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RESEARCH ARTICLE

Fractal motor activity regulation and sex differences in preclinical Alzheimer's disease pathology

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Abstract

Introduction: Degradation in fractal motor activity regulation (FMAR), a measure of multiscale self-similarity of motor control, occurs in aging and accelerates with clinical progression to Alzheimer's disease (AD). Whether FMAR changes occur during the pre-symptomatic phase of the disease in women and men remains unknown.

Methods: FMAR was assessed in cognitively normal participants (n = 178) who underwent 7 to 14 days of home actigraphy. Preclinical AD pathology was determined by amyloid imaging-Pittsburgh compound B (PiB) and cerebrospinal fluid (CSF) phosphorylated-tau181 (p-tau) to amyloid beta 42 (A β 42) ratio.

Results: Degradation in daytime FMAR was overall significantly associated with preclinical amyloid plaque pathology via PiB+ imaging (beta coefficient $\beta = 0.217$, standard error [SE] = 0.101, $P = .034$) and increasing CSF tau181-A β 42 ratio ($\beta = 0.220$, SE = 0.084, $P = .009$). In subset analysis by sex, the effect sizes were significant in women for PiB+ ($\beta = 0.279$, SE = 0.112, $P = .015$) and CSF ($\beta = 0.245$, SE = 0.094, $P = .011$) but not in men (both P s > .05). These associations remained after inclusion of daily activity level, apolipoprotein E ϵ 4 carrier status, and rest/activity patterns.

Discussion: Changes in daytime FMAR from actigraphy appear to be present in women early in preclinical AD. This may be a combination of earlier pathology changes in females reflected in daytime FMAR, and a relatively underpowered male group. Further studies are warranted to test FMAR as an early noncognitive physiological biomarker that precedes the onset of cognitive symptoms.

KEYWORDS

actigraphy, amyloid positron emission tomography imaging, amyloid plaque pathology, amyloid beta 42, fractal regulation, interdaily stability, intradaily variability, phosphorylated tau, Pittsburgh compound B, preclinical Alzheimer's disease, sex differences

1 | INTRODUCTION

Alzheimer's disease (AD) continues to lack early and readily obtained biomarkers of risk in earlier life.¹ There has been increasing interest in

the role of continuous monitoring of motor activity in free-living adults in predicting cognitive decline.^{2,3} Recently, it was shown that the self-similarity of actigraphy-derived motor activity fluctuations when magnified across different time scales, known as fractal motor activity

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regulation (FMAR), is linked to AD; and alterations in FMAR coincided with cognitive decline, accelerating during progression to mild cognitive impairment (MCI), through mild/moderate/severe dementia.⁴⁻⁶

In fact, complex temporal patterns including fractal patterns have been observed in many physiological signals⁷⁻⁹ such as gait,¹⁰ mobility,¹¹ motor function,¹² and activity patterns,^{4,5} all of which have been linked to AD and pathology.¹³⁻¹⁶ It has been accepted that fractal patterns are generated by multiple such processes in an ongoing feedback loop.⁷ In addition to AD diagnosis, perturbed daytime FMAR has been associated with increased disability, frailty, and mortality in the elderly.^{3,15,17,18} However, much of this evidence has either been close to AD diagnosis^{3,19} or thereafter.⁶ The relationship between daytime FMAR and early, preclinical AD pathology in cognitively normal individuals is unknown.

In this study, we analyzed the relationship between daytime FMAR and both imaging and cerebrospinal fluid (CSF)-derived amyloid and tau AD biomarkers in cognitively normal participants who underwent 7 to 14 days of actigraphy in their home environment. We accounted for apolipoprotein E (APOE) $\epsilon 4$ carrier status and examined potential sex differences in FMAR given prior evidence for links between sex and AD pathology.²⁰

2 | METHODS

2.1 | Subjects

All participants were from the Washington University Knight Alzheimer's Disease Research Center (ADRC) in St. Louis, Missouri. Inclusion criteria were age over 45 years, no cognitive impairment (Clinical Dementia Rating score 0), and no abnormal movement of the nondominant arm. Participants provided written, informed consent for an add-on actigraphy study, described in detail elsewhere.^{16,21} We included 178 participants (mean age [standard deviation (SD)] 65.9 [8.3] years) who completed the actigraphy study, and had at least one AD biomarker available through the ADRC. Participant procedures were approved by the Washington University Human Research Protection Office. This current analysis was approved by the Partners Healthcare, Inc. Institutional Review Board and was part of the Knight ADRC-approved project D1821 (Neuropathology for disrupted multiscale activity control in Alzheimer's disease).

2.2 | Biomarkers of AD pathology

Pittsburgh compound B (PiB) positron emission tomography (PET) amyloid imaging was performed in 150 and cerebrospinal fluid (CSF) was obtained in 149 participants (121 participants had both, whereas 57 had one AD biomarker only). An a priori cut-off value of total mean cortical standard-uptake-value ratio > 1.42 as PiB positive (PiB+), using the regional spread function technique; those ≤ 1.42 were deemed PiB negative (PiB-).²² CSF was obtained via lumbar puncture as previously described.²³ Amyloid beta 42 (A β 42) and phosphorylated

RESEARCH IN CONTEXT

- 1. Systematic review:** Recent studies indicate that fractal motor activity regulation (FMAR) may be a novel biomarker for Alzheimer's disease (AD), particularly in elderly subjects during the years prior to diagnosis. However, the relationship between FMAR degradation and preclinical AD pathology in younger, cognitively normal adults is unknown.
- 2. Interpretation:** This study showed for the first time a link between FMAR and AD via preclinical pathology in women that was independent of age, race, education, daily activity, and apolipoprotein E $\epsilon 4$ status.
- 3. Future directions:** Future studies may aim to (1) replicate the associations between FMAR and preclinical AD pathology in larger samples of men; (2) determine what mechanisms underlie these associations; (3) test the relationship between FMAR alterations and other types of dementia; and (4) explore whether interventions can modulate FMAR as a way to delay the onset of AD.

HIGHLIGHTS

1. Fractal motor activity regulation (FMAR) is associated with preclinical Alzheimer's disease (AD) pathology in cognitively normal women.
2. The relationship is independent of age, physical activity, rest-activity pattern fragmentation, and apolipoprotein E $\epsilon 4$ carrier status.
3. FMAR may represent a novel biomarker for preclinical AD pathology.

tau181 (p-tau) were measured by the ADRC Biomarker Core using enzyme-linked immunosorbent assay (INNOTEST; Innogenetics).¹⁶ CSF p-tau-to-A β 42 ratio was calculated as a sensitive and specific biomarker for AD-related neurodegeneration given its specificity for preclinical AD, and conversion to symptomatic AD.²⁴ Consistent with a recent study, all participants had biomarker data from 3 years before to 0.5 years after actigraphy recording included in this study, and irreversibility of AD pathology was assumed.¹⁶ In summary, biomarkers of preclinical AD pathology used in this study were (1) PiB status (PiB+ or PiB-) as a dichotomous variable, and (2) p-tau-to-A β 42 ratio as a continuous variable.

2.3 | Data collection and preprocessing

Motor activity was continuously monitored for 14 days using an actigraph monitor (Actiwatch2; Phillips-Respironics) worn on the non-

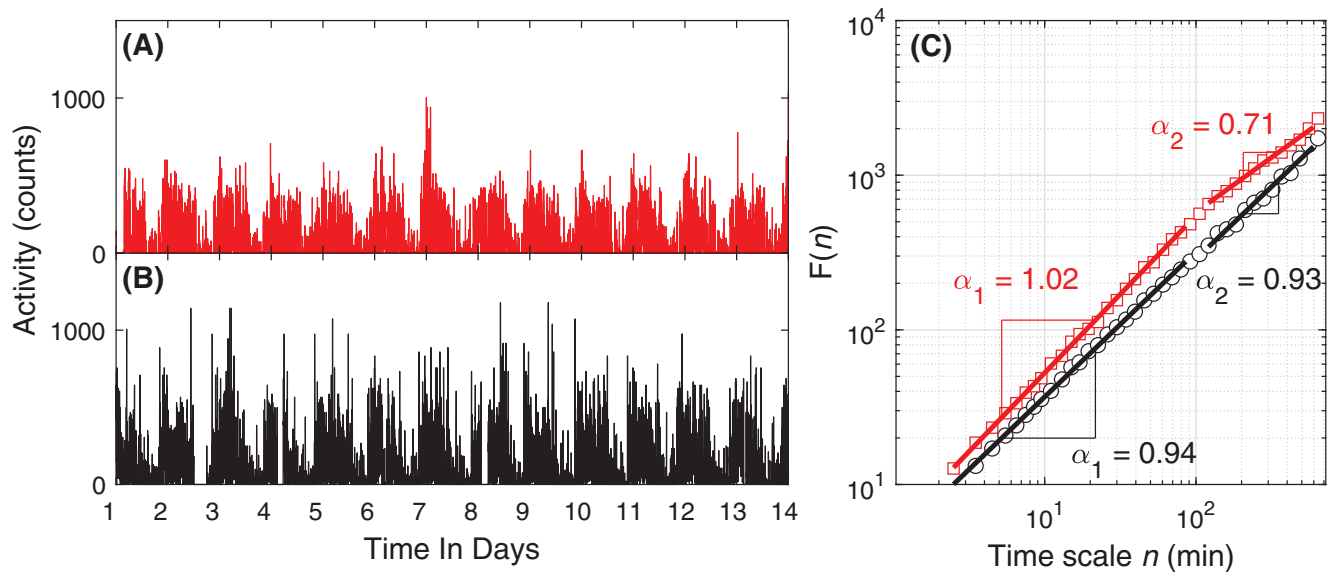


FIGURE 1 Fractal motor activity regulation measurement. Representative motor activity recordings from actigraphy over one full representative week for two participants, with $\Delta\alpha$ values in the 90th (A: in red) and 10th percentiles (B: in black) are shown. Gray shading indicates 7 PM to 11 AM data, which were excluded. C, $F(n)$ is fitted using a power law, indicating a fractal structure in the fluctuations, and is plotted against time on a log-log scale. $F(n)$ is fitted separately in two regions: 1.25 to 90 minutes, and 120 to 600 minutes. The slopes of the lines in the two regions are α_1 and α_2 , respectively. $\Delta\alpha$ is the difference between the two slopes, α_1 and α_2 ; higher $\Delta\alpha$ is worse, indicating an inconsistency of fractal motor activity regulation between the shorter and longer time scales

dominant wrist. Data were sampled at 32 Hz and integrated into 30-second epochs. To ensure good signal quality, recordings were checked using an established MATLAB GUI program (Ver. R2015a, the MathWorks Inc.)^{15,25,26} and quality issues such as (1) isolated spikes with amplitude beyond 10 SD away from the individual global mean levels; and (2) sequences of zeros with duration > 60 minutes during the daytime (likely representing off-wrist periods) were identified and marked as gaps.^{27,28} Finally, each recording was manually inspected to confirm quality control prior to FMAR assessment.

2.4 | Fractal motor activity regulation

To assess FMAR, we investigated the temporal correlation property of motor activity fluctuation at an array of timescales by performing detrended fluctuation analysis (DFA) with two-order polynomial detrending.^{28,29} The DFA calculates the fluctuation amplitude, $F(n)$, as a function of time scale n . A power-law form of $F(n)$, that is, $F(n) \sim n^\alpha$, indicates a fractal structure in the fluctuations (Figure 1). The temporal correlation in the fluctuations can be quantified by the scaling exponent, α , where 0.5 indicates no correlation in the fluctuations (“white noise”), and > 0.5 indicates positive, whereas < 0.5 indicates negative temporal correlations. Positive temporal correlation implies that adjacent values in time tend to have similar values (i.e., large values more likely followed by large values), and negative temporal correlation suggests that adjacent values in time are more likely different from each other (i.e., large values more likely followed by small values). Mathematically, the upper limit for α is 3 for the DFA using two-order polynomial detrending (stronger correlations for larger values),²⁷ but most

physiological outputs under healthy conditions have a value close to 1.0.²⁸ This imitates the behavior of “pink” (1/f) noise, a signal/process in which the power spectral density is inversely proportional to the signal frequency; it represents a delicate balance between total randomness (white noise) with no control and excessive regularity (periodic signals), with too rigid a control (no response or flexibility). In fact, this is one of the most common patterns in the output of healthy biological systems,³⁰ including the brain activity; recent evidence suggests that pink noise can enhance slow-wave sleep (associated with memory consolidation) in patients with MCI.³¹

FMAR degradation can be assessed from the changes in $F(n)$ and α . One typical change is decreases in α values with age (i.e., motor activity fluctuations become more like white noise).^{3,7,32} However, the rate of decrease appears to be disproportionate over two time scale regions in AD and dementia with faster decline at time scales > 2 hours (up to 24 hours, α_2) than < 90 minutes (α_1); this leads to the deviation of $F(n)$ from a power-law form (a straight line) with $\alpha_1 > \alpha_2$.^{4–6,32} Therefore, we used the difference, that is, $\Delta\alpha = \alpha_1 - \alpha_2$, to assess such degradation in FMAR (Figure 1). Increased $\Delta\alpha$ was previously observed to be more strongly linked with neurodegeneration,³² particularly in the suprachiasmatic nucleus, and with cortical amyloid plaque burden, versus core body temperature and motor activity derived rest/activity measures.³³ In addition, we focused on peak daytime activity data (i.e., 11 AM–7 PM) to assess FMAR changes independent of the potential effects of altered sleep that may cause nocturnal motor activity. Collectively, considering an epoch length of 30 seconds and the decreased length of consecutive data recordings due to the exclusion of nighttime period/gaps, we quantified α_1 in the range of 3 to 90 minutes and α_2 in the range of 2 to 8 hours.

TABLE 1 Participant characteristics

| Characteristic | All (n = 178) Mean (SD) or N (%) | PiB+ (n = 33) | PiB- (n = 117) | P |
|-----------------------------|-------------------------------------|------------------|-------------------|-------|
| Age, years | 65.9 (8.3) | 69.8 (5.4) | 64.6 (8.6) | .001 |
| Sex, women | 117 (66%) | 20 (61%) | 80 (68%) | .44 |
| Education, years | 16.2 (2.4) | 15.6 (2.5) | 16.3 (2.4) | .14 |
| Race, non-Hispanic white | 167 (94%) | 32 (97%) | 110 (94%) | .68 |
| APOE ϵ 4 carrier | 66 (37%) | 18 (55%) | 38 (32%) | .02 |
| log(p-tau-to-A β 42)* | NA | -0.89 (0.26) | -1.21 (0.18) | <.001 |

Abbreviations: A β , amyloid beta; APOE, apolipoprotein E; PiB, Pittsburgh compound B; SD, standard deviation.

Notes: APOE ϵ 4 carrier (1 or 2 alleles); log(pTau-to-A β 42) cerebrospinal fluid phosphorylated Tau 181 (pTau) to amyloid- β -42 (A β 42) ratio, log transformed for non-normal distribution.

*121 participants with both PiB and log(pTau-to-Ab42) available.

2.5 | Assessment of covariates

Age was in years at start of actigraphy recording. Biological sex at birth, race (non-Hispanic White, Black, or other), education (years) were self-reported. APOE ϵ 4 genotype was dichotomized to carrier (one or two alleles) versus noncarrier. Mean daily activity was estimated from the extent of actigraphy accelerations in arbitrary units (a.u.). We also considered the following measures of rest/activity patterns using published results and methodology from this cohort:^{16,34,35} (1) interdaily stability (IS) of daily activity rhythm (similarity between days; higher values indicate more day-to-day stability);³⁶ and (2) intradaily variability (IV; how consolidated the rest/activity rhythms are). Low IV results occur when there is a continuous period of high activity and a continuous period of minimal activity during each day; higher IV indicates more fragmentation of the rest/activity pattern.³⁵

2.6 | Statistical analysis

We examined all continuous variables for normal distribution by visual inspection of histograms and the Kolmogorov-Smirnov test. The p-tau-to-A β 42 ratio was log-transformed due to non-normal distribution. Comparisons between two groups (PiB+ and PiB- status) were conducted using independent t tests for normally distributed continuous variables, Mann-Whitney U tests if non-normally distributed, or Chi-squared tests for categorical variables. Correlations were assessed with Pearson's correlation.

We constructed multiple regression models with PiB status as a dichotomous predictor, and separately with log (p-tau/A β 42) as a continuous predictor, accounting for available covariates that may affect both FMAR and preclinical AD pathology; these were entered stepwise in the following order: our core model (Model A) included demographics (age, sex, education years, and ethnicity), Model B additionally included mean daily activity level, Model C added APOE ϵ 4 genotype, and Models D1 and D2 added two rest/activity measures one at a time given their known collinearity. The effects of the time lag between AD biomarker assessment and FMAR assessment on all associations

were explored, but were not significant. Therefore, the time lag was not included as a covariate to preserve degrees of freedom. Related to this, to assess clinical utility of FMAR (alongside age, sex, race, education, daily activity, and APOE) in the prediction of AD biomarker status, we also included further analysis examining the odds of prior PiB+ at the time of imaging, based on the upper half (\geq median) and lower half ($<$ median) of $\Delta\alpha$, assuming that AD pathology was irreversible. All tests were two-sided, with an α level of 0.05. Statistical analyses were performed using JMP Pro (Ver. 14, SAS Institute).

3 | RESULTS

3.1 | Participant characteristics

Demographics and characteristics of participants are summarized in Table 1. Overall, the participants were more likely to be female (66%, n = 117), aged (mean [SD]) 65.9 [8.3] years, and have had 16.2 [2.4] years of education (Table 1). Among the 150 participants with PiB PET imaging, 22% (n = 33) were PiB+ and, compared to PiB- participants, they were older (69.8 [5.4] vs. 64.6 [8.6] years, $P = .001$), more often APOE ϵ 4 carriers (55% vs. 32%, $P = 0.02$), and with higher log(p-tau/A β 42) (-0.89 [0.26] vs. -1.21 [0.18], $P < .001$), in a subset of 121 with both markers available. Figure 1 shows motor activity recordings over 1 week, and the corresponding FMAR ($\Delta\alpha$) from two representative female participants at the same age (78 years), one PiB+ with $\Delta\alpha$ in the 90th centile of the cohort, and one PiB- with $\Delta\alpha$ in the 10th centile. FMAR was normally distributed, with a median value of 0.10, and ranged from -0.45 to +0.48 (Figure 2).

The effects of age, sex, daily activity level, and APOE ϵ 4 genotype on daytime FMAR are shown in Figure 3. With increasing age, there was a trend toward increased $\Delta\alpha$ but this effect was not significant ($r = 0.11$, $P = .13$; Figure 3A). After adjusting for age, women had higher $\Delta\alpha$ (0.10 vs. 0.04 in men, $P = .016$; Figure 3B). Daily activity level had no significant effect on $\Delta\alpha$ ($r = -0.08$, $P = .25$; Figure 3C). There was no significant difference in $\Delta\alpha$ between APOE ϵ 4 carriers and non-carriers (0.076 present vs. 0.074 absent, $P = .88$; Figure 3D).

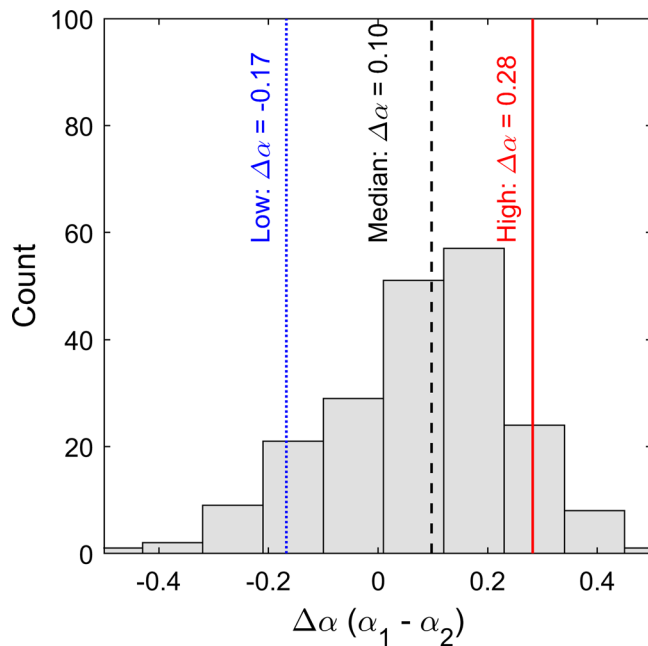


FIGURE 2 The distribution of the fractal motor activity regulation $\Delta\alpha$ metric. The median value of 0.10 is represented by the black dotted line. Red line represents 10th centile whereas the blue dotted line represents the 90th centile

3.2 | AD biomarkers and FMAR ($\Delta\alpha$)

We compared PiB+ participants ($n = 33$) to PiB- participants ($n = 119$) to examine the effect of amyloid plaque pathology on FMAR. PiB+ participants had significantly higher daytime $\Delta\alpha$ than PiB- participants in our core multivariate model after accounting for the potential effects of age, sex, education, and race (Figure 3E). The magnitude of this difference in $\Delta\alpha$ was 21.7% of the SD when “All” subjects were included (Table 2, Model A: estimate = 0.217, standard error [SE] = 0.101, $P = .034$). This relationship remained unchanged after including mean daily activity level (Model B: estimate = 0.226, SE = 0.102, $P = .028$), and APOE $\epsilon 4$ genotype (Model C: estimate = 0.223, SE = 0.105, $P = .035$). After inclusion of individual rest/activity measures (IS and IV), the associations between PiB status and FMAR remained significant (Models D1-D2; Table 2). In further analysis, when a participant had an assessed $\Delta\alpha$ in the upper half (≥ 0.10 , median value in Figure 2), there was significantly increased odds for prior PiB+ at the time of imaging, compared to those in the lower half (odds ratio [OR] 3.32, 95% confidence interval [CI] 1.33–8.30, $P = .010$); this was independent of age, sex, education, race, daily activity, and APOE (see Table S1 in supporting information).

We also examined CSF $\log(p\text{-tau}/A\beta 42)$ as a continuous measure of AD-specific pathological burden. There was a positive correlation between $\log(p\text{-tau}/A\beta 42)$ and daytime $\Delta\alpha$ for all participants with available CSF biomarkers (Figure 3F). In our core model, every 1-SD increase in $\log(p\text{-tau}/A\beta 42)$ was associated with a 22.0% SD increase in $\Delta\alpha$ (Table 2, Model A: estimate = 0.220, SE = 0.084, $P = .009$). This relationship also remained unchanged after inclusion of daily activity

(Model B: estimate = 0.228, SE = 0.083, $P = .007$) and APOE genotype (Model C: estimate = 0.218, SE = 0.087, $P = .013$). Similarly, the inclusion of IS/IV in Models D1-D2 did not affect the association. Full model results for PiB status and $\log(p\text{-tau}/A\beta 42)$ on $\Delta\alpha$ are summarized in Tables S2-S3 in supporting information.

Given that we observed significantly higher $\Delta\alpha$ in women, a subset analysis by sex was performed (Table 2). The associations of $\Delta\alpha$ with AD pathology measures were significant in women for both PiB+ ($\beta = 0.279$, SE = 0.112, $P = .015$) and CSF $\log(p\text{-tau}/A\beta 42)$ ($\beta = 0.245$, SE = 0.094, $P = .011$), but not in men for either PiB+ ($\beta = 0.187$, SE = 0.201, $P = .357$) or CSF $\log(p\text{-tau}/A\beta 42)$ ($\beta = 0.130$, SE = 0.167, $P = .438$).

4 | DISCUSSION

This study identified for the first time an association between FMAR and preclinical AD biomarkers that warrants further investigation and validation. We found that changes in daytime FMAR (higher $\Delta\alpha$) were associated with preclinical AD pathology in healthy, cognitively normal adults, as measured by amyloid imaging (PiB status) or CSF p-tau-to- $A\beta 42$ ratio. These associations were significant after inclusion of age, sex, education, race, mean daily activity, and APOE $\epsilon 4$ carrier status. However, women had higher daytime FMAR degradation, and appeared to drive the above associations. These findings suggest that daytime FMAR imparts new information, particularly in women, about AD pathogenesis at the early stage of the disease prior to the onset of cognitive symptoms.

Fractal regulation has been used to characterize health status and clinical outcome in many diseases,⁷ including the prediction of MCI and AD dementia.^{4–6} We recently showed for the first time that FMAR predicted incident clinical AD by 5 years on average.³ However, given that preclinical AD pathology may develop more than 10 to 20 years prior to symptomatic cognitive impairment,^{37,38} this is the first study demonstrating an association between early preclinical AD pathology and FMAR changes. Additionally, $\Delta\alpha$ significantly associated with CSF p-tau-to- $A\beta 42$ ratio, a continuous measure of AD-specific pathology, suggesting that FMAR may be able to serve as a marker of preclinical AD progression.

Interestingly, FMAR appeared to be more degraded in women than men ($P = .016$, Figure 3B). This is in keeping with a prior study in healthy subjects in which FMAR degradation appeared steeper in females, starting as early as young adulthood between 30 and 40 years of age.³⁹ However, in an elderly community cohort (also predominantly women, but ≈ 20 years older than our cohort on average), FMAR degradation was higher with age, but no difference in FMAR degradation was observed between sexes.^{3,6} In this study, FMAR degradation also trended higher with age, but was not significant. Thus, FMAR's link to sex may well be age dependent. $\Delta\alpha$, as one of many accepted FMAR measures, may only reflect an aspect of FMAR change that is influenced by sex, but only in younger cohorts.

Most importantly, though results were significant for the whole cohort, the associations between AD pathology and FMAR remained

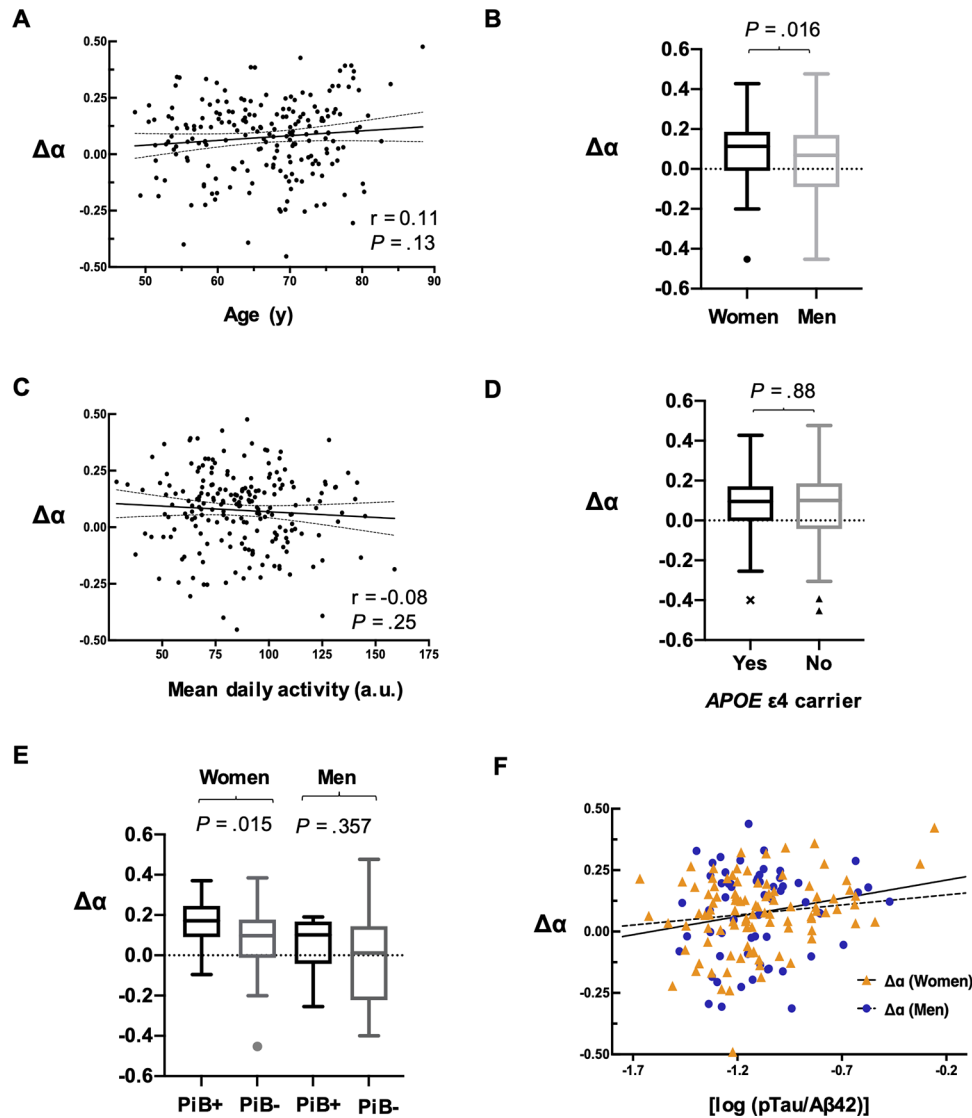


FIGURE 3 Effect of Alzheimer's disease (AD) biomarkers and demographic characteristics on fractal motor activity regulation. All plots show $\Delta\alpha$ on the y axis, with higher values indicating more degradation of fractal motor activity regulation. A, Increasing age in years (y) was non-significantly associated with higher $\Delta\alpha$. B, Women had higher $\Delta\alpha$. C, Decreased mean daily activity (in arbitrary units) was non-significantly associated with higher $\Delta\alpha$. Scatterplot shows linear regression line plus 95% confidence interval. D, There was no difference in $\Delta\alpha$ between APOE $\epsilon 4$ carriers and non-carriers. E, Women with preclinical AD pathology, as defined by Pittsburgh compound B (PiB) positron emission tomography (PET) positivity (PiB+), had higher $\Delta\alpha$ than participants who were PiB negative (PiB-). F, Greater AD-specific pathological burden, as measured by cerebrospinal fluid phosphorylated tau 181 (p-tau) to amyloid beta 42 (A β 42) ratio [\log (p-tau/A β 42)], was significantly correlated with higher $\Delta\alpha$ in women (orange triangles and solid line; $r = 0.26$, $P = .011$), but not in men (blue circles and dashed line; $r = 0.10$, $P = .438$). Box plots show interquartile range (IQR) as boxes, median as center line, and 1.5 x IQR as whiskers. Outliers are represented as individual markers. P values adjusted for age (B) or age, sex, education, and race (C-F)

significant only in females. The effect sizes for PiB+ on FMAR appeared larger in women, but in formal testing, being female did not significantly augment the effects of amyloid plaque positivity on FMAR degradation (data not shown). The makeup of the Washington University ADRC, in which the female sample size was larger than the male sample (66% women, Table 1), resulted in lower standard errors (narrower confidence intervals) for women, and/or greater variability in men (Figure 3B), which may contribute to the sex differences for significance thresholds being reached in our fully adjusted models. However, power differences may not fully explain the significantly higher $\Delta\alpha$ in women

(0.10 vs. 0.04 in men, $P = .016$). The possibility for earlier AD pathology changes in women is supported by the other findings showing that women have higher prevalence of AD,⁴⁰ faster cognitive decline⁴¹ and differences in underlying AD pathology, on both neuroimaging⁴² and CSF.⁴³ Taken together, this warrants further work within larger samples to examine FMAR changes during middle age,¹ as well as the trajectory of FMAR with aging in both women and men using longitudinal within-subject study designs.

Mechanistically, poor or impaired motor function, and low physical activity levels have all been linked to MCI, AD, and cognitive

TABLE 2 Sex-specific preclinical AD amyloid plaque pathology and disease burden on fractal motor activity regulation

| β , SE | PiB+/PiB- | | | log(p-tau/A β 42) | | |
|----------------------|--------------|--------------|--------------|-------------------------|--------------|--------------|
| | All | Female | Male | All | Female | Male |
| <i>P</i> value | n = 150 | n = 100 | n = 50 | n = 149 | n = 93 | n = 56 |
| Model A | 0.217, 0.101 | 0.279, 0.112 | 0.187, 0.201 | 0.220, 0.084 | 0.245, 0.094 | 0.130, 0.167 |
| (core) | 0.034 | 0.015 | 0.357 | 0.009 | 0.011 | 0.438 |
| Model B | 0.226, 0.102 | 0.280, 0.112 | 0.199, 0.207 | 0.228, 0.083 | 0.231, 0.094 | 0.236, 0.176 |
| (+daily activity) | 0.028 | 0.014 | 0.341 | 0.007 | 0.017 | 0.187 |
| Model C | 0.223, 0.105 | 0.272, 0.115 | 0.215, 0.217 | 0.218, 0.087 | 0.224, 0.100 | 0.240, 0.188 |
| (+APOE ϵ 4) | 0.035 | 0.020 | 0.327 | 0.013 | 0.026 | 0.209 |
| Model D1 | 0.225, 0.106 | 0.267, 0.116 | 0.197, 0.221 | 0.224, 0.089 | 0.224, 0.089 | 0.201, 0.105 |
| (+IS) | 0.036 | 0.024 | 0.378 | 0.013 | 0.013 | 0.309 |
| Model D2 | 0.214, 0.106 | 0.287, 0.118 | 0.204, 0.214 | 0.201, 0.092 | 0.279, 0.106 | 0.208, 0.200 |
| (+IV) | 0.044 | 0.017 | 0.347 | 0.030 | 0.010 | 0.594 |

Notes: Effects of amyloid plaque pathology (PiB, Pittsburgh compound B status) and cerebrospinal fluid (CSF) AD-specific disease burden biomarker log(p-tau/A β 42) on fractal motor activity regulation (FMAR) in all subjects, and by sex. β represents change in $\Delta\alpha$ in standard deviations (SDs), alongside corresponding standard errors (SE) and *P* values, for PiB+ compared to PiB-, or per each SD increase in log(p-tau/A β 42). The core Model A included age, sex, education, and ethnicity. Model B additionally included mean physical activity level. Model C additionally included APOE ϵ 4 status. Models D1 and D2 additionally included for rest/activity measures IS interdaily stability, and IV intradaily variability.

decline.^{2,13,14,46,47} The current study showed a strong and consistent association between preclinical AD pathology and FMAR, raising the possibility that motor dysfunction and FMAR share common underlying pathophysiology (i.e., neurodegeneration). While activity level is only one domain in the assessment of motor function, we did not observe a strong association between FMAR and daily activity levels. Motor function is multifaceted and likely only partially reflected in FMAR. In addition, FMAR may involve the other physiological control systems that interact with the motor control system.⁴⁸ More work is required to understand how FMAR reflects healthy motor function beyond simply total activity levels.

Finally, there is increasing evidence that rest/activity patterns, a proxy for underlying circadian regulation (the body's daily rhythm and control of physiological processes), is an early sign of AD preceding the onset of cognitive symptoms.^{16,49,50} At the same time, our work has shown that the maintenance of fractal activity patterns requires intact circadian regulation.^{33,51} Given that higher IV, a measure of rest/activity pattern fragmentation, was also positively correlated with AD pathology in the same cohort,¹⁶ it is not surprising that FMAR degradation trended toward a positive correlation with higher IV (Figure S1 in supporting information). However, the relationship between FMAR and preclinical AD remained significant despite the inclusion of IV in our final model. We would argue these results for FMAR show consistency with prior circadian links to AD. Taken together, we believe FMAR better encompasses physiological processes relevant to cognitive decline than age alone, individual measures of activity levels, rest/activity patterns, and even genetic predisposition by revealing unique information in preclinical AD. Future studies determining the neural circuitry for FMAR may shed light on the neuroanatomical/neuropathological changes underlying these findings.

Among the strengths of this study, to the best of our knowledge, these are the first results incorporating fractal regulation and in vivo AD biomarkers (both CSF and PiB PET imaging). The Knight ADRC cohort is significant given the nature of the data collected, with detailed clinical and dementia assessments that ensure consistent phenotyping. Actigraphy was collected for 14 days, providing an excellent source data for analyses, in combination with established FMAR analysis protocols. When we assume irreversibility of AD pathology, having an assessed value for $\Delta\alpha$ greater than the 50th centile value in this cohort was associated with more than 1-fold increased odds of being PiB+ at the time of imaging, which was comparable to the odds of PiB+ from being a APOE ϵ 4 carrier versus a non-carrier (Table S1). The potential application of FMAR measures in screening people with a high probability of AD pathology should be desirable because AD biomarkers such as amyloid and tau are expensive or invasive to obtain. To improve upon its utility, future work should combine this unobtrusive monitoring method in participants' natural environment, with other inexpensive/non-invasive clinical measures; this makes it more feasible to identify higher risk individuals at an earlier stage, who may then go onto lumbar puncture or AD imaging.⁵²⁻⁵⁵

We acknowledge some limitations of our study. The cohort was relatively homogeneous; therefore, we were unable to fully consider race or ethnicity in our analyses. It is possible that changes in FMAR occurred during up to 3-year's lag between actigraphy recording and AD biomarker measurement. However, assuming irreversibility of AD pathology and the strength of association within the two separate AD pathology measures, it seems probable that the time lag would have biased our findings toward the null. It is also possible that the observed relationships are caused by non-amyloid/tau pathologies in the aged brain. In particular, sleep disordered breathing is common and can influence amyloid burden,⁵⁶ but was not assessed in this cohort.

The relationship between FMAR alterations and other types of dementia has also not yet been explored. Ultimately, external validation and replication are needed with more male subjects, in undiagnosed participants with MCI, and accounting for comorbidities and medications that may affect both motor activity patterns and AD pathology.

In summary, we found that FMAR degrades with preclinical AD pathology, and that this effect was largely driven by female participants. The proposed FMAR measure is independent of age, APOE ϵ 4 status, mean daily activity, and rest/activity patterns. These results warrant further investigation to establish the potential of fractal regulation as a passively obtained, non-cognitive and physiological biomarker for AD. To improve the prediction/detection of AD dementia, future studies may combine FMAR with other imaging and/or behavioral measures and use advanced techniques of machine learning to extract the best features or biomarkers for AD risk.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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REFERENCES

- Khoury R, Ghossoub E. Diagnostic biomarkers of Alzheimer's disease: a state-of-the-art review. *Biomark Neuropsychiatry*. 2019;1:100005. <https://doi.org/10.1016/j.bionps.2019.100005>.
- Buchman AS, Boyle PA, Yu L, Shah RC, Wilson RS, Bennett DA. Total daily physical activity and the risk of AD and cognitive decline in older adults. *Neurology*. 2012;78:1323-1329. <https://doi.org/10.1212/WNL.0b013e3182535d35>.
- Li P, Yu L, Lim ASP, et al. Fractal regulation and incident Alzheimer's disease in elderly individuals. *Alzheimers Dement J Alzheimers Assoc*. 2018;14:1114-1125. <https://doi.org/10.1016/j.jalz.2018.03.010>.
- Hu K, Van Someren EJW, Shea SA, Scheer FAJL. Reduction of scale invariance of activity fluctuations with aging and Alzheimer's disease: involvement of the circadian pacemaker. *Proc Natl Acad Sci U S A*. 2009;106:2490-2494. <https://doi.org/10.1073/pnas.0806087106>.
- Hu K, Riemersma-van der Lek RF, Patxot M, et al. Progression of dementia assessed by temporal correlations of physical activity: results from a 3.5-Year. *Longitudinal Randomized Controlled Trial Sci Rep*. 2016;6:27742. <https://doi.org/10.1038/srep27742>.
- Li P, Yu L, Yang J, et al. Interaction between the progression of Alzheimer's disease and fractal degradation. *Neurobiol Aging*. 2019;83:21-30. <https://doi.org/10.1016/j.neurobiolaging.2019.08.023>.
- Goldberger AL, Amaral LAN, Hausdorff JM, Ivanov PC, Peng C-K, Stanley HE. Fractal dynamics in physiology: alterations with disease and aging. *Proc Natl Acad Sci U S A*. 2002;99(Suppl 1):2466-2472. <https://doi.org/10.1073/pnas.012579499>.
- Gao L, Smielewski P, Czosnyka M, Ercole A. Cerebrovascular signal complexity six hours after intensive care unit admission correlates with outcome after severe traumatic brain injury. *J Neurotrauma*. 2016;33:2011-2018. <https://doi.org/10.1089/neu.2015.4228>.
- Gao L, Smielewski P, Li P, Czosnyka M, Ercole A. Signal Information prediction of mortality identifies unique patient subsets after severe traumatic brain injury: a decision-tree analysis approach. *J Neurotrauma*. 2020;37:1011-1019.
- Dierick F, Nivard A-L, White O, Buisseret F. Fractal analyses reveal independent complexity and predictability of gait. *PLoS One*. 2017;12:e0188711. <https://doi.org/10.1371/journal.pone.0188711>.
- Dolatabadi E, Van Ooteghem K, Taati B, Iaboni A. Quantitative mobility assessment for fall risk prediction in dementia: a systematic review. *Dement Geriatr Cogn Disord*. 2018;45:353-367. <https://doi.org/10.1159/000490850>.
- Ehsani H, Parvaneh S, Mohler J, et al. Can motor function uncertainty and local instability within upper-extremity dual-tasking predict amnesic mild cognitive impairment and early-stage Alzheimer's disease?. *Comput Biol Med*. 2020;120:103705. <https://doi.org/10.1016/j.combiomed.2020.103705>.
- Buchman AS, Yu L, Wilson RS, Schneider JA, Bennett DA. Association of brain pathology with the progression of frailty in older adults. *Neurology*. 2013;80:2055-2061. <https://doi.org/10.1212/WNL.0b013e318294b462>.
- Buchman AS, Schneider JA, Leurgans S, Bennett DA. Physical frailty in older persons is associated with Alzheimer disease pathology. *Neurology*. 2008;71:499-504. <https://doi.org/10.1212/01.wnl.0000324864.81179.6a>.
- Li P, Lim ASP, Gao L, et al. More random motor activity fluctuations predict incident frailty, disability, and mortality. *Sci Transl Med*. 2019;11:eaax1977. <https://doi.org/10.1126/scitranslmed.aax1977>.
- Musiek ES, Bhimasani M, Zangrilli MA, Morris JC, Holtzman DM, Ju Y-ES. Circadian rest-activity pattern changes in aging and preclinical Alzheimer disease. *JAMA Neurol*. 2018;75:582-590. <https://doi.org/10.1001/jamaneurol.2017.4719>.
- Li P, Morris CJ, Patxot M, et al. Reduced tolerance to night shift in chronic shift workers: insight from fractal regulation. *Sleep*. 2017;40:zsx092. <https://doi.org/10.1093/sleep/zsx092>.
- Li P, To T, Chiang W-Y, Escobar C, Buijs RM, Hu K. Fractal regulation in temporal activity fluctuations: a biomarker for circadian control and beyond. *JSM Biomark*. 2017;3:1008.
- Li P, Gao L, Gaba A, et al. Circadian disturbances in Alzheimer's disease progression: a prospective observational cohort study of community-based older adults. *Lancet Healthy Longev*. 2020;1:e96-105. [https://doi.org/10.1016/S2666-7568\(20\)30015-5](https://doi.org/10.1016/S2666-7568(20)30015-5).
- Mazure CM, Swendsen J. Sex differences in Alzheimer's disease and other dementias. *Lancet Neurol*. 2016;15:451-452. [https://doi.org/10.1016/S1474-4422\(16\)00067-3](https://doi.org/10.1016/S1474-4422(16)00067-3).
- Ju Y-ES, McLeland JS, Toedebusch CD, et al. Sleep quality and preclinical Alzheimer disease. *JAMA Neurol*. 2013;70:587-593. <https://doi.org/10.1001/jamaneurol.2013.2334>.
- Jack CR, Wiste HJ, Weigand SD, et al. Defining imaging biomarker cut-points for brain aging and Alzheimer's disease. *Alzheimers Dement J Alzheimers Assoc*. 2017;13:205-216. <https://doi.org/10.1016/j.jalz.2016.08.005>.
- Vos SJ, Xiong C, Visser PJ, et al. Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. *Lancet Neurol*. 2013;12:957-965. [https://doi.org/10.1016/S1474-4422\(13\)70194-7](https://doi.org/10.1016/S1474-4422(13)70194-7).
- Tapiola T, Alafuzoff I, Herukka S-K, et al. Cerebrospinal fluid {beta}-amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain. *Arch Neurol*. 2009;66:382-389. <https://doi.org/10.1001/archneurol.2008.596>.

25. Gao L, Li P, Hu C, et al. Nocturnal heart rate variability moderates the association between sleep-wake regularity and mood in young adults. *Sleep*. 2019;42:zs034. <https://doi.org/10.1093/sleep/zsz034>.
26. Gao L, Lim ASP, Wong PM, et al. Fragmentation of rest/activity patterns in community-based elderly individuals predicts incident heart failure. *Nat Sci Sleep*. 2020;12:299-307. <https://doi.org/10.2147/NSS.S253757>.
27. Hu K, Ivanov PC, Chen Z, Carpena P, Stanley HE. Effect of trends on detrended fluctuation analysis. *Phys Rev E*. 2001;64:011114. <https://doi.org/10.1103/PhysRevE.64.011114>.
28. Hu K, Ivanov PC, Chen Z, Hilton MF, Stanley HE, Shea SA. Non-random fluctuations and multi-scale dynamics regulation of human activity. *Phys -Stat Mech Its Appl*. 2004;337:307-318. <https://doi.org/10.1016/j.physa.2004.01.042>.
29. Xu LM, Ivanov PC, Hu K, Chen Z, Carbone A, Stanley HE. Quantifying signals with power-law correlations: a comparative study of detrended fluctuation analysis and detrended moving average techniques. *Phys Rev E*. 2005;71:051101. <https://doi.org/10.1103/PhysRevE.71.051101>.
30. Szendro P, Vincze G, Szasz A. Pink-noise behaviour of biosystems. *Eur Biophys J EBJ*. 2001;30:227-231. <https://doi.org/10.1007/s002490100143>.
31. Papalambros NA, Santostasi G, Malkani RG, et al. Acoustic enhancement of sleep slow oscillations and concomitant memory improvement in Older Adults. *Front Hum Neurosci*. 2017;11:109. <https://doi.org/10.3389/fnhum.2017.00109>.
32. Hu K, Harper DG, Shea SA, Stopa EG, Scheer FAJL. Noninvasive fractal biomarker of clock neurotransmitter disturbance in humans with dementia. *Sci Rep*. 2013;3:2229. <https://doi.org/10.1038/srep02229>.
33. Hu K, Meijer JH, Shea SA, et al. Fractal patterns of neural activity exist within the suprachiasmatic nucleus and require extrinsic network interactions. *PLoS One*. 2012;7:e48927. <https://doi.org/10.1371/journal.pone.0048927>.
34. Nelson W, Tong YL, Lee JK, Halberg F. Methods for cosinorhythmometry. *Chronobiologia*. 1979;6:305-323.
35. van Someren EJW, Hagebeuk EEO, Lijzenga C, et al. Circadian rest-activity rhythm disturbances in alzheimer's disease. *Biol Psychiatry*. 1996;40:259-270. [https://doi.org/10.1016/0006-3223\(95\)00370-3](https://doi.org/10.1016/0006-3223(95)00370-3).
36. Witting W, Kwa IH, Eikelenboom P, Mirmiran M, Swaab DF. Alterations in the circadian rest-activity rhythm in aging and Alzheimer's disease. *Biol Psychiatry*. 1990;27:563-572. [https://doi.org/10.1016/0006-3223\(90\)90523-5](https://doi.org/10.1016/0006-3223(90)90523-5).
37. Roe CM, Fagan AM, Grant EA, et al. Amyloid imaging and CSF biomarkers in predicting cognitive impairment up to 7.5 years later. *Neurology*. 2013;80:1784-1791. <https://doi.org/10.1212/WNL.0b013e3182918ca6>.
38. Villemagne VL, Pike KE, Darby D, et al. Abeta deposits in older nondemented individuals with cognitive decline are indicative of preclinical Alzheimer's disease. *Neuropsychologia*. 2008;46:1688-1697. <https://doi.org/10.1016/j.neuropsychologia.2008.02.008>.
39. Joustra SD, Gu C, Rohling JHT, et al. Decrease in scale invariance of activity fluctuations with aging and in patients with suprasellar tumors. *Chronobiol Int*. 2017;1-10. <https://doi.org/10.1080/07420528.2017.1407779>.
40. Andersen K, Launer LJ, Dewey ME, et al. Gender differences in the incidence of AD and vascular dementia: the EURODEM Studies. EURODEM Incidence Research Group. *Neurology*. 1999;53:1992-1997. <https://doi.org/10.1212/wnl.53.9.1992>.
41. Sundermann EE, Biegon A, Rubin LH, et al. Better verbal memory in women than men in MCI despite similar levels of hippocampal atrophy. *Neurology*. 2016;86:1368-1376. <https://doi.org/10.1212/WNL.0000000000002570>.
42. Buckley RF, Mormino EC, Rabin JS, et al. Sex differences in the association of global amyloid and regional Tau deposition measured by positron emission tomography in clinically normal older adults. *JAMA Neurol*. 2019;76:542-551. <https://doi.org/10.1001/jamaneurol.2018.4693>.
43. Altmann A, Tian L, Henderson VW, Greicius MD. Alzheimer's Disease Neuroimaging Initiative Investigators. Sex modifies the APOE-related risk of developing Alzheimer disease. *Ann Neurol*. 2014;75:563-573. <https://doi.org/10.1002/ana.24135>.
44. Cornelis MC, Wang Y, Holland T, Agarwal P, Weintraub S, Morris MC. Age and cognitive decline in the UK Biobank. *PLoS One*. 2019;14:e0213948. <https://doi.org/10.1371/journal.pone.0213948>.
45. Doherty A, Jackson D, Hammerla N, et al. Large scale population assessment of physical activity using wrist worn accelerometers: the UK Biobank Study. *PLoS One*. 2017;12:e0169649. <https://doi.org/10.1371/journal.pone.0169649>.
46. Buchman AS, Yu L, Wilson RS, Boyle PA, Schneider JA, Bennett DA. Brain pathology contributes to simultaneous change in physical frailty and cognition in old age. *J Gerontol A Biol Sci Med Sci*. 2014;69:1536-1544. <https://doi.org/10.1093/gerona/glu117>.
47. Buchman AS, Yu L, Boyle PA, et al. Microvascular brain pathology and late-life motor impairment. *Neurology*. 2013;80:712-718. <https://doi.org/10.1212/WNL.0b013e3182825116>.
48. Pittman-Polletta BR, Scheer FAJL, Butler MP, Shea SA, Hu K. The role of the circadian system in fractal neurophysiological control. *Biol Rev Camb Philos Soc*. 2013;88:873-894. <https://doi.org/10.1111/brv.12032>.
49. Wu Y-H, Swaab DF. Disturbance and strategies for reactivation of the circadian rhythm system in aging and Alzheimer's disease. *Sleep Med*. 2007;8:623-636. <https://doi.org/10.1016/j.sleep.2006.11.010>.
50. Hu K, Li P, Sleep GL. Rest-activity rhythms and aging: a complex web in Alzheimer's disease?. *Neurobiol Aging*. 2021. <https://doi.org/10.1016/j.neurobiolaging.2021.02.017>.
51. Hu K, Scheer FAJL, Ivanov PC, Buijs RM, Shea SA. The suprachiasmatic nucleus functions beyond circadian rhythm generation. *Neuroscience*. 2007;149:508-517. <https://doi.org/10.1016/j.neuroscience.2007.03.058>.
52. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement J Alzheimers Assoc*. 2011;7:280-292. <https://doi.org/10.1016/j.jalz.2011.03.003>.
53. Caselli RJ, Reiman EM. Characterizing the preclinical stages of Alzheimer's disease and the prospect of presymptomatic intervention. *J Alzheimers Dis JAD*. 2013;33(Suppl 1):S405-416. <https://doi.org/10.3233/JAD-2012-129026>.
54. Cummings J, Aisen PS, DuBois B, et al. Drug development in Alzheimer's disease: the path to 2025. *Alzheimers Res Ther*. 2016;8:39. <https://doi.org/10.1186/s13195-016-0207-9>.
55. Bobkova N, Vorobyov V. The brain compensatory mechanisms and Alzheimer's disease progression: a new protective strategy. *Neural Regen Res*. 2015;10:696-697. <https://doi.org/10.4103/1673-5374.156954>.
56. Yun C-H, Lee H-Y, Lee SK, et al. Amyloid burden in obstructive sleep apnea. *J Alzheimers Dis JAD*. 2017;59:21-29. <https://doi.org/10.3233/JAD-161047>.

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