# Divergent Associations of Slow-Wave Sleep versus Rapid Eye Movement Sleep with Plasma Amyloid-Beta

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**Objective:** Recent evidence shows that during slow-wave sleep (SWS), the brain is cleared from potentially toxic metabolites, such as the amyloid-beta protein. Poor sleep or elevated cortisol levels can worsen amyloid-beta clearance, potentially leading to the formation of amyloid plaques, a neuropathological hallmark of Alzheimer disease. Here, we explored how nocturnal neural and endocrine activity affects amyloid-beta fluctuations in the peripheral blood.

**Methods:** We acquired simultaneous polysomnography and all-night blood sampling in 60 healthy volunteers aged 20–68 years. Nocturnal plasma concentrations of amyloid-beta-40, amyloid-beta-42, cortisol, and growth hormone were assessed every 20 minutes. Amyloid-beta fluctuations were modeled with sleep stages, (non)oscillatory power, and hormones as predictors while controlling for age and participant-specific random effects.

**Results:** Amyloid-beta-40 and amyloid-beta-42 levels correlated positively with growth hormone concentrations, SWS proportion, and slow-wave (0.3–4Hz) oscillatory and high-band (30–48Hz) nonoscillatory power, but negatively with cortisol concentrations and rapid eye movement sleep (REM) proportion measured 40–100 minutes previously (all $t$ values > |3|, $p$ values < 0.003). Older participants showed higher amyloid-beta-40 levels.

**Interpretation:** Slow-wave oscillations are associated with higher plasma amyloid-beta levels, whereas REM sleep is related to decreased amyloid-beta plasma levels, possibly representing changes in central amyloid-beta production or clearance. Strong associations between cortisol, growth hormone, and amyloid-beta presumably reflect the sleep-regulating role of the corresponding releasing hormones. A positive association between age and amyloid-beta-40 may indicate that peripheral clearance becomes less efficient with age.

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In recent years, a metabolic homeostatic function of sleep has been put forward. In rodents, an increase in the interstitial space surrounding tissue cells has been observed during sleep, resulting in an increased clearance of potentially neurotoxic metabolic products, particularly the amyloid-beta (Aβ) protein.[1] In humans, experimental sleep deprivation or interference with slow-wave sleep (SWS) inhibits the overnight reduction of Aβ in cerebrospinal fluid (CSF) and a subsequent increase in plasma Aβ.[2–4] Specifically, a study that collected paired blood and CSF samples found that during sleep deprivation, mean overnight concentrations of CSF Aβ1-40 and Aβ1-42 increased by ∼35% above baseline, whereas plasma Aβ decreased by ∼5% below baseline.[5] In the cross-sectional study including 70 cognitively healthy older adults, shorter self-reported sleep duration and poorer sleep quality were associated with greater Aβ burden as measured by carbon 11-labeled Pittsburgh compound B positron emission tomography (PET).[6]

The important role of sleep in Aβ clearance is further supported by the finding that in Alzheimer disease (AD), impaired sleep and pathological accumulation of cortical Aβ are reported long before (sometimes up to 20 years) the onset of clinical symptoms.[7] Moreover, it has been suggested that impaired sleep can lead to Aβ accumulation, which in turn can drive the progression of the disease.[7]

Other lines of evidence report that Aβ clearance can be affected by abnormally increased cortisol concentrations, another common feature of AD.[8] High levels of circulating cortisol are usually associated with sustained stress. Within a normal circadian cycle, cortisol levels increase during the second half of the night, when rapid eye movement (REM) sleep predominates. The lowest cortisol levels are observed during the first half of the night, which in turn is associated with a maximal amount of SWS and a surge of growth hormone (GH).[9] These associations suggest common regulators of neural and endocrine activity during sleep and possibly of the endocrine and metabolic functions of sleep.

This study explores associations between sleep features, cortisol, GH, and plasma Aβ fluctuations using concurrent all-night plasma sampling and polysomnography in the to-date largest sample of healthy participants. We assume that plasma Aβ fluctuations can represent changes in central Aβ production or clearance, because it has been shown that plasma Aβ kinetics reflect the amyloidosis pathology of the central nervous system similarly to CSF.[10] Likewise, plasma markers have been validated with high sensitivity and specificity for Aβ pathology, while being less invasive, cheaper, and more practical than CSF, which has limitations for establishing it in routine clinical practice, as lumbar puncture is a modestly invasive procedure.[10]

Based on the evidence that brain clearance occurs during SWS, we hypothesize that SWS and the GH peak (which temporally coincides with SWS) would be followed by an increase in Aβ plasma levels. Given that REM sleep is accompanied by wakelike neural activity,[9] we hypothesize that the REM episodes and the cortisol peak (which temporally coincides with REM sleep) are accompanied by cerebral waste accumulation. However, we have no prior hypothesis on the direction of the correlation (if any) between REM sleep and plasma Aβ, because brain clearance during REM sleep has not been reported in the literature so far. In addition, we explore the temporal dynamics between sleep features and plasma Aβ fluctuations, speculating that they might reflect the rate of the waste removal from the brain to the periphery. In summary, our study replicates the known associations between SWS and plasma Aβ and reveals a new link between REM sleep and plasma Aβ, while both are seen in the broader context of hormone modulation and age. This work, therefore, contributes to a holistic understanding of the effect of sleep on plasma Aβ fluctuations.

## Subjects and Methods

### Participants

In this cross-sectional study, we analyzed plasma samples and polysomnographic recordings from previous unpublished endocrinological studies conducted at the Max Planck Institute of Psychiatry, using only nights with no pharmacological or endocrine intervention. The data were collected during 2004–2007. The sample consisted of 60 healthy volunteers (32 females) aged 39.8 ± 16.0 years (range = 20–68). The exclusion criterion was a diagnosed neurological, psychiatric, or sleep disorder, including sleep-disordered breathing. Study eligibility was assessed by psychiatrists trained in somnology, taking the past and current medical history; screening for depressive symptoms, as depression is mostly associated with sleep disturbances; and performing a physical examination and screening tests (eg, routine laboratory parameters, drug screening).

All studies and data reanalyses were approved by the ethics committee of the University of Munich. All participants gave written informed consent. Due to the retrospective nature of this study, information regarding participants' usual sleep habits, medications, chronotype, and self-reported sleep questionnaires was unavailable. The apolipoprotein E (APOE) status and amyloid deposition of the participants were not assessed.

### Plasma Measurement

During the experimental night in the sleep laboratory, 4ml of blood was drawn every 30 minutes (20:00–22:00) or 20 minutes (22:00–07:00) from the adjacent room, using an intravenous cannula and a tube extension. Free GH and cortisol

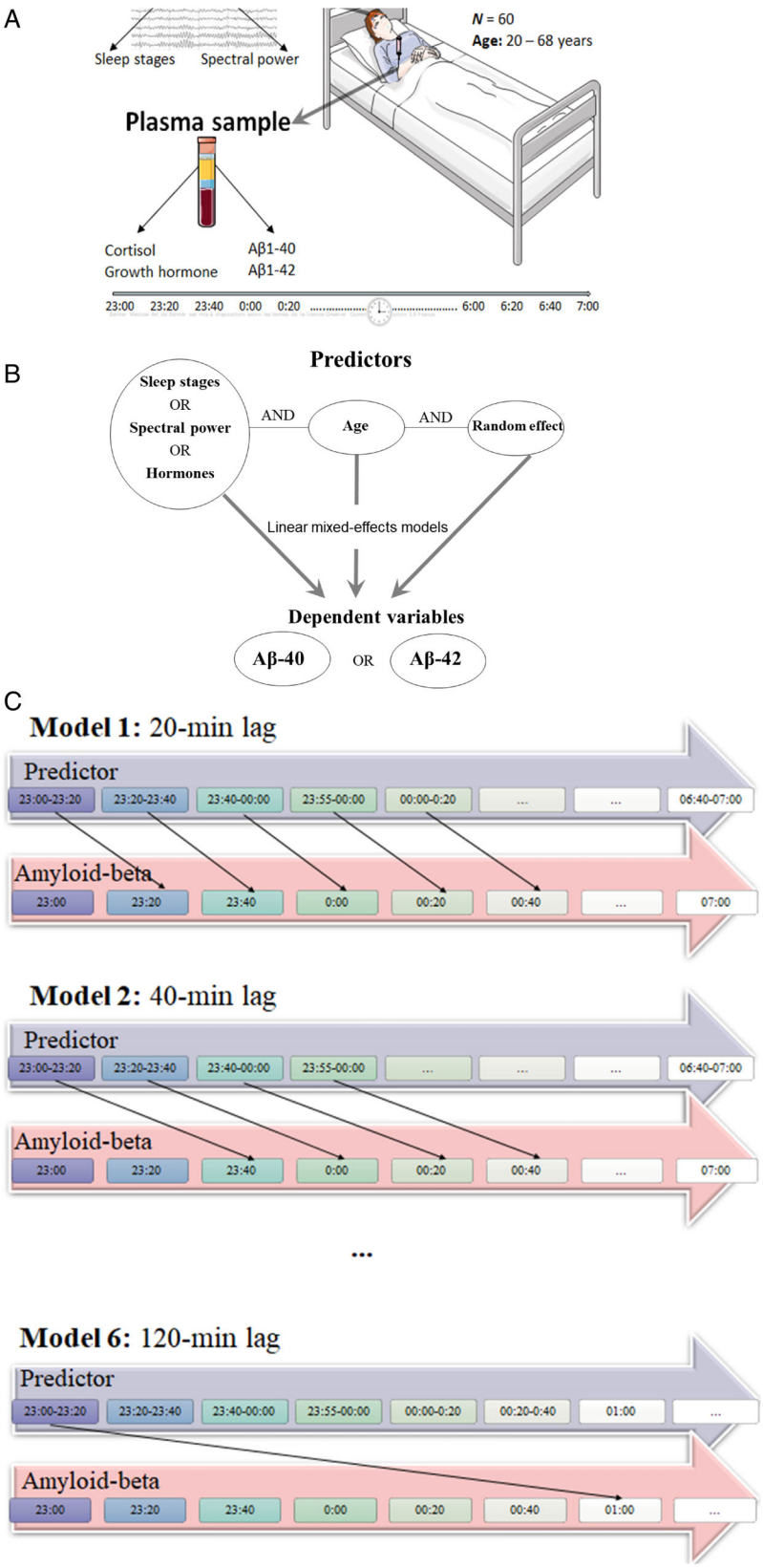


FIGURE 1: Study design and models. (A) Simultaneous polysomnography and all-night blood sampling were acquired in 60 healthy volunteers aged 20–68 years. Plasma concentrations of amyloid-beta 1–40 (Aβ1-40) and Aβ1-42, cortisol, and growth hormone were assessed for every 20 minutes of sleep from 23:00 to 7:00. (B) Predictors and dependent variables used in the mixed models. (C) For each predictor (sleep/hormone feature), we ran 6 different models corresponding to the time lags between the predictor and Aβ ranging from 120 to 20 minutes in 20-minute steps while controlling for multiple comparisons. [Color figure can be viewed at www.annalsofneurology.org]

concentrations were measured by radioimmunoassay. Aβ1-40 and Aβ1-42 were analyzed with commercially available Euroimmun enzyme-linked immunosorbent assays (ELISAs; plasma protocol[11]) according to the manufacturer's instructions by an expert blind to the subject characteristics and sleep data. Only the samples drawn from 23:00 to 7:00 were analyzed (Fig 1). All samples from one subject were measured on the same ELISA plate in the same run. The average coefficients of variation equaled 8.7% for Aβ1-40 and 11.6% for Aβ1-42, which is in line with a general guideline that ELISA coefficient of variation should be <15%.[11] This is, however, higher than that reported by Ovod et al,[10] who measured coefficients of variation of 8.48% for Aβ1-40 and 6.81% for Aβ1-42. Notably, our Aβ plasma assay is not able to reflect brain Aβ pathology and thus does not differentiate amyloid status of the participants.

### Polysomnography

The experimental night was preceded by an adaptation night in the sleep laboratory. Polysomnography was recorded from 23:00 to 07:00, stored, and analyzed with a digital recorder (Comlab 32 Digital Sleep Lab, Brainlab V 3.3 software; Schwarzer, Munich, Germany) from F3, F4, C3, C4, P3, P4, O1, and O2 leads, electro-oculogram, and mental/submental electromyogram, with a sampling rate of 250Hz (filtered from 0.3 to 70Hz). Sleep data were scored according to the American Academy of Sleep Medicine standards by experts not involved in the study. Epochs with electromyographic and electroencephalographic (EEG) artifacts were manually excluded by an experienced scorer before all automatic analyses (average percentage of all excluded epochs was <0.1%).

### Spectral Power

Total spectral power was calculated for each 30-second epoch for each channel and then differentiated to its aperiodic (ie, fractal, 1/f, scale-free) and oscillatory components using Irregularly Resampled Auto-Spectral Analysis.[12] To implement the algorithm, we used the ft_freqanalysis function of the Fieldtrip toolbox[13] as described elsewhere.[14,15] The function was called twice, with cfg.output = "fractal" and cfg.output = "original" for the total power and its aperiodic component, respectively. The aperiodic power component was transformed to log–log coordinates by standard least-squares regression. To estimate the power-law exponent (the rate of the spectral decay), we calculated the slope of the aperiodic component as a marker of excitation-to-inhibition ratio.[16] The oscillatory component was calculated by subtracting the aperiodic component from the total power. All values higher than 3 standard deviations above the mean were automatically replaced by NaN (not-a-number) values.

### Sleep Outcome Measures

Sleep features were characterized with 6 different variables, specifically, the proportion of N1, N2, SWS, and REM sleep, oscillatory power component in the 0.3–4Hz band (slow-wave activity [SWA]) as an objective EEG marker of SWS, and the slope of the aperiodic power component in the 30–48Hz band as an objective marker of REM sleep (Fig S6, Supplementary Material).[17]

The analysis was limited to 48Hz due to recording line noise (50Hz in Europe). All variables were averaged over each 20 minutes of sleep. Spectral power variables were averaged over F3 and F4 electrodes, as this location is associated with the highest SWA.

As an exploratory subanalysis, we also calculated the oscillatory power component in the theta (4–8Hz), alpha (8–11Hz), and beta (15–30Hz) frequency bands, as well as the slope of the aperiodic power component in the 0.3–35Hz band and averaged them over the frontal electrodes.

In the Supplementary Material, we report the associations between spectral power over additional topographical areas (S1) as well as the effect of atonia (S2), autonomic functioning (S3), wakefulness after sleep onset (S4), and age (S5) and plasma Aβ.

### Statistical Analysis

To assess whether sleep features or hormones (predictors) can explain changes in the subsequent Aβ1-40 or Aβ1-42 plasma levels (dependent variables), we used univariable mixed-effects models using the R package *mgcv*. Specifically, each model included a fixed (explanatory) effect of one of the sleep features or hormones, a fixed effect of age, and a participant-specific random intercept (to control for individual-specific heterogeneities). The code is provided in Supplementary Material S6.

Given that we did not expect that participants' sex might influence Aβ, seen together with the result of the supplementary analysis that revealed no effect of sex on cortisol or GH, we did not include participants' sex as a predictor in the models, to keep them as parsimonious as possible.

For each sleep feature/hormone, we ran 6 different models using different time lags between the predictor and Aβ. Namely, the lags ranged from 120 to 20 minutes in 20-minute steps (see Fig 1). The choice of the time lag range was justified by the work by Ovod et al,[10] who used plasma Aβ stable isotope labeling kinetics to show that labeled Aβ rapidly appears in plasma <2 hours after infusing label.

To control for multiple comparisons, we used Benjamini–Hochberg adjustment with a false discovery rate set at 0.05. Due to the semiexploratory nature of this study, all corrections were done per a given sleep feature/hormone (6 different tests) with the α level set in the 0.008–0.050 range.

To assess model quality, we calculated the $R^2$ and Akaike information criterion (AIC). Given that the number of observations ranged from 19 per subject for the models using the 120-minute lag to 24 per subject for the models using the 20-minute lag, we excluded the last 1–5 observations from the longer datasets to end up with an equal number of observations (~19 per subject) in each model. We note that results are not directly comparable across time lags, as they are not based on the exact same set of data points. Nevertheless, assuming that the entire sample is representative, our models can serve as initial descriptive visualizations able to

hint at which time lag should be chosen for the next-level analysis.

In Supplementary Material S7, we also explored the nonlinear features of the association between the predictors and Aβ, using Generalized Additive Mixed Models. We found that the results obtained by linear and nonlinear models were comparable (Table S3).

## Results

The demographic, sleep, and plasma characteristics of the participants are reported in Table 1.

### Plasma Measurements

Nocturnal plasma concentrations of Aβ and hormones expressed as the percent of the mean and averaged over all participants are shown in Figure 2A. Absolute values are shown in Figure S7 of the Supplementary Material. The averaged Aβ level decrease from evening to morning equaled 12%. The averaged cortisol concentrations increased 5.9 times from 23:00 to 7:00, which is in line with the broadly reported observation that during the second half of the night, when REM sleep predominates, cortisol levels increase. On average, the maximal GH level during the first part of the night was 17.8 times higher compared to the baseline level measured at 23:00. After the peak, GH levels started to decrease. This is in line with literature reporting that the GH peak coincides with SWS, where both predominate during the first part of the night.

### Mixed-Effects Models

Figure 2B,C visualizes the relationships between different predictors and plasma Aβ measured 80 minutes afterwards averaged over all participants, whereas Figure 3 shows nonaveraged values of all participants for models using the 80-minute lag (the best models as assessed by their $R^2$ and AIC). For each predictor, we performed 6 different models with 6 different time lags between the predictor and Aβ (range = 120–20 minutes in 20-minute steps). The slope estimates of each model are presented in Figure 4 and Table 2.

### Sleep Stages

SWS proportions predicted higher Aβ1-40 measured 40–100 minutes thereafter and Aβ1-42 measured 20–80 and 100–120 minutes thereafter. REM sleep proportions measured at 40–100 minutes prior to a blood measurement predicted lower subsequent levels of Aβ1-40 and Aβ1-42. The proportions of N1 and N2 had no effect on subsequent Aβ (see Fig 4A).

**TABLE 1. Demographic, Plasma, and Sleep Characteristics of the Participants**

| Characteristic | Mean | SD | Range or % |
|---|---|---|---|
| Age, yr | 39.80 | 16.05 | 20–68 |
| Gender ratio, F/M | 32/28 | - | 53%/47% |
| Aβ1-40, pg/ml | 93.36 | 23.46 | 83.47–154.88 |
| Aβ1-42, pg/ml | 24.13 | 6.00 | 21.96–33.85 |
| Cortisol, ng/ml | 75.24 | 25.32 | 32.18–48.55 |
| Growth hormone, ng/ml | 2.30 | 1.94 | 0.60–9.36 |
| Non-REM stage 1, min (%) | 36.26 | 24.58 | 9% |
| Non-REM stage 2, min (%) | 200.87 | 41.26 | 51% |
| Slow-wave sleep, min (%) | 77.56 | 40.32 | 20% |
| REM sleep, min (%) | 80.32 | 28.34 | 20% |
| WASO, min | 68.38 | 49.18 | - |
| Total non-REM time, min | 314.68 | 35.96 | 80% |
| TST, min | 395.00 | 48.80 | - |
| Sleep efficiency, % | 85 | 10.56 | - |

The percentage of each sleep stage is given relative to TST. Sleep efficiency = TST/(TST + WASO).
Aβ = amyloid-beta; F = female; M = male; REM = rapid eye movement; SD = standard deviation; TST = total sleep time (without WASO); WASO = wake after sleep onset.

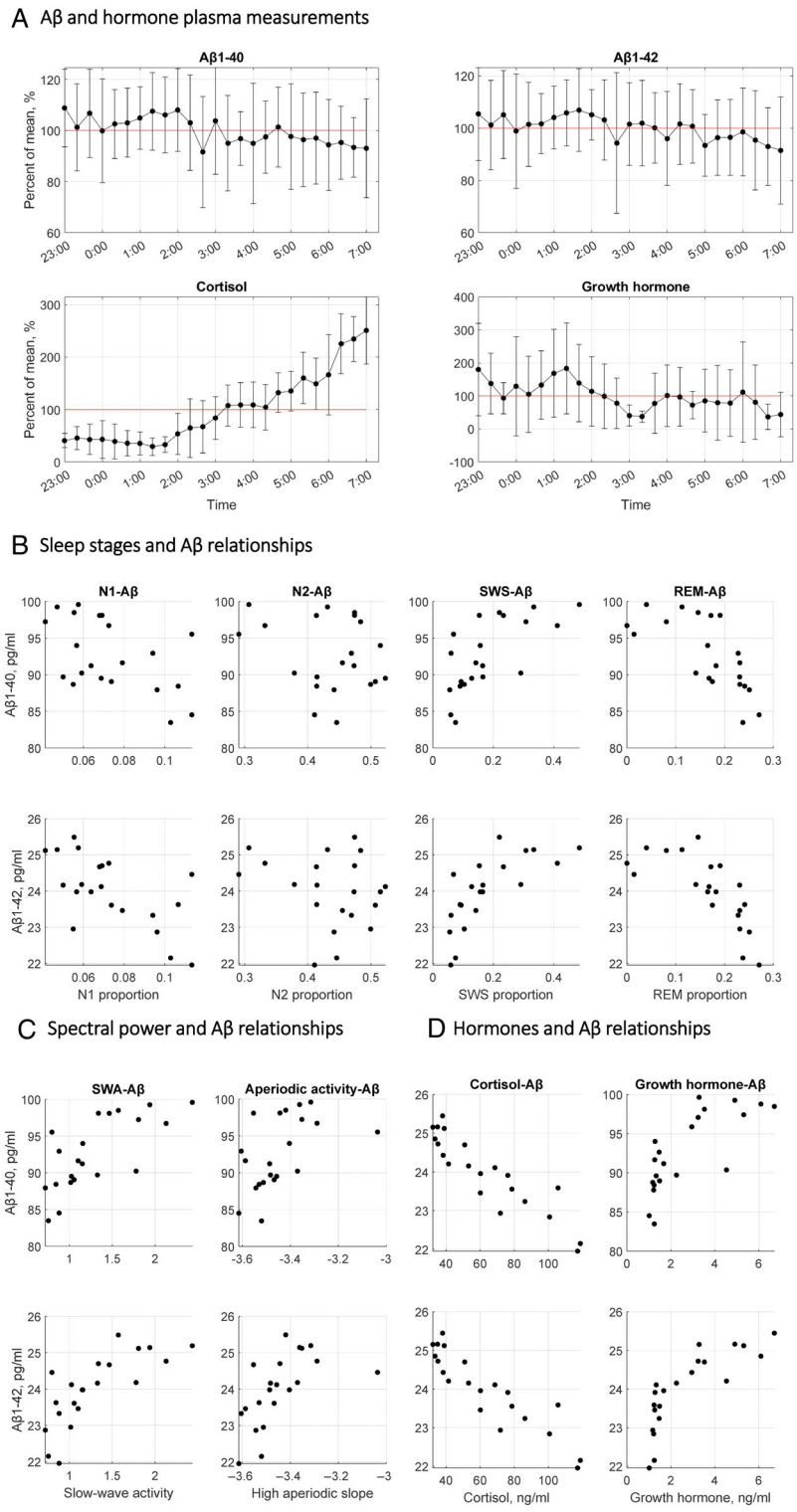


**FIGURE 2: Amyloid-beta (Aβ), hormones, and sleep features. (A) Standardized concentrations of plasma Aβ, cortisol, and growth hormone plasma concentrations calculated as the percent change from the first measurement and averaged over all participants. The measurements were taken every 20 minutes from 23:00 until 7:00. Error bars denote standard deviations between the individuals. On average, plasma Aβ levels decreased by 12% across the night. Cortisol levels increased toward morning, whereas growth hormone peaked during the first part of the night and then decreased. (B–D) Visualization of the relationships between the group-level averaged sleep stages (B), spectral power (C), and hormones (D) and plasma levels of Aβ measured 80 minutes thereafter. Both Aβ1-40 and Aβ1-42 correlated positively with growth hormone concentrations, slow-wave sleep (SWS) proportion, frontal slow-wave activity (SWA), and aperiodic high-band slope, but negatively with cortisol concentrations and rapid eye movement (REM) sleep proportion as revealed by the mixed-effects models (see Figs 3 and 4). No statistically significant associations were observed between Aβ and N1 or N2 sleep proportions. [Color figure can be viewed at www.annalsofneurology.org]**

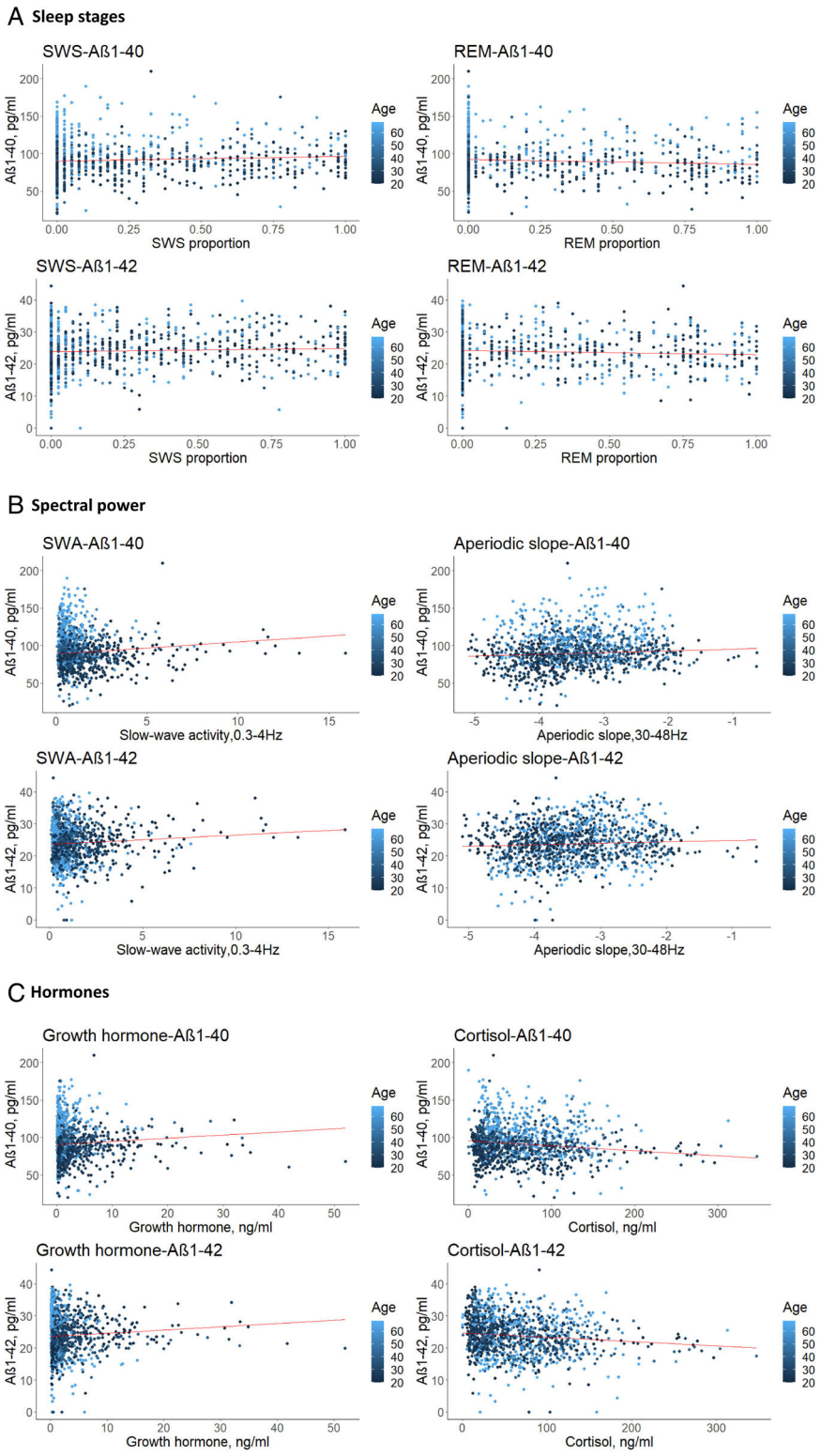


**FIGURE 3: Mixed-effects models. (A) The slow-wave sleep (SWS) and rapid eye movement (REM) sleep proportions, (B) frontal slow-wave activity (SWA; 0.3–4Hz) and the slopes of the frontal high-band aperiodic power (30–48Hz), and (C) cortisol or growth hormone levels were entered into (separate) linear mixed-effects models as fixed factors together with the "age" as an additional fixed factor and the "participant" as a random factor to predict the plasma levels of amyloid-beta 1–40 (Aβ1-40) and Aβ1-42 measured 80 minutes thereafter. Within an 80-minute delay, the Aβ1-40 and Aβ1-42 plasma levels correlated positively with growth hormone concentrations, SWS proportion, frontal SWA, and aperiodic high-band slope, but negatively with cortisol concentrations and REM sleep proportion. Younger age predicted lower plasma levels of Aβ1-40 (as reflected by the higher density of darker dots in the lower part of the graphs), whereas older age predicted higher plasma levels of Aβ1-40 (as reflected by the higher density of lighter dots in the higher part of the graphs). The age had no effect on Aβ1-42. [Color figure can be viewed at www.annalsofneurology.org]**

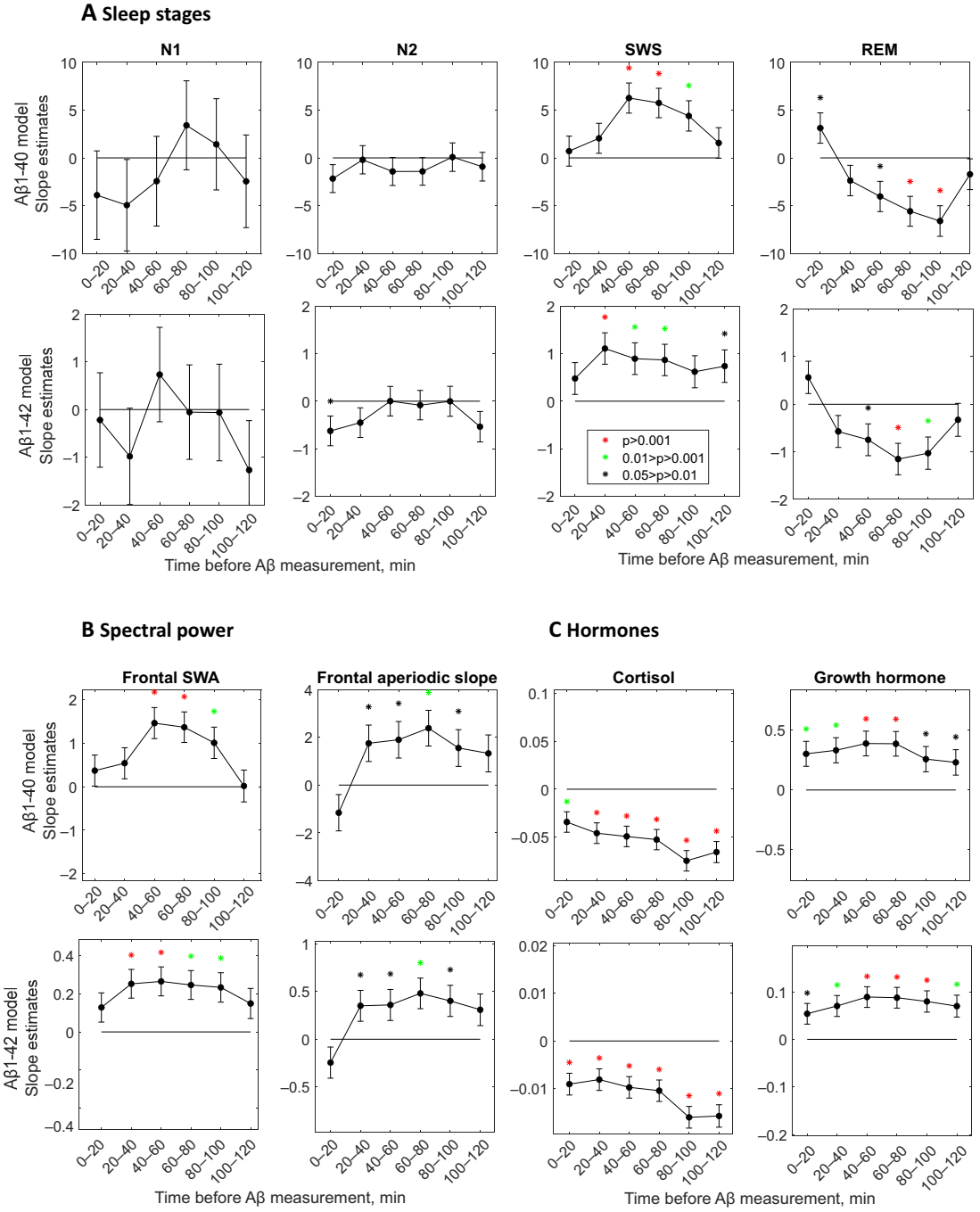


**FIGURE 4: Slope estimates of the amyloid-beta (Aβ) predictors. (A) The proportions of N1, N2, slow-wave sleep (SWS), and rapid eye movement (REM) sleep, (B) frontal spectral power, and (C) cortisol and growth hormone levels were entered as predictors of Aβ1-40 and Aβ1-42 into 6 different mixed-effects models using 20–120-minute lags between the predictors and subsequent Aβ. The slope estimate of the fixed effect of each predictor and its standard error are presented. The asterisks mark the slope estimates for which the null hypothesis (stating that a predictor does not affect Aβ) should be rejected. The models that further passed Benjamini–Hochberg correction for multiple comparisons (6 different models for each predictor) are listed in the main text. The SWS proportion, slow-wave activity (SWA), growth hormone, and high aperiodic slopes predict an increase in the subsequent Aβ levels (significantly positive slopes), and the REM sleep proportion and cortisol predict a decrease (significantly negative slopes) in the subsequent Aβ levels, whereas N1 and N2 have no effect (close to zero slopes) on Aβ. Red asterisks correspond to $p < 0.001$, green to $0.01 > p > 0.001$, and black to $0.05 > p > 0.01$. [Color figure can be viewed at www.annalsofneurology.org]**

### *Spectral Power*

SWA (an EEG marker of SWS) predicted higher Aβ1-40 measured 40–100 minutes afterward and Aβ1-42 measured 20–100 minutes afterward (see Fig 4B). Oscillatory spectral power in the theta, alpha, and beta bands had no effect on Aβ. The high-band (30–48Hz) aperiodic

**TABLE 2. Linear Mixed-Effects Models**

| Dependent Variable | Aβ1-40 Models | | | | | | Aβ1-42 Models | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Predictor | Slope Estimate | SE | *t* | *P* | $R^2$ | AIC | Slope Estimate | SE | *t* | *p* | $R^2$ | AIC |
| Age | 0.647 | 0.128 | 5.055 | $5 \times 10^{-7}$ | 0.610 | 9,954 | −0.019[a] | 0.041[a] | −0.447[a] | 0.655[a] | 0.726[a] | 6,231[a] |
| N1 | −1.767[a] | 4.430[a] | −0.399[a] | 0.690[a] | 0.610[a] | 9,956[a] | −1.154[a] | 0.946[a] | −1.219[a] | 0.223[a] | 0.726[a] | 6,232[a] |
| N2 | −0.015[a] | 1.391[a] | −0.011[a] | 0.991[a] | 0.610[a] | 9,956[a] | 0.230[a] | 0.296[a] | 0.779[a] | 0.436[a] | 0.726[a] | 6,232[a] |
| SWS | 6.566 | 1.529 | 4.293 | $2 \times 10^{-5}$ | 0.616 | 9,937 | 1.183 | 0.327 | 3.623 | $3 \times 10^{-4}$ | 0.729 | 6,220 |
| REM | −6.465 | 1.475 | −4.384 | $10^{-5}$ | 0.616 | 9,936 | −1.471 | 0.313 | −4.698 | $3 \times 10^{-6}$ | 0.731 | 6,210 |
| SWA | 1.541 | 0.345 | 4.471 | $9 \times 10^{-6}$ | 0.617 | 9,935 | 0.310 | 0.074 | 4.177 | $3 \times 10^{-5}$ | 0.730 | 6,215 |
| Aperiodic slope | 2.470 | 0.730 | 3.385 | 0.001 | 0.614 | 9,944 | 0.551 | 0.157 | 3.515 | $5 \times 10^{-4}$ | 0.728 | 6,221 |
| Cortisol | −0.067 | 0.010 | −6.960 | $6 \times 10^{-12}$ | 0.629 | 9,488[b] | −0.014 | 0.002 | −6.707 | $3 \times 10^{-11}$ | 0.742 | 5,915[b] |
| Growth hormone | 0.426 | 0.102 | 4.162 | $3 \times 10^{-5}$ | 0.614 | 9,349[b] | 0.100 | 0.022 | 4.612 | $4 \times 10^{-6}$ | 0.734 | 5,845[b] |

Each row represents the main effect of a fixed factor from an independent mixed-effects model. There were ∼21 observations per subject. Time lag between the predictors and Aβ = −80 minutes. Number of subjects = 60. Number of observations for sleep feature models ∼1,208, for cortisol models ∼1,154, for growth hormone models ∼1,135.

AIC = Akaike information criterion; Aβ = amyloid-beta; REM = rapid eye movements sleep; SE = standard error; SWA = slow-wave activity; SWS = slow-wave sleep.

[a]Nonsignificant *p* values or *p* values that did not pass Benjamini–Hochberg correction for multiple comparisons.

[b]AICs of the sleep feature and hormone models cannot be compared directly due to the unequal number of observations.

slopes (an EEG marker of REM sleep) predicted higher Aβ1-40 measured 20–80 minutes later and Aβ1-42 measured 20–100 minutes afterward (see Fig 4B). The low-band (0.3–35Hz) aperiodic slopes had no effect on Aβ.

### *Hormones*

Cortisol correlated negatively whereas GH correlated positively with Aβ1-40 and Aβ1-42 measured 0–120 minutes thereafter (see Fig 4C). Figures S1 and S2 in the Supplementary Material further show the relationships between hormone levels and sleep proportions.

### *Age*

The mixed-effects models showed that participants' age predicted higher plasma levels of Aβ1-40 but not Aβ1-42 (see Table 2, Fig 3). Further in-depth analysis revealed that after the correction for multiple comparisons (6 tests), the presleep (measured at 23:00) and mean Aβ1-40 levels positively correlated with the participants' age. Postsleep (measured at 7:00) Aβ1-40 levels did not correlate with the participants' age (Fig S3, Supplementary Material). In addition, Figures S3 and S4 further show averaged plasma Aβ and hormone concentrations in young and old participants separately, and Figure S5 shows the relationship between the participants' age and SWS and REM proportions. Supplementary Material S6 reports mixed-effect models separately in younger and older participants (Table S2).

## Discussion

The present study investigated associations between nocturnal neural and endocrine activity and plasma Aβ fluctuations using a large sample of healthy individuals aged 20–68 years. The results show that the Aβ1-40 and Aβ1-42 plasma levels correlate positively with GH concentrations, SWS proportion, SWA, and high-band aperiodic activity, but negatively with cortisol concentrations and REM sleep proportion measured 40–100 minutes before. Older participants show higher plasma levels of Aβ1-40, but not Aβ1-42, compared to the younger ones.

### *Slow-Wave Sleep*

We found that a single night of normal sleep is accompanied by a 12% decrease in Aβ1-40 and Aβ1-42 plasma levels, in line with other reports on a ∼10% reduction in plasma Aβ.[18-20] Moreover, plasma levels of Aβ1-40 and Aβ1-42 could be predicted by preceding SWA (assessed

by EEG power) and the SWS proportion (assessed by visual sleep scoring). This is in line with previous observations that total sleep disruption, selective disruption of SWS, or sleep fragmentation (eg, repetitive sleep interruptions such as in physicians on-call) reduces or abolishes the overnight Aβ clearance.[2,3,20] Interestingly, several nights of partial sleep deprivation (4 hours of sleep per night), where REM and total sleep were reduced, but SWS was not, did not change plasma or CSF Aβ levels,[21] indicating that the effect is specific for SWS.

The abovementioned studies contrast with the PET study in healthy adults in late midlife, reporting that SWA is not related to early Aβ accumulation in the medial prefrontal cortex.[22] A possible explanation for the discrepancy is a difference in the sensitivity of the approaches used. Thus, we used a within-subject analysis design, where we analyzed the participants' data within their own time series, whereas Chylinski et al used a correlational approach.[22] Of note, other PET studies found associations between the Aβ burden in the medial prefrontal cortex and the severity of SWA impairment and even suggested that it may directly contribute to hippocampus-dependent cognitive decline in the elderly.[23,24] Moreover, the authors reported that SWA can forecast the longitudinal Aβ cortical deposition.[24]

In summary, we interpret the positive association between SWS and subsequent peripheral Aβ levels as a finding that confirms major literature on SWS's contribution to cerebral Aβ clearance.

### *Aβ Kinetics from Brain to Periphery*

Interestingly, the association between SWS and Aβ plasma levels could be observed for time lags of ~40–100 minutes only. This is in line with the study that used plasma Aβ stable isotope labeling kinetics to show that labeled Aβ rapidly appears in plasma <2 hours after label infusion.[10] Interestingly, the half-life of Aβ in the central nervous system is approximately 9 hours, suggesting that peripheral clearance mechanisms and/or transport rates might be faster than the central ones.[10] Ovod et al.[10] further report faster turnover of plasma Aβ1-42 relative to Aβ1-40. This also is in line with our findings of shorter lags between SWS and Aβ1-42 compared to Aβ1-40 (20–100 minutes vs 40–100 minutes, respectively).

### *Age*

Following a well-known aging-related decrease in SWS (Fig S5, Supplementary Material), one could hypothesize that older adults present reduced brain clearance, which might be expressed as lower plasma Aβ. However, we found similar Aβ1-42 and higher Aβ1-40 in older compared to younger participants (Fig S3, Supplementary Material). This is only partially in line with the study by Huang et al,[19] who found that both Aβ1-40 and Aβ1-42 plasma concentrations are higher in older than in young participants. Nevertheless, in Huang et al,[19] the correlation between age and Aβ1-40 was considerably higher than between age and Aβ1-42 ($r = 0.7$ vs $r = 0.4$). It is also worth mentioning that the sample size in Huang et al[19] was relatively small compared to our study and comprised only young and old but not middle-aged participants. Notably, Aβ1-42 is the principal Aβ peptide in Alzheimer plaques, whereas Aβ1-40 is a predominant (~90%) form of Aβ peptide in the brain, CSF, and plasma. Aβ1-40 is not as pathogenic as Aβ1-42 and may even have protective effects against Aβ plaque formation.

### *Peripheral Clearance*

A possible explanation for the positive association between age and plasma Aβ1-40 relates to the finding that brain-derived Aβ is also cleared by the liver and kidneys (Fig 5B). Following the broadly documented age-related reduction of renal function,[25] we hypothesize that older persons might have less efficient peripheral Aβ clearance, which might be expressed as higher baseline levels of plasma Aβ1-40 (Fig S3, Supplementary Material). Other medical comorbidities, such as vascular disease, may impair clearance or alter plasma AD biomarkers as well.[5]

Peripheral clearance is very important; according to the peripheral sink hypothesis, cerebral and peripheral soluble Aβ are in equilibrium such that peripheral Aβ clearance induces Aβ removal from the brain into blood.[26] This leads us to the hypothesis that if an age-related decrease in this efflux exists and persists, it can contribute to cerebral amyloid accumulation and, subsequently, plaque formation and AD development.

The finding that Aβ brain homeostasis is maintained by the brain–periphery equilibrium taken together with the finding that REM sleep typically follows NREM sleep can explain the negative association between REM sleep and subsequent plasma Aβ levels observed here. Possibly, intensive clearance during SWS leads to an increase of Aβ concentration in the blood, which in turn slows down or even inhibits Aβ efflux from the brain to the periphery during the following sleep stages (see Fig 5A).

This explanation should also hold for the N2 stages that occur after SWS. However, given that some of the N2 epochs precede SWS whereas some of them follow SWS, the effect (if any) should sum to zero, as was revealed by our results (ie, no association between the amount of N2 and Aβ; see Fig 5A). No links between the amount of N1 and Aβ could be explained by too few N1 epochs, which accounted for only 9% of total sleep time.

### REM Sleep

Given that REM sleep is a stage with wakelike neural activity, one would expect it to be accompanied by high production of metabolic waste. This view cannot explain the negative association between REM sleep and Aβ observed here. High waste production, however, does not necessarily imply a concurrent high clearance rate. If this is the case, then our findings could be explained by low/ceased central clearance (in addition to the possible effects of REM sleep timing and peripheral clearance discussed above). This view is in line with the functional magnetic resonance imaging study in naturally sleeping pigeons that showed a decrease in ventricular CSF flow in REM compared to non-REM sleep.[27] The authors further interpret this as less efficient waste clearance, suggesting that brain activation during REM sleep comes at the expense of clearance. In healthy older humans, lower theta power during REM sleep was linked to higher neocortical amyloid deposition.[28] This finding may reflect both higher waste production and lower central clearance. However, at this stage, its link to our observation is unclear.

Another possibility is that the negative association between REM sleep and Aβ reflects decreased waste production. At first glance, this is at odds with the very definition of REM sleep as a neurally active state (which as such should be accompanied by increased waste production). This discrepancy, however, might be explained by the research line studying aperiodic neural activity, that is, nonoscillatory 1/f activity with no defining temporal scale.[16,17] Thus, in both intracranial and scalp human EEG studies, REM and SWS show steeper slopes (faster spectral decay) of the aperiodic power component in the 30–50Hz frequency band as compared to wakefulness.[17] These findings were replicated here as well (Fig S6, Supplementary Material). Given that aperiodic slopes presumably reflect the ratio between excitatory and inhibitory neural currents,[16,17] steeper aperiodic slopes observed during REM sleep can reflect the shift of this ratio in favor of inhibition.

This is in line with a calcium imaging study in rodents that revealed an overall decrease in cortical firing during REM and SWS.[29] Specifically, reduced firing rates during REM sleep were accompanied by a selectively increased activity of inhibitory parvalbumin interneurons. These interneurons mediate reduced cortical activity and increased inhibition of pyramidal neurons,[29] the major source of the EEG signal. Based on these results, Niethard et al suggest that at the cellular level, REM sleep is a period of prevalent suppression of neural activity where a subset of neurons with high activity during the wake period is activated.[29]

Such a view offers a likely mechanistic explanation for our observation. Namely, we found that steeper slopes of high-band aperiodic activity (a marker of REM sleep) were associated with lower subsequent levels of plasma Aβ and thus strengthened the finding of the negative association between REM sleep amount and Aβ. If REM sleep coincides with cortical inhibition and thus decreased synaptic activity, it should be accompanied by decreased cerebral waste production presumably followed by a lower peripheral Aβ level. This view is in line with the study in a mouse model of AD showing that optogenetically inducing gamma (40Hz, which is expected to be accompanied by flatter slopes), but not other frequencies, reduces Aβ levels in the hippocampus.[30]

Here, we speculate that during REM sleep, both central waste production and clearance decrease/cease (see Fig 5B). This, however, should be further confirmed by studies that, for example, pharmacologically manipulate the amount of REM sleep.

### Holistic Effect of Sleep on Aβ

The assumption that both REM and SWS are associated with cortical inhibition raises the question of why these sleep stages show divergent associations with the subsequent plasma Aβ levels. One possible explanation relates to the timing of REM sleep discussed above (see Fig 5A). An alternative explanation considers the relative dominance of the oscillatory versus nonoscillatory neural activity during SWS and REM, respectively.[31] For example, it has been suggested that during SWS, prominent slow oscillatory neuronal activity leads to oscillations in blood volume, drawing CSF into and out of the brain.[32] Our findings are in line with this theory as here, Aβ fluctuations were associated specifically with SWA (0.3–4Hz) and not with the oscillatory activity in other frequency bands or broadband (0.3–35Hz) aperiodic activity.

Possibly, all stages of non-REM sleep are involved in brain clearance (with different efficiency), whereas during REM sleep, clearance is stopped altogether or reduced massively, potentially even compared to wakefulness. If this scenario is true, no brain clearance during REM sleep (the hypothetical ground truth) can be expressed as a negative correlation between the amounts of REM sleep and plasma Aβ (the current observation). REM-related ceasing of clearance could stem from the relative dominance of aperiodic compared to oscillatory neural activity during this stage,[31] unfavorable brain–periphery Aβ equilibrium, or another, unknown mechanism.

In summary, a positive association between the SWS and subsequent Aβ plasma levels can be explained by efficient cerebral clearance possibly via the coupling of slow-wave oscillations with blood and CSF flow. A negative

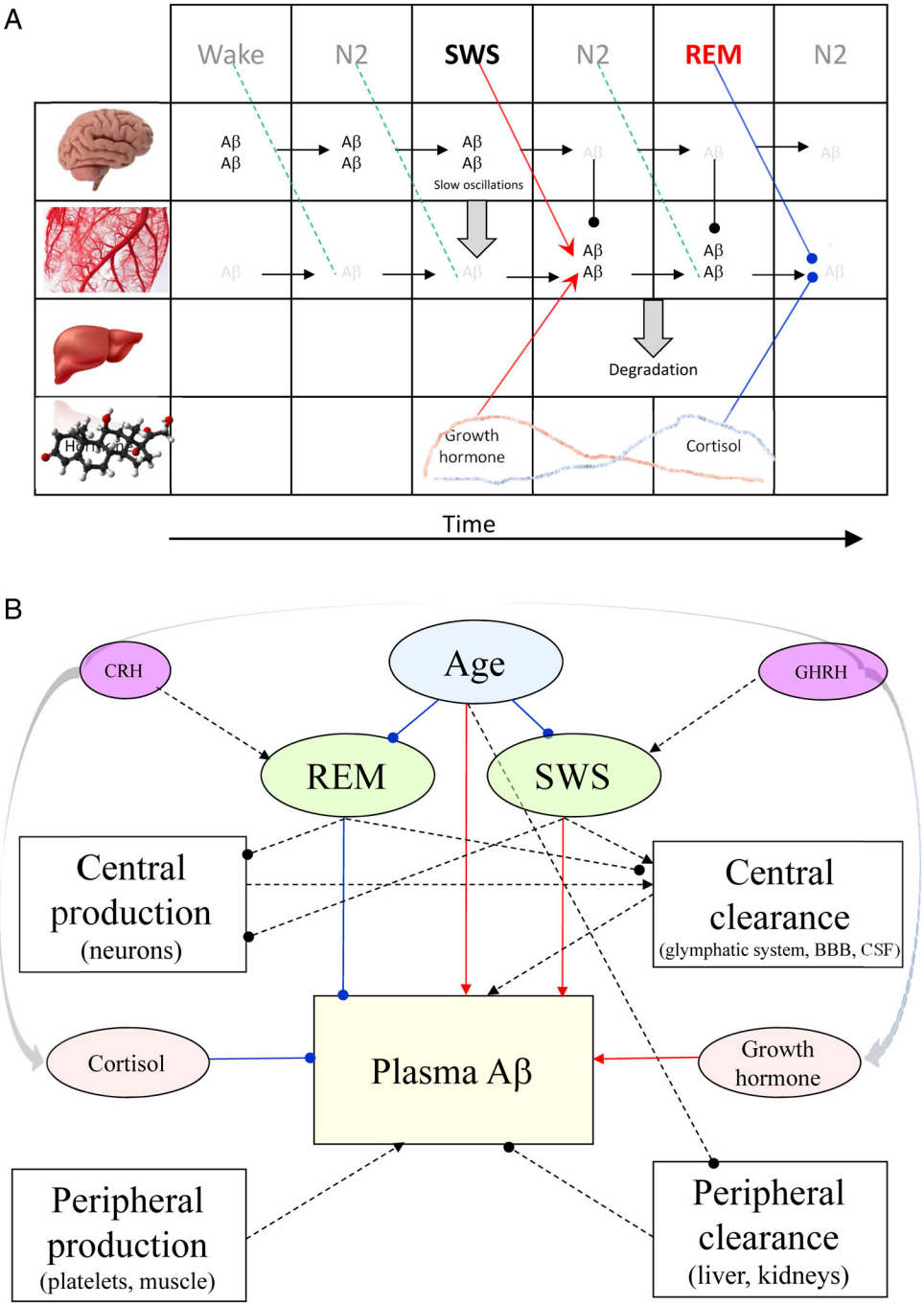


**FIGURE 5: Summary and limitations. (A) Temporal relationships between sleep stages/hormones and amyloid-beta (Aβ) turnover from the brain to periphery. (B) The effects of different factors on Aβ. Slow-wave sleep (SWS) is associated with higher subsequent plasma Aβ levels, possibly through increased central clearance and decreased central production of cerebral Aβ. Rapid eye movement (REM) sleep is associated with lower subsequent plasma Aβ levels through an unknown mechanism, possibly some combination between decreased central Aβ production and clearance. Healthy aging is associated with decreased SWS and REM sleep and higher plasma levels of Aβ1-40 (but not Aβ1-42) possibly through inefficient peripheral clearance. It should be kept in mind that Aβ is also synthesized and cleared in the periphery. Aβ negatively correlates with cortisol and positively with growth hormone. Growth hormone-releasing hormone (GHRH) increases SWS and growth hormone. Corticotrophin-releasing hormone (CRH) elevates cortisol and REM sleep. Red solid arrows indicate positive associations observed in the current study; blue solid lines indicate negative associations observed in the current study; green dashed lines indicate nonsignificant relationships; black dashed lines/arrows indicate associations reported/suggested in the literature. BBB = blood–brain barrier; CSF = cerebrospinal fluid. [Color figure can be viewed at www.annalsofneurology.org]**

association between REM sleep and subsequent Aβ might reflect a complex combination of several factors, such as decreased waste production due to neural inhibition, decreased central clearance due to a relative shift to the dominance of nonoscillatory activity or another, unknown mechanism, and nonefficient Aβ brain–periphery efflux

due to an increased peripheral sink condition observed as an aftereffect of SWS (see Fig 5).

### Hormone Effect on Aβ

In view of the considerable endocrine activity accompanying sleep, we also explored associations between nocturnal fluctuations of hormones and Aβ. We found that Aβ positively correlated with GH and negatively correlated with cortisol plasma levels measured 0–120 minutes before. The broad range of significant time lags can be explained by the finding that cortisol readily crosses the blood–brain barrier and binds to its receptors in the brain.[33] A small but significant amount of GH also passes the blood–brain barrier and acts on the neuronal GH receptors with a modulatory effect on memory, working capacity, and cognition.[34]

In animal models and cell cultures, glucocorticoids have been shown to mediate enhanced production of cerebral Aβ, reduce degradation, facilitate plaque formation, enhance Aβ-mediated neuronal toxicity, and increase tau accumulation (Fig S8, Supplementary Material).[33] Specifically, glucocorticoid treatment in vitro and in monkeys reduced the activity of the insulin-degrading enzyme, a candidate protease in the clearance of Aβ in the brain, which is decreased in AD patients.[33] Cortisol likely increases the transcription of the amyloid precursor protein (*APP*) gene via the glucocorticoid-response binding element, leading to the increased Aβ production observed in vitro and in vivo. An *APP* protein increase leads to increased processing of *APP* to C99, which is consequently cleaved by the γ-secretase to release Aβ.[33]

These findings are highly relevant for clinical research, because it is established that early sporadic AD patients show elevated cortisol levels, which along with other environmental and genetic risk factors contribute to increased Aβ production and exacerbate existing AD pathologies.[33] Besides AD, elevated cortisol levels can be caused by administration of exogenous glucocorticoids (eg, for inflammation treatment) and a stressful lifestyle (Fig S8, Supplementary Material), factors that are very common in modern society.

Interestingly, whereas one night of sleep deprivation increases the overnight concentration of Aβ in CSF, it does not significantly affect cortisol in plasma or CSF, suggesting that sleep deprivation-related changes in CSF Aβ are not mediated by stress or circadian disruption as measured by cortisol.[35]

Alternatively, the observed associations can be explained by the timing of the hormone's release and not by their involvement in Aβ clearance. For example, the effect could be explained by the sleep-regulating role of the corresponding releasing hormones (see Fig 5B). Thus, it is well documented that the GH-releasing hormone synchronizes both SWS and GH release. The corticotropin-releasing hormone regulates both REM sleep as well as the release of adrenocorticotropin by the pituitary gland and cortisol by the adrenal gland.[9] Undoubtedly, further studies are needed to clarify the mechanisms of the associations between hormone and plasma Aβ fluctuations. At this stage, our findings suggest that one's hormone profile may serve as a marker of one's plasma Aβ status.

### Limitations

First, even though plasma is a more accessible and less invasive source than CSF for estimating Aβ concentrations in circulation, peripheral Aβ is not a direct surrogate for central Aβ. Only 30%–50% of plasma Aβ originates from the central nervous system through Aβ transport across the blood–brain barrier and CSF,[24] whereas the rest is synthesized in the periphery by platelets, muscle, blood vessels, and other cells.[36] Nevertheless, it has been shown that plasma Aβ kinetics reflect the amyloidosis pathology of the central nervous system similarly to CSF.[10]

Besides central and peripheral production and central clearance, which change as a function of a wake–sleep cycle, plasma Aβ levels are also influenced by peripheral clearance (see Fig 5B). In addition, the hydrophobic nature of Aβ makes the peptide bind to numerous binding plasma proteins (e.g., APOE, albumin, Aβ-specific IgG), which could result in "epitope masking" and other analytical interferences.[36] Of note, our study was not designed to differentiate between different Aβ sources.

Second, the APOE and amyloid plaque status of the participants was impossible to define due to the retrospective nature of this study and because our plasma Aβ assay is not able to reflect brain Aβ pathology and thus does not differentiate the amyloid status of the participants. Our findings need to be confirmed using other, more sensitive plasma Aβ assays.

Third, the presence/absence of sleep apnea, which has an impact on Aβ accumulation and may also modify the levels of various hormones, including GH and cortisol, was not confirmed polysomnographically.

Fourth, we used univariable models with a single sleep feature/hormone and a fixed time lag (but corrected for age and participant-specific random intercepts) rather than multivariable mixed-effects models with multiple sleep features/hormones at several time lags. Our models serve as a descriptive tool and to gain first insights into the data. However, separate univariable regressions are not directly comparable with each other, as they are not based on the exact same set of data points. Future studies using advanced statistical analyses and multivariable regressions based on our initial descriptive visualizations might be

able to overcome this limitation and thereby allow for comparison across time.

## Conclusions

Using simultaneous polysomnography and all-night blood sampling in healthy volunteers, this study demonstrated that specific sleep and hormonal features can predict nocturnal Aβ plasma fluctuations. The associations between sleep, hormones, and plasma Aβ levels suggest that SWS and REM sleep have different homeostatic functions due to divergent neural and endocrine activity. Of note, here, we assume that Aβ plasma fluctuations possibly represent changes in central Aβ production or clearance. However, future studies should confirm this link and provide a deeper understanding of the mechanism involved in brain clearance and the pathogenesis of AD and other neurodegenerative conditions, potentially leading to the development of innovative and evidence-based prevention and intervention techniques.

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## Author Contributions

M.D. and M.M.V. contributed to the conception and design of the study. A.S., M.P., O.S., E.L., S.T., M.S., I.K., M.U., M.M.V., M.D., and Y.R. contributed to the acquisition or analysis of data. Y.R., N.K., L.B. and M.D. contributed to drafting the text or preparing the figures.

## Potential Conflicts of Interest

Nothing to report.

### *Data Availability*

Deidentified individual-level data are shared in the Supplementary Material. The participants' privacy has been protected in accordance with applicable laws and regulations. Any additional information required to reanalyze the data reported in this paper is available from the corresponding author upon request.

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