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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 (PET)-based β -amyloid ($A\beta$), hippocampal volume and cognitive function in aged controls. Lower $A\beta$ burden was associated with a lifestyle comprising high cognitive engagement and low vascular risk, particularly in apolipoprotein E (APOE) $\epsilon 4$ carriers. While cognitive function was related to high lifetime cognitive engagement and low vascular risk, $A\beta$ 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 lifespan 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.

Keywords

aging; amyloid; APOE; hippocampus; PIB

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

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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 to many other factors including genetics and socioeconomic status (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).

While 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, 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; Vemuri et al., 2014). In statistical models the interrelation between lifestyle variables has been mainly addressed by treating other lifestyle factors as co-variables or moderator variables, by defining lifestyle indices, e.g. 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; Vemuri et al., 2014). All of 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 in order (i) to try to parse how various lifestyle elements co-vary with or differ from one another, and (ii) to 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 (BACS). Subjects were recruited from the community by advertisements and word of mouth. Criteria for study inclusion were a Geriatric Depression Scale (GDS) score ≥ 10 , a Mini Mental Status Examination (MMSE) score ≥ 25 , normal cognitive functions (all cognitive scores within ± 1.5 standard deviation [SD] of age-, gender- and years of education-adjusted norms on two 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 MRI and [^{11}C] Pittsburgh-compound-B (PIB) and [^{18}F] Fludeoxyglucose (FDG)-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 healthcare 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 APOE ϵ 4 (APOE ϵ 4+), as homozygote APOE ϵ 3 (APOE ϵ 3+) and as heterozygote or homozygote APOE ϵ 2 (APOE ϵ 2+) allele carriers. The available sample included all 118 individuals from previous publications (Landau et al., 2012; Wirth et al., 2014b; Wirth et al., 2014a) that focused on the investigation of the relationships between cognitive activity, physical activity and cortical amyloid- β (A β) 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 socioeconomic status

Assessment of cognitive activity, physical activity and socioeconomic status (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, 40 years retrospectively, and current age). Responses were provided on a five-point frequency scale (one = once a year or less, five = 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 two or more cognitive activity measurements (mean [SD] time interval between two measurements 18 [6.3] months), calculated intraclass correlation coefficients (ICC, test-retest reliability) were 0.94 (95% 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 two-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 one walking mile) during a typical, recent one-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 two or more physical activity measurements (mean [SD] time interval between two measurements 18 [6.3] months), calculated ICCs 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 one-week period and 0.68 (95% CI: 0.54, 0.78) for hours seated during a 24hour period.

Socioeconomic status 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, qualitative) data (FAMD) using FactoMineR v1.27 (Husson et al., 2014) 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, socioeconomic status, education), quantitative measures of physical activity (total kilocalories of energy expended during the last year, walking miles during a one-week period, hours seated during a 24-hour period) and qualitative variables referring to the subjects' vascular risk profile (arterial hypertension, hyperlipidemia, diabetes, smoking status).

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

We extracted four components with eigenvalues greater than one, 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: 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), 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 four-factor solution (BCC_0 [Browne-Cudeck criterion] = 0, BIC_0 [Bayes information criterion] = 0, $\chi^2/\text{degrees of freedom}$ [df] = 0.6, Bentler-Bonett normed fit index [NFI] > 0.9, RMSEA [root mean square error of approximation] < 0.03). The largest sample size for which one would accept the hypothesis that this model is correct was 272 (Hoelter's critical N, $p = 0.05$).

2.4 Cognitive factor scores

Cognitive factor scores were extracted from a baseline sample of 307 healthy individuals (mean [SD] age 74 [7] years, education 17 [2.1] years, MMSE 29 [1.3], number of males 98 [32 %]) with complete data on various cognitive tests, and with a GDS score 10, a MMSE score 25, normal cognitive functions (all cognitive scores within -1.5 SD of age-, gender-

and years of education-adjusted norms), and an age between 60 and 90 years at the first visit. This approach was chosen to generate robust and reliable data on a sample as large as possible. The 307 subjects included all 152 participants who were included in the present study. The additional 155 subjects were BACS participants recruited identically but who did not undergo PET imaging.

Using that baseline sample, we performed a maximum likelihood estimation factor analysis with oblique rotation to extract factors representing various cognitive functions/domains from 19 different cognitive tests.

Cognitive tests were selected as appropriate for the factor analysis inclusion if 1) all scores/variables were normally distributed, 2) no excessive co-linearity existed between any two variables, 3) all variables were correlated with at least one other variable, 4) data loss was minimized. Finally, 14 cognitive tests were entered into the factor analysis, from which one (Letter Fluency (Spreeen and Benton, 1977)) was subsequently removed as it did not load significantly into any factor.

The scree method (Cattell, 1966), parallel analysis (Humphreys and Montanelli, 1975) and Kaiser's criterion (Kaiser, 1960) each suggested a three factor solution, which demonstrated a significant goodness-of-fit ($\chi^2 = 67.9$, $df = 42$, $p < 0.01$, RMSEA = 0.05) and explained 56% of the total data variance.

Table 2 lists the cognitive tests that loaded onto each factor. Based on the pattern of test loading, factor 1 was interpreted as episodic memory, factor 2 as working memory and factor 3 as processing speed/executive function. Factor scores were calculated by multiplying the sum of each z-scored variable and its analysis-derived, variable-specific factor weight.

2.5 Co-variables

GDS was related to lifestyle variables/dimensions (see Results). Depression might moreover influence self-assessment, and thus the participants' reports on lifestyle variables that were based on self-assessment. Statistical models were thus adjusted for GDS, used as measure of depression (Yesavage et al., 1982), to assess robustness of the data and to control for potential bias or confounding effects.

2.6 Neuroimaging biomarkers

2.6.1 MRI and assessment of hippocampal volume—Structural MRI scans were acquired at LBNL on a 1.5 T Magnetom Avanto system (Siemens Medical Systems, Iselin, NJ, USA; 12 channel head-coil, triple mode). High-resolution T1-weighted magnetization-prepared rapid gradient echo axial scans were collected using the following parameters: repetition time = 2110 ms, echo time = 3.6 ms, flip angle = 15°, field of view = 256 × 256 mm, number of slices = 160 with a 50% gap, voxel size = 1 × 1 × 1 mm³. For each individual the hippocampal volume was obtained from the native-space MRI scans using the automated subcortical FreeSurfer 5.1 parcellation (Fischl et al., 2002). All reconstructed data were visually checked for segmentation accuracy. Hippocampal segmentation was considered to have failed, (i) if parts of the cerebrospinal fluid (CSF), white matter, cortex or amygdala

were identified as hippocampus or, (ii) if parts of the hippocampus were identified as CSF, white matter, cortex or amygdala (Mulder et al., 2014). Segmentation failures were corrected manually in all participants. For subsequent statistical analysis, the manually corrected hippocampal volume segmentation was summed across hemispheres and normalized to the FreeSurfer 5.1–derived total intracranial volume (ICV).

2.6.2 FDG- and PIB-PET—[¹¹C] PIB and [¹⁸F] FDG PET scanning was performed with 15 mCi of [¹¹C] PIB followed by 6–10 mCi of [¹⁸F] FDG (2 hours timespan between injections) at LBNL (Siemens ECAT EXACT HR PET or Siemens Biograph PET/CT scanner). Images were attenuation corrected using either a transmission scan or CT. PIB data were collected over a 90-minute measurement interval (four frames × 15 s, eight × 30 s, nine × 60 s, two × 180 s, eight × 300 s, three × 600 s), and FDG over a 30-minute measurement interval (six frames × 5 minutes, starting 30 minutes postinjection). After smoothing (4 mm Gaussian kernel with scatter correction) and preprocessing, FDG-images were intensity normalized to the mean glucose metabolism within the pons, manually edited from the subcortical FreeSurfer 5.1 brainstem segmentation (Fischl et al., 2002). PIB data processing used Logan graphical analysis with a cerebellar gray reference region to construct distribution volume ratio (DVR) images (Landau et al., 2012; Wirth et al., 2014b).

2.6.3 Assessment of PIB index and mean FDG—A global cortical PIB index (continuous variable) was calculated to estimate the subjects' Aβ burden. The native-space PIB-PET images were co-registered to the native-space MRI scans and a mean DVR value was derived from FreeSurfer parcellated frontal, temporal, parietal, and anterior/posterior cingulate regions of interest (ROIs, for details see supplemental Table 1) using the automated Desikan-Killiany parcellation (Desikan et al., 2006).

FDG mean uptake was determined within a set of predefined and validated metaROIs (for details see (Landau et al., 2011)). ROI-specific values were averaged and for each subject, a composite ROI measure (mean FDG) was generated from the mean of the metaROIs (right and left inferior temporal and lateral parietal regions, bilateral posterior cingulate-precuneus region) relative to the mean of the pons (reference region).

2.7 Statistical analysis

Using the IBM SPSS Amos statistical software package (version 22.0) direct effects (i) of lifestyle dimensions on biomarkers, (ii) of lifestyle dimensions on cognitive functions, and (iii) of biomarkers on cognitive functions, as well as indirect (mediation) effects of lifestyle dimensions on cognitive factor scores with biomarkers as mediator variables were modeled. Initial models included at once (A) all four lifestyle dimensions (exogenous composites), all three biomarkers (intermediate endogenous observed variables: PIB index, mean FDG, hippocampal volume, and the residual covariances among the three biomarkers) and our three cognitive factor scores (downstream endogenous composites: episodic memory, working memory and processing speed/executive function, and the residual covariances among the three cognitive factor scores), or (B) all four lifestyle dimensions, all three biomarkers and their residual covariances as well as global cognition as a downstream endogenous latent variable (composed of episodic memory, working memory and

processing speed/executive function). Both models were overidentified (for A $df = 6$, for B $df = 21$) and they did exhibit good measures of fit ($\chi^2/df < 1$, NFI > 0.9 , RMSEA < 0.01). Reduced models were created by dropping several paths, resulting in further df increase (for A $df = 29$, for B $df = 29$) while maintaining same good model fit. Simplified models are displayed in Figure 1A & B and all final analyses were conducted on those reduced models. Multi-group analysis included the pairwise comparison of path coefficients (= regression weights) between APOE $\epsilon 3$ carriers ($\epsilon 3\epsilon 3$) and APOE $\epsilon 4$ carriers; critical ratios or 1.96 were deemed to be significant at $p < 0.05$. Unstandardized (B) and standardized estimates (β) of direct and indirect effects are reported, and indirect effects were evaluated for significance at $p = 0.05$ using 95% bias-corrected confidence intervals (Monte Carlo method, 5000 bootstrap samples). Unless otherwise reported all direct and indirect effects remained significant after outlier exclusion (z -score < 2.68 or > 2.68). In cases where significant direct lifestyle dimension effects were found, follow-up linear regression models were computed to understand what lifestyle variable was driving the significant effect; in each model, the respective outcome variable was regressed simultaneously on all lifestyle variables. Linear regression models were conducted using SPSS, version 22.0 and statistical significance was defined as $p = 0.05$. All statistics were performed using the standardized regression residuals of each variable controlling for age and gender, and results refer to those analyses. Unless otherwise reported, direct and indirect effects, as well as critical ratios derived from multi-group analysis, remained unchanged when the standardized regression residuals of each variable were additionally controlled for GDS.

3 Results

3.1 Characteristics of participants

Descriptive statistics of the participants' demographics, lifestyle variables and biomarkers are given in Table 3. Self-reports of physician-diagnosed arterial hypertension, hyperlipidemia and diabetes were present in respective 34%, 38% and 7% of all investigated cases, and a history of cigarette smoking was indicated by 30% of the participants. Forty-two participants (29%) had at least one APOE $\epsilon 4$ allele, with two (1.4%) homozygous APOE $\epsilon 4$ carriers; 13 (9%) of participants had at least one APOE $\epsilon 2$ allele, and there were no homozygous APOE $\epsilon 2$ carriers; 90 (63%) had two APOE $\epsilon 3$ alleles. APOE carrier status was unknown in 9 subjects.

Compared to APOE $\epsilon 3$ subjects, APOE $\epsilon 4$ carriers were significantly younger ($t(101) = -2.2$, $p = 0.03$), had a higher PIB index ($t(46) = 3.6$, $p = 0.001$), larger hippocampal volumes ($t(118) = 2.4$, $p = 0.02$) and higher processing speed/executive function scores ($t(105) = 2.3$, $p = 0.02$). While higher processing speed/executive function scores in APOE $\epsilon 4$ carriers were explained by their younger age ($t(105) = 1.7$, $p = 0.09$), larger hippocampal volumes were not ($t(118) = 2.1$, $p = 0.04$) (age and gender adjusted independent samples t -test). Further demographics, lifestyle variables, lifestyle dimensions, mean FDG and the remaining cognitive factor scores did not differ between APOE $\epsilon 4$ and APOE $\epsilon 3$ carriers (independent samples t -test, χ^2 -test) (supplemental Table 2).

Age was positively correlated with lifestyle dimension low PhysAct/high VascRisk ($r = 0.2$, $p < 0.01$), and negatively correlated with hippocampal volume ($r = -0.34$, $p < 0.01$), mean

FDG ($r = -0.27$, $p < 0.01$), episodic memory ($r = -0.34$, $p < 0.01$), processing speed/executive function ($r = -0.34$, $p < 0.01$) and global cognition ($r = -0.29$, $p < 0.01$).

GDS was positively correlated with lifestyle dimension low PhysAct/high VascRisk ($r = 0.23$, $p < 0.01$) and with hours seated during a 24-hour period ($r = 0.18$, $p = 0.03$); smokers had higher GDS ($t(149) = 2.4$, $p = 0.02$) compared to non-smokers.

Subjects who reported arterial hypertension were significantly older than participants without arterial hypertension ($t(150) = 2.6$, $p = 0.01$). Compared to men, women had significantly larger relative hippocampal volumes ($t(138) = 2.6$, $p = 0.01$), higher mean FDG values ($t(144) = 5.1$, $p < 0.01$) and episodic memory scores ($t(114) = 3.1$, $p < 0.01$), a higher cigarette smoking prevalence ($\chi^2(1) = 4.1$, $p = 0.04$), but lower scores for lifestyle dimension high SES/high edu/low smoking ($t(150) = -2.7$, $p < 0.01$).

There were no further relationships between age, gender, GDS and the remaining lifestyle variables, lifestyle dimensions, biomarkers or cognitive factor scores (nonparametric correlations, independent samples t-test, χ^2 -test).

3.2 Direct effects

Statistical models revealed a significant inverse effect of lifestyle dimension high CogAct/low VascRisk on PIB index ($B = -0.23$, $\beta = -0.23$, $p < 0.01$; Figure 2A), which was most strongly related to a significant association between middle life cognitive activity and PIB ($B = -0.25$, $\beta = -0.24$, $p < 0.04$). A significant positive effect of lifestyle dimension high SES/high edu/low smoking on hippocampal volume ($B = 0.2$, $\beta = 0.2$, $p < 0.02$; Figure 2B) was also found; when hippocampal volume was regressed simultaneously on education, socioeconomic status and smoking, no single lifestyle variable explained the relationship between lifestyle dimension high SES/high edu/low smoking and hippocampal volume. Excluding socioeconomic status from the regression model, however, results in a significant association between education and hippocampal volume ($B = 0.22$, $\beta = 0.21$, $p < 0.02$).

Lifestyle dimension high CogAct/low VascRisk was moreover related to better episodic memory ($B = 0.22$, $\beta = 0.23$, $p < 0.01$), resulting from a significant association between current life cognitive activity and episodic memory ($B = 0.26$, $\beta = 0.26$, $p < 0.03$), and to better global cognition ($B = 0.16$, $\beta = 0.29$, $p < 0.04$), resulting from a significant relationship between early life cognitive activity and global cognition ($B = 0.26$, $\beta = 0.25$, $p = 0.02$) (Figure 2C).

There were additional significant effects of hippocampal volume on episodic memory ($B = 0.24$, $\beta = 0.25$, $p < 0.01$), on processing speed/executive function ($B = 0.21$, $\beta = 0.21$, $p < 0.02$) and on global cognition ($B = 0.19$, $\beta = 0.35$, $p < 0.01$) (Figure 2D).

3.3 Mediation effects

There were significant indirect effects of lifestyle dimension high SES/high edu/low smoking on episodic memory ($\beta = 0.05$, 95% CI: 0.01, 0.11, $p = 0.05$), on processing speed/executive function ($\beta = 0.04$, 95% CI: < 0.01, 0.1, $p = 0.05$) and on global cognition ($\beta = 0.07$, 95% CI: < 0.01, 0.09, $p = 0.05$), mediated by hippocampal volume (Figure 3A – C).

After outlier exclusion only the indirect effect of high SES/high edu/low smoking on global cognition remained significant ($\beta = 0.06$, 95% CI: < 0.01 , 0.08 , $p = 0.05$), while the indirect effects of high SES/high edu/low smoking on episodic memory ($\beta = 0.04$, 95% CI: < -0.01 , 0.1 , $p = 0.05$) and on processing speed/executive function ($\beta = 0.03$, 95% CI: < -0.01 , 0.09 , $p = 0.05$) did not.

Table 4 provides an overview of all direct, indirect, and total effects derived from the mediation models.

3.4 Multi-group analysis

Multi-group analysis revealed a significant inverse association between high CogAct/low VascRisk and PIB index in APOE ϵ 4 carriers ($B = -0.51$, $\beta = -0.37$, $p < 0.01$), but not in APOE ϵ 3 carriers ($B = -0.04$, $\beta = -0.06$, $p = 0.59$). Difference on path coefficients (= critical ratio) was 2.3 ($p < 0.05$), which remained on a trend-level after outlier exclusion (critical ratio = 1.9). Detailed results of the multi-group analysis are presented in supplemental Table 3.

4 Discussion

In cognitively normal elderly, we identified dimensions of lifestyle characterized by common variance between (1) high lifetime cognitive activity and a low vascular risk profile, (2) low current physical exercise and high cardiovascular risk, (3) high socioeconomic status, high education and low smoking status, and (4) the simultaneous presence of various vascular risk factors. Beside their explanatory power for certain “lifestyles” and behaviors, these dimensions were particularly associated with brain pathology and cognitive functions. The composite of lifetime cognitive activity and a low vascular risk profile was related to lower cortical A β retention, and preserved episodic memory and global cognition. Additionally, the composite of high socioeconomic status, high education and low lifetime smoking status was associated with larger hippocampal volumes, which mediated indirect effects on episodic memory, processing speed and global cognition (Figure 4). The composite of high lifetime cognitive activity and a low vascular risk profile was related to lower A β burden in APOE ϵ 4 carriers.

Our results suggest that lifestyle should be thought of as a complex construct composed of discrete elements, including cognitive and physical activity, education, socioeconomic status, and vascular risk factors. Importantly, in our study, not all lifestyle variables were related to one another, but certain lifestyle variables demonstrated meaningful covariance reflecting interrelated lifestyle and behavioral patterns. Of note is the strong common variance between cognitive activity and vascular health, and independently from this particular lifestyle, the strong covariance between physical inactivity and vascular risk.

Our data further support the growing literature reporting on an interaction between genetics and lifestyle on markers of brain health and disease. We replicate previous findings from our cohort that cortical A β load in elderly APOE ϵ 4 carriers can be moderated by lifetime cognitive activity (Wirth et al., 2014b). This supports the notion that individuals at higher

genetic risk for AD may be especially sensitive to the biological effects of lifestyle conditions and behaviors.

Our data also corroborate previous findings reporting on the association between vascular risk factors and cortical A β accumulation (Reed et al., 2012; Reed et al., 2014; Rodrigue et al., 2013). We found A β retention was not independently associated with vascular risk variables, but was instead associated with a composite variable containing information associated with both leisure activity and vascular risk profile, especially in subjects at higher genetic risk for AD. Vascular health helps to maintain paravascular amyloid drainage/clearance mechanisms, and lifelong cognitive activity has been conjectured to result in lower neural activity-linked A β release (Hawkes et al., 2012; Iadecola, 2014; Jagust and Mormino, 2011; Snyder et al., 2014; Zlokovic, 2008). Those multiple mechanisms may be important in lowering amyloid burden, or mitigating its increase, especially in APOE ϵ 4 carriers. Vascular risk may therefore have played a role in prior findings stating relationships between cognitive activity and cortical A β load (Landau et al., 2012; Wirth et al., 2014b; Wirth et al., 2014a) or, alternatively, cognitive activity may have played a role in previous reports of the effects of vascular risk (Reed et al., 2012; Reed et al., 2014; Rodrigue et al., 2013).

The relationship between education, adult socioeconomic status, smoking status and hippocampal volume supports common evidence that early life environmental influences may affect brain structure development. Higher childhood socioeconomic status has previously been reported as associated with larger hippocampal volume and brain size in late life (Staff et al., 2012). Childhood socioeconomic status seems moreover to predict smoking habits in adulthood (Giesinger et al., 2014; Laitinen et al., 2013) and duration of education, which in turn is a proxy of adult socioeconomic status (Staff et al., 2012). Our results thus suggest that enduring developmental effects on brain structure may be explained by the association of early life experience with education, adult socioeconomic status and adulthood smoking prevalence.

Based on our results, we suggest that various lifestyle dimensions and brain biomarkers are related via two distinct pathways. The first pathway includes the association between lifelong and current life conditions and behaviors on amyloid burden and cognition, which we consider as a “dynamic lifestyle” pathway because it is presumably changing over the lifecourse. While the dynamic pathway affects episodic memory and global cognition, those associations are not explained by the pathway’s A β lowering impact but rather perhaps through a shared intermediate mechanism. Such mechanisms might include neural compensation (Elman et al., 2014) or neural efficiency (Jagust and Mormino, 2011). The second pathway includes the ongoing relationship between early life environmental influences and hippocampal volume, and this can be considered as a “static developmental” pathway. In our study, this latter “static” pathway was not related to cortical amyloid load, and its substantial association with various cognitive domains was mediated by sustained hippocampal volume. The “static development” pathway may confer protective benefits on brain structure, which keeps subjects in the normal category even in the presence of neurodegeneration/amyloid burden (Brayne et al., 2010; Erten-Lyons et al., 2009). These two pathways may reinforce one another, especially in APOE ϵ 4 carriers. As an example, larger hippocampal volumes in APOE ϵ 4 positives – compared to APOE ϵ 3 carriers - may

result from subjects with better static endowments who have remained cognitively normal despite an A β load.

Our study has several limitations. Our cohort is characterized by particularly high levels of lifetime leisure activity, socioeconomic status and education, and participant recruitment by advertisement or word of mouth may have excluded subjects of lower socioeconomic status. In addition, our sample exhibits a lower variance in education level and a lower vascular risk prevalence compared to more population-based samples. The lack of associations between mean FDG and e.g. cognitive function, for instance, may result from missing meaningful variations in the predefined AD signature meta-ROIs (used to generate mean FDG) in that particularly healthy and well-educated cohort. The generalizability of some of the results presented has thus yet to be demonstrated. Furthermore, no assumption on causality can be drawn from the covariance pattern between various lifestyle variables, and the causality assumption of the detected associations between lifestyle, biomarkers and cognition cannot be proven by the present cross-sectional study design and must be confirmed by longitudinal surveys. Another study limitation is that certain lifestyle variable data - in particular, cognitive activity, physical exercise and smoking status - are self-reported, and thus might have been influenced by undetected bias. A final limitation is presented by the fact that our sample size may be too small to detect more subtle relationships between various lifestyle factors, brain biomarkers and cognition. For example, a recent meta-analysis of 16 cross-sectional studies including around 1,300 cognitively normal elderly revealed that amyloid burden has a modest, but significant effect on episodic memory (Hedden et al., 2013). However, a sample size nearly three times larger than the number of participants included in the present analysis would be necessary to detect those small effect sizes (Hedden et al., 2013). This may, at least in part, account for the absent association between A β load and cognition in our data set.

In conclusion, our data show that particular modifiable lifestyle factors share common variance that together result in various independent healthier or less healthy lifestyle patterns. These lifestyle patterns are related to brain health via a “dynamic lifestyle” pathway, including the association between lifelong cognitive activities and amyloid retention, in particular in APOE ϵ 4 carriers, and via a “static developmental” pathway, including the associations between early life experiences and hippocampal volume and cognition. Overall, our results emphasize the mutual importance of an intellectually enriched lifestyle accompanied by vascular health on both cognition and presumed neural mediators of cognition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Lifestyle is a complex construct of distinct covarying lifestyle elements
- Lifestyle affects the brain via two pathways that reinforce one another
- Cortical A β retention is related to APOE ϵ 4 carrier status
- This relationship is modified by leisure activities and vascular risk factors
- Hippocampal volume is related to early life environmental influences

Figure 1. Reduced final models used for path analysis and multi-group analysis

Models included the four lifestyle dimensions (blue in **A & B**), the three biomarkers (pink in **A & B**), the three cognitive factor scores (orange in **A & B**) and global cognition as a latent variable (**B**). Gray arrows display covariances among variables. HV, hippocampal volume, e, error term.

Figure 2. Associations between lifestyle dimensions, biomarkers and cognitive domains
A, Relationship between lifestyle dimension high CogAct/low VascRisk and PIB index; **B**, Relationship between lifestyle dimension high SES/high edu/low smoking and hippocampal volume; **C**, Regression lines demonstrate relationships between high lifetime cognitive activity and a low vascular risk profile on episodic memory (EM) and global cognition (GC); **D**, Graphs conceptualize the significant positive associations between hippocampal volume and various cognitive domains. PS, processing speed/executive function. All variables are standardized residuals adjusted (adj.) for age and gender.

Figure 3. Indirect effects of lifestyle dimension high SES/high edu/low smoking on cognitive domains

Age and gender adjusted mediation models revealed significant indirect effects of lifestyle dimension high SES/high edu/low smoking on episodic memory (A), processing speed/executive function (B) and global cognition (C) mediated by hippocampal volume (AC). * p 0.05, CI – confidence interval.

Figure 4. Overview of significant associations between lifestyle dimensions, amyloid retention, hippocampal volume and cognitive functions

Associations between lifestyle dimensions, biomarkers and cognition derived from two lifestyle classifications, from high lifetime cognitive activity combined with a low vascular risk profile (high CogAct/low VascRisk, effects are shown in gray), and from the composite of high socioeconomic status, high education and low smoking status (high SES/high edu/low smoking, effects are shown in light green). Figure includes direct and indirect effects. Standardized regression coefficients are presented; † inverse direct association between high CogAct/low VascRisk and PIB index was detected in APOEε4 carriers (see results), * $p < 0.05$.

Table 1

Factor loadings of the quantitative lifestyle variables and category loads of the qualitative variables contributing to each lifestyle dimension.

Lifestyle variable	Dimension loadings			
	Dimension 1	Dimension 2	Dimension 3	Dimension 4
	High lifetime cognitive activity and low vascular risk profile	Low current physical activity and high vascular risk profile	High socioeconomic status/ education and low smoking prevalence	High vascular risk profile
Early life cognitive activity	0.45	0.25	-0.18	0.08
Middle life cognitive activity	0.54	0.19	-0.09	0.06
Current life cognitive activity	0.52	0.18	-0.01	0.01
Education	0.26	0.03	0.50	0.01
Socioeconomic status	<0.01	0.16	0.65	0.05
Total kilocalories of energy expended during the last year	0.21	-0.49	-0.02	0.26
Walking miles during a one-week period	0.16	-0.39	0.02	0.29
Hours seated during a 24-hour period	-0.10	0.51	0.08	-0.28
Arterial hypertension_yes	-0.26	0.48	-0.23	0.73
Arterial hypertension_no	0.24	-0.22	0.04	-0.32
Hyperlipidemia_yes	-0.19	0.35	-0.08	0.83
Hyperlipidemia_no	0.17	-0.09	-0.11	-0.42
Diabetes_yes	0.08	0.47	-0.24	0.85
Diabetes_no	-0.10	-0.22	0.05	-0.45
Smoking_yes	0.02	0.22	-0.65	0.03
Smoking_no	-0.04	0.03	0.46	0.38

The category loads are applied to binary variables that are 1 if the individual belongs to the respective category, 0 if not. Signs and spread between a variable's category loads indicate the influence of the respective qualitative variable.

Table 2

Factor loading scores of the individual cognitive tests contributing to each cognitive factor.

Cognitive tests	Factor loadings		
	Factor 1 Episodic memory	Factor 2 Working memory	Factor 3 Processing speed/ Executive function
CVLT 1–5 FR	0.86	−0.09	−0.14
LM A plus B1	0.59	0.13	−0.07
Category total	0.55	−0.00	0.19
LS recall total	0.53	0.32	0.07
VR long delay	0.49	0.01	0.22
DS backward	0.04	0.84	−0.12
DS forward	−0.05	0.66	0.00
Arithmetic tasks	0.07	0.46	0.21
Symbol digit	0.41	0.06	0.51
Stroop correct in 60s	0.24	0.1	0.5
Mental control	0.04	0.32	0.48
Trail making A	0.18	−0.04	0.4
Finger taps per second	−0.09	0.00	0.38

CVLT, California Verbal Learning Test, DS, digit span, FR, free recall, LM, logical memory, LS, listening span, VR, visual reproduction.

Table 3

Characteristics of participants.

Demographics	Participants, number	152
	Age at PIB PET in years, mean (SD)	76 (6)
	Male, number (%)	65 (43)
Lifestyle variables	Education in years, mean (SD)	17 (2.1)
	Socioeconomic status, mean score (SD)	50 (13.2)
	Early age cognitive activity, mean score (SD)	3.4 (0.7)
	Middle age cognitive activity, mean score (SD)	3.6 (0.5)
	Current age cognitive activity, mean score (SD)	3.8 (0.5)
	Total kcal of energy expended during the last year, mean score (SD)	110000.1 (95330.3)
	Walking miles during a one-week period, mean score (SD)	4 (6.4)
	Hours seated during a 24-hour period, mean score (SD)	16 (3.6)
	Arterial hypertension, number of affected subjects (%)	51 (34)
	Hyperlipidemia, number of affected subjects (%)	57 (38)
	Diabetes, number of affected subjects (%)	11 (7)
	Cigarette smoking (ever), number (%)	46 (30)
Neuroimaging biomarkers ⁺	PIB index, mean (SD)	1.09 (0.17)
	Mean FDG [†] , mean (SD)	1.35 (0.1)
	Hippocampal volume normalized to ICV, mean (SD)	4.1×10^{-3} (0.5×10^{-3})

SD, standard deviation, kcal, kilocalories; PIB, Pittsburgh-Compound-B, FDG, Fludeoxyglucose, ICV, intracranial volume

⁺ mean time intervals in months (SD) between the neuroimaging measurements and neuropsychological test session were as follows: neuropsychological test session and MRI 4 (4.2), neuropsychological test session and PET 3 (1.9), MRI and PET 1 (3.5);

[†] mean FDG represents a composite ROI generated from the mean of five metaROIs relative to the mean of the pons (see 2.6.3).

Table 4

Standardized direct, indirect and total effects derived from mediation models.

	Direct effect	Indirect effect	Total effect
PIB on high CogAct/low VascRisk	-0.23*	-	-0.23*
Mean FDG on high CogAct/low VascRisk	0.06	-	0.06
EM on high CogAct/low VascRisk	0.23*	0	0.23*
GC on high CogAct/low VascRisk	0.29*	0.01	0.3*
Mean FDG on low PhysAct/high VascRisk	0.11	-	0.11
EM on low PhysAct/high VascRisk	0.1	0	0.1
GC on low PhysAct/high VascRisk	0.17	0	0.17
Mean FDG on high SES/high edu/low smoking	-0.12	-	-0.12
HV on high SES/high edu/low smoking	0.2*	-	0.2*
EM on high SES/high edu/low smoking	0.06	0.05*	0.11
PS on high SES/high edu/low smoking	-0.03	0.04*	0.02
GC on high SES/high edu/low smoking	0.04	0.07*	0.11
GC on PIB	-0.05	-	-0.05
EM on HV	0.25*	-	0.25*
PS on HV	0.21*	-	0.21*
GC on HV	0.35*	-	0.35*

High CogAct/low VascRisk, high lifetime cognitive activity and low vascular risk profile, low PhysAct/high VascRisk, low current physical activity and high vascular risk profile, high SES/high edu/low smoking, high socioeconomic status /education and low smoking prevalence, high VascRisk, high vascular risk profile, PIB, Pittsburgh-Compound-B (= PIB index), FDG, Fludeoxyglucose (mean FDG represents a composite ROI generated from the mean of five metaROIs relative to the mean of the pons (see material & methods)), HV, hippocampal volume, EM, episodic memory, PS, processing speed/executive function, GC, global cognition,

* p 0.05