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Persistent blood-brain barrier dysregulation in patients with obstructive sleep apnea following long-term continuous positive airway pressure treatment

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ABSTRACT

Introduction: Blood-brain barrier (BBB) dysfunction has been hypothesized to be a triggering factor in neurodegeneration. This study compared moderate-severe obstructive sleep apnea (OSA) patients with controls to evaluate the effects of this sleep disorder on BBB integrity, as well as explore the impact of continuous positive airway pressure (CPAP) treatment on BBB.
Methods: This study included moderate-severe OSA patients, OSA patients being treated with CPAP for at least 12 months (OSA-CPAP), and a control group with no neurological or psychiatric diseases. Participants underwent neurological examination, cognitive assessment (to exclude cognitive impairment) and lumbar puncture for cerebrospinal-fluid (CSF) biomarkers analysis [β-amyloid42 (Aβ$_{42}$), total-tau, phosphorylated tau, ratio between CSF and serum albumin levels (Qalb)].
Results: 38 moderate-severe OSA patients (mean age 65.50 ± 9.16), 12 patients with OSA treated with CPAP (OSA-CPAP, mean age 65.42 ± 6.45) and 25 controls (mean age 65.64 ± 8.10) were included. Moderate-severe OSA patients showed higher Qalb than controls ($p = 0.026$); also OSA-CPAP patients presented higher Qalb than controls ($p = 0.044$). Qalb did not differ comparing moderate-severe OSA and OSA-CPAP groups. OSA patients showed lower CSF Aβ$_{42}$ levels compared to both controls ($p < 0.001$) and the OSA-CPAP patients ($p < 0.001$).
Conclusions: These findings confirmed CSF Aβ$_{42}$ alteration and documented BBB dysfunction, as indicated by the higher Qalb, in OSA patients. The metabolic and oxidative damage caused by hypoxia could account for these phenomenona; however, the BBB impairment seems to be not reversible, as OSA-CPAP patients presented the BBB alteration although normal CSF Aβ$_{42}$ levels. Further studies exploring BBB function and its clinical implication for neurodegeneration in OSA are needed.

1. Introduction

The impact of obstructive sleep apnea (OSA) on brain health has gained increasing attention, as its prevalence continues rising among adults and older adults. Furthermore, OSA has been recognized as a potential risk factor for cognitive impairment and neurodegenerative diseases (Liguori et al., 2021).

OSA-related intermittent hypoxia can contribute to cognitive impairment by triggering neuronal loss in both the hippocampus (Goldbart et al., 2003) and wake-promoting regions (Zhu et al., 2007). Moreover, sleep fragmentation and impairment related to OSA condition may lead to the dysfunction of the glymphatic system (Lee et al., 2022), causing the accumulation of neurotoxins. This accumulation can impair synaptic plasticity, driving cognitive impairment and early neuropathological changes due to Alzheimer's disease (AD) (Lim and Pack, 2014).

Previous research demonstrated that intermittent hypoxia leads to endothelial dysfunction, increases pro-inflammatory cytokines

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production, and compromises tight junction integrity, ultimately contributing to blood-brain barrier (BBB) dysregulation (Li et al., 2021; Palomares et al., 2015). The BBB plays a crucial role in maintaining central nervous system (CNS) homeostasis by regulating the exchange of molecules between the bloodstream and the brain. Disruption of this barrier can increase its permeability, facilitating the entry of harmful substances, triggering neuroinflammation, and accelerating neurodegenerative processes (Sweeney et al., 2019). Although BBB dysfunction is recognized as an early pathological event in neurodegeneration (Janelidze et al., 2017), its role in OSA-related neuropathological processes remains poorly understood. Among the potential biomarkers considered for screening and diagnosing neurodegenerative processes, the ratio between cerebrospinal-fluid (CSF) and serum albumin levels (Qalb) has been considered a reliable index of BBB integrity (Tibbling et al., 1977). High Qalb levels indicate an increased exchange of proteins between the blood and the CSF, reflecting BBB dysfunction. Additionally, alterations in CSF β-amyloid$_{42}$ (Aβ_{42}) levels have been associated to impaired amyloid clearance mechanisms, further supporting the role of BBB dysregulation in neurodegeneration (Baril et al., 2018; Bubu et al., 2019).

Given the growing evidence linking OSA to neurodegenerative diseases, including AD (Liguori et al., 2021), and the presence of biomarkers consistent with AD pathology in patients with this sleep disorder (Liguori et al., 2021), understanding whether BBB dysfunction represents an early marker of OSA-related cerebral damage is crucial. Although continuous positive airway pressure (CPAP) is the standard treatment for OSA and effectively improves sleep-related symptoms and oxygenation, its effects on BBB integrity remains unexplored. While existing literature suggests that CPAP may help normalizing certain neurodegenerative biomarkers (such as CSF Aβ_{42}), it may not fully reverse vascular and endothelial damage caused by prolonged intermittent hypoxia (Baril et al., 2018; Rosenzweig et al., 2015). Assessing whether long-term CPAP treatment can mitigate BBB dysfunction is essential for understanding OSA pathophysiological mechanisms and its long-term cerebral impact. Therefore, this study aimed to assess BBB integrity in moderate-severe OSA patients by measuring Qalb and CSF AD biomarkers, comparing untreated OSA patients to CPAP-treated OSA patients and controls.

2. Materials and methods

2.1. Study design and setting

This study constitutes a secondary analysis of a previous investigation focused on assessing CSF orexin and AD biomarker levels, nocturnal sleep impairment and cognition in moderate-severe OSA patients (Liguori et al., 2019). For this study, three groups of participants were included: patients newly diagnosed with moderate-severe OSA (Apnea-Hypopnea Index – AHI - ≥ 15/h); a group of OSA patients who received CPAP treatment for at least 12 months; a group of controls similar in age and sex, admitted to the center for suspected polyneuropathy, which was ruled out after diagnostic investigations. All groups were enrolled at the Neurology Unit of the University Hospital of Rome Tor Vergata between October 2015 and December 2018.

In this study, differently from the previous one (Liguori et al., 2019), the primary aim was to measure Qalb in moderate-severe OSA patients compared to both OSA patients treated with CPAP (OSA-CPAP) and controls. OSA and the beneficial effect of CPAP treatment were evaluated by the nocturnal polysomnographic recording (PSG, SOMNOscreen, SOMNOmedics GmbH, Randersacker, Germany), which was performed according to American Academy of Sleep Medicine criteria (Berry et al., 2017), as previously reported (Liguori et al., 2019).

All participants also underwent a clinical and neurological evaluation, brain magnetic resonance imaging, and lumbar puncture for the evaluation of CSF AD biomarker levels. Moreover, the following exclusion criteria were considered in order to not affect biomarker analysis: cognitive impairment, also evaluated by using the clinical dementia rating (CDR ≥ 0.5), abnormal cell count (>4 cells/mcL) at the CSF sample analysis. Inclusion criteria for OSA-CPAP patients were: at least 12 months of CPAP therapy; good compliance to CPAP therapy, which is generally defined as the usage of CPAP ≥ 4 h per night during > 5 nights per week; efficacy of the CPAP treatment documented by the ventilator software report (AHI <5 per hour) and confirmed by the polysomnographic recording.

The exclusion criteria for controls were the following: intake of CNS active drugs; intake of melatonin supplements or hypnotics; consumption of caffeine, tobacco and/or alcohol at the time of the sleep laboratory investigation; previous diagnosis of other neurological and/or psychiatric diseases.

The study protocol was considered observational by the Independent Ethical Committee of the University Hospital of Rome Tor Vergata and was then performed according to the STROBE statement. Patients and controls provided informed consent to the study.

2.2. Biomarker analysis

Lumbar puncture was conducted between 8 and 10 AM in the decubitus position using atraumatic needles to obtain CSF samples, which have been analyzed for Qalb, total tau (t-tau), phosphorylated tau (p-tau), and Aβ_{42} levels according to indications and recommendations previously published (Liguori et al., 2016). To distinguish between normal and pathological biomarker CSF values, clinically established cut-off were applied: Aβ_{42} levels < 500 pg/mL, t-tau > 375 pg/mL, p-tau > 52 pg/mL, Qalb > 9 and ratio t-tau/Aβ_{42} > 0.52 (Duits et al., 2014; Fernandes et al., 2022; Mulder et al., 2010).

2.3. Statical analysis

Data analysis was conducted with the statistical program SPSS for Windows version 25.0 (IBM, 2020). Descriptive statistics were initially computed to describe the demographic and clinical data of the sample. Data were reported as mean ± standard deviation or medians and interquartile ranges, according to data distribution. Categorical data were reported as counts and percentages. Kruskal Wallis tests were used to compare the demographic, clinical and CSF biomarkers between patients with OSA, patients with OSA treated with CPAP (OSA-CPAP) and controls. For further analysis, moderate-severe OSA patients were stratified based on pathological CSF Aβ_{42} levels and the t-tau/Aβ_{42} ratio. The Mann-Whitney *U* test was then performed to assess differences in Qalb levels between these subgroups. The p-value was set at $p < 0.05$ for statistical significance.

3. Results

Thirty-eight patients newly diagnosed with moderate-severe OSA (76.3 % males, mean age 65.50 ± 9.16), twelve OSA-CPAP patients (83.3 % males, mean age 65.42 ± 6.45) and twenty-five controls (60 % males, mean age 65.64 ± 8.10) were included in this study. No differences were found in terms of sex ($\chi 2 = 2.9014$. $p = 0.234$) and mean age between the three groups ($H(2) = 0.007$; $p = 0.997$). Demographics and CSF biomarker data are summarized in Table 1.

Considering the CSF biomarkers, significant differences between the three groups were found for Qalb [$H(2) = 8.593$, $p = 0.014$; Fig. 1)] Specifically, both moderate-severe OSA patients and the OSA-CPAP patients showed higher Qalb than controls ($p = 0.026$; $p = 0.044$, respectively). No significant differences were found in Qalb levels between moderate-severe OSA patients and the OSA-CPAP patients ($p = 0.572$). Among the other biomarkers (Fig. 2), there was only a significant difference in CSF Aβ_{42} levels between the three groups [$H(2) = 25.507$, $p < 0.001$]. In particular, patients with moderate-severe OSA showed lower CSF Aβ_{42} levels compared to both the OSA-CPAP patients ($p < 0.001$) and controls ($p < 0.001$). No differences were

Table 1
Participants' demographic and CSF biomarkers data.

	Groups												
	OSA Patients (n = 38)				OSA-CPAP Patients (n = 12)				Controls (n = 25)				*p*-values
	Median	Percentile 25	Percentile 75	N (%)	Median	Percentile 25	Percentile 75	N (%)	Median	Percentile 25	Percentile 75	N (%)	
Age (years)	67.00	58.00	73.00		65.50	60.00	70.50		66.00	60.00	72.00		0.997
Sex Males				29 (76.3 %)				10 (83.3 %)				15 (60 %)	
Females				9 (23.7 %)				2 (16.7 %)				10 (40 %)	0.234
MMSE	25.00	23.85	27.00		27.50	24.25	30.00		28.60	28.00	30.00		< 0.001 *
AHI	39.00	26.00	44.00		4.00	0.90	4.80		NA				NA
Qalb (pg/mL)	7.00	5.00	9.00		7.00	5.50	9.50		5.21	3.66	6.31		0.014 *,#
$A\beta_{42}$ (pg/mL)	485.00	394.00	682.00		846.50	750.50	988.50		950.00	662.00	1021.00		< 0.001 *,§
t-tau/$A\beta_{42}$ ratio	0.37	0.23	0.81		0.26	0.19	0.38		0.22	0.16	0.28		0.003 *
t-tau (pg/mL)	208.00	131.00	348.00		238.00	160.00	288.00		208.00	151.00	231.00		0.550
p-tau (pg/mL)	39.50	27.00	56.00		41.00	32.50	51.50		39.00	32.00	45.00		0.712

Abbreviations: MMSE, Mini Mental State Examination; AHI, Apnea-Hypopnea Index; $A\beta_{42}$, β-amiloid$_{42}$; t-tau, total-tau; p-tau, phosphorylated tau; Qalb, ratio between CSF and serum albumin levels: NA, Not Applicable
* OSA Patients vs Controls
# OSA-CPAP Patients vs Controls
§ OSA Patients vs OSA-CPAP Patients

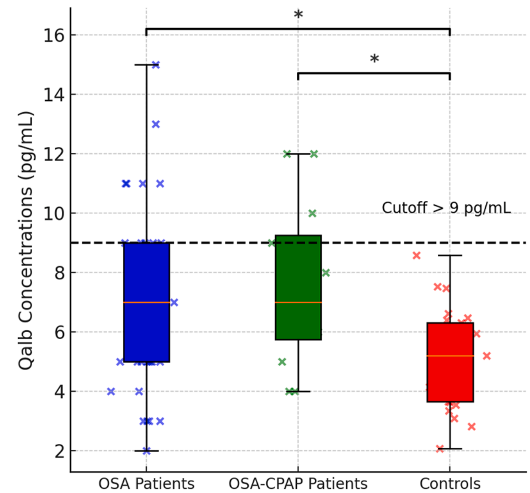

Fig. 1. Qalb values of untreated moderate-severe OSA patients, OSA patients treated by long-term CPAP, and controls.

observed between the OSA-CPAP patients and the controls in the CSF $A\beta_{42}$ levels (p = 0.930).

Among the moderate-severe OSA patients (n = 38), 52.6 % (20/38) exhibited pathological CSF $A\beta_{42}$ levels, suggesting cerebral amyloid cascade impairment, while 31.5 % (12/38) demonstrated high Qalb values, indicative of BBB alteration. In contrast, no participants in the OSA-CPAP group exhibited pathological CSF $A\beta_{42}$ levels, although 33.3 % (4/12) presented abnormal Qalb values. In the control group, no pathological values were observed regarding the CSF biomarkers analyzed (Table 2). Among moderate-severe OSA patients, 9 (23.7 %) patients showed pathological values of CSF t-tau levels, 13 (34.2 %) patients showed pathological values of CSF p-tau levels, and 14 patients (36.8 %) had pathological t-tau/$A\beta_{42}$ ratio (Table 2). However, Qalb levels did not significantly differ between patients with and without pathological CSF AD biomarkers (U=202.50, p = 0.515 for CSF $A\beta_{42}$; U=226.0, p = 0.82 for t-tau/$A\beta_{42}$ ratio). Since no pathological values in CSF $A\beta_{42}$ and t-tau levels, and in t-tau/$A\beta_{42}$ ratio were observed in the OSA-CPAP group, no comparisons of Qalb between subgroups were conducted (Table 2). The only comparison in the OSA-CPAP group regarded patients with and without pathological CSF p-tau levels, and no significant differences in Qalb between subgroups were evident (Table 2).

4. Discussion

The present study documented an alteration of the CSF marker of BBB integrity, as expressed by the Qalb, in patients with moderate-severe OSA compared to controls. All OSA patients included in this study demonstrated normal cognitive function, and thus the impact of OSA on BBB was evident prior to the possible onset of cognitive impairment. BBB is essential for maintaining brain health since it represents an important filter in the interchange of substances between CNS and blood flow. BBB activity is maintained by the integrity of the microvascular endothelium that can protect from the effects of many inflammatory and vascular/hemodynamic changes, affecting in turn the homeostasis of the CNS (Chow and Gu, 2015). Normal aging impacts BBB integrity and functionality, by affecting its homeostasis. Consistently, in neurodegenerative disorders, structural and functional BBB changes are exacerbated and the impairment of the BBB integrity can be measured by analyzing the Qalb, a marker obtained by comparing the albumin levels between CSF and serum (Liguori et al., 2016), which has been demonstrated higher in patients with neurodegenerative disorders, such as AD, compared to cognitively intact participants, with an increase of the damage along with the disease progression (Musaeus et al., 2023).

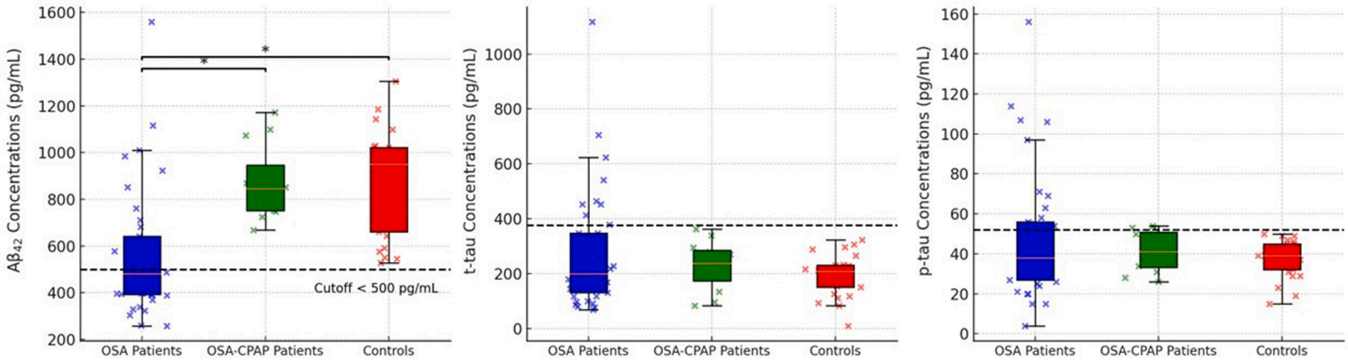

Fig. 2. CSF AD biomarkers of untreated moderate-severe OSA patients, OSA patients treated by long-term CPAP, and controls.

Table 2
Comparison of Qalb levels among participants classified according to the pathological thresholds of CSF biomarkers.

CSF Biomarker	Group	Participants with pathological biomarker, n (%)	Qalb Analysis		
			Qalb Levels in Normal Biomarkers Group[a](Mean ± SD)	Qalb Levels in Pathological Biomarkers Group[a](Mean ± SD)	Qalb Comparison (U, p)
CSF $A\beta_{42}$	Moderate-Severe OSA (n = 38)	20 (52.6 %)	8.50 ± 9.06	7.25 ± 2.47	U = 202.5, p = 0.52
(pathological value <500 pg/mL)	OSA-CPAP (n = 12)	0 (0 %)	–	–	–
	Controls (n = 25)	0 (0 %)	–	–	–
Ratio t-tau/$A\beta_{42}$	Moderate-Severe OSA (n = 38)	14 (36.8 %)	7.75 ± 7.90	8.00 ± 2.66	U = 226.0, p = 0.82
(pathological value >0.52)	OSA-CPAP (n = 12)	0 (0 %)	–	–	–
	Controls (n = 25)	0 (0 %)	–	–	–
t-tau	Moderate-Severe OSA (n = 38)	9 (23.7 %)	7.86 ± 7.24	7.78 ± 2.73	U = 162.0, p = 0.29
(pathological value >375 pg/mL)	OSA-CPAP (n = 12)	0 (0 %)	–	–	–
	Controls (n = 25)	0 (0 %)	–	–	–
p-tau	Moderate-Severe OSA (n = 38)	13 (34.2 %)	7.96 ± 7.69	7.62 ± 2.96	U = 200.5, p = 0.25
(pathological value >52 pg/mL)	OSA-CPAP (n = 12)	3 (25.0 %)	8.22 ± 2.86	5.33 ± 1.15	U = 5.50, p = 0.15
	Controls (n = 25)	0 (0 %)	–	–	–

Abbreviations: $A\beta_{42,}$ β-amiloid$_{42}$; t-tau, total-tau; p-tau, phosphorylated tau; Qalb, ratio between CSF and serum albumin levels; CSF, cerebrospinal-fluid; OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure; SD, Standard Deviation

[a] "Normal Biomarker Group" and "Pathological Biomarker Group" refer to participants classified based on established pathological thresholds for each CSF biomarker: CSF $A\beta_{42}$: pathological if < 500 pg/mL; t-tau/$A\beta_{42}$ ratio: pathological if > 0.52; t-tau: pathological if > 375 pg/mL; p-tau: pathological if > 52 pg/mL Note: No comparisons were performed in case of absent cases with pathological biomarker levels.

Therefore, the documentation of the BBB leakage in patients with moderate-severe OSA can be added to the already demonstrated detrimental effects of this sleep disorder on brain health, thus further increasing the risk for neurodegeneration.

CSF AD biomarker levels were also analyzed, and a significant reduction of CSF $A\beta_{42}$ levels was documented in patients with moderate-severe OSA when compared to both controls and the OSA-CPAP group. Noteworthy, there were no significant differences in CSF $A\beta_{42}$ levels between OSA patients treated by CPAP and controls. This finding concords with previous literature, which reports that OSA patients show early alterations in CSF AD biomarker levels (Bubu et al., 2019). Moreover, considering the subgroup of moderate-severe OSA patients, in the current study, no differences were observed in Qalb between OSA patients with pathological CSF $A\beta_{42}$ levels (<500 pg/mL), and those OSA patients with normal CSF $A\beta_{42}$ levels. These findings highlight the alteration of BBB in patients with moderate-severe OSA, and this BBB impairment seems not to be directly associated with Aβ cerebral pathology. Several mechanisms can contribute to BBB impairment in patients with OSA, including oxidative stress, intermittent hypoxia, and increased inflammation (Lim and Pack, 2014). Notably, inflammation can also be caused by Aβ deposition, oxidative stress, and cellular damage, leading to a cascade effect involving Aβ deposition, BBB pathology, and further oxidative stress. Considering that CPAP treatment has the potential to restore CSF $A\beta_{42}$ levels, it could be hypothesized that CPAP might also contribute to the restoration of BBB functionality and integrity (Baril et al., 2018). However, in the present study OSA patients under long-term CPAP treatment exhibit Qalb values comparable to those of untreated OSA patients, and higher than those of the control participants. This suggests a maintenance of BBB impairment despite receiving CPAP treatment for at least 12 months. Although these results suggest that the negative effects of the mechanisms impairing the BBB can lead to its permanent alteration, it is important to consider that these findings could also be influenced by the duration of OSA, as well as the length of CPAP treatment. Hence, further studies should consider longer follow-up assessments and detailed CPAP adherence data to assess the potential reversibility of BBB impairment and whether higher CPAP treatment exposure may mitigate its persistence. Notably, the BBB breakdown begins relatively early in aging, even before the onset of cognitive impairment (Takeda et al., 2014). Hence, the present results further add to the previous literature showing the risk of OSA in inducing cognitive decline and AD, by also altering the BBB. Based on this evidence, it is plausible that OSA can alter the AD biomarkers and trigger AD pathology, especially given the chronic impact on the BBB, which appears to be enduring and not positively influenced by CPAP treatment.

Despite the novelty of the present findings, this study has several limitations that need to be acknowledged. First, the small sample size across the three groups, which reduced the statistical power of the analysis. Second, the cross-sectional nature of the study and thus the lack of longitudinal data in the groups of patients in order to determine the direct effect of OSA and the impact of CPAP treatment on the BBB. Third, the lack of detailed CPAP adherence data beyond the minimum compliance criteria prevented us from assessing potential dose-dependent effects of CPAP on Qalb. Future research should incorporate adherence metrics, such as average nightly use and longitudinal CPAP compliance, to determine whether higher CPAP treatment exposure influences BBB function. Another limitation of this study is the lack of inclusion of further AD biomarkers, such as Sβ100, an astrocytic activation marker implicated in BBB dysfunction and neuroinflammation. Finally, sleep apnoea was screened through a sleep amnestic interview in the control group. Therefore, the absence of a PSG recording in the control group does not allow further assessments.

5. Conclusion

OSA has been extensively associated with cognitive decline, with a large amount of literature data describing the link between OSA and AD (Fernandes and Liguori, 2025). BBB impairment may also be identified as one of the pathological events induced by OSA and triggering neurodegeneration. Nevertheless, the lack of beneficial effects of CPAP treatment on BBB function and structure warrants further investigation. Furthermore, these findings emphasize the need for clinicians to be vigilant in the early recognition of OSA in individuals at risk for cognitive decline and AD since not all the detrimental effects of OSA can be fully reversed by CPAP treatment.

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CRediT authorship contribution statement

Placidi Fabio: Methodology. **Fernandes Mariana:** Writing – review & editing, Investigation, Formal analysis. **Nuccetelli Marzia:** Formal analysis. **Izzi Francesca:** Methodology. **Mercuri Nicola Biagio:** Writing – review & editing, Supervision. **Bernardini Sergio:** Supervision. **Liguori Claudio:** Writing – review & editing, Writing – original draft, Conceptualization.

Conflict of interest

All authors declare that they have no conflict of interest to declare.

Declaration of Competing Interest

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

Data Availability

The data that support the results reported in this study are available from the corresponding author upon reasonable request.

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