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Absence of Relationship Between Self-Reported Sleep Measures and Amyloid Load in Elderly Subjects

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Objective: To determine the relationships between self-reported sleep profile and cortical amyloid load in elderly subjects without dementia.

Methods: This cross-sectional study included 143 community-dwelling participants aged ≥70 years (median: 73 years [70–85]; 87 females) with spontaneous memory complaints but dementia-free. Sociodemographic characteristics, health status, neuropsychological tests, sleep, and 18F-florbetapir (amyloid) PET data were collected. The clinical sleep interview evaluated nighttime sleep duration, but also daytime sleep duration, presence of naps, and restless leg syndrome (RLS) at time of study. Validated questionnaires assessed daytime sleepiness, insomnia, and risk of sleep apnea. The cortical standardized uptake value ratio (SUVr) was computed across six cortical regions. The relationship between sleep parameters and SUVr (cut-off ratio> 1.17 and tertiles) was analyzed using logistic regression models.

Results: Amyloid-PET was positive in 40.6% of participants. Almost 40% were at risk for apnea, 13.5% had RLS, 35.5% insomnia symptoms, 22.1% daytime sleepiness, and 18.8% took sleep drugs. No significant relationship was found between positive amyloid PET and nighttime sleep duration (as a continuous variable, or categorized into <6; 6–7; ≥7 h per night). Logistic regression models did not show any association between SUVr and daytime sleep duration, 24-h sleep duration, naps, RLS, daytime sleepiness, insomnia symptoms, and sleep apnea risk (before and after adjustment for APOEε4 and depressive symptoms).

Conclusion: Our study did not confirm the association between amyloid-PET burden, poor sleep quantity/quality in elderly population, suggesting that the interplay between sleep, and amyloid is more complex than described.

Keywords: amyloid, amyloidosis, sleep, elderly, PET—positron emission tomography, NAPS, dementia, cognition
**INTRODUCTION**

Experimental and human studies suggest that sleep-wake alterations contribute to brain amyloid-beta (A\(\beta\)) dysregulation and showed that A\(\beta\) load in interstitial fluid proportionally increases with time awake (1). Short sleep duration, sleep fragmentation, and reduced slow-wave sleep may thus affect A\(\beta\) brain deposition, one of the key pathophysiological mechanisms of Alzheimer’s disease (AD) (1–3). Sleep-wake disturbances (i.e., sleep fragmentation, frequent and long awakenings, and excessive daytime sleepiness), and sleep disorders (i.e., insomnia and sleep apnea syndrome) are frequently found in patients with AD at early and also late stages of the disease (4–10).

One reference study on 62 older adults found that people with self-reported short sleep had higher A\(\beta\) burden than long sleep/night (5). Other studies on cognitively healthy individuals at risk of developing AD reported associations between amyloid load and other sleep parameters (i.e., sleep quality, sleep latency, sleep efficiency, wake after sleep onset, excessive daytime sleepiness, and napping) (5–8, 11–14). Similarly, in a 1-year prospective study, we found that the risk of cognitive decline is higher in frail elderly subjects with excessive daytime sleepiness and longer nighttime in bed (15). However, all these results need to be replicated due to the frequent sleep misperception in older people, and the differences in sleep assessment methodology, populations and sample size, treatment intake, confounding factors and study design (5–14). Moreover, the relationships between sleep profile, cognitive status, and amyloid load measured by positron imaging tomography (PET) remain unknown in elderly population with memory complaints.

The main aim of this study was to determine the relationship between self-reported nighttime sleep duration and cortical amyloid load, measured by PET with the \(^{18}\text{F-florbetapir}\) amyloid ligand (\(^{18}\text{F-florbetapir PET}\)), in elderly subjects with memory complaints. We also assessed using a detailed, and comprehensive clinical interview the relationships between other sleep characteristics and brain amyloid load.

**METHODS**

**Participants**

The MAPT-AV45 sleep ancillary study (www.clinicaltrials.gov NCT00672685) included 143 community-dwelling participants aged ≥70 years (median age: 73 years-old; range [70 to 85]; 87 females) with spontaneous memory complaints, but free of dementia (16–19). Sociodemographic characteristics, health status, and neuropsychological test results were available for all patients who also underwent sleep assessment and \(^{18}\text{F-florbetapir-PET}\) brain imaging.

The MAPT-AV45 study and the sleep ancillary study were approved by the Toulouse ethics committee (Comité de Protection des Personnes- Sud-Ouest et Outre-Mer I et II). The methods were carried out in accordance with the approved guidelines. Each participant signed legal consent forms. Informed consent was obtained from all subjects.

**\(^{18}\text{F-florbetapir-PET Brain Imaging}\)**

Brain imaging was performed using five different hybrid PET-CT scanners. Image acquisition started 50 min after injection of 4 MBq/kg of \(^{18}\text{F-florbetapir}\). PET sinograms were reconstructed with an iterative algorithm, with corrections for randomness, scatter, photon attenuation, and decay, producing images with an isotropic voxel of 2 × 2 × 2 mm\(^3\), and a spatial resolution of approximately 5-mm full width at half maximum at the field of view center. \(^{18}\text{F-florbetapir}\) images were coregistered to a template provided by Avid Radiopharmaceuticals (Philadelphia, PA) (20) using SPM for normalization to the Montreal Neurological Institute (MNI) space. Tracer retention in the cerebral cortex was quantified using the standardized uptake value ratio (SUVR) relative to the whole cerebellum. The SUV of the cortical retention index were computed in six cortical regions of interest (i.e., frontal, parietal, temporal, precuneus, anterior, and posterior cingulate cortices). Cortical SUV ratios were obtained by normalizing the cortical SUV with the mean uptake relative to the whole cerebellum that defines the amyloid load. According to a previously established cut-off, the amyloid PET scan was considered positive when the global cortical SUVr value was higher than 1.17\(^2\). As threshold may depend of the targeted population, we further grouped participants according to the tertiles of their global cortical SUVr, the highest tertile group compared with the other two.

**Self-Reported Sleep Parameters**

All participants had a face-to-face interview to assess last month the duration of nighttime sleep (in hour and also categorized as <6; 6–7; ≥7 h per night according to a reference study (10)), daytime sleep (in minutes), presence and duration of naps (recorded as: no naps, naps <30 min, naps ≥30 min per day), total sleep time (daytime and nighttime sleep), and sleep efficiency (i.e., total sleep time divided by time spent in bed reported by subjects, expressed as a percentage). The presence of restless legs syndrome [RLS; on the basis of the five minimal diagnostic criteria (21)], and of rapid eye movement sleep behavioral disorder (RBD; violent nocturnal agitation accompanied by shouting often at the end of the night and associated with dreamlike memories) were also investigated by a semi-structured clinical interview. Participants completed, with the help of medical staff when required, the following sleep questionnaires: the Epworth Sleepiness Scale (ESS) to evaluate excessive daytime sleepiness (EDS; cut-off score ≥11) (22); the 7-item self-report Insomnia Severity Index (ISI) to evaluate insomnia symptoms [score <8: low insomnia; score (3–9): sub-threshold insomnia; and score ≥15: moderate-severe insomnia] (23); and the Berlin questionnaire to assess the risk of sleep apnea (24).

**Other Biological and Clinical Characteristics**

A standardized interview with questions on sociodemographic characteristics, health status and use of medications was performed at baseline and each year during the 5-year follow-up. Drugs were coded according to the World Health
Organization's Anatomical Therapeutic Chemical Classification. Hypnotics were classified as benzodiazepine, benzodiazepine-like compounds (zolpidem, zopiclone), sedative antidepressants, and miscellaneous medications (including barbiturates, antihistamines, and other pharmacological categories, such as neuroleptics). Drugs administered during the year of the 18F-florbetapir-PET were taken into account for the analysis. Height and weight were measured and used to calculate the body mass index. Cerebro-cardiovascular and metabolic diseases were defined as self-report history of stroke and cardiovascular events, diabetes, or hypertension (defined by measured systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥95 mmHg, or current antihypertensive treatment). Depressive symptoms were evaluated using the Beck Depression Inventory II (BDI-II) scale (25) (no depressive symptoms: 0–11 score; moderate to severe depressive symptoms, when score ≥12).

Based on the Clinical Dementia Rating (CDR) scale and the validated Petersen criteria (26), participants with a CDR score = 0.5 were classified as having Mild Cognitive Impairment (MCI). Participants with dementia at baseline (CDR score ≥ 1) were not included. The Mini Mental State Examination (MMSE) test was performed in all participants.

APOE was genotyped using a classical PCR digestion method (primers: 5’-GGGACGGCTGTCCAAGGAGCTG-3’ and 5’-TCGCGGGCCGGCCTGGTA CACT-3’; restriction enzyme: HhaI).

Statistical Analysis
The sample was described using percentages for categorical variables, and medians [range] for quantitative variables, because the Shapiro-Wilk test indicated the data distribution was mostly skewed. The negative and positive amyloid PET groups were compared using univariate logistic regression models. Sociodemographic and clinical variables associated with brain amyloid load at p < 0.10 in the univariate analysis were included in logistic models to estimate the adjusted odds-ratios (OR) and their 95% confidence intervals (CI) for sleep parameters. For all analyses, the significance level was set at p < 0.01. Analyses were performed using the SAS statistical software (version 9.4; SAS Inc, Cary, North Carolina).

RESULTS

Clinical Characteristics, Sleep Profile, and Amyloid PET
For the whole population (n = 143), the education level was intermediate in 45.5% and high in 33.6% of participants, and the median MMSE score was 29 [20–30]. Moreover, 25% of participants had MCI, and 28.5% were APOEε4 allele carriers. Regarding the vascular and metabolic profile, 41.3% were overweight, 17.5% obese, and 65.7% reported history of cardiovascular and/or metabolic diseases. Moderate to severe depressive symptoms were reported by 30.0% of participants.

The median sleep duration was 7 h [3.25–9.5] for nighttime and 20 min [0–120] for daytime. About 56% of participants were nappers, and 29.5% had naps longer than 30 min. The median sleep efficiency was 87.5% [44.4–100]. Almost 40% of participants were at risk of sleep apnea, 13.5% had RLS (mild in 52.6% of them), 22.1% had EDS, 35.5% presented insomnia symptoms (moderate to severe for 8.5% of them), 8.2% had clinically-defined RBD, and 18.8% took often hypnotics.

Amyloid PET was positive (global cortical SUVr > 1.17) in 40.6% of participants (Table 1). Participants with positive amyloid PET were more frequently APOE4 carriers (p = 0.003) and had more often depressive symptoms (BDI-II score ≥12) (p = 0.03) (Table 1).

| Variable          | Global cortical SUVr | p   |
|-------------------|----------------------|-----|
|                   | ≤1.17 N = 85         | >1.17 N = 58 |
| N                 | %                    | %     |
| Sex               |                      |       |
| Men               | 55                   | 64.71 | 52.17 | 0.25 |
| Women             | 30                   | 35.29 | 44.83 |       |
| Age, in years      |                      |       |
| 74                         | 73                       |       |
| [70–85]          | 70–85                |       |
| (a)               |                      |       |
| Educational level  |                      |       |
| Low               | 22                   | 25.88 | 8     | 13.79 | 0.20 |
| Intermediate      | 35                   | 41.18 | 30    | 51.72 |       |
| High              | 28                   | 32.94 | 20    | 34.48 |       |
| MMSE score(a)     |                      |       |
| 29                         | 29                       |       |
| [24–30]          | 24–30                |       |
| MCI               |                      |       |
| No                | 65                   | 76.47 | 42    | 72.41 | 0.58 |
| Yes               | 20                   | 23.53 | 16    | 27.59 |       |
| APOE4             |                      |       |
| Not carrier       | 62                   | 81.58 | 31    | 57.41 | 0.003 |
| Carrier           | 14                   | 18.42 | 23    | 42.59 |       |
| BMI, kg/m2        |                      |       |
| <25               | 33                   | 38.82 | 26    | 44.83 | 0.75 |
| [25–30]          | 36                   | 42.35 | 23    | 39.66 |       |
| ≥30               | 16                   | 18.82 | 9     | 15.62 |       |
| BDI-II score      |                      |       |
| <12               | 67                   | 78.82 | 35    | 61.40 | 0.03 |
| ≥12               | 18                   | 21.18 | 22    | 38.60 |       |
| Cardiovascular events |                |       |
| No                | 29                   | 34.12 | 20    | 34.48 | 0.96 |
| Yes               | 56                   | 65.88 | 38    | 65.52 |       |
| Hypnotic intake   |                      |       |
| No                | 70                   | 82.35 | 46    | 79.31 | 0.65 |
| Yes               | 15                   | 17.65 | 12    | 20.69 |       |

18F-florbetapir-PET was performed within a median interval of 134 [10–360] days from the sleep evaluation. No significant
| Variable                                      | ≤1.17 N = 85 | >1.17 N = 56 | Model 0 | Model 1 | ≤1.22 N = 94 | >1.22 N = 49 | Model 0 | Model 1 |
|----------------------------------------------|--------------|--------------|---------|---------|--------------|--------------|---------|---------|
| Nighttime sleep duration, hours             |              |              |         |         |              |              |         |         |
| <6                                           | 13           | 11           | 16.37   | 1.03    | 1            | 0.89         | 17      | 14.29   | 1       | 0.38    | 1       | 0.39    |
| 6–7                                          | 44           | 32           | 55.17   | 0.86    | 1.01         |              | 46      | 61.22   | 1       | 1.58    | 2.15    |
| ≥7                                           | 28           | 15           | 25.86   | 0.63    | 0.82         |              | 31      | 24.49   | 0.94    | 1.53    | 0.425   | 0.56    |
| Nighttime sleep duration, hours ≥7 [4–10]   | 7            | 4            | 87.67   | 0.33    | 0.89         | 0.47         | 7 [4–10]| 7 [4.5–9]| 0.92    | 0.60    | 0.98    | 0.90    |
| Daytime sleep duration, minutes             |              |              |         |         |              |              |         |         |
| Daytime sleep duration, min (1)             |              |              |         |         |              |              |         |         |
| 0–120                                       | 15           | 20           | 43.23   | 1.00    | 0.97         | 1.01         | 15      | 20      | 1.00    | 0.97    | 1.01    | 0.55    |
| Naps                                         |              |              |         |         |              |              |         |         |
| No                                          | 35           | 23           | 45.46   | 1.00    | 0.97         | 1.01         | 37      | 21      | 1.00    | 0.97    | 1.01    | 0.55    |
| Yes <30 min                                   | 21           | 12           | 23.08   | 0.87    | 0.81         |              | 23      | 10      | 1.03    | 1.03    | 1.03    | 1.03    |
| Yes ≥30 min                                   | 21           | 17           | 32.69   | 1.23    | 0.54         | 0.573        | 24      | 14      | 1.03    | 1.03    | 1.03    | 1.03    |
| Sleep efficiency (%)                         |              |              |         |         |              |              |         |         |
| <8.35                                        | 28           | 19           | 32.76   | 0.90    | 0.85         |              | 29      | 18      | 0.77    | 1.01    | 0.61    | 0.61    |
| 8.35–93.75                                   | 29           | 18           | 31.03   | 0.91    | 0.86         |              | 32      | 15      | 0.76    | 0.76    | 0.67    | 0.67    |
| ≥93.75                                       | 28           | 21           | 36.21   | 1.11    | 0.56         | 0.59         | 33      | 16      | 0.78    | 1.05    | 1.05    | 1.05    |
| Sleep efficiency (%) (2)                     | 87.5 [44.4–100]| 88.9 [50–100]| 1.01    | 0.39    | 1.02         | 0.12         | 87.5 [44.4–100]| 87.5 [62.5–100]| 1.01    | 0.64    | 1.02    | 0.18    |
| ESS score                                    |              |              |         |         |              |              |         |         |
| <11                                          | 66           | 40           | 76.57   | 1.02    | 1            | 0.68         | 71      | 35      | 1.06    | 1       | 0.98    | 1       |
| ≥11                                          | 18           | 12           | 21.43   | 1.10    | 1.22         |              | 21      | 9       | 0.87    | 1.01    | 0.372   | 0.77    |
| ESS score (3)                                | 6 [0–21]     | 6 [1–15]     | 1.01    | 0.86    | 1.01         | 0.89         | 6 [0–21]| 6 [1–14]| 0.89    | 0.82    | 0.89    | 0.84    |
| Insomnia severity scale                      |              |              |         |         |              |              |         |         |
| <8                                           | 55           | 36           | 65.48   | 1.08    | 1            | 0.44         | 60      | 31      | 1.08    | 1       | 0.44    | 1       |
| 8–14                                         | 21           | 17           | 25.00   | 1.08    | 1            |              | 22      | 16      | 1.08    | 1.08    | 1.08    | 1.08    |
| ≥15                                          | 8            | 4            | 9.52    | 0.76    | 0.93         |              | 10      | 4       | 0.89    | 0.89    | 0.89    | 0.89    |
| Insomnia severity scale (3)                  | 5 [0–23]     | 4 [0–23]     | 9.52    | 0.81    | 0.95         | 0.25         | 5 [0–23]| 4 [0–15]| 0.96    | 0.96    | 0.96    | 0.96    |

(Continued)
relationship was found between positive amyloid PET and nighttime sleep duration [taken as a continuous variable and categorized into $<6$; $6-7$; $\geq 7$ h per night as previously reported (3)] before and after adjustment for APOE4 and depressive symptoms (BDI-II score $\geq 12$) (Table 2 and Figure 1). Similarly, no association was found between amyloid PET status and other sleep characteristics: daytime sleep duration, 24-h sleep duration, napping, sleep efficiency, EDS, insomnia symptoms, risk of sleep apnea, RLS, and clinically-defined RBD (Table 2). These results remained unchanged after excluding subjects with MCI ($n = 36$).

Comparison of participants subdivided in two groups according to their global cortical SUVr values in tertiles (highest tertile, SUVr $>1.22$, vs. the other two) showed almost similar results, with no between-group differences (Table 2).

### DISCUSSION

Our study provides an extensive assessment of the sleep-wake profile and brain amyloid load measured with $^{18}$F-florbetapir-PET in a cohort of elderly subjects without dementia. No association was found between the global cortical (using the pathological cut-off of 1.17 and tertiles of the population) and nighttime sleep duration, but also with daytime sleep duration, naps, daytime sleepiness, insomnia, risk of apnea, clinically-defined RBD, and sleep efficiency in unadjusted and adjusted models for APOE4 and depressive symptoms.

A similar key study on 62 community-dwelling older adults found that people with self-reported sleep $\leq 6$ h/night had higher Aβ burden measured by $^{11}$C-Pittsburgh compound B (PIB) PET in cortical and precuneus areas than those with $>7$ h of sleep/night. Amyloid burden was intermediate in subjects with 6–7 h of sleep per night (5). These results remained significant after adjustment for potential confounders (APOE4 carrier status, comorbidities and sleep-related treatments) (5). Despite similar self-reported assessment of sleep duration among both studies, our study did not confirm such association in unadjusted and adjusted models for APOE4 status and depressive symptoms. Conversely, the number of participants (143 in our study vs. 62), amyloid tracer ($^{18}$F-florbetapir vs. $^{11}$C-PiB), tracer uptake quantification (SUVr vs. distribution volume ratio), segmentation method (PET vs. MRI template), and cognitive profile (25.2% of subjects with MCI in our population vs. cognitively normal participants; but results from our study remained unchanged after excluding subjects with MCI) were different (5). Except for the low sample size at risk of obtaining a Type I error, other differences are less likely to explain such result discrepancies. We also reanalyzed our data using linear instead of logistic regression models, like in the previous study (5), but results remain unchanged. Also, we found no association between amyloid load in the precuneus specifically and nighttime sleep duration (data not shown).

Although the potential relationship between sleep duration and amyloid load (1, 16) is attractive in the context of amyloid clearance, sleep-wake patterns (27), orexin involvement (28), and glymphatic alterations in AD (29–31), the links between sleep and AD pathology are complex, often bidirectional and
variable during disease progression (32). Extracellular amyloid accumulation could be reduced during sleep and increased during wakefulness (33). Recent studies performed in young healthy adults showed that slow-wave sleep, rather than the entire sleep period, plays a key role in regulating the cerebrospinal fluid (CSF) levels of Aβ (34). As slow waves change in amplitude, frequency and shape with aging (35), we could hypothesize that the links between sleep and production/clearance of soluble amyloid proteins are different in older individuals compared with young people. Nevertheless, our current findings do not confirm that insufficient sleep duration is a clinically significant risk factor for brain amyloid deposition in elderly subjects.

Our study also did not find any association between amyloid PET positivity and napping, EDS, and sleep efficiency.
Conversely, a study with a different design (actigraphy and CSF Aβ quantification in 142 healthy volunteers) showed an association between low CSF Aβ42 levels and frequent napping, sleep efficiency, but again not with nighttime sleep duration (12). A cross-sectional study on 184 cognitively normal participants older than 60 years found that longer sleep latency was associated with higher levels of amyloid burden (by PET), independently of the APOEe4 status (14). Similarly, another study found that cognitively healthy adults with less adequate sleep, more sleep problems, and greater somnolence (assessed using the Sleep Scale from the Medical Outcomes Study) had higher amyloid load in angular gyrus, frontal medial orbital cortex, cingulate gyrus, and precuneus (6). However, amyloid burden was not associated with the daytime sleepiness assessed by ESS (6). On the other hand, a recent study on 283 ≥70-year-old participants without dementia found that baseline excessive daytime sleepiness (ESS score ≥10) was significantly associated with longitudinal Aβ accumulation in the anterior and posterior cingulate, precuneus and parietal regions within a mean interval between two 11C-PiB-PET scans of 2.2 years (36). Unfortunately, the absence of reported cross-sectional results on amyloid burden, sleep profile, particularly nighttime sleep duration and excessive daytime sleepiness, does not allow comparing our findings. Using the Berlin questionnaire, we did not find any association between amyloid PET status and the risk of sleep apnea. In contrast, several recent studies underlined the impact of self-reported clinical diagnosis of obstructive sleep apnea on the longitudinal increases in florbetapir PET uptake in normal and MCI subjects (37, 38). The mechanistic processes that link sleep apnea to accumulation of amyloid plaques and dementia need to be better assessed before proposing novel targets for intervention (37, 38).

The strengths of our study are the well-characterized population with spontaneous memory complaints but free of dementia, the standardized 18F-florbetapir-PET imaging with cortical SUVr measurements, the clinical face-to-face sleep interview associated with validated questionnaires, and the analysis of a large number of potential confounding factors. The absence of relationship between positive amyloid PET and nighttime sleep duration persists despite adjustment for APOEe4 and depressive symptoms. To fill the gap between cognitively normal participants and prodromal AD, subjects with memory complaints constitute a well-targeted population.

The present study also presents some limitations. The sleep profile assessment was self-reported only, based on a clinical interview and questionnaires completed by the patients with the help of a caregiver/clinical team member if required, to detail sleep characteristics and complaints at time of study instead of objective measurements, such as actigraphy or polysomnography. The self-reporting nature of the evaluation could have led to recall biases and lack of accuracy in the responses, with potential unstable sleep phenotype/complaints and sleep misperception. However, the use of self-reported questionnaires to detect individuals with sleep disturbances is particularly relevant in the clinical practice and was easier and less expensive than polysomnography in a sleep laboratory but preclude to detect sleep apneas. Finally, we are aware that small sample size is often a limitation especially when reporting negative results. However, the number of participants was more than twice that of the previous study (5). We have computed a post-hoc statistical power calculation between the groups in our population. With the SUVr threshold of 1.17 and the means of sleep duration of 6.83 h in subjects below 1.17 and 6.63 h in those above, common standard deviation of 1.2 and alpha risk of 0.05, 567 subjects per group (1,134 in total) would have been necessary to show significant between-group differences with a power of 0.80. To date, no study arranges data with both PET-amyloid and sleep assessments on more than 1,000 participants at-risk to develop AD.

CONCLUSIONS

Our study failed to confirm previous findings on the association between poor sleep quantity/quality and amyloid load, despite the fairly large population, the detailed, and comprehensive sleep profile, the large number of potential confounding factors, and the cortical amyloid load measurements by 18F-florbetapir-PET. Conversely, our results show that the interplay between sleep and amyloid is more complex than previously described. Before developing tailored therapeutic approaches, the sleep profile of subjects with amyloid pathology at different disease stages need to be better understood.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the supplementary files.

ETHICS STATEMENT

The MAPT-AV45 study and the sleep ancillary study were approved by the Toulouse ethics committee (Comité Protection des Personnes- Sud-Ouest et Outre-Mer I et II). The methods were carried out in accordance with the approved guidelines. Each participant signed legal consent forms. Informed consent was obtained from all subjects.

AUTHOR CONTRIBUTIONS

YD and AG: drafting, revising the manuscript for content, including medical writing for content, study concept or design, interpretation of data analysis, study supervision, and coordination. L-AG, CB, and IJ: revising the manuscript for content, interpretation of data analysis, study concept or design, and statistical analysis. FB and DM-G: revising the manuscript for content, interpretation of data analysis, and acquisition of data. SN, DD, CG, KB, CM, RD, SA, BV, and PP: revising the manuscript for content and acquisition of data.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.