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RESEARCH ARTICLE

Late-midlife lifestyle and brain and cognitive changes in individuals on the AD versus non-AD continuum

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Abstract

INTRODUCTION: We investigated whether a composite measure of late-midlife lifestyle was associated with (1) longitudinal brain changes and (2) cognitive changes when adjusting for these brain changes.

METHODS: We used linear mixed models to examine whether the LIfestyle for BRAin Health (LIBRA) index was associated with changes in tau, white matter hyperintensity, neurodegeneration, and cognition and whether changes were similar in amyloid positive (A+; > 17 Centiloids) and negative participants.

RESULTS: We included 324 individuals from the Wisconsin Registry for Alzheimer's Prevention (39% apolipoprotein E [*APOE*] ε4 carrier, 30% A+, prior baseline age 67 [50–75]). The LIBRA index was not associated with biomarker trajectories or the primary cognitive composite outcome trajectory. There were inconsistent effects on secondary domain-specific cognitive trajectories. In contrast, tau and neurodegeneration were strongly associated with cognitive trajectories.

DISCUSSION: In the age-range and disease-range studied, lifestyle did not exhibit a meaningful effect on Alzheimer's disease or vascular biomarker accumulation and was not consistently associated with cognitive trajectories.

KEYWORDS
Alzheimer's disease, biomarkers, cognition, global brain atrophy, hippocampal volume, lifestyle, LIfestyle for BRAin Health index, tau PET, white matter hyperintensity, Wisconsin Registry for Alzheimer's Prevention

Highlights

- In this age-range, the LIfestyle for BRAin Health (LIBRA) index was not associated with biomarker trajectories.
- The LIBRA index was not consistently associated with cognitive trajectories.
- Effects of lifestyle, if any, may take more time to manifest.

1 | INTRODUCTION

Although the association of lifestyle with cognitive decline and dementia has been established,[1] the underlying mechanism(s) have not been fully elucidated. Alzheimer's disease (AD), the most common cause of dementia, is characterized by abnormal accumulation of amyloid and tau. Rates of accumulation of amyloid have been shown to be highly predictable and similar from person to person.[2–5] We recently examined the impact of lifestyle on amyloid burden and temporal features including accumulation rate and amyloid onset age, and did not identify any associations with lifestyle and these amyloid features.[6]

The literature examining the effect of lifestyle factors on AD biomarkers is mixed, and largely cross-sectional, with most previous studies focused on amyloid only.[6–19] There is limited evidence for a direct association between lifestyle and amyloid pathology, largely confirming our prior observation.[6] Several questions remain unanswered regarding the effect of lifestyle on brain health including the other AD proteinopathy—tau—as well as the effect of vascular disease in the brain, which may have a more plausible connection to lifestyle health factors, and neurodegeneration detectable with magnetic resonance imaging (MRI), which is a non-specific marker.

To address these unanswered questions, longitudinal study designs are needed that will enable an examination of biomarker level and trajectory over time in relationship to prior indicators of lifestyle health. Improving our understanding of the contribution of lifestyle factors to brain and cognitive changes in the pre-dementia stage, both in the presence or absence of amyloid pathology will be informative in research and clinical prevention settings.

The Wisconsin Registry for Alzheimer's Prevention (WRAP) is a longitudinal cohort studying mid-life predictors of cognitive decline. As such, it is ideally situated to study these associations. In the current study, we examined whether a composite measure of late-midlife lifestyle was associated with (1) longitudinal brain changes in measures of tau burden, vascular burden, and neurodegeneration and (2) longitudinal cognitive changes when adjusting for changes in these biomarkers. We were specifically interested in looking at whether a less brain-healthy lifestyle was associated with deleterious changes in tau burden, cerebrovascular disease (white matter hyperintensity [WMH]), neurodegeneration (hippocampal volume [HV], global brain atrophy [GBA]) and cognitive decline (Preclinical Alzheimer's Cognitive Composite [PACC-3], memory and executive performance) and whether patterns were similar in individuals on the AD continuum (i.e., amyloid positive [A+]) versus not.

RESEARCH IN CONTEXT

1. **Systematic reviews**: The authors reviewed the literature using traditional databases such as PubMed. Previous work suggests that modifiable factors may be protective in the development of symptoms of all-cause dementia, but there is limited evidence for an association between lifestyle factors and amyloid accumulation. Moreover, it is unclear whether lifestyle is associated with other longitudinal brain changes including fibrillar tau deposition, vascular burden, and neurodegeneration, and whether lifestyle is associated with cognitive decline when adjusting for these brain changes.
2. **Interpretation**: In the age-range and disease-range studied, lifestyle did not exhibit a meaningful effect on Alzheimer's disease (AD) or vascular biomarker accumulation and was not consistently associated with the longitudinal cognitive outcomes.
3. **Future directions**: Results of the current study underscore the need to strengthen the evidence surrounding the potential benefits of adopting or adhering to healthy lifestyle behaviors to prevent AD-related pathophysiology.

2 | METHODS

2.1 | Participants

Participants were recruited from WRAP,[20] which had enrolled 1790 late-middle age adults at the time of these analyses (median age at first cognitive assessment 58 [range: 40–69]). At each study visit, WRAP participants undergo neuropsychological testing and are assigned a cognitive status by a multi-disciplinary consensus diagnosis panel (for details, see Langhough Koscik et al.[21]). Participants are diagnosed as being cognitively unimpaired, having mild cognitive impairment (MCI[22,23]), being impaired-not MCI, or having dementia in line with the National Institute on Aging–Alzheimer's Association (NIA-AA) workgroup diagnostic criteria.[24] None of the participants had dementia at the WRAP study baseline and none of the participants were part of any intervention study.

WRAP participants who underwent tau positron emission tomography (PET) and/or T1-weighted volumetric and T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI and had received a diagnosis within 2 years of the earliest biomarker imaging panel were included in this study. We excluded participants for whom no amyloid PET assessment was available. Participants with incomplete apolipoprotein E (*APOE*) $\varepsilon 4$, incomplete lifestyle data, and/or a diagnosis of dementia were also excluded from this study. The final sample consisted of 324 individuals. Detailed inclusion/exclusion criteria can be found in Figure S1. The cohort is enriched for AD risk via oversampling for parental history of dementia ($n = 251$; 77.5%) resulting in the enrichment of proportion of participants positive for at least one allele of the known AD genetic risk factor *APOE* $\varepsilon 4$ ($n = 126$; 38.9%).

2.2 | Lifestyle for BRAin Health (LIBRA) index

The Lifestyle for BRAin Health (LIBRA) index is a weighted component score that comprises 12 modifiable risk and protective factors for cognitive decline and dementia: low/moderate alcohol use, coronary

artery disease, physical inactivity, renal dysfunction, diabetes, high cholesterol, smoking, obesity, hypertension, depression, cognitive activity, and Mediterranean diet adherence.[25,26] WRAP participants were classified as being "at risk" or "not at risk" for each modifiable factor, according to the risk definitions given in Table S1 and described more comprehensively in the previous paper by Cody et al.[6]

The LIBRA score ranges from −5.9 to 12.7, with higher scores indicating a less brain-healthy lifestyle and an expected increased risk of dementia. To compute overall lifestyle in late-midlife, we averaged LIBRA scores over all of a participant's study visits before age 70 at which all 12 LIBRA components were assessed (mean [SD] years of follow-up before age 70: 3.9 [1.8]; median number of complete visits: 2; detailed in Table S2). Although LIBRA was included as a continuous score in all analyses, we used data-driven tertiles to create low (score −5.9 to −0.070), intermediate (score −0.069 to 1.60), and high-risk (score 1.61 to 12.7) lifestyle groups for visualization purposes.

2.3 | Cognitive assessment

WRAP participants completed cognitive assessments at their initial study visit and approximately every 2 years after this. The full battery is described in Johnson et al.[20] Cognitive performance was assessed in this study using a validated WRAP version of the Preclinical Alzheimer's Cognitive Composite [PACC-3], a composite modeled after Donohue et al.[27,28] The WRAP PACC-3 includes the Rey Auditory Verbal Learning Test total learning score (sum of trials 1–5), Wechsler Memory Scale-Revised Logical Memory delayed recall score, and the Wechsler Adult Intelligence Scale Digit Symbol test score. In addition, to assess domain-specific cognitive changes, we examined performance in the memory domain (composite consisting of the Rey Auditory Verbal Learning Test delayed recall, Logical Memory delayed recall score, and Brief Visuospatial Memory Test-Revised delayed recall) and the executive function domain (composite consisting of the Trail Making Test Part B, Wechsler Adult Intelligence Scale–Digit Symbol test and Letter Fluency). All cognitive scores were *z*-scored based on a reference group consisting of first observations from cognitively unimpaired WRAP participants.[28] The mean follow-up duration for the cognitive outcomes was 6.3 years (SD 3.3, $n = 318$) for the PACC-3, 5.8 years (SD 2.9, $n = 317$) for the memory composite, and 6.3 years (SD 3.3, $n = 321$) for the executive function composite (median number of cognitive visits: 3).

2.4 | Positron emission tomography (PET) imaging

PET image processing and quantification methods have been detailed previously.[8,29] In summary, amyloid burden was assessed as a global cortical average 11[C] Pittsburgh Compound B (PiB) distribution volume ratio (DVR; Logan graphical analysis, cerebellum gray matter reference region), and amyloid positivity (A+) was determined using a previously established threshold of DVR >1.16, which is equivalent to a Centiloid of 17.[2] To better capture all participants on the AD continuum, amyloid status was defined on the basis of the most recent amyloid PET scan available for that participant. The average time between lifestyle assessment and amyloid PET scan was 4.0 years (SD 1.75).

A subset of individuals underwent tau PET imaging ($n = 259$). MK-6240 standardized uptake value ratios (SUVRs; 70–90 min, inferior cerebellar gray matter reference region) were used to assess regional tau burden in two regions of interest (ROIs): the entorhinal cortex (EC), the earliest region of tau deposition on PET imaging, and a meta-temporal composite (MTC), a measure of widespread tau in the temporal lobe, encompassing the EC, amygdala, parahippocampal gyrus, fusiform gyrus, and inferior and middle temporal gyri.[29] Tau SUVRs were *z*-scored based on a reference group of amyloid negative (PiB DVR ≤1.16), cognitively unimpaired individuals younger than 60 years of age.[30] The mean follow-up duration for tau PET was 2.5 years (SD 0.6; median no. of visits: 1; $n = 100$; Table S3).

2.5 | Magnetic resonance imaging (MRI)

A subset of individuals underwent T1 and T2 FLAIR MRI ($n = 319$). Methods for MRI acquisition, processing, and quantification and the method for determining *z*-scores for WMH, HV, and GBA have been described previously.[31] Briefly, a reference group of cognitively unimpaired, amyloid negative (PiB DVR ≤1.16) participants was defined and a regression-based approach that encompassed adjustment for total intracranial volume (TICV) was used to compute *z*-scores. WMH *z*-scores were used to measure cerebrovascular burden ($n = 252$) and HV and GBA *z*-scores were used to measure neurodegeneration ($n = 318$). The mean follow-up duration for the WMH assessment was 2.6 years (SD 0.8; median no. of visits: 1, $n = 106$; Table S3) and the mean follow-up duration for the HV and GBA assessments was 5.7 years (SD 3.1; median no. of visits: 2, $n = 236$; Table S3). HV *z*-scores were inversed such that higher *z*-scores correspond to lower HV for ease of interpretation.

2.6 | Statistical analysis

Differences in demographic and clinical characteristics of participants at different levels of lifestyle risk were assessed using analysis of variance (ANOVA) or chi-square test for continuous and categorical variables, respectively.

2.6.1 | Analyses Aim 1

For Aim 1, baseline was defined as the first biomarker assessment for a participant. We assessed the Spearman correlations between the LIBRA score, amyloid burden, tau burden, vascular burden, and neurodegeneration. We used mixed-effects models (random intercept) to investigate whether the LIBRA score was associated with longitudinal brain changes in measures of tau burden, vascular burden, and

neurodegeneration, and whether changes were similar in individuals on the AD continuum (i.e., A+) versus not (i.e., amyloid by age interactions). We created models adjusted for sex, *APOE* ε4 carrier status, and the time between LIBRA index and first biomarker assessment for each individual biomarker outcome. Age was the time variable and was centered at the mean. To assess the effect of LIBRA on AD-related brain changes, we began with a three-way LIBRA*amyloid status*age interaction. A backward stepwise approach, removing highest-order non-significant interactions sequentially, was followed to determine the final model for each brain outcome.

2.6.2 | Analyses Aim 2

For Aim 2, baseline was defined as the first cognitive assessment for a participant. We used mixed-effects models (random slope, random intercept; unstructured covariance) to investigate whether the LIBRA score was associated with cognitive trajectories on the PACC-3 (the primary outcome) and memory and executive domains (secondary outcomes) and whether changes were similar in those on the AD continuum (i.e., A+) versus not (i.e., amyloid by age interactions) when adjusting for tau burden and neurodegeneration (defined on basis of the most recent MRI scan available for each participant). Specifically, for each cognitive outcome, we created models adjusted for sex, baseline Wide Range Achievement Test-III reading recognition subtest (WRAT) score,[32] practice effects (the number of previous exposures to the test), and amyloid status. Age was the time variable and was centered at the mean.

We first assessed the effects of the MTC and GBA *z*-score on each cognitive outcome. We then assessed the effect of LIBRA on amyloid-related decline, adding the LIBRA-related terms to the model, and beginning with a three-way LIBRA*amyloid status*age interaction. A backward stepwise approach, removing highest-order non-significant interactions sequentially, was followed to determine the final model for each cognitive outcome. As sensitivity analysis, we repeated the models for the primary cognitive outcome (1) without adjustment for MTC and GBA *z*-scores and (2) when including a quadratic age term.

Analyses were performed using the lme4 Package in R (version 4.3.2, The R Foundation for Statistical Computing), and two-sided *p*-values < 0.05 were considered statistically significant.

3 | RESULTS

3.1 | Participant characteristics

Sample characteristics according to lifestyle risk tertile are presented in Table 1. Seventy-three percent of participants were female, 30% were amyloid positive, and 39% were *APOE* ε4 carriers. The median age at the first biomarker assessment was 67 years (range: 50–75) and the median age at first included cognitive assessment was 58 years (range: 40–69). The median age at the first complete lifestyle visit was 63 (range: 44–70). Participants had 16 years of education on average and 1% of participants had MCI at baseline. Participants with lower LIBRA scores were more likely to have more years of education, higher WRAT scores, and higher PACC-3 scores, and were more likely to have tau pathology at biomarker baseline. Participants with higher LIBRA scores were more likely to have higher GBA at biomarker baseline.

3.2 | Aim 1: Biomarker outcomes

Spearman correlations are presented in Figure S2. In the mixed-effects models of longitudinal biomarker outcomes, no significant LIBRA*amyloid status*age interactions or LIBRA*age (after removing the non-significant three-way) were observed. Final (reduced) models indicated a main effect of LIBRA on baseline tau MTC and GBA *z*-scores, such that higher LIBRA scores, indicative of worse brain-lifestyle, were associated with lower MTC *z*-scores (indicating lower tau burden) and higher GBA *z*-scores (indicating more atrophy; $\beta = -0.15$, $p = .017$ and $\beta = 0.05$, $p = .018$, respectively; see Table S4 for final reduced models). Figure 1 shows raw data plots of biomarker outcomes by age, panelled by LIBRA risk tertile.

3.3 | Aim 2: Cognitive outcomes

MTC tau and GBA were associated with PACC-3, memory, and executive function composite trajectories (Table S5). In the mixed-effects models of longitudinal cognitive outcomes, no significant LIBRA*amyloid status*age interaction or LIBRA*age (after removing the non-significant three-way) was observed for PACC-3 *z*-scores, our primary outcome (See Table 2 and Table S6 for model output, visualized in Figure S3). For PACC-3, the LIBRA main effect was also not significant. Patterns were essentially the same for the memory composite (Table S7 and Figure S4).

The LIBRA*amyloid status*age interaction was significant in the model examining executive function. Late-midlife LIBRA was differentially associated with executive function composite trajectories in amyloid positive and negative participants (*p* for interaction 0.019; Table S7). In the group of participants at lower lifestyle risk, amyloid positive participants seem to decline faster than amyloid negative participants (Figure 2).

In sensitivity analyses, we found a LIBRA*amyloid status*age interaction for PACC-3 *z*-scores if the model was not adjusted for biomarkers (visualized in Figure S5). Inclusion of a quadratic age term in the model did not change results.

4 | DISCUSSION

The aim of the current study was to examine whether a composite measure of late-midlife lifestyle was associated with (1) longitudinal brain changes in measures of tau burden, vascular burden, and neurodegeneration and (2) longitudinal cognitive changes when adjusting for change in these biomarkers. We found that, in the age range, disease

TABLE 1 Participant characteristics.

	Total group $N = 324$	Low lifestyle risk[a] $N = 121$	Intermediate lifestyle risk $N = 106$	High lifestyle risk $N = 97$	*p*-value*
Age at biomarker baseline, median (range)	66.8 (50.3–74.5)	58.11 (50.3–75.6)	56.3 (40.2–55.3)	57.7 (44.8–68.8)	0.72
Age at baseline cognitive assessment, median (range)	57.5 (40.2–69.4)	58.1 (44.3–69.4)	56.3 (40.2–65.3)	57.8 (44.8–68.8)	0.58
Female, *n* (%)	235 (72.5%)	89 (73.6%)	81 (76.4%)	65 (67.0%)	0.31
Non-Hispanic White, *n* (%)	306 (94.4%)	115 (95.0%)	101 (95.3%)	90 (92.8%)	0.54
Cognitively impaired at baseline cognitive assessment, *n* (%)	3 (0.93%)	0 (0.0%)	0 (0.0%)	3 (3.1%)	0.13
Education, median (range)	16.0 (12.0–20.0)	17.0 (12.0–20.0)	16.0 (12.0–20.0)	16.0 (12.0–20.0)	< 0.001
Wide Range Achievement Test-III score, median (range)	107.0 (66.0–119.0)	107.0 (66.0–119.0)	107.0 (75.0–119.0)	105.0 (68.0–119.0)	0.0057
Amyloid positive, *n* (%),[b]	96 (29.6%)	41 (33.9%)	26 (24.5%)	29 (29.9%)	0.31
APOE ε4 carrier, *n* (%)	126 (38.9%)	49 (40.5%)	43 (40.6%)	34 (35.1%)	0.65
Family history of dementia, *n* (%)	251 (77.5%)	95 (78.5%)	80 (75.5%)	76 (78.4%)	0.84
Average late-midlife LIBRA score, median (range)	0.6 (−4.9–7.4)	−1.4 (-4.9–−0.1)	0.8 (0.0–1.6)	2.6 (1.7–7.4)	< 0.001
tau EC *z*-score at baseline > 1.5 SD, *n* (%)	58 (22.4%)	32 (32.7%)	12 (13.5%)	14 (19.4%)	0.0056
tau MTC *z*-score at baseline > 1.5 SD, *n* (%)	39 (15.1%)	25 (25.5%)	5 (5.6%)	9 (12.5%)	0.0057
WMH *z*-score at baseline > 1.5 SD, *n* (%)	13 (5.2%)	6 (6.5%)	1 (1.1%)	6 (8.5%)	0.087
HV *z*-score at baseline > 1.5 SD, *n* (%)	21 (6.6%)	9 (7.6%)	6 (5.8%)	6 (6.3%)	0.86
GBA *z*-score at baseline > 1.5 SD, *n* (%)	11 (3.5%)	1 (0.84%)	3 (2.9%)	7 (7.4%)	0.032
PACC-3 *z*-score at baseline, median (range)	0.23 (−3.5–2.5)	0.32 (−2.3–2.5)	0.34 (−2.9–2.4)	−0.050 (−3.5–2.0)	0.0024

Abbreviations: ANOVA, analysis of variance; *APOE*, apolipoprotein E; EC, entorhinal cortex; DVR, distribution volume ratio; GBA, global brain atrophy; HV, hippocampal volume; LIBRA, LIfestyle for BRAin Health; PET, positron emission tomography; PACC-3, Preclinical Alzheimer's Cognitive Composite; WMH, white matter hyperintensity.

*p-values from chi-square test (categorical variables) or ANOVA (continuous variables).

[a]Based on data-driven tertiles of average LIBRA scores: low risk (score -5.9–−0.070), intermediate risk (score −0.069–1.60), and high risk (score 1.61–12.7).

[b]DVR > 1.16, equivalent to a Centiloid of 17.[2] Based on most recent amyloid PET scan.

range, and time span studied, late-midlife lifestyle as operationalized here was not associated with tau, WMH, and neurodegeneration trajectories. The effect of lifestyle on cognitive trajectories was not consistent, with lifestyle showing modest effects on executive function but not PACC-3 or memory trajectories. In contrast, and as one might expect, inferolateral temporal lobe tau burden and a measure of GBA were significantly associated with cognitive trajectories on the PACC-3 and memory and executive function composites. Overall, the findings are at odds with prevailing views regarding the effect of lifestyle on AD, although it must be pointed out that this is largely a preclinical cohort and that the effects of lifestyle, if any, may take more time to manifest.

Evidence on both the cross-sectional and longitudinal association of lifestyle with tau burden is sparse. In the current study, we found that LIBRA was not associated with longitudinal change in tau burden, which mirrors prior work on lack of a LIBRA effect on amyloid PET trajectories and lack of a LIBRA effect on longitudinal cerebrospinal fluid (CSF) p-tau181.[6,33] Previous studies that did report associations included cross-sectional studies reporting associations

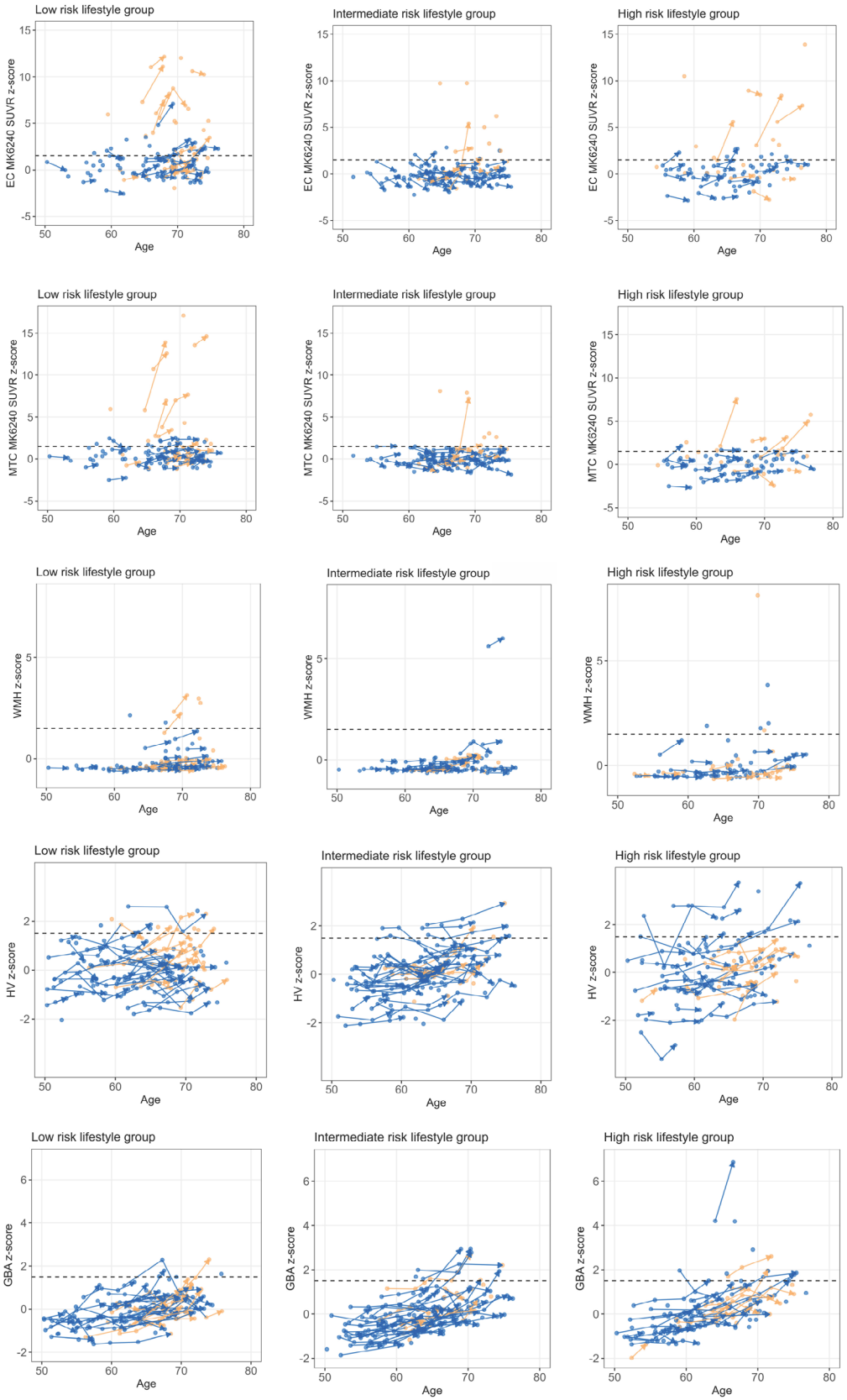

FIGURE 1 Raw data plots of age by tau *z*-scores, WMH *z*-score, HV *z*-score, and GBA *z*-score. Plots were paneled by tertile-based late-midlife LIBRA risk category and colored according to amyloid status (blue = amyloid negative, orange = amyloid positive). GBA, global brain atrophy; HV, hippocampal volume; LIBRA, Lifestyle for BRAin Health; WMH, white matter hyperintensity.

TABLE 2 Results PACC-3.

	Model 1		Model 2		Model 3	
	Estimate (95% CI)	*p*-value	Estimate (95% CI)	*p*-value	Estimate (95% CI)	*p*-value
Coefficient						
Intercept	0.30 (0.16–0.45)	**< 0.001**	0.31 (0.16–0.45)	**< 0.001**	0.31 (0.16–0.45	**< 0.001**
LIBRA score	−0.03 (-0.09–0.03)	0.41	−0.03 (−0.09–0.03)	0.29	−0.03 (−0.08–0.02)	0.18
GBA *z*-score*age	−0.02 (−0.02–−0.01)	**< 0.001**	−0.02 (−0.02–−0.01)	**< 0.001**	−0.02 (−0.02–−0.01)	**< 0.001**
tau MTC *z*-score*age	−0.01 (−0.02–−0.01)	**< 0.001**	−0.01 (−0.02–−0.01)	**< 0.001**	−0.02 (−0.02–−0.01)	**< 0.001**
LIBRA score*age	0.00 (−0.01–0.00)	0.87	0.00 (0.00–0.01)	0.34		
LIBRA score*amyloid status	−0.06 (−0.17–0.05)	0.31	−0.03 (−0.13–0.08)	0.63		
Age*amyloid status	0.00 (−0.02–0.02)	0.75	0.00 (−0.02–0.02)	0.94		
LIBRA score*age*amyloid status	0.01 (0.0–0.02)	0.073				
Observations	1242		1242		1242	
Marginal R^2/Conditional R^2	0.332/0.835		0.334/0.836		0.334/0.835	

Note: Age was the time variable. Random effects included both a random intercept and a random slope for age, with correlation permitted between intercept and slope. Models were adjusted for sex, baseline Wide Range Achievement Test-III reading recognition subtest (WRAT) score and practice effects (not presented).

Abbreviations: CI, confidence interval; GBA, global brain atrophy; LIBRA, Lfestyle for BRAin Health; MTC, meta-temporal composite; PACC-3, Preclinical Alzheimer's Cognitive Composite.

*indicates the interaction between the listed variables.

Significant *p*-values (< 0.05) are in bold font.

between alcohol consumption, lower social network scores, and multidomain lifestyle risk and increased CSF p-tau levels in cognitively unimpaired participants,[17,19,34] as well as a longitudinal study reporting associations between sleep impairment and longitudinal change in tau PET burden in predominantly cognitively impaired participants (Alzheimer's Disease Neuroimaging Initiative).[35] Differences in sample composition (cognitive status, multi- vs single-center studies) and measurement modality likely contribute to the heterogeneity of results. Our results may also have been affected by the fact that participants with lower LIBRA scores were more likely to have tau pathology at study baseline. More longitudinal studies, preferably with long follow-up durations, will be needed to fully establish the association between lifestyle and tau accumulation.

Previous studies on lifestyle, WMH, and neurodegeneration have largely been focused on physical activity and diet. They suggest mostly favorable associations of healthy lifestyle behaviors with (change in) WMH and markers of neurodegeneration,[12,36–45] replicated here for baseline GBA. Conversely, we did not find associations of lifestyle with WMH or HV trajectories. Lifestyle may be associated with GBA and not HV, as GBA is a more global measure of brain health, whereas HV is more specifically affected in certain diseases such as AD or limbic-predominant age-related TDP-43 encephalopathy.

Previous work provides clear evidence for associations of lifestyle with both cognitive functioning and decline.[25,26,36,46,47] The observation that LIBRA was not associated with PACC-3 or memory trajectories if adjusted for biomarkers and our previously identified lack of effect of LIBRA on amyloid- and *APOE*-related decline[6] may suggest that the effects of lifestyle on cognition, if any, are nominal in comparison to the effect of biomarker accumulation on cognitive decline within this age and disease burden range. The observation that late-midlife LIBRA was differentially associated with executive function trajectories in amyloid positive and negative participants may be explained partially by the fact that participants with lower LIBRA scores were more likely to have pathology at biomarker baseline. We also observed this in a previous study in our cohort,[6] and it may be due to participants at familial risk being more highly motivated to adhere to a healthy lifestyle pattern, although we did not observe clear associations between LIBRA risk category and family history at study baseline.

The current study has several limitations. Assessment of lifestyle through a summed composite score may not have allowed us to capture the full complexity of lifestyle over the late-midlife period and may have introduced a risk of reverse causality. The LIBRA score moreover does not include (detailed) information on all lifestyle factors that have been

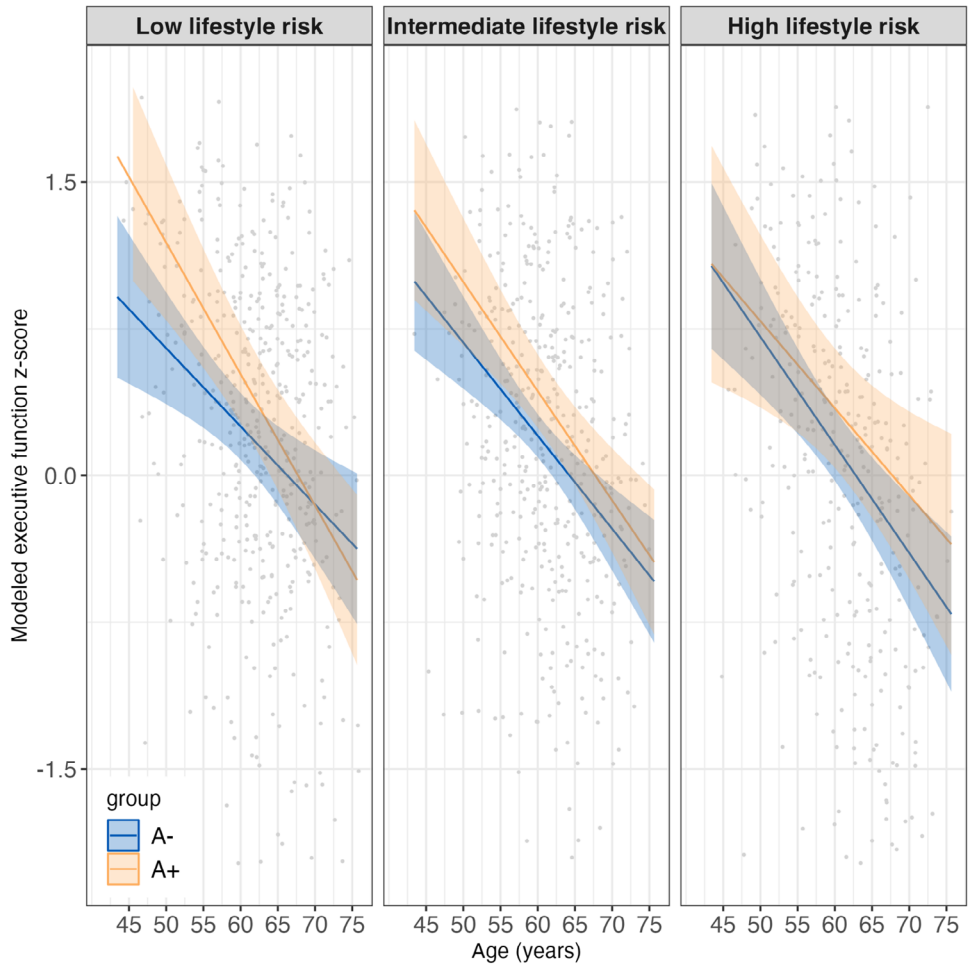

FIGURE 2 Modeled trajectories on executive function *z*-score by amyloid status, paneled by lifestyle risk tertile. Raw data points in gray. Based on the model including the three-way LIBRA*amyloid status*age interaction. The model was adjusted for sex, baseline Wide Range Achievement Test-III reading recognition subtest (WRAT) score, practice effects, most recent tau SUVR MTC *z*-score and most recent GBA *z*-score, and the interactions of both the tau MTC and GBA *z*-scores with age. Age was the time variable. Random effects included both a random intercept and a random slope for age, with correlation permitted between intercept and slope. A+, amyloid positive; A−, amyloid negative; GBA, global brain atrophy; MTC, meta-temporal composite; SUVR, standardized uptake value ratios.

identified recently as risk factors for dementia.[1] However, the utility of the LIBRA score in assessing brain health has been confirmed in multiple settings. Because participants start assessments in the presymptomatic time frame, with biomarker abnormalities emerging and a limited presence of objective cognitive decline over follow-up, the study may have been underpowered to detect associations between lifestyle and brain and cognitive changes over time. For instance, only a small proportion (15%) of the cohort was tau positive, and only a limited number of the participants included in this study showed a change in WMH burden. The rates of conversion to MCI or dementia are also still low in this largely preclinical cohort. However, the WRAP study is ideally situated to detect biomarker and cognitive changes during this presymptomatic time frame, to which most lifestyle interventions are targeted. The study of multiple biomarker and cognitive outcomes in the same samples provides an integrative and more comprehensive picture of the role of lifestyle in brain and cognitive changes. As the WRAP study primarily includes participants from the upper Midwest population, generalizability of the results may be limited.

In this longitudinal study, lifestyle as encapsulated by the LIBRA index, was not associated with tau accumulation, vascular ischemic change, or atrophy. Nor was LIBRA consistently associated with cognitive decline. Results are consistent with prior work in this cohort, which did not identify associations between lifestyle and AD biomarkers or cognitive decline[6,31,47,48] but demonstrated striking effects of both AD and vascular biomarkers on cognitive change.[3,30,31,48,49] The results of the current study suggest that potential beneficial effects of adhering to a healthy lifestyle in late-midlife, if any, may take more time to manifest and underscores the need to strengthen the evidence and clarify communication surrounding the potential benefits of adopting or adhering to healthy lifestyle behaviors to prevent AD-related pathophysiology. Continued longitudinal evaluation of lifestyle and biomarker accumulation will be necessary to fully determine

whether lifestyle moderates accumulation in the context of AD clinical endpoints such as time to dementia diagnosis.

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CONFLICT OF INTEREST STATEMENT

S.C.J. has in the past 3 years served on advisory boards for Enigma Biomedical and AlzPath. No other conflicts of interest were reported.

CONSENT STATEMENT

All subjects provided informed consent and study procedures were approved by the University of Wisconsin–Madison Institutional Review Board and conducted in accordance with the Declaration of Helsinki.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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