–based β-amyloid (Aβ), hippocampal volume, and cognitive function in aged controls. Lower Aβ burden was associated with a lifestyle comprising high cognitive engagement and low vascular risk, particularly in apolipoprotein E ε4 carriers. Although cognitive function was related to high lifetime cognitive engagement and low vascular risk, Aβ load had no relation to current cognitive function. The covariance between high adult socioeconomic status, high education, and low smoking prevalence predicted better cognitive function and this was mediated by larger hippocampal volume. Our data show that lifestyle is a complex construct composed of associated variables, some of which reflect factors operating over the life span and others which may be developmental. These factors affect brain health via different pathways, which may reinforce one another. Our findings moreover support the importance of an intellectually enriched lifestyle accompanied by vascular health on both cognition and presumed cerebral mediators of cognitive function.

1. Introduction

Up to half of all worldwide dementia cases may be attributable to modifiable lifestyle factors (Barnes and Yaffe, 2011). Many investigators have attempted to address the effects of lifestyle factors on both the risk of developing Alzheimer's disease (AD) (Snowdon et al., 1996; Verghese et al., 2003) as well as the specific effects of lifestyle on the brain that may mediate AD risk (Landau et al., 2012; Reed et al., 2014; Valenzuela et al., 2008; Vemuri et al., 2012; Villeneuve et al., 2014). In these studies, factors such as cognitive engagement, physical activity, leisure activities, diet, and disease-related variables that may reflect health behaviors (such as cardiovascular risk) have been examined. "Lifestyle" is, thus, a very complex set of behaviors and exposures that are related to one another and many other factors including genetics and socioeconomic status (SES; Jagust and Mormino, 2011). Furthermore, many such lifestyle factors often serve as proxies for unmeasurable constructs such as brain reserve or resilience (Murray et al., 2011).

Although the individual impact of various lifestyle factors has been repeatedly investigated, only a few studies have addressed their covariance and combined relationships to brain and cognition. The evaluation of multiple lifestyle variables—education and occupational and leisure cognitive/social activities combined into a composite lifestyle variable—has revealed an effect of lifestyle on cerebral small vessel disease features, neuronal density, cortical thickness, and brain weight (Valenzuela et al., 2012), and on global cognitive function (Vemuri et al., 2012, 2014). In statistical models, the inter-relation between lifestyle variables has been mainly addressed by treating other lifestyle factors as covariates or moderator variables, by defining lifestyle indices, for example, by summing binary scores for each lifestyle variable (Aleksandrova et al., 2014; Chiuve et al., 2008; Hamer and Stamatakis, 2008) or by using combinations of a priori grouping of variables and principal component analysis (Vemuri et al., 2012, 2014). All these methods introduce assumptions about the relationships between variables that may not be valid.

The present study approached the problem of lifestyle as a coherent and broader construct of separate domains (1) to try to

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parse how various lifestyle elements co-vary with or differ from one another and (2) investigate how those co-varying lifestyle variables differently affect brain biomarkers and cognition by evaluating multiple pathways at once.

2. Material and methods

2.1. Selection of participants

The study included 152 cognitively normal older people representing a convenience sample, the Berkeley Aging Cohort Study. Subjects were recruited from the community by advertisements and word of mouth. Criteria for study inclusion were a geriatric depression scale (GDS) score $\leq$10, a mini mental status examination (MMSE) score $\geq$25, normal cognitive functions (all cognitive scores within −1.5 standard deviation [SD] of age-, gender-, and years of education-adjusted norms on 2 delayed recall memory tests: California verbal learning test long delay free recall and Wechsler III visual recall long delay free recall), and an age between 60 and 90 years at the first visit. Each participant underwent a standardized neuropsychological test session, as well as magnetic resonance imaging (MRI), [^{11}C] Pittsburgh-compound-B (PIB), and [^{18}F] fludeoxyglucose (FDG)-positron emission tomography (PET) scanning. None of the individuals reported current serious medical, neurologic, or psychiatric illnesses. Participants indicated whether they had a past or present medical history of arterial hypertension, hyperlipidemia, and diabetes diagnosed by a health care professional and whether they had ever smoked cigarettes. Apolipoprotein E (APOE) genotyping was performed using DNA obtained from blood samples, and subjects were classified as heterozygote or homozygote APOEε4 (APOEε4+), as homozygote APOEε3 (APOEε3+), and as heterozygote or homozygote APOEε2 (APOEε2+) allele carriers. The available sample included all 118 individuals from previous publications (Landau et al., 2012; Wirth et al., 2014a, 2014b) that focused on the investigation of the relationships between cognitive activity, physical activity, and cortical amyloid-β (Aβ) retention. Written informed consent was obtained from each participant in accordance with the Institutional Review Boards of the University of California, Berkeley and Lawrence Berkeley National Laboratory (LBNL).

2.2. Cognitive activity, physical activity, and SES

Assessment of cognitive activity, physical activity, and SES has been reported in detail previously.

Lifetime cognitive activity was assessed using a validated 25-item questionnaire (Wilson et al., 2003) recording the frequency of common cognitively demanding activities (e.g., reading, writing letters) at various age epochs (6, 12, 18, and 40 years retrospectively and current age). Responses were provided on a 5-point frequency scale (1 = once a year or less, 5 = every day or almost every day). Three cognitive activity measures were created by calculating the mean of each age epoch for every participant: early life (average over the age epochs 6, 12, and 18), middle life (average over the age epoch 40), and current life (average over the current age epoch) cognitive activity. Based on 118 individuals who fully completed 2 or more cognitive activity measurements (mean [SD] time interval between 2 measurements 18 months [6.3]), calculated intraclass correlation coefficients (test-retest reliability) were 0.94 (95% confidence interval [CI], 0.92–0.96) for early life cognitive activity, 0.82 (95% CI, 0.73–0.87) for middle life cognitive activity, and 0.79 (95% CI, 0.69–0.85) for current life cognitive activity.

Current physical activity was quantified using the modified Minnesota leisure-time activities questionnaire (Geffken et al., 2001; Taylor et al., 1978). The participants indicated the frequency they participated in physical and leisure activities during a typical, recent 2-week period and during how many months per year. Frequency and duration information were multiplied using an activity-specific intensity code indicating calorie expenditure (Taylor et al., 1978) and summed to represent the intensity of physical activity (total kilocalories of energy expended) during the last year. Separately, the subjects assessed their walking miles or walking blocks (10 walking blocks equated with 1 walking mile) during a typical, recent 1-week period and their hours seated (including e.g., sleeping, eating and any other time sitting down) during a usual 24-hour period. Based on 115 individuals who fully completed 2 or more physical activity measurements (mean [SD] time interval between 2 measurements 18 months [6.3]), calculated intraclass correlation coefficients were 0.80 (95% CI, 0.71–0.86) for total kilocalories of energy expended during the last year, 0.82 (95% CI, 0.74–0.87) for walking miles during a 1-week period, and 0.68 (95% CI, 0.54–0.78) for hours seated during a 24-hour period.

SES was estimated from the participants' self-reported professional backgrounds, based on the 1990 occupation classification systems of the U.S. Bureau of the Census (Hauser and Warren, 1997).

2.3. Lifestyle dimensions

We applied a factor analysis for mixed (quantitative and qualitative) data (FAMD) using FactoMineR version 1.27 (Husson et al., 2011) to identify uncorrelated clusters of variables that segregate into various lifestyle domains, to intentionally capture covariance patterns between distinct lifestyle variables. FAMD can be roughly considered as a composite of principal component analysis for quantitative variables and multiple correspondence analysis for qualitative data, balancing the influence of both continuous and categorical variables in the analysis. FAMD extracts components or dimensions, which represent clusters of variables that correlate highly with one another.

We included the following lifestyle variables in the analysis: quantitative cognitive lifestyle variables (early life cognitive activity, middle life cognitive activity, current life cognitive activity, SES, and education), quantitative measures of physical activity (total kilocalories of energy expended during the last year, walking miles during a 1-week period, and hours seated during a 24-hour period), and qualitative variables referring to the subjects' vascular risk profile (arterial hypertension, hyperlipidemia, diabetes, and smoking status).

For individuals with multiple assessments, variables closest to PET scanning were chosen.

We extracted 4 components with eigenvalues >1, which explained 54% of the variance in the data. To best illustrate results, components were named based on the individual variables that expressed the highest dimension loading score for the respective dimension as follows: dimension 1 - high lifetime cognitive activity and low vascular risk profile (high CogAct/low VascRisk), dimension 2 - low current physical activity and high vascular risk profile (low PhysAct/high VascRisk), dimension 3 - high socioeconomic status/education and low smoking prevalence (high SES/high edu/low smoking), and dimension 4 - high vascular risk profile (high VascRisk; Table 1).

Exploratory factor analysis by stepwise heuristic specification search and subsequent confirmatory factor analysis, each conducted using the IBM SPSS Amos statistical software package (version 22.0), revealed a good model fit of this 4-factor solution (BCC_0 [Browne-Cudeck criterion] = 0, BIC_0 [Bayes information criterion] = 0, χ^2/degrees of freedom [df] = 0.6, Bentler-Bonett normed fit index [NFI] >0.9, and RMSEA [root mean square error of approximation] <0.03). The largest sample size for which one