Title

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Protective effects of sleep duration and physical activity on cognitive performance are influenced by β-amyloid and brain volume but not tau burden among cognitively unimpaired older adults

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ABSTRACT

Background and objectives: Sleep and physical activity have gained traction as modifiable risk factors for Alzheimer's disease. Sleep duration is linked to amyloid-β clearance while physical activity is associated with brain volume maintenance. We investigate how sleep duration and physical activity are associated with cognition by testing if the associations between sleep duration or physical activity to cognition are explained by amyloid-β burden and brain volume, respectively. Additionally, we explore the mediating role of tau deposition in sleep duration—cognition and physical activity—cognition relationships.

Methods: This cross-sectional study obtained data from participants in the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) study, a randomized clinical trial. In trial screening, cognitively unimpaired participants (age 65–85 years) underwent amyloid PET and brain MRI; *APOE* genotype and lifestyle questionnaire data were obtained. Cognitive performance was assessed using the Preclinical Alzheimer Cognitive Composite (PACC). Self-reported nightly sleep duration and weekly physical activity were the primary predictors. Regional Aβ and tau pathologies and volumes were the proposed variables influencing relationships between sleep duration or physical activity and cognition.

Results: Aβ data were obtained from 4322 participants (1208 with MRI, 59% female, 29% amyloid positive). Sleep duration was associated with a Aβ composite score (β = −0.005, CI: (−0.01, −0.001)) and Aβ burden in the anterior cingulate (ACC) (β = −0.012, CI: (−0.017, −0.006)) and medial orbitofrontal cortices (MOC) (β = −0.009, CI: (−0.014, −0.005)). Composite (β = −1.54, 95% CI:(−1.93, −1.15)), ACC (β = −1.22, CI:(−1.54, −0.90)) and MOC (β = −1.44, CI:(−1.86, −1.02)) Aβ deposition was associated with PACC. Sleep duration—PACC association was explained by Aβ burden in path analyses. Physical activity was associated with hippocampal (β = 10.57, CI: (1.06, 20.08)), parahippocampal (β = 9.3, CI: (1.69, 16.91)), entorhinal (β = 14.68, CI: (1.75, 27.61), and fusiform gyral (β = 38.38, CI: (5.57, 71.18)) volumes, which were positively associated with PACC ($p < 0.02$ for hippocampus, entorhinal cortex and fusiform gyrus). Physical activity—cognition relationship was explained by regional volumes. PET tau imaging was available for 443 participants. No direct sleep duration—tau burden, physical activity by tau burden, or mediation by regional tau was observed in sleep duration—cognition or physical activity—cognition relationships.

Discussion: Sleep duration and physical activity are associated with cognition through independent paths of brain Aβ and brain volume, respectively. These findings implicate neural and pathological mechanisms for the relationships between sleep duration and physical activity on cognition. Dementia risk reduction approaches that emphasize the adequate sleep duration and a physically active lifestyle may benefit those with risk for Alzheimer's disease.

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1. Introduction

With limited Alzheimer's disease (AD) modifying drugs, dementia risk reduction through lifestyle changes is of critical importance. Sleep duration and physical activity are two highly promising prevention approaches with established mechanisms of action for modifying AD risk. In AD mouse models, the disease-modifying effects of sleep regulation suggest that sleep deprivation accelerates amyloid-β (Aβ) accumulation by promoting a higher level of neuronal Aβ release, altering extracellular Aβ fluctuation patterns, or through disrupting secretase function to change Aβ production (Musiek and Holtzman, 2015; Kang et al., 2009; Musiek and Holtzman, 2016). Human sleep studies have shown complementary evidence of sleep and dementia risk, such that individuals with sleep disturbances and disorders perform worse on cognitive assessments and are at increased risk of incident AD (Yaffe et al., 2014; Fortier-Brochu et al., 2012). Associations between sleep duration and AD-related pathologies were also observed, in which increased plasma and cortical Aβ levels were related to sleep deficits and shorter sleep duration for individuals with cognitive symptoms or amyloid positivity (Sanchez-Espinosa et al., 2014; Insel et al., 2021; Spira et al., 2013). Evidence suggests that sleep—Aβ deposition relationship is consistent among regions of early Aβ deposition (Insel et al., 2021; Winer et al., 2021) (medial orbitofrontal cortex (MOC), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), and precuneus) (Palmqvist et al., 2017; Villeneuve et al., 2015). Complementary evidence from participants with Down syndrome also suggests that sleep is associated with Aβ deposition and cognitive features of preclinical AD (Cody et al., 2020), warranting a further assessment of these relationships among persons at risk of AD.

Physical activity has been shown to improve memory and behavioral performance and regulate hippocampal neurogenesis in rodent models (Kim et al., 2014; Khodadadi et al., 2018; Zarezadehmehrizi et al., 2021; Rossi Daré et al., 2020; Sun et al., 2018). These findings are corroborated by human studies in which those who engage in physical activity have increased brain volumes (Erickson et al., 2011) and functional connectivity (Gu et al., 2021; Dorsman et al., 2020), which are two inferred causes of cognitive benefits seen in randomized clinical trials of physical activity in older adults (Lautenschlager et al., 2008; Chapman et al., 2016; Williamson et al., 2009). Evidence suggests that beneficial effects of exercise are primarily driven by a change in cerebral hypoperfusion of hippocampus (Maass et al., 2015) and are manifested through improved memory (Whiteman et al., 2016; Ma et al., 2017; Vaynman et al., 2004; Tao et al., 2019). The number of studies investigating the relationship between physical activity, cognition and all regions associated with memory processing (not necessarily focusing on hippocampus) is limited.

There is emerging evidence highlighting the role of tau burden in sleep—cognition relationship. Among cognitively normal older adults, self-reported changes in sleep duration were associated with tau burden (Winer et al., 2019). Moreover, sleep deprivation was associated with greater tau protein aggregation rate in neural networks (Wang and Holtzman, 2020), implicating a potential pathway linking sleep, tau, and cognitive decline. Similar associations were observed for physical activity. In a small sample of cognitively normal older adults, participants with higher physical activity had lower neocortical tau burden, as well as lower regional burden in the temporoparietal and prefrontal cortices (Brown et al., 2018). Additionally, older adults with lower total tau concentration and high physical activity had a 27% slower cognitive decline, while older adults with higher levels of total tau concentrations had 41% slower cognitive decline compared to little physical activity (Desai et al., 2021), postulating tau as a potential moderator in physical activity—cognition relationship. While there is evidence linking poorer sleep with medial temporal lobe tau burden (Winer et al., 2019), the role of regional tau in other tau PET *meta*-ROI regions (entorhinal, amygdala, parahippocampal, fusiform, and inferior temporal regions) (Jack et al., 2017) in sleep—cognition and physical activity—cognition relationships among amyloid positive participants remains underexplored.

The mechanisms linking sleep duration, physical activity, and cognition have not been evaluated in a large, deeply-phenotyped, cognitively unimpaired cohort with neuroimaging biomarkers. The goal of the present study was to evaluate the independent paths through which sleep duration and physical activity modify brain Aβ and tau deposition and brain volumes to confer cognitive function. We hypothesized that global Aβ levels, as well as Aβ burden in early accumulation regions influence the sleep duration-cognition relationship in path analyses. Aβ levels in temporal region, a region traditionally implicated in clinical stages in AD progression, was used to confirm whether these associations are specific to the early accumulation regions or not. Additionally, we hypothesized that brain volumes of regions implicated in memory processing (hippocampus, entorhinal cortex (EC), parahippocampal cortex, and fusiform gyrus (FG)) (Crane et al., 2012) influence the physical activity-cognition relationship in a sample of cognitively unimpaired, amyloid positive, healthy older adults. We also explored the role of tau burden in regions comprising tau PET *meta*-ROI in sleep duration—cognition and physical activity—cognition relationships. We hypothesized that tau burden of regions in *meta*-ROI, regions in medial temporal lobe where ligand uptake appears first,(Jack et al., 2017) influence the sleep duration—cognition and physical activity-cognition relationship in a sample of cognitively unimpaired, amyloid positive, healthy older adults with available tau PET imaging.

2. Materials and methods

2.1. Participants

Study participants were selected from the screening visit of the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) study. The A4 study is a randomized clinical trial conducted in 67 trial sites in the US and internationally. Eligible participants were age 65 and older, cognitively normal, and did not have major health problems (Sperling et al., 2014). As a part of the screening visit, demographic, family history, and lifestyle questionnaires were completed. Participants underwent medical and cognitive screenings, and blood was collected to determine APOE4 carrier status. All participants underwent amyloid PET imaging. Amyloid-positive individuals also underwent structural MRI scans which were used in the current study (Sperling et al., 2014; Sperling et al., 2020). All participants provided written informed consent. Institutional review board approval was obtained at each of the trial sites.

2.2. Imaging

Study participants underwent PET (Sperling et al., 2020) imaging for Aβ deposition, acquired 50 to 70 min after receiving an injection of 10 mCi of F 18-florbetapir (FBP) (Sperling et al., 2020). Images were acquired with a 128x128 matrix and reconstructed with iterative or row action maximization likelihood algorithm with post-reconstruction Gaussian filter (Clark et al., 2012). Images were realigned, averaged, and spatially aligned to a standard space template (Insel et al., 2020). Semiautomated quantitative analysis calculated the mean signal of predefined anatomically relevant cortical regions of interest (frontal, temporal, parietal, precuneus, anterior and posterior cingulate) (Clark et al., 2012). Cerebellum was a reference region for the calculation of standardized uptake value ratio (SUVr) (Clark et al., 2012; Insel et al., 2020). For the purposes of our study, Aβ levels in ACC, MOC, PCC, and precuneus regions were derived from PET scans. Additionally, we used the Aβ levels in the temporal region for secondary analyses. Composite Aβ levels were calculated from global neocortical region. Evidence of elevated Aβ was assessed by the A4 clinical team (Sperling et al., 2020). Participants with a standardized uptake value ratio (SUVr) of 1.15 or more or with SUVr between 1.10 and 1.15 and 2-reader visual consensus

were categorized as amyloid positive (Sperling et al., 2020). Amyloid positive participants underwent structural MR imaging. Imaging was done on 3 T machines and included T1 MPRAGE, FLAIR, T2 SE, T2*, DWI, and resting state fMRI. For T1 MPRAGE, gradient nonlinearity was applied when necessary. Their T1-weighted MRI scans were processed using NeuroQuant (https://www.cortechs.ai/products/neuroquant/); regional volumes of hippocampus, parahippocampal cortex, entorhinal cortex and fusiform gyrus were used in the current analyses. A subset of participants with MRI scans also underwent tau PET imaging using [18F] Flortaucipir (FTP) tracer and collected in 4x5min frames from 90 to 110 min post-injection. Individual frames were realigned and averaged to create a static image which was then smoothed with a 3 mm Gaussian kernel. Standardized uptake value ratio (SUVr) images were created with intensity normalization by mean inferior cerebellar gray matter (Baker et al., 2017; Maass et al., 2017). FTP SUVR images were co-registered and resliced to each participant's structural MRI and mean SUVRs were calculated for FreeSurfer-v7-defined anatomical regions (Desikan et al., 2006) of entorhinal cortex, amygdala, parahippocampus, fusiform gyrus, and inferior and middle temporal gyri.

2.3. Cognitive testing

The Preclinical Alzheimer Cognitive Composite (PACC) was the primary cognitive outcome in the study. PACC includes 4 components: Mini-Mental State Examination (MMSE) score, Digit Substitution Test, Logical Memory Delayed Recall-IIa score, and the Free and Cued Selective Reminding Test. Standardized component z-scores were calculated and added together for the composite score (Donohue et al., 2014).

2.4. APOE genotyping

All participants were genotyped on the Illumina Global Screening Array at Columbia University (Deters et al., 2021). 115 APOE2/4 carriers (2.7% of sample) were excluded from the current study, because APOE2 may have protective effects against AD risk. Participants were categorized as APOE4 carriers if they had at least one ε4 allele.

2.5. Physical activity and sleep measures

Physical activity and sleep duration measures were collected with self-report questionnaires on current habits. Physical activity was defined as the weekly aggregate of aerobic exercise (measured in hours/week). Nighttime sleep duration was measured as the number of hours slept at night. Daytime sleep duration was measured as the number of hours asleep during the day.

2.6. Statistical analyses

Analyses were conducted in R (version 4.1.1). The distributions of variables of interest were inspected visually. Demographic variables were compared between Aβ-positive and Aβ-negative participants using t-tests for continuous variables and $\chi 2$ tests for categorical variables. Statistical tests were considered significant if the corresponding 2-sided p-value was less than or equal to 0.05. A corresponding 95% confidence interval (CI) is reported for the analyses. Associations between lifestyle factors, Aβ, tau, regional volumes, and cognition were tested using linear regression. Regression assumptions were checked through statistical testing and visual inspection. Participants were assumed to be independent from one another a priori. Homoskedasticity assumptions were tested using visual inspection of the regression residuals vs. fitted values. Normality assumption was tested using a combination of visual and quantitative inspections of the distribution of residuals. Linearity assumption was tested using fractional polynomials and visual inspection.

Path analyses using structural equation modeling (SEM) were conducted using the lavaan statistical package. Models assessed whether cognitive performance was explained by sleep duration (exogenous variable) and composite and regional Aβ load (endogenous biological variable). Similarly, models assessed whether cognitive performance was explained by physical activity (exogenous variable) and regional volumes (endogenous biological variable). These analyses were repeated with regional tau as the endogenous variable of interest. Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), and Root Mean Square Error of Approximation (RMSEA) associated with path analysis models were reported. CFI and TLI close to 1, and RMSEA <0.05 indicated good fit of the data to the models.

Mediation package was used to test for mediation effects and estimate potential mediation parameters. Mediation effects in sleep duration—Aβ burden—cognition, physical activity—regional volume—cognition, and sleep duration (physical activity)—regional tau—cognition paths were classified using terminology of Zhao and colleagues (Zhao et al., 2010). The terminology differentiates between complementary mediation, competitive mediation, and indirect-only mediation, as well as direct-only non-mediation, and no-effect non-mediation.

Age, sex, education, and APOE4 carrier status were jointly tested as confounders. A confounding event was observed if adding the potential confounders in the model changed the magnitude of the association coefficients by>15%. Women that are not carriers of APOE4 allele were used as the referent group in the analyses. Analyses pertaining to brain region volumes included total gray matter volume as a covariate. Participants in the analyses had no missing data.

Sensitivity analyses were conducted when a variable of interest failed the assumptions of regression. If the variable failed the assumption of linearity, polynomial terms were used if they provided statistically better fit than the linear model. Additionally, literature-based cut points were used to dichotomize variables for interpretability purposes. If the variable failed the normality assumption, variable transformation was considered. Sleep duration path analyses were repeated using daytime sleep as the variable of interest. Additional post-hoc sensitivity analyses were conducted if any influential points were identified. The analyses were repeated with the influential points removed. An observation was considered influential if its leverage value was $> 2(k + 1)/n$ where k is the number of covariates, n is the number of observations, and if its studentized difference in fits was $> 2\sqrt{(k/n)}$. According to these criteria, influential points were identified for physical activity only, and analyses were repeated after removing these points.

Secondary analyses explored the role of Aβ burden in physical activity—cognition relationship, and the role of neurodegeneration in sleep duration—cognition relationship. Exploratory analyses tested whether regional tau burden mediates the effect of sleep duration or physical activity on cognition.

The chosen regions of interest are expected to be correlated since they have similar pathological signature or process similar tasks, thus findings from one region are expected to mirror findings from related regions. To account for these, p-values of comparisons were adjusted using Benjamini-Hochberg procedure.

2.7. Data availability statement

Data is available through LONI IDA upon successful completion of user agreement (https://ida.loni.usc.edu/collaboration/access/appLicense.jsp).

3. Results

3.1. Participant demographics

There were 4,322 cognitively unimpaired participants (59.5% female, mean age (SD): 71.3 ± 4.7 years) who met criteria for our study. Demographic and lifestyle variables, Aβ SUVr measures, brain region volumes, and PACC performance are summarized in Table 1. Amyloid-

Table 1
Participant characteristics. Means and standard deviations are reported. Characteristic differences based on amyloid positivity were tested by Student's *t*-test for continuous variables and with $\chi 2$ test for categorical variables. Effect size (ES) was determined using Cohen's D for continuous variable and Cramer's V for categorical variables. PACC = Preclinical Alzheimer Cognitive Composite.

VARIABLES	All (4322)	Aβ + (1272)	Aβ- (3050)	Effect Size	p value
Age (years)	71.28 (4.66)	72.10 (4.9)	70.94 (4.52)	0.25	<0.001
Gender (%Female)	59.49	59.28	59.57	0.32	0.86
Education (years)	16.58 (2.83)	16.58 (2.79)	16.59 (2.84)	0.01	0.7
APOE4 carrier status (%Carrier)	33.2	56.5	23.5	0.32	<0.01
PACC score	0.01 (2.54)	−0.41 (2.70)	0.19 (2.45)	0.24	<0.001
Physical Activity (h/week)	2.88 (3.80)	2.87 (3.81)	2.92 (3.76)	0.04	0.72
Night-time sleep (h/night)	7.11 (1.07)	7.07 (1.08)	7.12 (1.07)	0.05	0.15
Daytime sleep (h/day)	0.21 (0.38)	0.21 (0.38)	0.19 (0.37)	0.05	0.13
Self-Reported Race				0.05	0.03
>1 race	0.62%	0.71%	0.59%		
American Indian	0.21%	0.16%	0.23%		
Asian	3.86%	2.36%	4.49%		
Black	3.47%	2.44%	3.90%		
Pacific Islander	0.05%	0%	0.07%		
Unknown	0.53%	0.55%	0.52%		
White	91.25%	93.79%	90.20%		
Amyloid PET					
Composite Aβ (SUVr)	1.09 (0.19)	1.33 (0.18)	1.00 (0.07)	2.89	<0.001
Temporal Aβ (SUVr)	1.13 (0.18)	1.33 (0.20)	1.04 (0.08)	2.3	<0.001
Anterior Cingulate Cortex Aβ (SUVr)	1.14 (0.23)	1.42 (0.22)	1.03 (0.11)	2.54	<0.001
Medial Orbitofrontal Cortex Aβ (SUVr)	0.96 (0.18)	1.16 (0.17)	0.88 (0.09)	2.44	<0.001
Posterior Cingulate Cortex Aβ (SUVr)	1.11 (0.22)	1.34 (0.21)	1.01(0.14)	2.02	<0.001
Precuneus Aβ (SUVr)	1.18 (0.25)	1.47 (0.24)	1.06 (0.11)	2.6	<0.001

negative participants were younger ($p < 0.001$) and had higher PACC ($p < 0.001$) than Aβ-positive participants. The frequency of APOE-ε4 carrier status significantly differed between Aβ status groups, with 56.5% of the Aβ-positive participants having at least one ε4 allele ($p < 0.001$). We did not observe significant differences between Aβ groups for education, self-reported daytime and night-time sleep, physical activity, or sex. We note that participants in both groups had high self-reported physical activity means. There was a significant difference between self-reported

Table 2
Demographic variables of participants with MR imaging and with FTP PET imaging. Means and standard deviations are reported. Characteristic differences based on imaging protocol inclusivity were tested by Student's *t*-test for continuous variables and with $\chi 2$ test for categorical variables. Effect size (ES) was determined using Cohen's D for continuous variable and Cramer's V for categorical variables. PACC = Preclinical Alzheimer Cognitive Composite.

Variables	***Participants with MR Imaging (N = 1208)***	***Participants with FTP (N = 443)***	***Effect Size***	***p value***
Age (years)	72.00 (4.84)	71.8 (4.81)	0.04	0.47
Gender (%Female)	59.11	55.10%		
Education (years)	16.57 (2.79)	16.2 (2.83)	0.12	0.04
APOE4 carrier status (%Carrier)	57%	48.80%	0.06	0.03
PACC score	−0.39 (2.69)	−0.375 (2.78)	0	0.94
Physical Activity (h/week)	2.93 (3.80)	2.91 (3.51)	0	0.91
Night-time sleep (h/night)	7.07 (1.06)	7.02 (1.04)	0.05	0.34
Daytime sleep (h/day)	0.19 (0.37)	0.18 (0.36)	0.02	0.7
Self-Reported Race			0.11	0.002
>1 race	0.75%	0.90%		
American Indian	0.25%	0.20%		
Asian	2.24%	4.50%		
Black	2.57%	2.50%		
Pacific Islander	0%	0%		
Unknown	0.58%	0.50%		
White	93.62%	86.90%		
Amyloid PET				
Composite Aβ (SUVr)	1.33 (0.18)	1.28 (0.197)	0.28	<0.001
Temporal Aβ (SUVr)	1.33 (0.20)	1.29 (0.200)	0.24	<0.001
Anterior Cingulate Cortex Aβ (SUVr)	1.41 (0.22)	1.36 (0.247)	0.22	<0.001
Medial Orbitofrontal Cortex Aβ (SUVr)	1.16 (0.17)	1.12 (0.183)	0.25	<0.001
Posterior Cingulate Cortex Aβ (SUVr)	1.34 (0.21)	1.28 (0.221)	0.28	<0.001
Precuneus Aβ (SUVr)	1.47 (0.24)	1.41 (0.262)	0.25	<0.001
Regional Volumes				
Hippocampal Volume (cm^3)	6.75 (0.81)	6.76 (0.81)	0.02	0.749
Entorhinal Volume (cm^3)	5.40 (1.07)	5.38 (1.07)	0.02	0.788
Parahippocampal Volume (cm^3)	4.42 (0.69)	4.41 (0.69)	0.02	0.717
Fusiform Gyral Volume (cm^3)	22.23 (2.50)	22.2 (2.61)	0.02	0.693
Tau PET				
Entorhinal FTP (SUVr)		1.17 (0.16)		
Amygdala FTP (SUVr)		1.26 (0.16)		
Parahippocampal FTP (SUVr)		1.14 (0.12)		
Fusiform Gyral FTP (SUVr)		1.22 (0.11)		
Inferior Temporal FTP (SUVr)		1.23 (0.12)		
Middle Temporal FTP (SUVr)		1.17 (0.11)		

Table 3
Linear regression parameter estimates (β, 95% CI) from daily night-time sleep—Aβ deposition relationship (upper) and from regional Aβ burden—PACC score relationship (lower). Column headers represent each region for the Aβ burden—PACC relationship. Age, sex, education, and APOE4 carrier status are confounders in the relationships. APOE4 non-carrier women were the reference group. Significant relationships of interest were bolded and italicized. ACC = Anterior Cingulate Cortex, MOC = Medial Orbitofrontal Cortex, PCC = Posterior Cingulate Cortex, PACC = Preclinical Alzheimer Cognitive Composite.

Night-Time Sleep Duration—Regional Aβ Burden Relationship						
Variable	***Composite***	***ACC***	***MOC***	***Temporal***	***PCC***	***Precuneus***
Sleep (h/Night)	***−0.005 (−0.01, −0.001)***	***−0.012 (−0.017, −0.006)***	***−0.009 (−0.014, −0.005)***	−0.005 (−0.009,0.001)	−0.003 (−0.008,0.003)	−0.004 (−0.01,0.003)
Age (years)	0.007 (0.006,0.008)	0.007 (0.006,0.009)	0.005 (0.004,0.006)	0.008 (0.007,0.009)	0.008 (0.006,0.009)	0.001 (−0.01,0.02)
Sex	−0.014 (−0.025, −0.003)	−0.004 (−0.02,0.01)	−0.042 (−0.052, −0.032)	−0.027 (−0.038, −0.017)	−0.044 (−0.057, −0.031)	0.004 (−0.01,0.02)
Education (years)	−0.001 (−0.003,0.001)	−0.001 (−0.003,0.001)	−0.001 (−0.002,0.001)	0 (−0.002,0.002)	−0.002 (−0.005,0)	−0.003 (−0.005,0)
APOE4	0.15 (0.139,0.161)	0.18 (0.17,0.19)	0.13 (0.12,0.14)	0.13 (0.12,0.14)	0.31 (0.12,0.15)	0.19 (0.17, 0.2)
Regional AB Burden —PACC Score Relationship						
Regional Burden (SUVr)	***−1.54 (−1.93, −1.15)***	***−1.216 (−1.535, −0.897)***	***−1.435 (−1.854, −1.016)***	***−1.228 (-1.629, −0.827)***	***−1.167 (−1.494, −0.841)***	***−1.297 (−1.597, −0.998)***
Age (years)	−0.141 (−0.16, −0.13)	−0.144 (−0.159, −0.129)	−0.146 (−0.161, −0.131)	−0.143 (−0.158, −0.128)	−0.144 (−0.159, −0.128)	−0.140 (−0.155, −0.125)
Sex	−1.26 (−1.4, −1.12)	−1.238 (-1.38, −1.096)	−1.294 (−1.437, −1.151)	−1.268 (−1.411, −1.126)	−1.286 (−1.428, −1.143)	−1.229 (−1.37, −1.087)
Education (years)	0.158 (0.134,0.183)	0.159 (0.134,0.183)	0.159 (0.135,0.184)	0.16 (0.136,0.185)	0.158 (0.133,0.182)	0.157 (0.133,0.181)
APOE4	0.032 (−0.125,0.189)	0.02 (−0.137,0.134)	−0.007 (−0.163,0.15)	−0.041 (−0.196,0.114)	−0.043 (−0.195, 0.11)	0.043 (−0.113,0.199)

race proportion among Aβ-positive and negative participants. Of 1272 Aβ-positive participants, T1 MRI data for 1208 participants, and tau PET data for 443 participants (12.8% Aβ-negative) were available at the time of data download. Characteristics of participants with MR and PET imaging protocols are summarized and compared in Table 2. There was a significant but not meaningful difference in education. There were also differences in self-reported race proportions, regional Aβ burdens such that participants in MR protocol had higher SUVr values, but no significant differences in lifestyle, cognitive, or regional volumetric measurements.

3.2. Sleep path analyses

3.2.1. Night-time sleep duration, amyloid deposition, and cognitive performance

Adjusting for age, sex, education, and APOE4 carrier status, night-time sleep duration was negatively associated with composite FBP SUVr (β = −0.005, 95% confidence interval (CI): (−0.01, −0.001), p = 0.045, Table 3, Fig. 1A). Night-time sleep duration was also negatively associated with ACC SUVr (β = −0.012, CI: (−0.017, −0.006), p < 0.001, Table 3, Fig. 1B) and MOC SUVr (β = −0.009, CI:(−0.014, −0.005), p < 0.001, Table 3, Fig. 1C). Night-time sleep duration was not significantly associated with temporal FBP SUVr (β = −0.003, CI: (−0.008,0.003), p = 0.07, Table 3, Fig. 1G), PCC FBP SUVr (β = −0.003, CI: (−0.008,0.003), p = 0.42, Table 3, Fig. 1H), or precuneus FBP SUVr (β = −0.004, CI: (−0.01,0.003), p = 0.32, Table 3, Fig. 1I).

No sleep by Aβ-status (positive vs. negative) interaction was observed for any of the regions or for the composite score (p(composite) = 0.73; p(ACC) = 0.07; p(MOC) = 0.72; p(PCC) = 0.29; p(precuneus) = 0.78)), thus no Aβ status-stratified analyses were conducted. There was no linear relationship between night-time sleep duration and PACC (β = 0.019, CI: (−0.046,0.083), p = 0.56, Table 4, Fig. 2A).

Aβ levels were negatively associated with PACC score. An increase in composite FBP SUVr was associated with lower PACC score (β = −1.54, CI: (−1.93, −1.15), p < 0.001, Table 3, Fig. 1D). An increase in ACC FBP SUVr was associated with a decrease in estimated PACC score (β = −1.216, CI: (−1.535, −0.897), p < 0.001, Table 3, Fig. 1E). The same pattern was observed regarding an inverse association of PACC score with MOC SUVr (β = −1.437, CI: (−1.855, −1.019), Table 3, Fig. 1F), temporal (β = −1.23, CI: (−1.632, −0.829), Table 3, Fig. 1J), PCC SUVr (β = −1.168, CI: (-1.494, −0.842), Table 3, Fig. 1K), and precuneus SUVr (β = −1.298, CI: (−1.598, −0.999), Table 3, Fig. 1L) (all p < 0.001).

Sleep—Aβ—cognition path analyses demonstrated that the hypothesized paths fit the observations well. Model CFI and TLI were both > 0.99, and model RMSEA was < 0.01 for composite, ACC, temporal, MOC, precuneus and PCC FBP SUVr. 15.5% of PACC variance was explained by sleep duration—composite Aβ path, 18.3% of PACC variance was explained by sleep duration—ACC Aβ path, 18% was explained by sleep duration—temporal Aβ path, 18.1% was explained by sleep duration—MOC Aβ path, 18.6 % was explained by sleep duration—precuneus Aβ path, and 18.2% was explained by sleep duration—PCC Aβ path (Fig. 3).

Additionally, composite FBP SUVr significantly mediated night-time sleep duration—PACC relationship (average causal mediation effect (ACME) = 0.01, CI: (<0.01, 0.02), p = 0.03)). Similarly, ACC and MOC FBP SUVrs were significant mediators (ACME = 0.01, CI: (<0.01,0.02), p < 0.01 for both). Regional and composite Aβ burdens were mediators in indirect-only mediation analyses. No mediation was observed for precuneus (ACME < 0.01, CI: (−0.01,0.01), p = 0.29), temporal FBP SUVR (ACME < 0.01, CI:(>-0.01, 0.01, p = 0.06), or PCC (ACME < 0.01, CI: (−0.01,0.01), p = 0.41). All p-values were adjusted using Benjamini-Hochberg procedure.

3.2.2. Night-time sleep duration and regional volumes

Sleep duration was not associated with regional brain volumes for any of our a priori selected regions.

3.2.3. Night-time sleep duration, tau deposition, and cognitive performance

Adjusting for age, sex, education, and APOE4 carrier status, no significant night-time sleep duration—FTP SUVr associations were observed for any of the regions of interest (p > 0.49 for all regions, Table 5). FTP SUVr was negatively associated with PACC score. An increase in entorhinal SUVr was associated with lower PACC score (β = −3.19, CI: (−4.78, −1.59), p < 0.001, Table 5). An increase in amygdala SUVr was associated with a decrease in estimated PACC score (β = −2.81, CI: (−4.387, −1.228), p < 0.001, Table 5). The same pattern was observed regarding an inverse association of PACC score with FG SUVr (β = −4.553, CI: (−6.865, −2.24), Table 5), inferior temporal (β = −4.473, CI: (−6.431, 2.516), Table 5), and medial temporal lobe SUVr

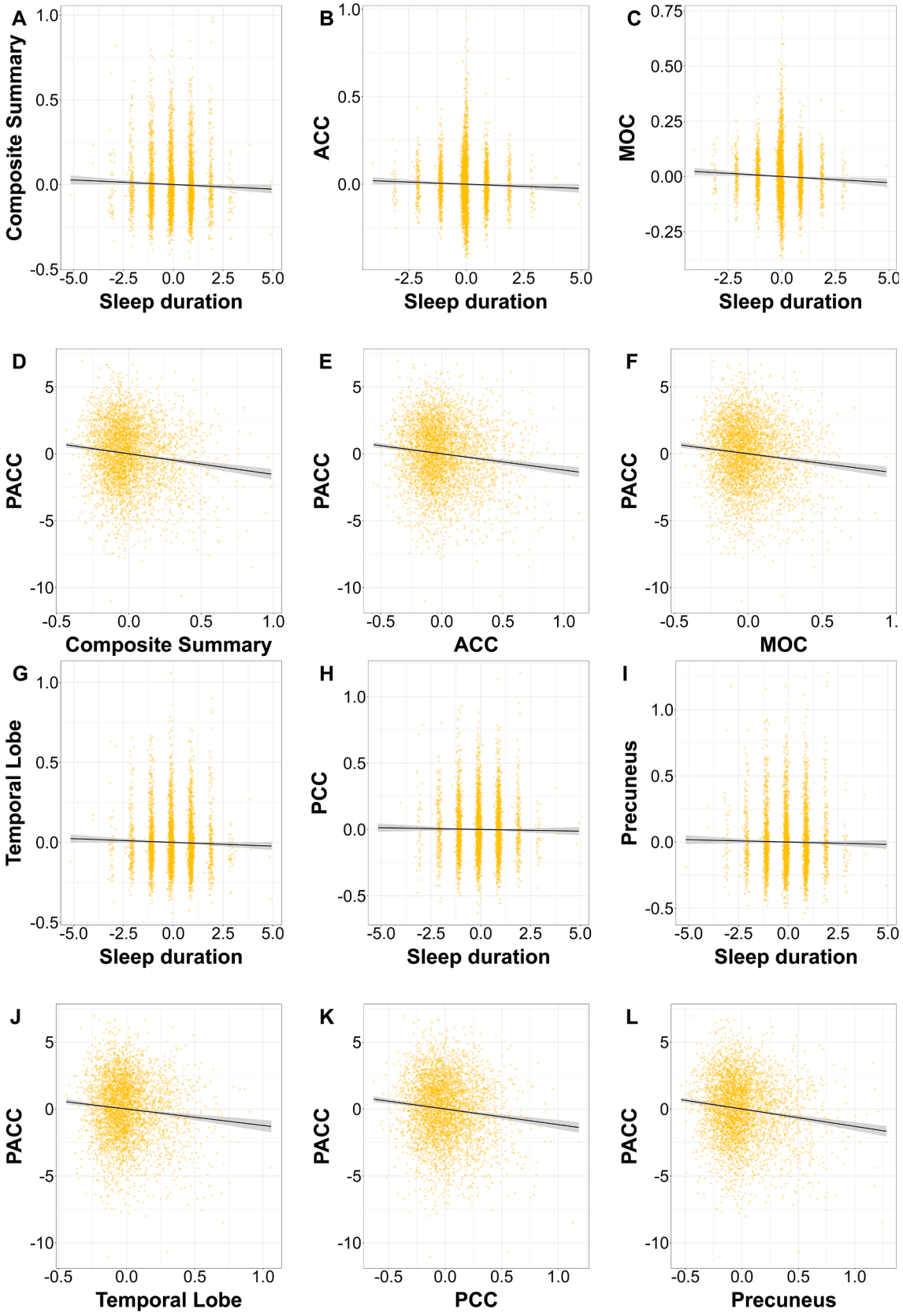

Fig. 1. Associations between sleep, regional amyloid burden, and cognition. The (added variable) plots demonstrate the association between sleep, and regional FBP SUVrs (A, B, C, G, H,I) and between the composite and regional FBP SUVrs and PACC scores (D, E, F, J, K, L) by regressing out the covariates from both the dependent and independent variables in each panel. ACC = Anterior Cingulate Cortex, MOC = Medial Orbitofrontal Cortex, PCC = Posterior Cingulate Cortex, PACC = Preclinical Alzheimer Cognitive Composite.

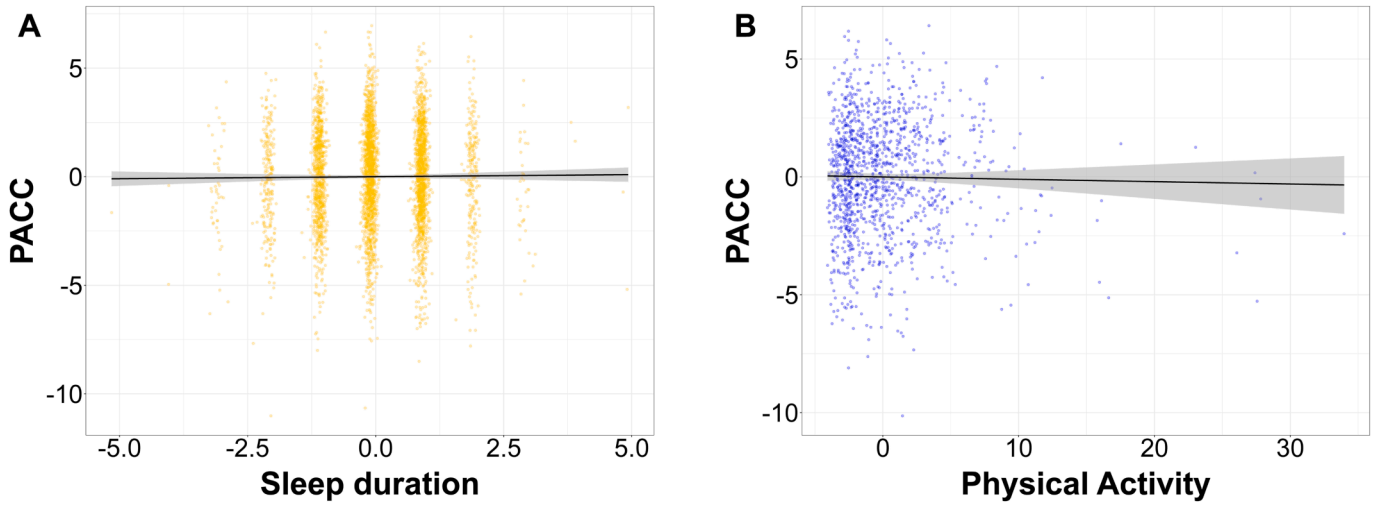

Fig. 2. Associations of physical activity and sleep with cognition. The (added variable) plots demonstrate the association between physical activity (A), sleep (B), and PACC scores by regressing out the covariates from both the dependent and independent variables in each panel. Sleep duration is measured in hours/night, physical activity is measured in hours/week. PACC = Preclinical Alzheimer Cognitive Composite.

Table 4
Linear regression parameter estimates (β, 95% CI) from weekly physical activity—PACC relationship (left) and sleep duration—PACC relationship (right). Age, sex, education, and APOE4 carrier status are confounders in the relationships. PACC = Preclinical Alzheimer Cognitive Composite.

Associations of sleep duration and physical activity with PACC score		
Variable	**Night-time Sleep Duration (h/night)**	**Physical Activity (h/week)**
Independent Variable	0.019 (−0.046,0.083)	0.173 (−0.201, 0.548)
Age (years)	−0.153 (−0.168,-0.138)	−0.184 (−0.213, −0.155)
Sex (Reference: Females)	−1.233 (−1.376, −1.09)	−1.195 (−1.481, −0.909)
Education (years)	0.16 (0.135, 0.185)	0.168 (0.118, 0.218)
APOE4 carrier status (Reference: Non-Carrier)	−0.199 (−0.346, −0.052)	−0.334 (−0.615, −0.05)

(β = −3.761, CI: (−6.092, −1.43), Table 5) (all p < 0.004). There was a negative trend between parahippocampal SUVr and PACC scores (β = −2.361, CI: (−4.514, −0.208), p = 0.07). Although the fit of the data for the sleep duration—regional tau burden—cognitive performance paths was good with a CFI and TLI > 0.99, and RMSEA < 0.01 for all regions, no significant mediation by regional tau burden was observed in the sleep duration—PACC relationship. All comparisons were adjusted using Benjamini-Hochberg procedure.

3.2.4. *Night-time sleep sensitivity analyses*

There was a significant non-linear night-time sleep duration—PACC score relationship. Two term fractional polynomial with an additional sleep duration term (square rooted) significantly improved the model compared to linear and 1 term polynomial models (p (sleep duration) < 0.001, p ($\sqrt{}$sleep duration) < 0.001). After categorizing night-time sleep variable into 3 categories (short: ≤6; normal: 6 < sleep duration < 9; and long: ≥9) based on findings of Winer and colleagues (Winer et al., 2021), we found that categorized nighttime sleep duration significantly improved the base model with only age, sex, education, and APOE4 carrier status as independent variable and PACC score as dependent variable (likelihood ratio $\chi^2_2 = 8.02$, p = 0.02). Participants with short and long sleep durations had lower covariate-adjusted PACC scores compared to participants who sleep 6–9 h nightly (β(short) = −0.17, CI: (−0.33, −0.01), p = 0.03; β (long) = −0.31, CI: (−0.6, −0.03), p = 0.03). These relationships were primarily driven by participants who slept<5 h or>10 h per day (n = 53, Fig. 4), and, after excluding them from the analyses, the model with polynomial terms had a similar shape to the linear one. All comparisons were adjusted for false discovery rate.

3.2.5. *Daytime sleep sensitivity analyses*

Daytime sleep was not significantly associated with composite FBP SUVr (β = −0.004, CI: (−0.018, 0.01), p = 0.61), ACC (β = −0.01, CI: (−0.027, 0.008), p = 0.48), or MOC (β = −0.01, CI: (−0.023, 0.003), p = 0.30) FBP SUVr in covariate-adjusted linear regressions. There was a negative non-significant association between daytime sleep and temporal FBP SUVr (β = −0.014, CI: (−0.028, 0.001), p = 0.18). No significant associations between daytime sleep and PCC (β = 0.007, CI: (−0.01, 0.024), p = 0.51) and precuneus (β = 0.008, CI: (−0.01, 0.026), p = 0.51) Aβ levels were observed. After adjusting for age, sex, education and APOE4 carrier status, daytime sleep was negatively associated with cognition (β = −0.45, CI: (−0.64, −0.27), p < 0.001). Daytime sleep—temporal FBP SUVr—cognition path had some deviations from theoretical fit. Path CFI was 0.17, TLI was −9.8, and RMSEA was 1.32 indicating a poor fit. Daytime sleep—temporal FBP SUVr explained 13.8% of PACC variance. Despite the poor fit, there was a significant complementary mediation (ACME = 0.02, 95% CI: (<0.01,0.04), p = 0.05). All p-values were adjusted for false discovery rate.

3.2.6. *Daytime sleep duration, tau deposition, and cognitive performance*

There was a significant positive association between daytime sleep and entorhinal FTP SUVr (β = 0.053, CI: (0.013, 0.092), p = 0.03) and a positive trend between daytime sleep and amygdala FTP SUVr (β = 0.047, CI: (0.007, 0.087), p = 0.051). No other significant daytime sleep—regional FTP SUVr associations were observed (p > 0.30 for other regions in *meta*-ROI, Table 6).

The fit of the data for the daytime sleep—entorhinal FTP SUVr—cognitive performance paths was good with a CFI of 0.99, TLI of 0.95, and RMSEA of 0.04. While entorhinal FTP SUVr—daytime sleep path explained 20.6% of the PACC variance, no significant mediation was observed (ACME = −0.16, CI: (−0.38, 0.01), p = 0.07). The fit of data for the daytime sleep—regional tau—cognition had RMSEA > 0.05 and TLI < 0.9 for all other regions and no mediation was observed for these regions.

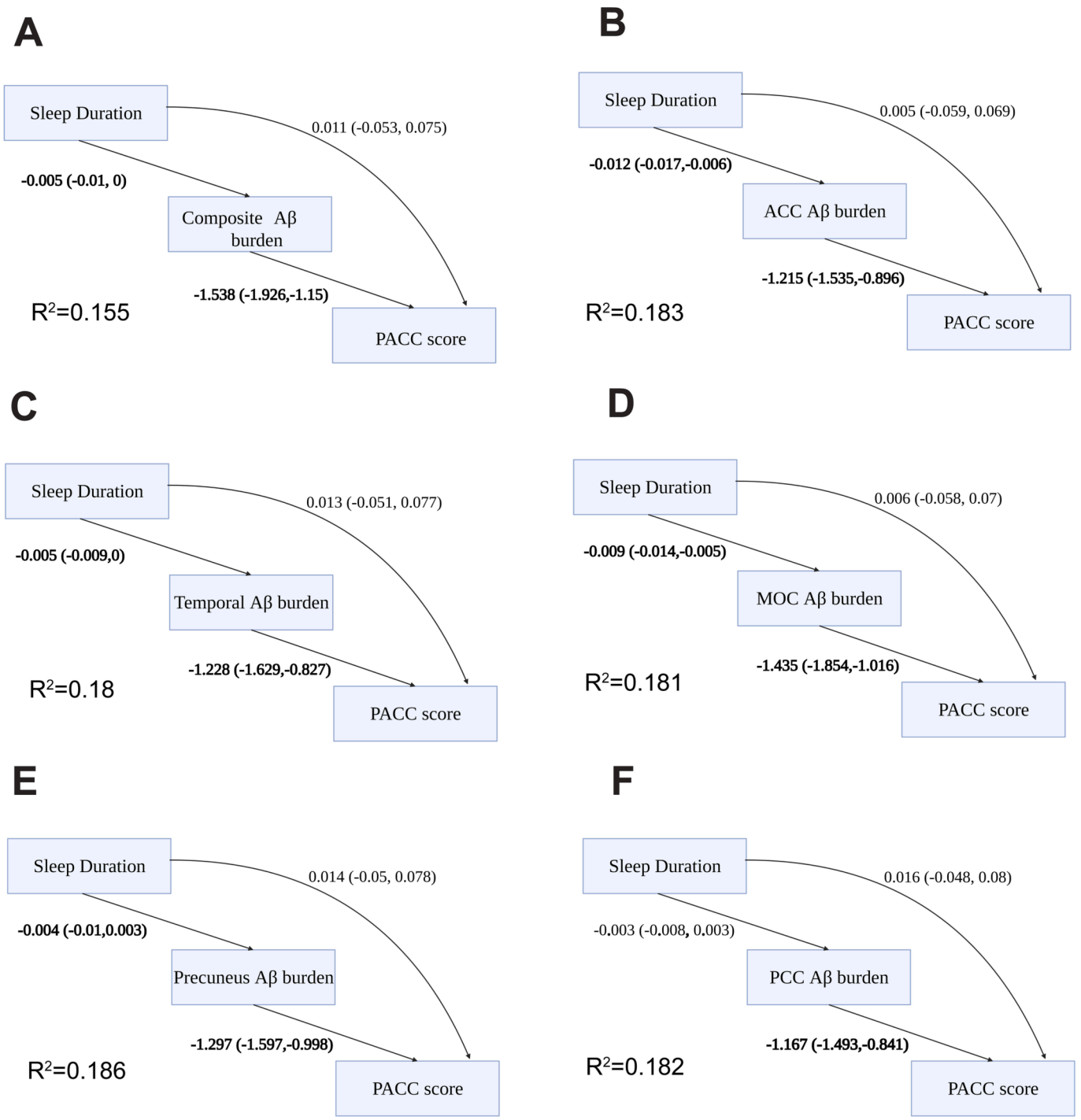

Fig. 3. Path models describing the relationships between sleep, amyloid burden and cognitive performance. Specific path coefficients and their corresponding 95% confidence intervals are shown on each arrow. Bold coefficients met the significance threshold of 0.05. Path R^2-s are presented at the bottom left of each path panel. ACC = Anterior Cingulate Cortex, MOC = Medial Orbitofrontal Cortex, PCC = Posterior Cingulate Cortex, PACC = Preclinical Alzheimer Cognitive Composite.

3.3. Physical activity path analyses

3.3.1. Physical activity and amyloid deposition

Physical activity (weekly aggregate of aerobic exercise) was not associated with regional or composite Aβ burden. Additionally, no significant physical activity—nighttime sleep duration association was observed.

3.3.2. Physical activity, regional volumes, and cognition among Aβ positive individuals

Adjusting for age, sex, education, APOE4 carrier status, and total gray matter volume, physical activity (measured as weekly hours of aerobic exercise) was positively associated with hippocampal volume (β = 10.57, CI: (1.06, 20.08), p = 0.039, Table 7, Fig. 5A), entorhinal volume (β = 14.68, CI: (1.75,27.61), p = 0.039, Table 7, Fig. 5B), parahippocampal volume (β = 9.3, CI: (1.69,16.91), p = 0.03, Table 7, Fig. 5C), and FG volume (β = 38.38, CI: (5.57,71.18), p = 0.039, Table 7, Fig. 5D). One weekly hour increases in physical activity increased PACC

Table 5
Linear regression parameter estimates (β, 95% CI) from daily night-time sleep\mathord{-} tau burden relationship (upper) and from regional tau burden—PACC score relationship (lower). Column headers represent each region for the tau burden—PACC relationship. Age, sex, education, and APOE4 carrier status are confounders in the relationships. APOE4 non-carrier women were the reference group. PACC = Preclinical Alzheimer Cognitive Composite.

Night-Time Sleep—Regional Tau Burden Relationship						
Variable	***Entorhinal Region***	***Amygdala***	***Parahippocampus***	***Fusiform Gyrus***	***Inferior temporal lobe***	***Middle temporal lobe***
Sleep (h/Night)	0	−0.008	−0.002	0	−0.004	−0.003
	(−0.013, 0.014)	(−0.022, 0.006)	(−0.012, 0.009)	(−0.01, 0.009)	(−0.015, 0.007)	(−0.013,0.006)
Age (years)	0.005	0.006	0.003	0.003	0.004	0.003
	(0.002, 0.008)	(0.003, 0.009)	(0.001, 0.006)	(0.001, 0.006)	(0.001, 0.006)	(0.001, 0.005)
Sex	−0.03	−0.007	0	−0.008	−0.007	−0.012
	(−0.06, 0.000)	(−0.037,0.024)	(−0.022, 0.023)	(−0.029, 0013)	(−0.032, 0.017)	(−0.033, 0.009)
Education (years)	0.003	0.004	0.002	0.002	0.002	0.002
	(−0.002, 0.008)	(−0.002, 0.009)	(−0.002, 0.006)	(−0.002, 0.006)	(−0.002, 0.006)	(−0.002, 0.005)
APOE4	0.082	0.093	0.046	0.039	0.046	0.045
	(0.053, 0.111)	(0.064, 0.122)	(0.024, 0.067)	(0.019, 0.059)	(0.023, 0.069)	(0.025, 0.064)
Regional Tau Burden —PACC Score Relationship						
Regional Burden (SUVr)	**−3.187**	**−2.807**	−2.361	**−4.553**	**−4.473**	**−3.761**
	(−4.783, −1.591)	**(−4.387, −1.228)**	(−4.514, −0.208)	**(−6.865, −2.24)**	**(−6.431, −2.516)**	**(−6.092, −1.43)**
Age (years)	−0.177	−0.175	−0.184	−0.176	−0.176	−0.181
	(−0.228, −0.126)	(−0.226, −0.123)	(−0.236, −0.133)	(−0.227, −0.125)	(−0.226, −0.125)	(−0.232, −0.129)
Sex	−1.257	−1.177	−1.16	−1.198	−1.192	−1.205
	(−1.757, −0.756)	(−1.677, −0.677)	(−1.665, −0.656)	(−1.696, −0.699)	(−1.687, −0.696)	(−1.707, −0.703)
Education (years)	0.126	0.127	0.122	0.126	0.125	0.124
	(0.041, 0.212)	(0.041, 0.213)	(0.036, 0.209)	(0.041, 0.212)	(0.04, 0.21)	(0.038, 0.21)
APOE4	−0.479	−0.481	−0.633	−0.562	−0.536	−0.574
	(−0.974, 0.015)	(−0.981, 0.019)	(−1.126, −0.14)	(−1.048, −0.077)	(−1.018, −0.053)	(−1.065, −0.083)

score by 0.173 but was not significant (CI: (−0.201, 0.548), p = 0.36, Table 4, Fig. 2B).

Regional volumes were associated with cognitive performance. PACC was positively associated with hippocampal volume (β = 0.04, CI: (0.02, 0.06), p < 0.001, Table 7, Fig. 5E), EC volume (β = 0.025, CI: (0.009,0.04), p = 0.005, Table 7, Fig. 5F) and FG volume (β = 0.007, CI: (0.001,0.013), p = 0.039, Table 7, Fig. 5H). There was a non-significant, trend-level relationship between parahippocampal volume and PACC (β = 0.021, CI: (−0.005, 0.045), p = 0.112, Table 7, Fig. 5G).

The fit of the data for the physical activity—hippocampal volume—cognitive performance paths was good with a CFI of 0.99, TLI of 0.99, and RMSEA of 0.02. A similar result was observed for the physical activity-entorhinal volume-PACC path with CFI > 0.99, TLI > 0.99, and RMSEA of 0.02. Physical activity —parahippocampal volume—PACC path had a CFI > 0.99, TLI of 0.99, and RMSEA of the path approximation was 0.02. Physical activity —FG volume—PACC path had a CFI and TLI > 0.99, and RMSEA of the path approximation was 0.02. 20.5% of the variance of PACC score was explained by physical activity-hippocampal volume path, 20% by physical activity—EC path, and 19.5% by parahippocampal volumes. 19.6% of the PACC variance was explained by physical activity—FG volume path (Fig. 6). While the direct physical activity—PACC association was not significant, hippocampal volumes significantly mediated that relationship (ACME < 0.01, 95% CI: (<0.01,0.01), p = 0.02), indicating an indirect-only mediating mechanism. No other significant regional volume mediations were observed. All analyses were adjusted for multiple comparisons using Benjamini-Hochberg procedure.

3.3.3. Physical activity and regional tau among Aβ positive individuals

No significant physical activity—regional FTP uptake associations were observed for all regions of interest (p > 0.61 for all regions, Table 8). The fit of the data for the physical activity—regional FTP SUVr—cognitive performance paths was good with a CFI and TLI > 0.99, and RMSEA < 0.01 for all regions. No significant mediation by regional FTP SUVr was observed in the physical activity—PACC relationship.

3.3.4. Physical activity sensitivity analyses

11 study participants had self-reported physical activity duration of over 20 h/week. Physical activity—regional volume associations were tested after removing data from those participants. After removing participants with high physical activity levels and adjusting for age, sex, education, APOE4 carrier status, and total gray matter volume, physical activity was associated with hippocampal volume (β = 14.97, CI: (3.01, 26.93), p = 0.01), entorhinal volume (β = 23.16, CI: (6.93, 39.38), p = 0.002), parahippocampal volume (β = 16.29, CI: (6.72, 25.86), p < 0.001), and FG volume (β = 43.98, CI: (5.33, 82.64), p = 0.03). Since the associations were similar with and without removing the outliers, no participant's data was ignored in the final analyses.

4. Discussion

Longer sleep duration and more aerobic physical activity were associated with better cognitive performance among study participants through lower Aβ load and bigger regional volumes, respectively. Individuals with longer sleep duration had lower levels of Aβ burden in MOC, ACC, PCC, and precuneus, notably areas where Aβ accumulates early in AD pathogenesis (Palmqvist et al., 2017). Aβ burden in these regions was negatively associated with higher PACC score. Higher physical activity levels were positively associated with bigger volumes in the hippocampus, EC, parahippocampal cortex, and FG, which are regions involved in episodic and long-term memory processing (Crane et al., 2012). These brain volumes were associated with higher PACC score.

Our findings regarding sleep—Aβ associations are consistent with previous findings (Insel et al., 2021; Winer et al., 2021). Our sensitivity analyses replicated Winer and colleagues' findings (Winer et al., 2021); however, for the current study, we treated nighttime sleep duration as a continuous variable, because the non-linear sleep-cognition relationship is primarily driven by outliers on lower and upper ends of the sleep duration. Our study focuses on the association among older adults with typical sleeping patterns, thus sleep duration was treated as a continuous variable to be more representative of adult sleeping patterns and to improve statistical power compared to an alternative categorical sleep duration variable. In our study, longer sleep duration was associated with lower MOC and ACC Aβ burden, and SUVr of these regions was negatively associated with cognition. Aβ burden in PCC and precuneus was negatively associated with cognitive performance. Aβ deposition in MOC, ACC, PCC, and precuneus explained the sleep-cognition relationship. These paths suggest that sleep regulation may indirectly

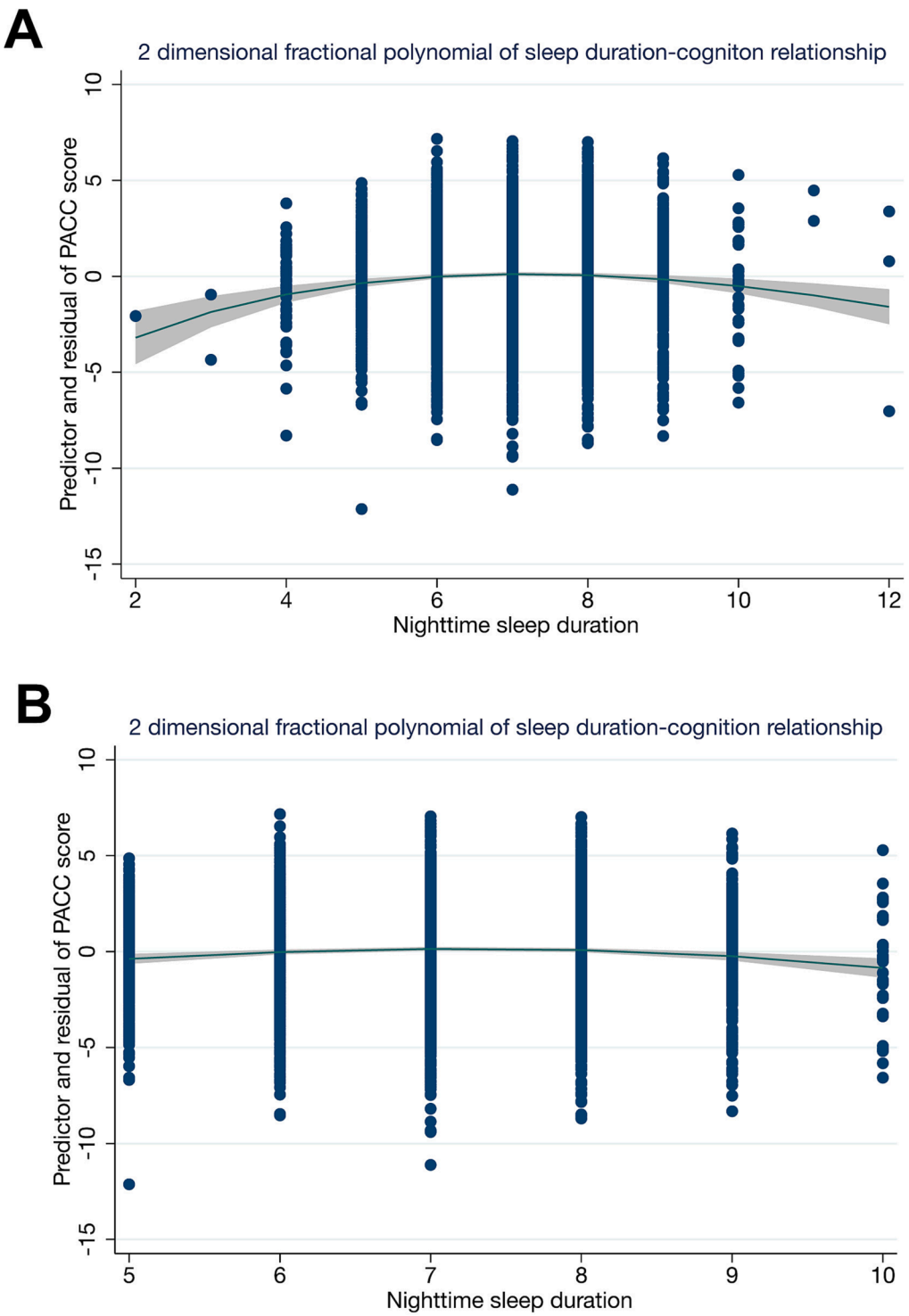

Fig. 4. Fractional polynomial plots depicting non-linear nighttime sleep duration—cognition relationship before (A) and after (B) removing participants with<5 h or>10 h of nighttime sleep. PACC = Preclinical Alzheimer Cognitive Composite.

prevent cognitive decline by reducing early amyloid deposition and delaying the progression of preclinical AD in those with unimpaired cognition. This path was also observed for composite Aβ, suggesting that the preventive effect of sleep on cognition is not restricted to initial regions of Aβ deposition.

Past studies have demonstrated a negative relationship between sleep disorders and cognitive performance. Compared with individuals with normal sleep patterns, individuals with insomnia had more impairment in key tasks related to episodic and working memory and problem solving; however, because those studies focused on individuals with sleeping disorders, questions remain regarding associations between more typical sleeping patterns and cognitive performance (Fortier-Brochu et al., 2012). Results from animal models suggest that an impaired sleep-wake cycle can promote a higher level of neuronal Aβ release (Musiek and Holtzman, 2015) and that Aβ accumulation follows circadian oscillations, increasing during the active period and decreasing during rest (Kang et al., 2009). Additionally, infusion of dual orexin receptor antagonists, which function as a sleeping aid, decrease

Table 6
Linear regression parameter estimates (β, 95% CI) from daytime sleep duration\mathord{-} tau deposition relationship. Column headers represent each region for the daytime sleep duration—regional tau burden relationship. Age, sex, education, and APOE4 carrier status are confounders in the relationships. APOE4 non-carrier women were the reference group.

Daytime Sleep—Regional Tau Burden Relationship						
Variable	***Entorhinal Region***	***Amygdala***	***Parahippocampus***	***Fusiform Gyrus***	***Inferior temporal lobe***	***Middle temporal lobe***
Daytime Sleep (hours/day)	**0.053**	**0.047**	0.019	0.012	0.015	0.019
	(0.0013,0.092)	**(0.007,0.087)**	(−0.011, 0.048)	(−0.016, 0.039)	(−0.018, 0.047)	(−0.008, 0.046)
Age (years)	0.005	0.006	0.003	0.003	0.004	0.003
	(0.002, 0.008)	(0.003, 0.009)	(0.001, 0.006)	(0.001, 0.006)	(0.001, 0.006)	(0.001, 0.005)
Sex	−0.035	−0.010	−0.001	−0.009	−0.008	−0.014
	(−0.065, −0.005)	(−0.041, 0.020)	(−0.024,0.021)	(−0.030, 0.012)	(−0.033, 0.016)	(−0.034, 0.007)
Education (years)	0.003	0.004	0.002	0.002	0.002	0.002
	(−0.002, 0.008)	(−0.002, 0.009)	(−0.002, 0.006)	(−0.002, 0.006)	(−0.002, 0.006)	(−0.002, 0.005)
APOE4	0.083	0.093	0.046	0.039	0.046	0.045
	(0.054, 0.111)	(0.064, 0.122)	(0.024, 0.068)	(0.020, 0.059)	(0.023, 0.069)	(0.025, 0.064)

Aβ plaque formation in APP transgenic mice, suggesting a mechanism through which sleep regulates Aβ deposition.

It has been established that sleep and Aβ deposition are negatively correlated among humans (Spira et al., 2013 ; Ju et al., 2014). Longer sleep duration is associated with decreased Aβ burden in early deposition regions, such as MOC and ACC, as well as with decreased global Aβ deposition (Insel et al., 2021). Studies have shown that Aβ levels in precuneus may be linked to cognitive decline through nocturnal awakenings among older adults with cognitive disorders (You et al., 2019). The present study extends this finding to a larger sample of older adults with unimpaired cognition. While the relationship between nighttime sleep hours and PCC Aβ burden is understudied, studies have shown that shortened rapid eye movement is associated with thinner PCC among MCI patients (Sanchez-Espinosa et al., 2014) and that excessive daytime sleeping was associated with higher PCC Aβ deposition (Carvalho et al., 2018). The current study suggests another path linking sleep duration, PCC Aβ burden, and cognition. There is evidence to suggest that the relationship between sleep and Aβ deposition is bidirectional (Wang and Holtzman, 2020; Ju et al., 2014). The cross-sectional nature of the current study limits the ability of assessing this claim. Ideally, the directionality of the relationship could be tested either through a longitudinal study where sleep patterns and Aβ accumulation patterns are collected, or through a randomized controlled trial (with amyloid lowering therapy as treatment and a measure of sleep as a (not necessarily primary) outcome. Animal studies and observational studies among older adults described above conclude that worse sleep measures are associated with higher Aβ levels cross-sectionally, which implies directionality from sleep duration to amyloid deposition (on which we based the hypotheses of the present study). Under this hypothesis, the mediating role of Aβ of early accumulation regions in sleep duration—cognition relationship was established. Overall, understanding the relationship between sleep duration and Aβ deposition in early Aβ accumulation regions may guide sleep interventions and supply insights about the mechanisms connecting sleep, amyloid deposition, and cognitive performance. Additionally, early sleep interventions may delay the development of detrimental sleeping habits and slow early Aβ accumulation.

This study reports the beneficial association of physical activity with hippocampal, entorhinal cortex, parahippocampal, and fusiform gyral volumes and cognition among Aβ-positive older adults. Although no direct association between physical activities and cognitive performance was observed, positive associations between physical activity and hippocampal volume and between hippocampus and cognition were evident among our sample, showing an indirect-only mediating

Table 7
Linear regression parameter estimates (β, 95% CI) from weekly physical activity—regional brain volume relationship (upper) and from regional volume—PACC score relationship (lower). Column headers represent each region for the regional volume—PACC relationship. Age, sex, education, and APOE4 carrier status are confounders in the relationships. APOE4 non-carrier women were the reference group. PACC = Preclinical Alzheimer Cognitive Composite.

Physical Activity—Regional Volume Relationship				
Variable	**Hippocampus**	**Entorhinal Cortex**	**Parahippocampus**	**Fusiform gyrus**
Physical Activity (h/week)	***10.57***	***14.68***	***9.3***	***38.38***
	(1.06, 20.08)	***(1.75, 27.61)***	***(1.69, 16.91)***	***(5.57, 71.18)***
Age (years)	−102.98	−66.31	−43.88	−154.22
	(−110.75, −95.22)	(−76.87, −55.75)	(−50.11, −37.68)	(−179.31, −129.12)
Sex	−40.18	843.88	528.84	633.57 3
	(−126.68, 46.33)	(726.26, 961.49)	(459.63, 598.04)	(354.49, 912.67)
Education (years)	0.46	4.9	16.51	67.77
	(−12.51, 13.44)	(−12.74, 22.54)	(6.13, 26.89)	(25.95, 109.59)
Cortical Gray Matter (mm^3)	358.74	307.45	282.96	1295.89
	(310.6, 406.86)	(242.01, 372.89)	(244.4, 321.46)	(1140.60, 1451.18)
APOE4	−117.75	−57.05	−29.68	−77.07
	(−190.99, −44.51)	(−156.61, 42.52)	(−88.26, 28.91)	(−313.71, 159.56)
Regional Volume—PACC Score Relationship				
Regional Volume (per 100 mm^3 change)	***0.04***	***0.025***	0.021	***0.007***
	(0.02, 0.06)	***(0.009, 0.04)***	(−0.005, 0.045)	***(0.001, 0.013)***
Age (years)	−0.15	−0.17	−0.178	−0.177
	(−0.18, −0.11)	(−0.2, −0.14)	(−0.208, −0.147)	(−0.207, 0.147)
Sex	−1.31	−1.475	−1.353	−1.309
	(−1.6, −1.02)	(−1.809, −1.14)	(−1.701, −1.006)	(−2.068, −0.147)
Education (years)	0.17	0.167	0.166	0.165
	(0.12, 0.22)	(0.117, 0.217)	(0.116, 0.216)	(0.115, 0.214)
APOE4	−0.289	−0.313	−0.32	−0.33
	(−0.569, −0.009)	(−0.593, −0.032)	(−0.602, −0.04)	(−0.06, −0.05)

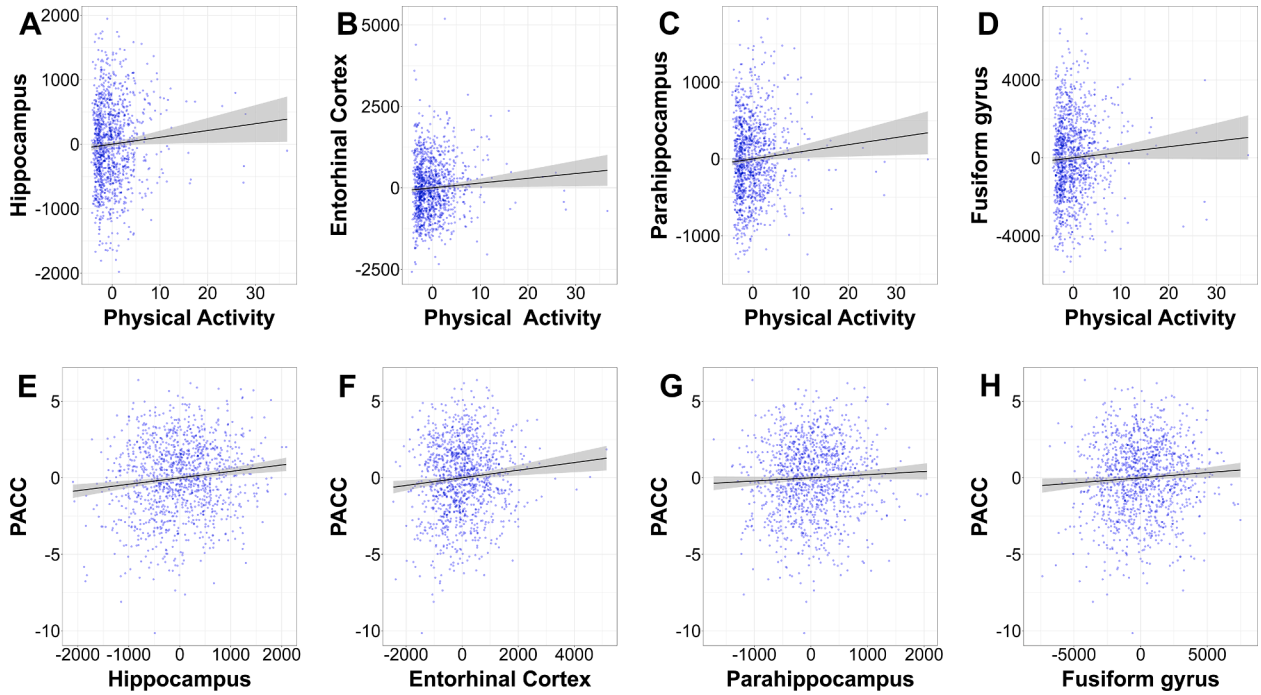

Fig. 5. Associations between physical activity, brain regions, and cognition. The (added variable) plots demonstrate the association between physical activity and volumes of hippocampus, entorhinal cortex, parahippocampus, and fusiform gyrus (A, B, C, D) and between volumes of hippocampus, entorhinal cortex, parahippocampus, and fusiform gyrus and PACC scores (E, F, G, H) by regressing out the covariates from both the dependent and independent variables in each panel. Volumes are measured in mm^3, physical activity in hours per week. PACC = Preclinical Alzheimer Cognitive Composite.

mechanism. Similarly, entorhinal cortex, parahippocampal, and fusiform gyral volumes were also found to explain the physical activity-cognition relationship in this cohort. Our findings suggest that the beneficial effect of physical activity on cognitive performance may be partially explained by brain regions responsible for memory processing, even among Aβ-positive participants.

Our results are consistent with findings from smaller animal and human studies that relate physical activity to decreased brain atrophy and increased cognition. Previous studies have identified associations of morphological changes in hippocampus, entorhinal cortex, parahippocampus, and fusiform gyral regions with memory performance (Crane et al., 2012; Yonelinas et al., 2007). The hippocampus is implicated in the relationship between physical activity and cognition (Maass et al., 2015). Physical activity in old age prevents hippocampal atrophy in humans, possibly through vascular plasticity and perfusion (Erickson et al., 2011; Maass et al., 2015). Physical activity-related increases in hippocampal volume have also been shown to mediate improvements in spatial memory (Erickson et al., 2010). Animal studies have shown that physical activity improved memory and cognitive performance in animals injected with Aβ peptides (Kim et al., 2014; Khodadadi et al., 2018; Zarezadehmehrizi et al., 2021; Dare et al., 2020). In human studies, hippocampal function improvements related to physical activity have been positively associated with cognitive performance changes (Ma et al., 2017; Vaynman et al., 2004; Tao et al., 2019). Physical activity has also been shown to induce positive changes in entorhinal cortex among animals (Pan et al., 2017; Stranahan et al., 2007), while human studies have shown that volume of entorhinal cortex was positively associated with aerobic fitness and cognitive performance in healthy young adults (Whiteman et al., 2016). However, no such findings have been reported for older adults. Physical activity may also increase neural excitability and gray and white matter volume in the parahippocampal cortex of older adults (Erickson et al., 2010; Loprinzi, 2019; Voss et al., 2013; Müller et al., 2017; Siddarth et al., 2018). Studies have also shown that older adults with higher levels of physical activity have thicker fusiform gyrus (Raffin et al., 2023).

While our findings did not warrant the assessment of the simultaneous effects of sleep and physical activities on cognition due to lack of significant physical activity—Aβ burden or sleep-duration—regional volume associations, evidence shows that sleep and physical activity may independently attenuate the negative impact of pathology on cognitive function (Falck et al., 2018; Sewell et al., 2021). Additionally, findings from the 2011–2014 National Health and Nutrition Examination Survey suggest that trading excess sleep with light physical activity or light physical activity with vigorous physical activity would relate with favorable cognitive outcomes (Wei et al., 2021).

The present study also explored whether regional tau burden in temporal *meta*-ROI, a combination of regions where ligand uptake is first observed in clinically normal aging populations (Jack et al., 2017), plays a mediating role in sleep duration—cognition and physical activity—cognition relationships. Physical activities and daily sleep duration did not have significant associations with regional tau deposition in the subset of amyloid positive cognitively normal participants. This may suggest that the interventions targeting sleep duration may be beneficial for earlier stages of AD pathology only, evidenced by the lack of sleep duration—tau and sleep duration—regional atrophy associations, and that mechanisms connecting physical activity to cognition may be independent of AD pathology, supported by associations through regional volumes but not through Aβ or tau. Earlier findings linking sleep duration to medial temporal lobe tau burden were based on data from a smaller sample of participants with mixed amyloid positivity status (Winer et al., 2019; Winer et al., 2021). Additionally, findings suggest that sleep quality, rather than duration, are closely associated with tau burden in medial temporal lobe (Winer et al., 2019; Wang and Holtzman, 2020; Winer et al., 2021). This may be supported by our finding linking daytime but not nighttime sleep and tau burden in entorhinal cortex. Daytime and nighttime sleep durations are negatively correlated and longer daytime sleep may be an indicator of poorer sleep quality. These assessments are outside of the scope of our study. Similar to findings with sleep duration, current evidence linking physical activity and tau burden comes from smaller samples with mixed Aβ positivity

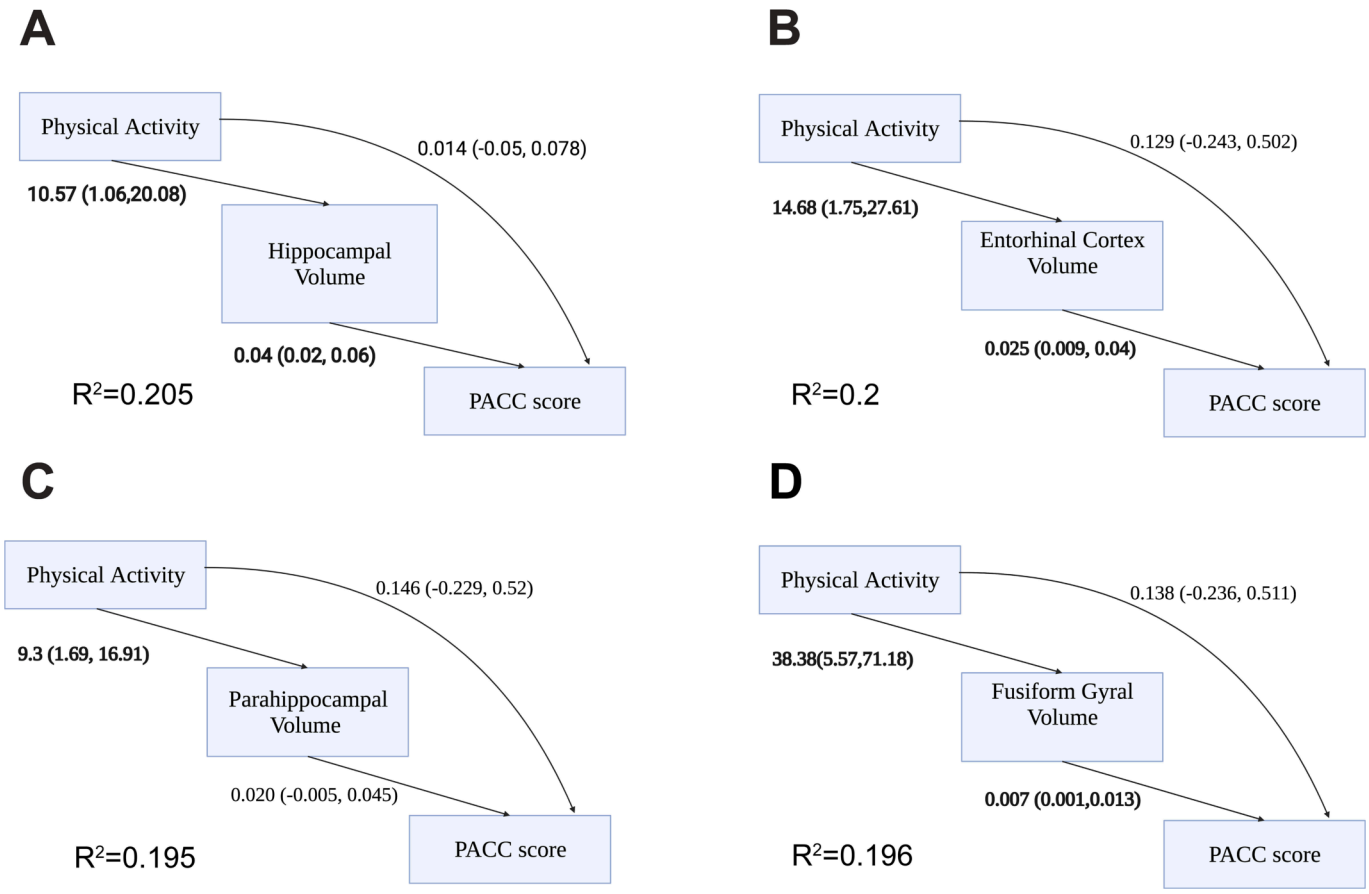

Fig. 6. Path models describing the relationships between physical activity, regional volume and cognitive performance. Specific path coefficients and their corresponding confidence intervals are shown on each arrow. Bold coefficients met the significance threshold of 0.05. Path R^2-s are presented at the bottom left of each path panel. The coefficients correspond to 100 mm^3 change in volumes. Physical activity is measured in hours per week. PACC = Preclinical Alzheimer Cognitive Composite.

Table 8
Linear regression parameter estimates (β, 95% CI) from weekly aerobic exercise duration\mathord{-} tau deposition relationship. Column headers represent each region for the physical activity—regional tau burden relationship. Age, sex, education, and APOE4 carrier status are confounders in the relationships. APOE4 non-carrier women were the reference group.

Physical Activity—Regional Tau Burden Relationship						
Variable	***Entorhinal Region***	***Amygdala***	***Parahippocampus***	***Fusiform Gyrus***	***Inferior temporal lobe***	***Middle temporal lobe***
Physical Activity (h/week)	0.001 (−0.004, 0.005)	0.001 (−0.003. 0.006)	0.002 (−0.002, 0.005)	0.001 (−0.002, 0.003)	0 (−0.003, 0.003)	0.001 (-0.002, 0.004)
Age (years)	0.005 (0.002, 0.008)	0.006 (0.003, 0.009)	0.003 (0.001, 0.006)	0.003 (0.001, 0.006)	0.004 (0.001, 0.006)	0.003 (0.001, 0.005)
Sex	−0.03 (−0.06, 0)	−0.007 (−0.037, 0.024)	−0.001 (−0.023,0.022)	−0.008 (−0.029, 0.012)	−0.012 (−0.033, 0.009)	−0.012 (−0.033, 0.009)
Education (years)	0.003 (−0.002, 0.008)	0.003 (−0.002, 0.009)	0.002 (−0.002, 0.006)	0.002 (−0.002, 0.006)	0.002 (−0.002, 0.006)	0.002 (−0.002, 0.005)
APOE4	0.082 (0.053, 0.111)	0.092 (0.063, 0.121)	0.045 (0.024, 0.067)	0.039 (0.019, 0.059)	0.046 (0.023, 0.069)	0.044 (0.024, 0.064)

(Brown et al., 2018; Coomans et al., 20222022; Merrill et al., 2016). Replication of our findings in larger cohorts with different biomarker profiles is needed for further conclusions.

4.1. Limitations

This study has limitations. Participants reported their physical activity and sleep times by answering single self-report questions from self-questionnaires on current lifestyle habits, instead of validated measures of physical activity and sleep. However, studies have suggested that 1-item questionnaires for physical activity and sedentary behavior, like the one used in the current study, has a similar validity and reliability compared to longer questionnaires and thus can be used as an indicator for physical activity (Bakker et al., 2020). Additionally, previous studies have concluded that subjective sleep time is a valid indicator of the sleep experience (Sperling et al., 2014). Future studies with the utilization of activity and sleep trackers would help extend and establish the validity of our findings. Our analyses exploring the role of physical activity are limited to Aβ-positive participants and aerobic exercises. It is possible that these findings would also be observed in Aβ-negative individuals, but this question could not be evaluated in the study sample. Similarly, only a subsample of participants underwent tau PET imaging, limiting

our findings to a smaller sample. Because of the cross-sectional nature of this study, causal claims in our interpretation are limited and would need to be assessed in a causal framework or clinical trial. Our analyses did not include other brain regions closely related to sleep duration (such as suprachiasmatic nucleus and locus coeruleus) due to unavailability of freesurfer-based ROIs for these regions. Measuring PET tracer uptake and structural volume in these regions in also limited by PET resolution and inaccurate segmentation of small subcortical structures. It is possible that pathology in these regions serves as a negative confound for sleep duration and may drive pathology in our regions of interest.

4.2. Conclusions

In this study we identified that regional Aβ deposition explains the sleep-cognition relationship. Region-specific analyses demonstrated that the sleep—Aβ relationship occurs in regions affected early in AD, indicating that sleep might be a candidate for a non-pharmacological intervention to hinder Aβ accumulation and cognitive decline. Identification of decreased sleep duration in late adulthood and employment of strategies to increase sleep quantity may help to delay the onset of cognitive symptoms associated with AD pathology. Additionally, we identified a potential protective path through which physical activity might preserve cognition. Regions associated with memory processing appear to explain the physical activity—cognition relationship among Aβ-positive older adults, indicating that engaging in physical activity may protect against cognitive decline even in those who are already Aβ-positive. Dementia risk reduction approaches that emphasize the adequate sleep duration and a physically active lifestyle may benefit those with risk for Alzheimer's disease.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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