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Fatigue after neurosurgery in patients with a brain tumor: The role of autonomic dysregulation and disturbed sleep

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ABSTRACT

Background

Fatigue is prevalent in patients with a brain tumor and high levels of fatigue persist after neurosurgical tumor resection. The underlying mechanisms are insufficiently understood and this study examines the role of autonomic nervous system dysregulation and objective sleep characteristics in fatigue among post-surgical patients.

Methods

Patients undergoing craniotomy ($N = 52$; age 52.1 ± 15.0 years; 44% women) were evaluated at 3 months after surgery (median = 86 days). Fatigue was measured using the Multidimensional Fatigue Inventory. Autonomic nervous system indices were based on 24-h heart rate variability (HRV) analysis. Sleep parameters were measured using actigraphy: total sleep duration, efficiency, onset latency and wake after sleep onset (WASO). Data analyses of this cross-sectional study included correlation and multiple regression analysis.

Results

Fatigue scores were significantly elevated in tumor resection patients compared to healthy reference norms (p's < 0.05) with no differences between patients with glioma ($N = 32$) versus meningioma ($N = 20$). Associations between HRV indices and fatigue were non-significant (r values <0.16, p values > 0.25). Sleep duration was associated with physical fatigue ($r = 0.35$, $p = 0.02$), whereas WASO was associated with mental fatigue levels ($r = 0.40$, $p = 0.006$). Disturbed sleep measures were associated with HRV indices of reduced parasympathetic nervous system activity in glioma patients but not in meningioma patients.

Conclusions

Multiple nocturnal awakenings may result in mental fatigue and longer sleep time was associated with physical fatigue, which may reflect compensatory sleep patterns. Future intervention studies addressing sleep quality may be beneficial in treating fatigue in patients following neurosurgery for tumor resection.

1. Introduction

Fatigue is one of the most common and debilitating symptoms in patients with a primary brain tumor and high levels of fatigue persist after neurosurgical tumor resection [1–3] Fatigue adversely affects quality of life in this patient group [4,5] and is associated with poor prognosis [6,7]. Cancer-related fatigue substantially interferes with patients' daily functioning and rest or sleep typically do not restore optimal functioning [1,8–10]. The prevalence of fatigue is higher in patients with a brain tumor than in other cancers [8,9]. Post-surgical radiation and chemotherapy may contribute to fatigue [2,11], but fatigue often persists well after completion of these cancer-related treatments [1,12–14]. A better understanding of fatigue in brain tumor survivors is important because of its impact on quality of life [4,5] and clinical outcomes [6,7].

Several factors that are specific to brain tumors may contribute to

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fatigue in addition to the general sequelae of radiation and chemotherapy. Damage to areas adjacent to the hypothalamus or pituitary gland following radiation may exacerbate fatigue and hormonal regulatory processes relevant to sleep [13,15–18]. The literature is inconsistent regarding the association between histological tumor grade and fatigue levels among patients with brain tumors [10,18–20]. Brain tumors may result in excess fatigue as a result of an overall loss of homeostasis because they may directly interfere with neural networks and neuroendocrine processes involved in energy regulation [13,15–17].

Studies in breast cancer survivors indicate that measures of reduced parasympathetic nervous system activity are related to higher levels of fatigue [11,21]. In addition, sleep is essential for optimal energy regulation and may therefore play an independent role in cancer-related fatigue. The association between fatigue and sleep has been studied in healthy individuals [22] and in a wide range of medical disorders [23–28]. In healthy individuals, disturbed sleep patterns and altered circadian rhythms result in autonomic dysregulation and an overall loss of homeostasis. The restfulness of sleep can be assessed by measuring the parasympathetic activity during sleep [29], and there is a bidirectional association between sleep and cardiovascular autonomic regulation [30]. However, no information is available about the interrelationship between fatigue, sleep, and autonomic dysregulation in patients with a brain tumor.

Based on this background of fatigue in patients with a primary brain tumor and the high levels of residual fatigue in patients following neurosurgical tumor resection, the present study examined: (1) the prevalence and severity of fatigue at 3 months post tumor resection; (2) whether autonomic nervous system dysregulation is associated with fatigue; and (3) the role of objective sleep characteristics in fatigue after tumor resection. These questions are important given the prevalence and impact of fatigue in patients with a brain tumor and the finding that persistent fatigue is associated with poor prognosis [6,7].

2. Methods

2.1. Patients

A total of 52 patients who underwent craniotomy for primary brain tumor resection (glioma or meningioma) at the National Neurosurgery Expert Center at Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands, were enrolled between April 2013 and March 2015. Data for the present analyses were obtained at 3 months post-surgery. Inclusion criteria were: (1) diagnosis of a first-time primary glioma (low-grade or high-grade) or meningioma; (2) age between 18 and 80 years; and (3) sufficient understanding of the Dutch language to complete the questionnaire assessments. Exclusion criteria were: (1) undergoing treatments for other cancers than the current brain tumor resection; (2) current treatment for psychiatric disorder other than mood or anxiety disorder; (3) major complications during surgery (e.g., severe hemorrhage); and (4) atrial fibrillation or other cardiac arrhythmias interfering with heart rate variability analysis. Patients were tested at 3 months post surgery after they completed their adjuvant treatments (radio- or chemotherapy). The study was approved by the Institutional Review Board (project # NL41422.008.12) and all patients provided written informed consent before participating in the study.

2.2. Design

The data presented in this paper are cross-sectional with fatigue as the primary outcome measure and multiple ambulatory measures (related to autonomic nervous system activity and sleep) as predictor variables.

2.3. Measures

2.3.1. Fatigue

The Multidimensional Fatigue Inventory (MFI) was used to assess fatigue. The MFI consists of 20 items, with statements (scored on a 5-point Likert scale) corresponding to the five dimensions of fatigue: general, physical and mental fatigue, reduced motivation and reduced activity [31]. The scale has good psychometric properties (total score Cronbach's $\alpha = 0.84$) and normative values have been published [32].

2.3.2. Autonomic nervous system measures

Heart rate variability (HRV) indices were used to measure autonomic nervous system activity. Patients were equipped with a 3-lead Holter monitor (modified V5, V1, and aVF: SEER Light; GE Medical Systems Information Technologies, Freiburg, Germany). HRV indices were derived from 24-h electrocardiography (ECG) assessments. Prior to HRV analyses, ECGs were examined by a trained technician to exclude abnormal beat-to-beat intervals (e.g., premature ventricular complexes and supraventricular beats) in order to prevent a biased index of HRV. Autonomic nervous system activity was inferred from the HRV (using MARS software version 7.2; GE Medical Systems Information Technologies) in the frequency domain using spectral analysis (High Frequency; HF-HRV: 0.15–0.40 Hz, and Low Frequency; LF-HRV: 0.04–0.15 Hz) and time domain (Root Mean Square of Successive Difference; RMSSD; Standard Deviation of successive N—N intervals; SDNN). Higher values of HF-HRV and RMSSD reflect higher levels of parasympathetic activity. Although the autonomic correlates of LF-HRV and SDNN are less well established, they are reported here to enable comparisons with other research in this area.

2.3.3. Sleep characteristics

Objective sleep measures were obtained using an ambulatory actigraphy device (Actiwatch Score, Royal Philips, Amsterdam, the Netherlands). Patients wore the activity monitoron their non-dominant wrist during 24 h [33]. The Actiwatch uses a piezo-electric accelerometer sensor that generates a voltage when the acceleration of the wrist with the device changes [34]. Sleep and wake time were checked by comparing the actigraph-based timepoints with a written diary to increase reliability of the timing of going to bed and getting up. The actigraphy analysis reveal the following objective sleep-related measures: total time in bed, total sleep time, sleep efficacy, sleep onset latency (SOL), and wake after sleep onset (WASO).

2.3.4. Covariates

Information about clinical history, brain tumor type and location, medication use and prior adjuvant treatment was obtained from the medical records. Self-report data were used to document sociodemographic measures and the severity of depressive symptoms was assessed using the Patient Health Questionnaire (PHQ-9) [35].

2.3.5. Statistical analysis

Data are presented as mean ± standard deviation (s.d.) or N and percentages. Analysis of variance (ANOVA) and Chi-square tests were used to analyze differences in patient characteristics between glioma and meningioma patients. Comparisons of fatigue scores in patients with a brain tumor with sex- and age-specific norm values were examined using one-sample *t*-tests. Pearson correlations were used to investigate associations between fatigue dimensions, sleep characteristics and HRV indices. Multiple regression analyses were used to adjust for sex and age. Prior to statistical analyses, data were examined for normality of data distribution, approximate linearity of the associations, and homoscedasticy of the residuals using visual inspection of scatter plots, which did not indicate violations of the assumptions for correlation and regression analysis. Data were analyzed using SPSS (version 24) and two-sided *p*-values are reported.

3. Results

3.1. Patient characteristics

Table 1 displays patient characteristics of the present sample (N = 52, mean age = 52.1 ± 15.0, range = 22–77 years; 44% were women). Patients with a glioma resection (N = 32; 56% high-grade) were younger than patients with a meningioma (N = 20; p = 0.02) and were more likely (p's < 0.001) to have received adjuvant treatment between the time of surgery and the current sleep and HRV assessments, reflecting standard clinical care (see Table 1). Assessments of fatigue, HRV, and actigraphy were obtained at a median 86 days (inter-quartile range = 79–93 days) following surgery.

3.2. Fatigue in post-surgical patients

Fig. 1 shows that fatigue levels were significantly higher in patients following brain tumor resection compared to age- and sex-based normative values (see [31]) for all MFI subscales (all p's < 0.05). The highest fatigue scores were found for physical fatigue (t(51) = 5.32, p < 0.001), activity-related fatigue (t(51) = 6.52, p < 0.001) and general fatigue (t(51) = 5.28, p < 0.001) compared to the normative reference values. No differences in fatigue levels were found between patients with glioma versus meningioma, or between patients with low-grade vs. high-grade glioma (p values > 0.10). Age was also not significantly related to the severity of fatigue (r values between 0.07 and 0.16). No sex differences were found in the fatigue subscales, except for mental fatigue levels which were higher in women than men (11.1 ± 4.5 vs. 8.5 ± 3.0; (t(50) = −2.55; p = 0.02).

3.3. The role of autonomic nervous system activity in fatigue

No significant differences between patients with a glioma versus those with a meningioma were found in HRV indices (all p values > 0.05, see Table 1). For all patients combined (N = 52), no significant associations were observed between HRV indices (HF-HRV, LF-HRV, RMSSD and SDNN) with fatigue measures (r values <0.16, p values > 0.25; see Table S1).

Table 1
Patient Characteristics.

	Total (N = 52)	Glioma (N = 32)	Meningioma (N = 20)	p
	mean ± s.d. or N (%)	mean ± s.d. or N (%)	mean ± s.d. or N (%)	
Age (years)	52.1 ± 15.0	48.3 ± 15.5	58.1 ± 12.4	0.02
Sex (female)	23 (44%)	9 (28%)	12 (60%)	0.07
Tumor location				
Frontal	24 (42%)	12 (38%)	12 (60%)	0.08
Temporal	17 (30%)	15 (47%)	2 (10%)	0.007
Parietal	10 (17%)	7 (22%)	3 (15%)	0.61
Occipital	5 (9%)	4 (13%)	1 (5%)	0.41
Central	3 (5%)	1 (3%)	2 (10%)	0.29
Insula	2 (4%)	2 (6%)	0 (0%)	0.28
Brainstem	1 (2%)	0 (0%)	1 (2%)	0.20
Multi-site	10 (19%)	8 (25%)	2 (11%)	0.08
Adjuvant treatment				
Radiotherapy	21 (48%)	19 (70%)	2 (12%)	<0.001
Chemotherapy	17 (39%)	17 (63%)	0 (0%)	<0.001
Anti-epileptics	15 (34%)	10 (37%)	5 (29%)	0.60
PHQ Depression score	5.1 ± 4.6	5.1 ± 4.4	5.1 ± 5.1	0.98
HRV indices				
HF-HRV (ln. ms^2)	4.6 ± 1.0	4.5 ± 1.1	4.8 ± 0.7	0.32
LF (ln.ms^2)	5.8 ± 1.0	5.9 ± 1.0	5.7 ± 0.9	0.41
RMSSD (ms)	26.7 ± 11.8	26.8 ± 12.8	26.4 ± 10.2	0.89
SDNN (ms)	129.7 ± 37.0	130.7 ± 39.5	128.0 ± 33.7	0.79

See text for abbreviations.

3.4. Association of objective sleep characteristics with fatigue

Patients with a glioma spent more time in bed than patients with a meningioma (9:09 ± 1:12 h. vs. 8:20 ± 1:10 h.; p = 0.04) and had a greater number of awakenings during their sleep (52 ± 19 vs. 39 ± 16; p = 0.02). These differences also remained significant when statistically adjusting for age and sex.

Table 2 displays the sleep characteristics (mean ± s.d.) and also the age and sex-adjusted associations of fatigue components with sleep characteristics. Significant associations were found between WASO and mental fatigue (r = 0.40, p = 0.006). The total sleep time was positively related to physical fatigue (r = 0.35, p = 0.02), activity-related fatigue (r = 0.37, p = 0.01) and general fatigue (r = 0.32, p = 0.33). As shown in Table 2, these associations remained significant when adjusting for age and sex (covariate-adjusted β coefficients are reported in Table 2).

3.5. Exploratory analyses of sleep and HRV indices

Significant correlations were found between sleep measures with HRV indices (HF-HRV, RMSSD and SDNN; see Table 3). In addition, the observed associations between sleep characteristics with HRV indices differed between patients with glioma versus those with meningioma. Among patients with glioma, the time spent in bed was positively correlated with RMSSD (r = 0.44; p = 0.02). Sleep onset latency was positively correlated with HF-HRV (r = 0.49; p = 0.01) and RMSSD (r = 0.57; p = 0.002). Sleep efficiency was inversely related to HF-HRV (r = 0.45; p = 0.02) and RMSSD (r = −0.60; p = 0.001) (see Table 3). Among patients with a meningioma, however, sleep characteristics showed no significant correlations with HRV indices.

4. Discussion

The unique aspect of this study is the simultaneous assessment of fatigue, autonomic nervous system-related HRV indices, and objective sleep characteristics in patients who underwent craniotomy for primary brain tumor resection. Patients displayed markedly elevated fatigue scores compared to norm-based reference values at 3 months post tumor resection. No differences in fatigue levels were observed between patients with a glioma versus those with a meningioma. Autonomic nervous system indices were not related to fatigue. However, fatigue was interrelated with sleep characteristics and we found that mental fatigue was primarily related to waking up after sleep onset, whereas physical fatigue and other fatigue dimensions were associated with longer time in bed. Exploratory analyses revealed significant correlations were found with sleep measures, particularly in glioma patients. These findings suggest that improving sleep quality may be an important target for future research and interventions for patients undergoing brain tumor resection, particularly in patients with glioma.

This study confirms that patients who had surgery for a primary brain tumor have elevated fatigue levels [1–3,12–14]. Impaired restorative sleep may be an important contributing factor to these heightened fatigue levels, which was found to differ across dimensions of fatigue. We found that mental fatigue was related to objective measures of waking up during the night. In contrast, physical fatigue (and other activity-related fatigue dimensions), was associated with time in bed and total sleep time. This finding could indicate a general lack of physical fitness of the patient as a consequence of reduced physical activity, as is also seen in patients with other types of cancer [36]. Intervention studies are needed to determine whether improved sleep hygiene (possibly combined with physical activity-related interventions) can be used to reduce physical and mental fatigue levels in patients with a brain tumor (see for example [37]).

Based on research in patients with breast cancer [11,21], we

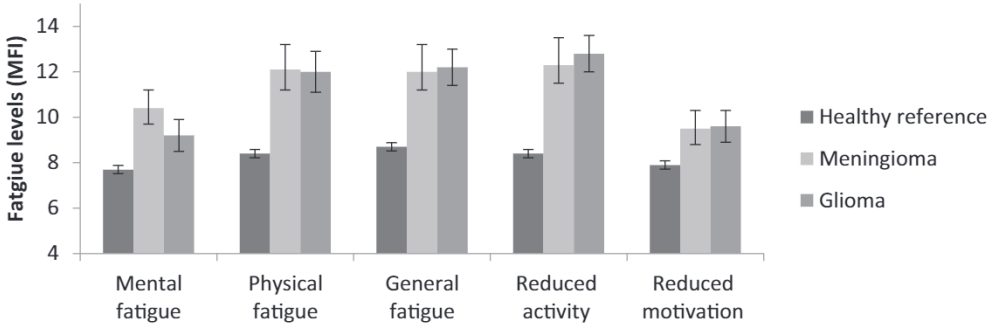

Fig. 1. Fatigue levels of patients with primary brain tumors compared to normative values.
$p < 0.0$ for all comparisons of patients with meningioma or glioma vs. the age- and sex-based normative data of healthy individuals. Patients with glioma did not differ from those with meningioma on the fatigue measures (all p-values > 0.10). Error bars denote standard errors of the mean.

Table 2
Regression analyses of the association between sleep characteristics with dimensions of fatigue.

	Time in bed (hrs)	Total sleep time (hrs)	Sleep Efficiency (%)	SOL (min)	WASO (min)
Mean ± s.d.	8:47 ± 1:14	7:34 ± 0:58	86.6 ± 7.1	19.6 ± 31.1	38.6 ± 20.7
Fatigue components[a]					
Mental	0.26	0.13	−0.28	0.06	0.35*
Physical	0.31*	0.33*	−0.04	0.05	0.10
General	0.33*	0.30*	−0.13	0.07	0.11
Reduced Activity	0.44*	0.36*	−0.22	0.15	0.28
Reduced Motivation	0.32*	0.29	−0.08	0.07	0.18
Total Fatigue	0.43*	0.36*	−0.20	0.11	0.25

SOL = sleep onset latency, WASO = wake after sleep onset.
[a] Data are standardized regression weights (β) adjusted for age and sex.
* = $p < 0.05$.

Table 3
Correlations between sleep characteristics and HRV indices of autonomic nervous system activity.

	Time in bed (hrs)	Total sleep time (hrs)	Sleep Efficiency (%)	SOL (min)	WASO (min)
All patients					
HF-HRV	0.17	−0.05	−0.28	0.39*	−0.03
LF-HRV	0.10	−0.13	−0.31*	0.37*	−0.02
RMSSD	0.39*	0.06	−0.47*	0.50*	0.19
SDNN	0.16	−0.13	−0.37*	0.46*	0.08
Glioma					
HF-HRV	0.24	−0.15	−0.45*	0.49*	0.05
LF-HRV	0.13	−0.16	−0.30	0.38	−0.03
RMSSD	0.44*	−0.05	−0.60*	0.57*	0.26
SDNN	0.18	−0.24	−0.45*	0.53*	0.06
Meningioma					
HF-HRV	0.19	0.24	0.10	0.08	−0.10
LF-HRV	−0.05	−0.18	−0.26	0.32	−0.05
RMSSD	0.28	0.20	−0.15	0.23	0.13
SDNN	0.04	−0.02	−0.11	0.10	0.08

See text for abbreviations.
* $p < 0.05$.

expected that fatigue would also be related to autonomic dysregulation in patients with brain tumors. However, we did not find support for this hypothesis. Instead we found that sleep measures reflecting disturbed sleep quality were correlated with HRV indices of reduced parasympathetic activity which is consistent with other sleep research (for review see Tobaldini and McEwen) [22,29]. Interestingly, the associations between sleep measures with HRV indices were primarily observed in patients who had a glioma and not in those with meningioma. Since patients with a glioma often have more invasive brain lesions compared to patients with a meningioma, more tissue damage and functional/disturbances are likely to play a role in glioma versus meningioma. It is possible that patients who have a glioma compensate their increased fatigue levels by spending more time in bed. This interpretation is further supported by the observed correlations between time spend in bed and dysregulated autonomic functioning.

Our findings are consistent with the theory developed by Wu and colleagues regarding dysregulations of the hypothalamic-pituitary-adrenal (HPA) axis as a common denominator of fatigue, sleep and cancer [15]. This theory postulates that primary brain tumors may result in excess fatigue as a result of an overall loss of homeostasis because brain tumors and their treatment may directly interfere with neural networks and neuroendocrine processes involved in energy regulation. This interpretation indicates that biobehavioral interventions that target neurocircuits relevant to sleep may result in reduced fatigue in patients with a brain tumor. HPA axis dysregulation often coincides with altered autonomic nervous system functioning, particularly a shift towards reduced parasympathetic activity. In addition to the HPA axis and autonomic nervous system output systems of the brain, neurocognitive problems and related compensatory mental efforts may result in disproportionally high levels of fatigue, consistent with the Coping Hypothesis of neurocognitive dysfunction and fatigue [38]. Incorporating these perspectives with the advantages of optimal sleep hygiene on homeostatic processes, as described by McEwen [22], it seems plausible that a general homeostatic imbalance underlies fatigue in patients with a brain tumor.

4.1. Limitations

The findings of this study need to be considered in the light of several limitations. Although the use of actigraphy provides an objective indication of sleep characteristics, this measure is less optimal than polysomnography to quantify specific sleep characteristics. For example, it can not be determined to what extent obstructive sleep apnea were present in the participating patients, or whether there was a relative reduction in restorative sleep stages such as slow-wave or N3 sleep. However, several studies have shown close correspondence between actigraphy- and polysomnography-based sleep indices [39,40]. Moreover, the use of wrist actigraphy enables more possibilities and less interference with normal routines than polysomnography for optimal sleep measurement in a patient's natural environment. Another limitation is that we did not measure sleep during multiple nights as optimal assessments of sleep patterns are better when 3–5 nights of observation are made. The number of participants is relatively small ($N = 52$) and the patient group is heterogeneous (patients with both low-grade and high-grade glioma and meningioma were included) and as a

consequence, the statistical power was such that only medium effect sizes could be detected; it is possible that smaller effect sizes exist, but those are probably clinically less important. We could also not fully correct for Type 1 error related to multiple testing. The comparison with normative data indicated that fatigue levels were very high in this post-surgical patient group, but we note that a between-groups design using controls with other types of cancer and/or age- and sex-matched comparison groups could have revealed other estimates. We also note that the normative data (based on $N = 2307$) used in this article (Schwarz et al., 2003) [32] are lower than those reported by the initial validation study by Smets et al. (2005) [31]. Finally, the cross-sectional design and potential fatigue-related consequences of post-surgical adjuvant therapies preclude causal inferences about the pathways linking fatigue, sleep characteristics and autonomic dysregulation. Future longitudinal and intervention studies are needed to replicate and expand on the present observations. These studies would also need to consider the patients' level of overall recovery and resumption of routine work-related and leisure activities as well as other biobehavioral pathways, such as physical activity and inflammation [7].

5. Conclusions

The results of this study show that patients who have undergone resection of a brain tumor display markedly elevated fatigue levels 3 months after surgery. Fatigue dimensions were differentially associated with sleep characteristics, such that mental fatigue was related to waking up during the night and physical fatigue (and other activity-related dimensions) related to longer sleep duration. These findings are relevant for the development of patient-centered treatment of neurosurgical patients and indicate an overall loss of homeostasis through multi-system disturbances, possibly as a direct consequence of neural network damage that particularly occurs in glioma patients. Moreover, HRV indices of reduced parasympathetic activity were primarily related to sleep-related measures in patients with a glioma and not in those with a meningioma. It is possible that psychological distress is a common factor in both sleep problems and fatigue in patients following brain surgery (e.g., [41–43]). It is also possible that spending more time in bed may be a compensatory behavior aimed to counter fatigue among patients who receive tumor resection. In order to confirm these findings, intervention studies directed at sleep hygiene and physical rehabilitation in patients following brain surgery are needed to confirm these findings and develop individual patient-targeted interventions.

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Data access and availability

Deidentified data on which the results of this article is based are available from the corresponding author.

Role of funding source

The funding agency provided salary (HdM) and equipment for the conduct of this study but was not involved in the data analyses and scientific report of this investigation. The authors had full access to all the data in the study and had final responsibility for the decision to submit the paper for publication.

Authorship

WJK, HdM, MMS and GJR developed the conceptual framework and design of the study. HdM, MWT and WMK acquired the data. WMK and WJK conduced the statistical analysis and drafted the manuscript. All authors (WMK, HdM, MWT, MMS, GJR, and WJK) reviewed and edited the final version of the manuscript.

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Declaration of competing interest

The authors have no conflicts of interest associated with this manuscript.

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