Lifestyle Affects Amyloid Burden and Cognition Differently in Men and Women

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Objective: Evidence on associations of lifestyle factors with Alzheimer's pathology and cognition are ambiguous, potentially because they rarely addressed inter-relationships of factors and sex effects. While considering these aspects, we examined the relationships of lifestyle factors with brain amyloid burden and cognition.
Methods: We studied 178 cognitively normal individuals (women, 49%; 65.0 [7.6] years) and 54 individuals with mild cognitive impairment (women, 35%; 71.3 [8.3] years) enrolled in a prospective study of volunteers who completed ^{18}F-Flutemetamol amyloid positron emission tomography. Using structural equation modeling, we examined associations between latent constructs representing metabolic/vascular risk, physical activity, and cognitive activity with global amyloid burden and cognitive performance. Furthermore, we investigated the influence of sex in this model.
Results: Overall, higher cognitive activity was associated with better cognitive performance and higher physical activity was associated with lower amyloid burden. The latter association was weakened to a nonsignificant level after excluding multivariate outliers. Examination of the moderating effect of sex in the model revealed an inverse association of metabolic/vascular risk with cognition in men, whereas in women metabolic/vascular risk trended toward increased amyloid burden. Furthermore, a significant inverse association between physical activity and amyloid burden was found only in men. Inheritance of an APOE4 allele was associated with higher amyloid burden only in women.
Interpretation: Sex modifies effects of certain lifestyle-related factors on amyloid burden and cognition. Notably, our results suggest that the negative impact of metabolic/vascular risk influences the risk of cognitive decline and Alzheimer's disease through distinct paths in women and men.

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Although an abundance of observational studies supports the possibility of preventing Alzheimer's disease (AD) and other dementias by following certain lifestyle habits,[1] disentangling the specific contribution of lifestyle-related factors to cognitive trajectories and brain pathologies remains a challenge. Metabolic or vascular risk (MVR) factors,[2] cognitive activity (CA),[3] and physical activity (PA)[4] can influence the onset and rate of cognitive decline in the aging population. Brain amyloid-beta (Aβ) plaques, a cardinal pathological feature and one of the earliest detectable biomarkers of AD,[5] has been reported to be associated with these lifestyle-related factors and numerous plausible physiological mechanisms have been described to support these associations.

Evidence suggests that accumulation of Aβ pathology is one of the main triggers that initiates AD by setting

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off a chain of events, which eventually causes downstream neurodegeneration, cognitive impairment and finally dementia.[5] Thus, preventing the accumulation of Aβ by reducing lifestyle-related risk factors might hold promise in delaying the onset of cognitive decline.[6–9] Increasing the resilience against age- and disease-related changes constitutes an additional important mechanism how an individual's lifestyle might offer protection against decline.[3,10] However, findings regarding possible protective mechanisms of individual lifestyle factors are mixed.[11–13]

A crucial factor that is increasingly recognized as a key variable in disease heterogeneity is sex.[14] Sex differences in lifestyle factors and their relation to amyloid burden and cognition might in part explain differences in susceptibility to AD. For instance, previous studies indicated more pronounced associations of higher MVR as well as lower PA with cognitive decline in women compared to men.[15,16] However, little is known about the role of amyloid burden in these potentially sex-specific effects of lifestyle-related factors on cognition.

The inter-relation of lifestyle-related risk factors and possible sex-related variation in AD risk factors call for novel approaches to further elucidate how various components interact. Using structural equation modeling, the present study aimed to investigate the role of sex in the associations of MVR, PA, and CA with amyloid burden and cognition. In a first step, we specified a structural equation model and examined how these lifestyle-related factors relate to individual differences in Aβ pathology and cognitive functions in our cohort of older adults. In a second step, we examined the model for differences between men and women. Given the broad differences in vascular physiology between men and women,[17,18] we hypothesized that sex differences will primarily be related to MVR.

Methods

Study Population

Study participants were recruited via newspaper ads and enrolled in the ID-cog study, a prospective study for long-term cognitive performance and healthy aging. Two hundred thirty-three residents (107 women and 126 men) of the greater Zurich area aged 50 to 89 years were included at baseline. Baseline data were collected between 2016 and 2020. To be enrolled, the participant had to be at least 50 years of age, free of clinically significant depression, any history of stroke, and diseases that interfere with compliance at the study visit. In the present study, we included all participants who had both Aβ-positron emission tomography (PET) imaging and APOE genotype assessment, leading to exclusion of one participant due to missing APOE information. Participants were determined to be cognitively unimpaired or fulfilling criteria for mild cognitive impairment (MCI) as determined by a diagnostic conference that included at least one experienced clinician and one neuropsychologist, incorporating all available clinical information and according to published diagnostic guidelines.[19] The study was approved by the ethics committee of the Canton Zurich. All participants gave written informed consent prior to the first study procedure.

Assessment of Physical and Cognitive Activity

PA and CA across different life stages were assessed using the corresponding questions in the Lifetime of Experience Questionnaire.[20] Scores were calculated for the 2 age stages "early life" (13–30 years) and "mid-life" (30–65 years). Because an individual's educational attainment is already part of the analysis as *Years of Education*, we aimed at quantifying the motivation to take part in extra-curricular, voluntary activities (eg, reading, writing, painting, and social activities). Thus, the CA scores involved only the "nonspecific" part of the questionnaire that refers to the implementation of cognitively stimulating activities in daily life (excluding questions concerning PA) in the 2 age stages. Further, the questionnaire addressed the usual frequencies of mildly energetic (eg, walking and general housework), moderately energetic (eg, playing golf and polishing a car), and vigorous PA (eg, running and playing tennis). Similar to previous publications[7,8] and deviant from the original scoring, we considered intensity and frequency of the activity for our scoring. Ratings of 1, 2, and 3 were assigned for mild, moderate, and vigorous PAs, respectively.[21] Total PA scores for the corresponding life stage were calculated by summing the product of frequency and intensity. Details regarding the derivation of the PA and CA scores are provided in the Supplementary Materials.

Because many participants did not yet reach the age of 65 years and thus did not complete the late-life section of the Lifetime of Experience Questionnaire, we used a separate questionnaire that addressed an individual's current (past 12 months) PA and CA.[13] Identical to the life-stage PA scores, we considered intensity and frequency of the activity for our PA scoring.

PET Imaging, Acquisition, and Analysis

Acquisition, processing, and regions of interest for amyloid PET scans using 18F-Flutemetamol have been described in detail in a previous publication.[22] We used the software PMOD NeuroTool 3.9 (PMOD Technologies LLC) to calculate the global Aβ standardized uptake value ratio (SUVR) for each participant by taking together frontal, temporal, and parietal lobe regions and anterior and

posterior cingulate normalized to the whole cerebellum. For descriptive purposes, we reported the number of participants with elevated amyloid at 2 previously established, relevant Centiloid project cutoff values.[23]

Clinical Data

Blood samples were collected in the morning after a fasting period of at least 8 hours. Four participants had their last food intake <8 hours before blood collection. The reported results did not change when the blood values of these subjects were excluded in a sensitivity analysis. In the present study, we used the following markers: triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), non-HDL cholesterol (non-HDL-C) and glycated hemoglobin (HbA1c). Non-HDL-C levels were calculated (non-HDL-C = total cholesterol – HDL-C). We preferred non-HDL-C to total cholesterol or low-density lipoprotein cholesterol because studies suggest that it is a better predictor of outcomes.[24] APOE genotyping was performed by commercially available Sanger Sequencing (Microsynth AG). Sex (self-reported as women or men), blood pressure, weight, and height for each participant were ascertained at the clinical visit.

Cognition Measures

Participants completed a battery of neuropsychological tasks. We assessed 4 cognitive domains defined by 16 (sub)tasks: working memory (Digit Span [backward], Corsi Block [backward]), executive functions (category fluency (animal), letter fluency (s), and figural fluency (5-point test), Stroop Test, Trail Making Test [B/A]), visual construction (Rey Complex Figure task [copy], and CERAD figures), and episodic memory (CERAD words [learning, recall, and recognition], and VLMT (German version of the RAVLT) [learning, late recall, and recognition], CERAD figures [recall]). We converted each individual test score to z scores using the mean and standard deviation of the cohort then averaged the scores to create the four domain scores. Details regarding the neuropsychological tests are provided in the Supplementary Materials.

Statistical Analysis

Subject Characteristics. Continuous variables were checked for normality. Differences between women and men were analyzed with Student's *t* test or Wilcoxon rank sum test, the chi-squared test, and age-adjusted analysis of covariance (ANCOVA) as appropriate. The SUVR was log-transformed before the calculation.

Confirmatory Factor Analysis. In a first step, we used confirmatory factor analysis (CFA) to identify the measurement model and establish the 3 lifestyle-related constructs. These (latent) constructs are variables that cannot be directly measured but represent the commonality of its indicators (ie, directly measured variables). For all constructs, we assumed one underlying factor that influences the expression of its indicators.[25] We used all available data about an individual's PA, CA, and MVR and defined initial constructs as follows: non-HDL-C, TG, HDL-C, systolic blood pressure, body mass index (BMI), and HbA1c were indicators assigned to the MVR construct; early life PA, mid-life PA, and current PA were indicators assigned to the PA construct; and early life CA, mid-life CA, current CA, and years of education were indicators assigned to the CA construct. In addition, Working Memory, Episodic Memory, Visual Construction, and Executive Function were assigned to the Cognition construct, which represents the fourth latent construct in the model. The initial model was used to identify indicators with low relevance for explaining the underlying factor. Indicators were included in the final model if the factor loadings were greater than 0.31.[26] Furthermore, we considered the overall fit of the model to select the final construct structures. Once the structure was obtained, we requested modification indices to arrive at the model that best represents the relationships between the analyzed variables. However, to avoid overfitting, only theoretical justified modifications that resulted in a notable improvement in model fit were made.

Structural Equation Modeling. In our primary analysis, we used structural equation modeling (SEM) to investigate the relationships between the lifestyle-related constructs (PA, CA, and MVR) established in the prior CFA, Aβ SUVR (amyloid burden) and cognitive performance (cognition). Based on published data, as described in the introduction, we specified the lifestyle-related constructs as predictors of both amyloid burden and cognition. Amyloid as one of the earliest markers for developing AD[5] was specified as a predictor of cognition and thus formed a potential mediator between the lifestyle-related constructs and cognition. Age was included as an exogenous variable and was specified as a predictor of amyloid burden, cognition, and MVR. *APOE4* (1/2 APOE4 allele vs no APOE4 allele) as a genetic risk factor for increased amyloid burden was specified as exogenous predictor of amyloid burden.[27] Because vascular risk may be influenced by an individual's APOE polymorphism,[28] we tested in an exploratory analysis, whether it would be meaningful to also specify APOE4 as a predictor of MVR. However, this path was not significant and was not included in the final model as it was not an a priori defined path.

Including sex as an exogenous variable in the model produced a substantial lack of fit, indicating large

differences in estimated parameters or the model structure between men and women. This led us to conduct a multigroup comparison analysis as a next step. In SEM, the examination of differences and similarities between groups becomes more informative and reliable when the underlying latent factor of the constructs is the same for both groups, that is, the constructs are invariant and measurement invariance is established. If measurement invariance is not supported, the group comparison is compromised because the meaning of the underlying factor becomes group specific. Measurement invariance of the scale's items across sex groups was tested based on published guidelines for establishing measurement invariance of models.[29,30] Establishing that construct and model structure is the same for both sexes allowed us to compare the estimated parameters.

Analyses were performed in R version 4.0.2 using maximum likelihood estimation in the *lavaan* package. SUVR was first log-transformed to better meet the model assumptions of normal distribution. All continuous variables were standardized prior to model entry. Apart from the measurement invariance testing procedure, we used a full information maximum likelihood (FIML) estimation to handle missing values, assuming missingness at random. We conducted the analyses with and without FIML; the use of FIML increased model power but did not substantially change any decisions regarding the parameters of interest. In total, 26 participants (11.2%) had one or more missing observation and less than 2% of the overall data was missing. We evaluated the model fit to data using the chi-squared statistic and several practical fit indices, including the root mean square error of approximation (RMSEA), comparative fit index (CFI), Tucker-Lewis index (TLI), and standardized root mean square residual (SRMR). RMSEA <0.05, CFI >0.95, TLI >0.95, and SRMR <0.08 indicate close model fit to data.

Sensitivity Analyses. We conducted the following post hoc analyses: (1) we used Mahalanobis distance ($p < 0.001$) to detect influential cases, which we excluded in follow-up models. Unless reported otherwise, results remained unchanged when influential cases were removed. (2) We tested whether single paths within the multigroup model significantly differ between men and women. (3) Because the meaning of the MVR and cognition constructs may differ by APOE4 carrier status,[28,31] we tested for measurement invariance in these constructs comparing APOE4 carriers with non-carriers. (4) Further analyses were performed using cognitively normal individuals only as well as APOE4 non-carriers only.

Results

Subject Characteristics

Table 1 summarizes demographics, baseline participant characteristics, and lifestyle variables. Subject characteristics are additionally provided for sex subgroups. Twenty-three (42.6%) of the 54 participants with MCI displayed elevated amyloid burden (Centiloid >12), 13 (24.1%) with established amyloid pathology (Centiloid >30).[23]

Confirmatory Factor Analysis

First, we applied CFA to establish the relationships between the observed indicators and latent constructs. The initial model, which included all the available variables, had an unacceptable fit (1. CFA in Table 2). Hence, we modified the model as described in the Method section. The following adjustments were made: (1) we removed current CA as an indicator of the CA construct and both non-HDL-C and systolic blood pressure as indicators of the MVR construct because of low factor loadings (<0.31); (2) we removed the negligible covariance between CA and MVR ($\beta = 0.033$, SE = 0.047, $p = 0.477$); (3) after requesting modification indices, we allowed correlated residuals between early life CA and mid-life CA. Both indicators were drawn from the same questionnaire and include identical questions, justifying this modification. Although we had to exclude information about an individual's CA as well as 2 potentially significant vascular risk factors, this model was preferred because it had a considerably better fit compared to the baseline model (2. CFA in Table 2).

Structural Equation Model

In a next step, we included age, APOE4, amyloid burden, and the structural paths (predictions) to the measurement model established in the CFA. Because sex could not be included as an exogenous variable in this model, we report first the results of the model that did not account for sex effects. This model fit the data well (1. SEM in Table 2) and is summarized in Figure 1. Detailed parameter estimates are available in Table 3.

Effects on Amyloid Burden and MVR. Both age and APOE4 were significant predictors of amyloid burden. In contrast, higher values in the PA construct significantly predicted lower amyloid burden. However, this association was weakened to a nonsignificant level after we excluded influential cases ($\beta = -0.153$, SE = 0.112, $p = 0.172$). Influential cases (n = 4, all of them MCI, 1 woman) are multivariate outliers and were identified using Mahalanobis distance. Neither MVR nor CA significantly predicted amyloid burden. Higher age predicted increased MVR.

TABLE 1. Study Cohort Description Overall and Stratified by Sex

	Overall (n = 232)	Men (n = 125; 53.9%)	Women (n = 107; 46.1%)
Age, years mean (SD) [range]	66.4 (8.2) [50–89]	67.7 (7.6) [50–81]	65.0 (8.8) [50–89]*
Education, years mean (SD)	15.5 (2.9)	16.5 (2.6)	14.3 (2.7)***
APOE-ε4 carrier, n (%)	54 (23.3)	24 (19.2)	30 (28.0)
MCI, n (%)	54 (23.3)	35 (28.0)	19 (17.8)
MMSE, mean (SD)	29.1 (1.2)	29.1 (1.1)	29.2 (1.3)
BMI, mean (SD)	25.4 (3.9)	26.5 (3.3)	24.2 (4.1)***
Diabetes mellitus, n (%)	9 (3.9)	7 (5.6)	2 (1.9)
CVD, n (%)	33 (14.2)	21 (16.8)	12 (11.2)
non-HDL-C, mean (SD)	3.84 (1.05)	3.72 (1.02)	3.97 (1.08)
HDL-C, mean (SD)	1.57 (0.38)	1.42 (0.31)	1.75 (0.37)***
Triglycerides, mean (SD)	1.10 (0.54)	1.13 (0.58)	1.05 (0.49)
Hemoglobin A1c	5.44 (0.48)	5.48 (0.55)	5.38 (0.38)
Systolic blood pressure	131.9 (15.2)	135.1 (13.8)	128.3 (15.9)***
Cognitive domains, mean (SD)[a]			
Working Memory	0 (0.79)	0.02 (0.77)	−0.02 (0.81)
Visual Construction	0 (0.80)	0.05 (0.75)	−0.04 (0.85)
Episodic Memory	0.02 (0.80)	−0.17 (0.74)	0.23 (0.81)**
Executive Function	0.01 (0.66)	0 (0.61)	0.02 (0.71)
Amyloid burden, SUVR median [range][a]	1.22 [1.02–2.37]	1.23 [1.02–2.23]	1.19 [1.03–2.37]
Centiloid >12, n (%)	77 (33.2)	51 (40.8)	26 (24.3)*
Centiloid >30, n (%)	27 (11.6)	15 (12.0)	12 (11.2)
Lifestyle variables			
PA Score, mean (SD)			
Early life	13.0 (9.5)	13.1 (9.9)	12.8 (9.1)
Mid-life	12.4 (9.6)	12.0 (10.0)	12.9 (9.1)
Current	10.0 (5.2)	9.9 (5.5)	10.1 (4.9)
CA Score, mean (SD)			
Early life	19.4 (4.4)	19.2 (4.3)	19.6 (4.5)
Mid-life	19.3 (4.6)	19.4 (4.7)	19.1 (4.5)
Current	23.3 (7.2)	22.8 (6.1)	23.9 (8.2)

Centiloid of 12 marks the transition from the absence of pathology to subtle pathology. Centiloid of 30 indicates the presence of established amyloid pathology. Blood markers are given in mmol/L. Note that the questionnaire used to assess early life and mid-life PA/CA differs from the questionnaire used to assess current PA/CA, thus, scales are not directly comparable. Abbreviations: BMI = body mass index; CA = cognitive activity; CVD = cardiovascular diseases; HDL-C = high-density lipoprotein cholesterol; MCI = mildly cognitive impaired; MMSE = Mini-Mental State Examination; PA = physical activity; SD = standard deviation; SUVR = standardized uptake value ratio.

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

[a]Group differences were assessed by age-adjusted analysis of covariance (ANCOVA).

TABLE 2. Indices of Fit for Confirmatory Factor Analysis and Structural Equation Models

		Statistical index of fit			Practical indices of fit			
Model	**Description**	χ^2	**df**	***p***	**RMSEA [CI]**	**SRMR**	**CFI**	**TLI**
1. CFA	Total cohort, all variables	210.5	113	0	0.061 [0.048, 0.074]	0.066	0.87	0.85
2. CFA	Total cohort, adjusted	81.1	71	0.193	0.025 [0.00, 0.047]	0.048	0.98	0.98
1. SEM	Total cohort	129.6	107	0.068	0.030 [0.00, 0.047]	0.054	0.97	0.96
2. SEM	Women only	151.2	107	0.003	0.062 [0.037, 0.084]	0.085	0.90	0.88
3. SEM	Men only	85.9	107	0.933	0.0 [0.00, 0.014]	0.067	1	1.09
MG-SEM	Total cohort	273.0	237	0.054	0.036 [0.00, 0.054]	0.083	0.96	0.95

A good model fit is indicated by nonsignificant χ^2 statistics ($p > 0.05$), RMSEA <0.05, SRMR <0.08, CFI >0.95, and TLI >0.95.
Abbreviations: CFA = confirmatory factor analysis; CFI = comparative fit index; CI = confidence interval; MG-SEM = multigroup structural equation model; RMSEA = root mean square error of approximation; SEM = structural equation model; SRMR = standardized root mean square residual; TLI = Tucker-Lewis index.

Effects on Cognition. Age and the CA construct significantly predicted cognitive performance, with the positive effect of CA on cognition being twice as large as the negative effect of age on cognition. In turn, neither the PA construct nor the MVR construct significantly predicted cognition. Because amyloid burden did not significantly predict cognition, we refrained from examining amyloid mediated effects on cognitive performance.

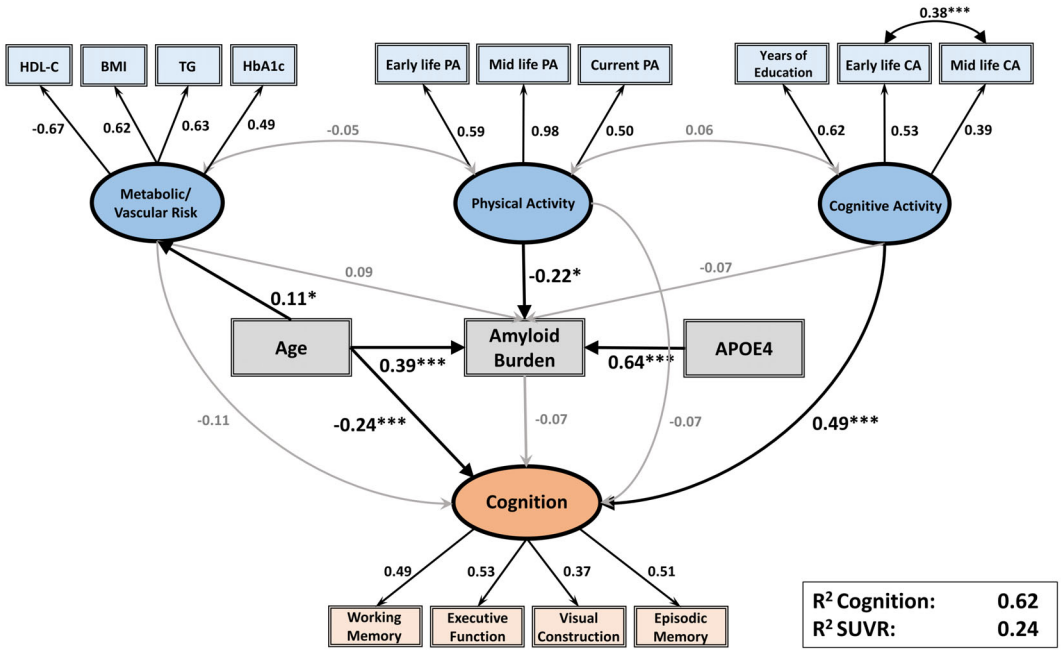

FIGURE 1: Path diagram picturing the structural model. Latent constructs of Metabolic/Vascular Risk, Physical Activity, and Cognitive Activity were used to investigate the relationship with Amyloid Burden (log-transformed) and the Cognition construct with Age and *APOE4* as exogenous variables. The ellipse-shaped variables represent the latent constructs. Black arrows indicate significant paths at *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$. Grey arrows indicate non-significant paths. Each single-headed arrow denotes a unidirectional effect of one variable on another and left–right-headed arrows indicate correlations between constructs or correlated residuals of indicators. Note that only estimates on paths going to a particular outcome variable are comparable as they are adjusted for each other. R^2 refers to the amount of variance in Cognition and Amyloid Burden accounted for by the model and involves significant and nonsignificant predictors. Abbreviations: BMI = body mass index; CA = cognitive activity; PA = physical activity; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; HbA1c = hemoglobin A1c; SUVR = standardized uptake value ratio. N = 232.

TABLE 3. Estimations of Model Parameters

Latent constructs	(Derived from)	Estimate	Std. Err.	*p*
Metabolic/vascular risk				
	BMI	0.620	0.072	<0.001
	HDL-C	−0.671	0.073	<0.001
	TG	0.627	0.072	<0.001
	HbA1c	0.486	0.75	<0.001
Physical activity				
	Early life PA	0.592	0.075	<0.001
	Mid-life PA	0.984	0.088	<0.001
	Current PA	0.503	0.073	<0.001
Cognitive Activity				
	Early life CA	0.532	0.092	<0.001
	Mid-life CA	0.385	0.093	<0.001
	Years of education	0.623	0.099	<0.001
Cognition				
	Working memory	0.492	0.049	<0.001
	Executive function	0.525	0.041	<0.001
	Episodic memory	0.508	0.050	<0.001
	Visual construction	0.370	0.053	<0.001
Regressions	**(Regressed on)**	**Estimate**	**Std. Err.**	***p***
Amyloid Burden				
	Age	0.392	0.060	<0.001
	APOE4	0.642	0.138	<0.001
	MVR	0.085	0.116	0.466
	PA	−0.215	0.109	0.049
	CA	−0.069	0.160	0.668
Cognition				
	Age	−0.236	0.038	<0.001
	Amyloid Burden	−0.067	0.036	0.064
	MVR	−0.107	0.062	0.082
	CA	0.490	0.128	<0.001
	PA	−0.066	0.062	0.290
Metabolic/Vascular Risk				
	Age	0.106	0.049	0.029
Covariances				
PA < - > MVR		−0.050	0.030	0.100
PA < - > CA		0.056	0.040	0.158
Early life CA < - > mid-life CA*		0.376	0.079	<0.001

Parameter estimate, standard error (Std. Err.), and *p* value for all indicators in the overall model. All estimates are standardized.
Abbreviations: BMI = body mass index; CA = cognitive activity; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; MVR = metabolic/vascular risk; PA = physical activity; TG = triglycerides.
*Residual covariance.

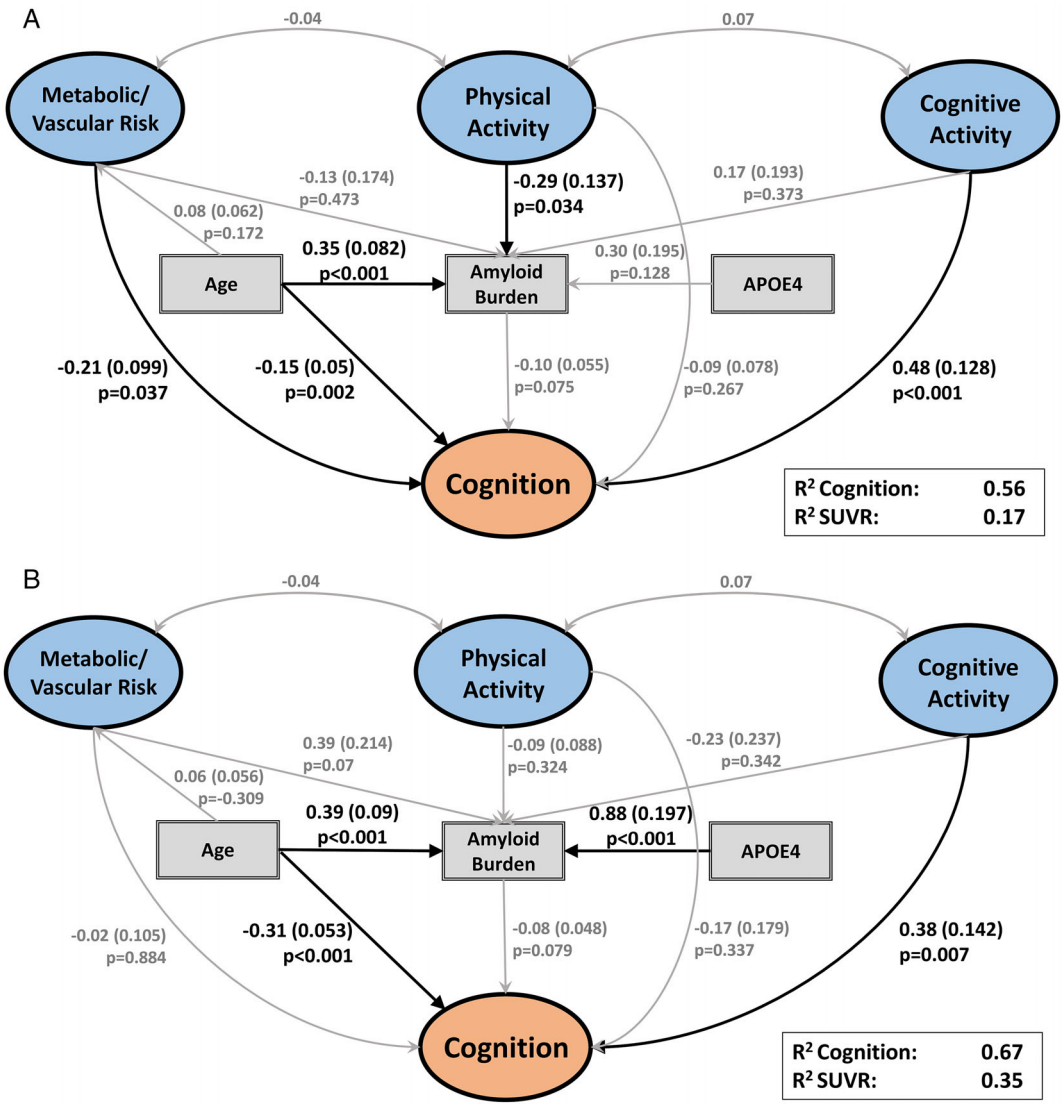

FIGURE 2: Multigroup comparison. Results of the multigroup analysis model depicted on separate models for (A) men (N = 125) and (B) women (N = 107). Factor loadings are the same for men and women and roughly correspond to the factor loadings in the full model (Fig 1). For a simplified representation, indicators and factor loadings were removed. Values on each path represent standardized estimates, standard error in parentheses, and *p* value. Abbreviation: SUVR = standardized uptake value ratio.

Multigroup Analysis

We then explored whether the relationships between the variables differ between women and men. For that, we first evaluated measurement invariance to determine construct comparability. For a detailed description of the measurement invariance testing procedure and the unabridged fit indices of each step, we refer the reader to the Supplementary Materials.

Measurement Invariance Testing. A first model, which was used to test whether the structure of the constructs is the same for both men and women, fit the data well. However, running individual models for each sex indicated a substantial better fit for men compared to women (2. and 3. SEM in Table 2), likely due to weaker associations among the variables in the women-only model. Further, the measurement invariance testing procedure revealed significant deterioration of the model fit when the indicator intercepts of episodic memory, years of education, BMI, and HDL-C were constrained. These were thus relaxed in the final group comparison model, that is, they were allowed to vary by sex. Otherwise, models were invariant, indicating equal structure, variance, and covariances of the constructs across sex.

Establishing measurement invariance enabled us to compare the structural parameters in the multigroup model. We depicted the result of the multigroup comparison in separate models for men and women in Figure 2.

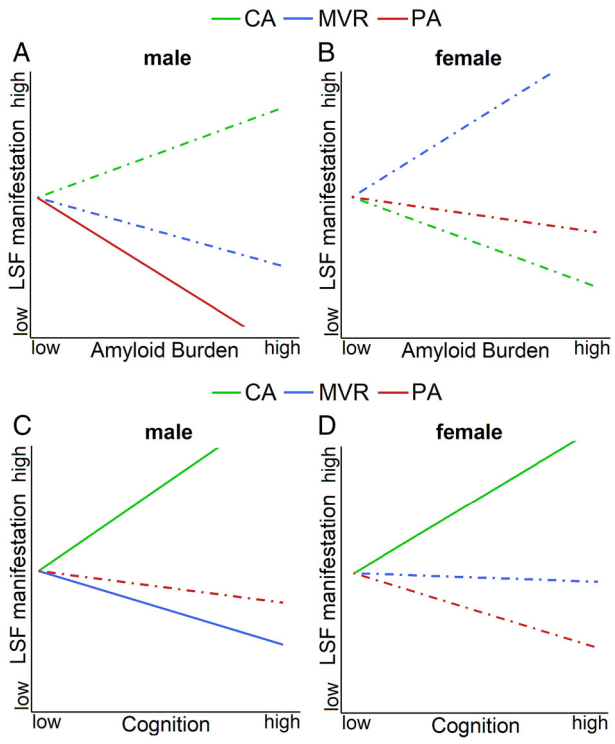

FIGURE 3: Summarized results of sex comparison. Solid lines indicate significant associations between the manifestation of the corresponding lifestyle-related factor and amyloid burden (A + B) and cognition (C + D). Dotted lines indicate non-significant paths. Plots are separately shown for men (A + C) and women (B + D). Abbreviations: CA = cognitive activity; LSF = lifestyle-related factor; MVR = metabolic/vascular risk; PA = physical activity.

Associations of lifestyle-related factors with cognition and amyloid burden are summarized in Figure 3.

Structural Parameters. In women, age was a slightly better predictor of amyloid burden and a much stronger predictor of cognition compared to men. APOE4 significantly predicted amyloid burden in women but not in men. In turn, only men showed a significant negative association between PA and amyloid burden and between MVR and cognition. As in the full model, the association between PA and amyloid burden was no longer significant after removing the influential cases mentioned above ($\beta = -0.194$, SE = 0.135, $p = 0.151$). Higher CA was the strongest predictor of better cognitive performance in both men and women. Both groups showed similar associations between amyloid and cognition, which approached significance in men ($p = 0.075$) and women ($p = 0.079$). The path from MVR to amyloid burden approached significance in women ($p = 0.07$) but not in men ($p = 0.473$).

Sensitivity Analysis

All post hoc models described below fit the data well (CFI >0.95, TLI >0.95, RMSEA <0.05, and SRMR <0.09). (1) Testing whether single paths in the model differed between men and women indicated significant group differences only in the APOE4-to-amyloid path and the age-to-cognition path ($p < 0.05$). (2) After excluding participants with MCI, the model displayed no association between PA and amyloid burden but showed a more pronounced effect of MVR. This became particularly evident when we compared men and women in this cognitively healthy subsample: there was a highly significant association between MVR and cognition in men ($\beta = -0.300$, SE = 0.115, $p = 0.009$) whereas the association was not significant in women ($\beta = -0.037$, SE = 0.105, $p = 0.723$). Conversely, higher MVR significantly predicted higher amyloid burden in women ($\beta = 0.389$, SE = 0.169, $p = 0.022$) but not in men ($\beta = -0.012$, SE = 0.161, $p = 0.940$). (3) We could establish measurement invariance in the MVR and cognition constructs by APOE4 carrier status (details in Supplementary Materials). (4) Finally, we excluded APOE4 carriers from the total cohort and examined the model with APOE4 non-carriers only. Because of convergence difficulties of the model due to the high factor loading of the mid-life PA indicator, we replaced the PA construct with the mid-life PA variable. The result of this model showed a significant association between MVR and cognition in the full APOE4 non-carrier sample. Otherwise, neither the full APOE4 non-carrier model nor the sex-subgroup APOE4 non-carrier model differed markedly from the overall sample.

Discussion

In our cohort of middle to higher aged adults, we found that a lifestyle high in PA was associated with lower amyloid burden and a lifestyle high in CA was associated with better cognitive performance. These results support existing evidence regarding their roles as modifiable risk factors for cognitive decline and are in line with the concept of cognitive reserve.[1,3] Multigroup analysis showed that higher MVR was associated with lower cognitive performance in men, whereas higher MVR tended to correlated with increased amyloid burden in women. These interactions were stronger in predefined sensitivity analyses restricted to cognitively healthy individuals and independent of APOE4 status. Although the associations revealed are based on cross-sectional data, the most likely interpretation, supported by previous reports without amyloid measurement, is that the adverse effects of vascular and metabolic risk factors increase the risk of cognitive decline and AD in women and men by partly different mechanisms.[32–34]

The significant association between higher MVR and lower cognitive performance in men is in line with a

higher incidence of cardiovascular events and vascular dementia in men than in women throughout much of the lifespan.[35] Many risk factors for cognitive impairment of vascular etiology, such as atrial fibrillation, atherosclerosis, and obesity, are more common among men.[35] Gender-related risk behavior and lifestyle likely contribute to the higher risk of vascular pathologies among men.[14] Although higher exposure to risk factors in men might have contributed to our finding, we note that the observed sex differences cannot simply be explained by a greater variance in the constructs, as we could establish equal variances across sex in the measurement invariance testing procedure. Women's vascular protection is commonly thought to be due to differences in estrogen concentration. Vasoprotective effects of estrogen include, for instance, the promotion of healthy endothelial function by increasing vasodilation in response to a vasodilatory stimulus.[36] A dysfunction of this response can often be observed during aging and is considered a crucial event in the development of many cardiovascular pathologies.[37] A decline of endothelial function has been found to begin around the fourth decade of life in men, whereas women maintain healthy vascular physiology for approximately another 10 years.[38] Other mechanisms for sex-related decreases in cognitive performance due to an increased MVR may be related to differences in cerebral blood flow, inflammatory processes, or blood brain barrier maintenance.[17] Our results suggest that MVR has an effect on cognition that is detectable already in healthy older adults and indicate that men in particular could beneficially impact cognition by striving for optimal cardiovascular health.

Different lines of evidence suggest that MVR might be causal to amyloid accumulation[39,40] but imaging studies also provide evidence for independent effects on brain health.[10] It is still debated whether vascular risk factors are risk factors for amyloid accumulation or for concomitant vascular pathologies that increase the likelihood of dementia.[41] Previous studies might have found ambiguous results because of a close relationship between vascular factors and Alzheimer's pathologies. Both may be intimately linked, making associations difficult to find.[39] MVR might act independently and/or synergistically with Aβ via enhanced inflammatory responses and activated pericytes to restrict capillary blood flow, ultimately promoting amyloid accumulation and blood–brain barrier dysfunction.[40,42] Further, it is plausible that MVR exerts a dual effect on brain health by promoting atherosclerosis and hypoperfusion on the one hand and amyloid accumulation via impaired clearance on the other hand.[39] Although our overall model would support the hypothesis that MVR and amyloid burden act independently, an association became visible in our multigroup models. Here, the MVR-to-amyloid path showed a trend toward significance in women and reached significance after excluding participants with MCI. Again, the broad sex differences in cerebrovascular function and pathology leave much scope for potential mechanisms that might make women more prone to amyloid accumulation in the presence of MVR.[17] For example, MVR might promote the generation of reactive oxygen species that further exacerbate an already enhanced state of oxidative stress observed in women after menopause.[17,43] Reactive oxygen species themselves have been shown to trigger Aβ generation by enhancing the amyloidogenic pathway.[44]

MVR showed stronger associations with cognition and amyloid burden in men and women, respectively, after excluding participants with MCI from our analysis. A potential explanation for this finding is that subjects with MCI reflect a heterogeneous population with amyloid accumulation and cognitive symptoms resulting from multiple etiologies that are not necessarily dependent on MVR.[45] Additionally, the relationship of vascular risk factors with dementia might not always be linear.[33] Jointly analyzing both MCI and cognitively healthy participants may have disturbed the ability of the MVR construct to associate with amyloid burden and cognition.

Interestingly, we found that the effect of APOE4 on amyloid burden was highly significant in women but not in men. Similarly, in a large autopsy study, Corder and colleagues reported a large increase in senile plaques in APOE4-carrying women between the ages 60 and 75 years compared to APOE4-carrying men in the same age range. This marked increase in accumulated amyloid was only seen in early neurofibrillary tangle stages (Braak I–III).[46] Furthermore, studies around menopause reported more pronounced amyloid burden in APOE4-carrying women compared to age- and genotype-matched men.[47] Despite some supporting evidence from the literature, we warrant caution in interpreting our finding because of the relatively small number of APOE4 carriers in our sample. Additionally, a large meta-analysis found no interaction between sex and APOE4 carrier status on amyloid abnormality.[27]

Besides the aforementioned differences in the sex-subgroup models, other associations were similar in men and women. The strong negative effect of age on cognition, which was particularly prominent in women, likely reflects the presence of brain pathologies not related or only partially related to amyloid (eg, TDP-43, microinfarcts, and neurofibrillary tangles) as well as other aging-related processes that affect cognitive abilities.[48] Age was also highly significantly associated with increased amyloid burden in both men and women. The path from CA

to cognition can be viewed as a proxy of an individual's cognitive reserve and reflects its ability to cope with age and disease-related changes.[3,10] Previous findings regarding the relationship of PA and amyloid burden are mixed.[11] We observed that higher PA was associated with lower amyloid burden; however, in sensitivity analyses, we found that the statistical significance of this association was driven by few men. Nevertheless, this finding would correspond to a recent study that also reported a significant association between amyloid burden and PA in men but not in women.[49]

We want to address some caveats regarding the interpretation of our results. As with all cross-sectional studies, we cannot provide direct causal evidence for protective roles of the studied lifestyle-related factors. Particularly PA and CA may be subject to reversed causality, that is, a lower burden of underlying pathology and/or higher cognitive capacity may facilitate maintaining an active life in older age.[50,51] Furthermore, we want to point out that volunteers in our study were recruited via newspaper advertisement and thus might represent a health-conscious cohort with many individuals still in early stages of neuropathology. However, as discussed above, an association between MVR and amyloid may be detectable particularly in the earliest stages of disease development.[52] In addition, the MCI group is not comparable to a memory clinic population and has therefore a lower proportion of subjects with prodromal AD. An important issue was the modest model fit for women. Factors not included in our model may better predict amyloid burden and cognitive performance in women (eg, sleep and stress).[14] Finally, excluding distinct subgroups in our sensitivity analyses may have modified the meaning of the constructs and thereby reduced the comparability of the models. However, factor loadings did not vary greatly among models and we could establish measurement invariance in distinct subgroups, which alleviates this concern. Replication of our findings in independent cohorts would be helpful to validate and possibly extend our results on different populations.

Given the multifactorial nature of AD and aging in general, SEM is a valuable tool to dissect the interconnectedness between lifestyle-related factors and their relative contributions to cognitive aging. Although single paths were not significantly different for the most part, we decided to choose a holistic approach to interpreting our findings that may be closer to reality where different factors (eg, MVR and PA) cannot definitely be separated. Furthermore, establishing latent constructs that assume a common causal factor that underlies the different indicators might also be more representative of the actual lifestyle factor instead of investigating single measures. Future research might focus on additional or more specific constructs that underlie the expression of clusters of vascular and metabolic risk indicators to gain a deeper understanding of the associations investigated in this work.

In summary, we confirm the positive impact of cognitive activity on cognition, which is an effect observable in both sexes. Additionally, we observed a tentative but significant association between physical activity and amyloid burden in this population that represents early amyloid accumulation. Most importantly, our results suggest that the negative impact of metabolic/vascular risk influences the risk of cognitive decline and AD through partly distinct paths in women and men. Acknowledging the interactions between lifestyle and sex will advance our understanding of AD and path the way toward individualized prevention and therapeutic strategies.

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Author Contributions

R.M.N., C.H., A.F.G., and V.T. contributed to the conception and design of the study. D.B., Z.J.R., A.B., I.Z., S.S., A.S., K.R., E.G., A.F.G., and V.T. contributed to the acquisition and analysis of data. D.B., V.T., and A.F.G. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

Nothing to report.

Data Availability

The raw data supporting the conclusions of this article will be made available by the authors upon reasonable request after evaluation by the authors and, if applicable, by the local ethics authority.

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