

## ANESTHESIOLOGY

# Electroencephalogram Burst-suppression during Cardiopulmonary Bypass in Elderly Patients Mediates Postoperative Delirium

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## EDITOR'S PERSPECTIVE

### What We Already Know about This Topic

- Associations between intraoperative burst-suppression and postoperative delirium have been reported.
- The causal significance of these associations is unknown.

### What This Article Tells Us That Is New

- In a retrospective observational substudy of 159 patients undergoing cardiac surgery, there is evidence that burst-suppression during cardiopulmonary bypass mediates the effect of physical function, temperature during cardiopulmonary bypass, and intraoperative electroencephalographic alpha power on postoperative delirium. Delirium was also associated with decreased broadband power in the intraoperative electroencephalogram.

Delirium is an acute brain dysfunction characterized by disturbances in attention, awareness, and cognition.<sup>1</sup> Normal aging,<sup>2</sup> poor physical function,<sup>3,4</sup> preexisting

## ABSTRACT

**Background:** Intraoperative burst-suppression is associated with postoperative delirium. Whether this association is causal remains unclear. Therefore, the authors investigated whether burst-suppression during cardiopulmonary bypass (CPB) mediates the effects of known delirium risk factors on postoperative delirium.

**Methods:** This was a retrospective cohort observational substudy of the Minimizing ICU [intensive care unit] Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS) trial. The authors analyzed data from patients more than 60 yr old undergoing cardiac surgery ( $n = 159$ ). Univariate and multivariable regression analyses were performed to assess for associations and enable causal inference. Delirium risk factors were evaluated using the abbreviated Montreal Cognitive Assessment and Patient-Reported Outcomes Measurement Information System questionnaires for applied cognition, physical function, global health, sleep, and pain. The authors also analyzed electroencephalogram data ( $n = 141$ ).

**Results:** The incidence of delirium in patients with CPB burst-suppression was 25% (15 of 60) compared with 6% (5 of 81) in patients without CPB burst-suppression. In univariate analyses, age (odds ratio, 1.08 [95% CI, 1.03 to 1.14];  $P = 0.002$ ), lowest CPB temperature (odds ratio, 0.79 [0.66 to 0.94];  $P = 0.010$ ), alpha power (odds ratio, 0.65 [0.54 to 0.80];  $P < 0.001$ ), and physical function (odds ratio, 0.95 [0.91 to 0.98];  $P = 0.007$ ) were associated with CPB burst-suppression. In separate univariate analyses, age (odds ratio, 1.09 [1.02 to 1.16];  $P = 0.009$ ), abbreviated Montreal Cognitive Assessment (odds ratio, 0.80 [0.66 to 0.97];  $P = 0.024$ ), alpha power (odds ratio, 0.75 [0.59 to 0.96];  $P = 0.025$ ), and CPB burst-suppression (odds ratio, 3.79 [1.5 to 9.6];  $P = 0.005$ ) were associated with delirium. However, only physical function (odds ratio, 0.96 [0.91 to 0.99];  $P = 0.044$ ), lowest CPB temperature (odds ratio, 0.73 [0.58 to 0.88];  $P = 0.003$ ), and electroencephalogram alpha power (odds ratio, 0.61 [0.47 to 0.76];  $P < 0.001$ ) were retained as predictors in the burst-suppression multivariable model. Burst-suppression (odds ratio, 4.1 [1.5 to 13.7];  $P = 0.012$ ) and age (odds ratio, 1.07 [0.99 to 1.15];  $P = 0.090$ ) were retained as predictors in the delirium multivariable model. Delirium was associated with decreased electroencephalogram power from 6.8 to 24.4 Hertz.

**Conclusions:** The inference from the present study is that CPB burst-suppression mediates the effects of physical function, lowest CPB temperature, and electroencephalogram alpha power on delirium.

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cognitive impairment,<sup>5,6</sup> sedative drugs,<sup>7</sup> sleep disturbance,<sup>8</sup> and inflammation<sup>9</sup> are risk factors that predispose patients to delirium. Although previously reported associations between delirium and increased mortality may not be causal,<sup>10</sup> delirium remains a leading cause of preventable

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morbidity in hospitalized elderly patients.<sup>10,11</sup> Thus, strategies to reduce the incidence of delirium and identify patients at risk for delirium are needed.

Burst-suppression during general anesthesia is associated with postoperative delirium.<sup>12-14</sup> Burst-suppression consists of alternations between isoelectricity and brief bursts of electrical activity.<sup>15</sup> Burst-suppression can be induced by anesthetic drugs that significantly modulate  $\gamma$ -aminobutyric acid type A receptors. Although sometimes induced intentionally for therapeutic purposes to treat refractory status epilepticus or increased intracranial pressure,<sup>16,17</sup> burst-suppression is generally considered potentially harmful and to be avoided. Whether burst-suppression is a modifiable risk factor for delirium *versus* merely an epiphenomenon or downstream readout for other factors that cause delirium is an open question.

If burst-suppression contributes causally to delirium, this argues for anesthetic protocols to reduce the incidence of intraoperative burst-suppression. Conversely, a noncausal association would argue for anesthetic protocols to identify patients with intraoperative burst-suppression for preoperative geriatric consultation. In a recent investigation, we found that patients with intraoperative burst-suppression during cardiopulmonary bypass (CPB) exhibited decreased alpha and beta oscillation power compared with age-matched control patients.<sup>18</sup> This finding suggests that patients exhibiting burst-suppression at age-adjusted anesthetic concentrations are neurobiologically distinct. Consistent with this finding, an electroencephalogram-guided anesthetic protocol reduced the incidence of intraoperative burst-suppression but not postoperative delirium.<sup>19</sup> Thus, the association between drug-induced intraoperative electroencephalogram burst-suppression and delirium in noncritically ill patients may not be entirely causal.

In this study we investigated associations between delirium risk factors, electroencephalogram burst-suppression during CPB, and postoperative delirium. We analyzed the electroencephalogram for burst-suppression during CPB, a period with stable and controlled anesthetic and physiologic management. Decreased alpha power has been associated with burst-suppression during CPB<sup>18</sup> and cognitive impairment.<sup>20,21</sup> Cognitive impairment has also been associated with postoperative delirium.<sup>5,6</sup> We hypothesized that preexisting cognitive impairment accounts for electroencephalogram burst-suppression during CPB. We also hypothesized that electroencephalogram burst-suppression during CPB mediates the effect of cognitive impairment on delirium.

## Materials and Methods

### Patient Selection and Data Collection

**Ethics Statement.** The Partners Human Research Committee approved this research study (Institutional Review Board 20168000742). This is a substudy of the

ongoing Minimizing ICU Neurologic Dysfunction with Dexmedetomidine-induced Sleep (MINDDDS) trial.<sup>22</sup> The MINDDDS trial is a 370-patient block-randomized, placebo-controlled, double-blinded, single-site, parallel-arm superiority trial of a sleep-inducing dose of dexmedetomidine for delirium prevention in elderly patients undergoing major cardiac surgery. For this substudy, data from eligible MINDDDS trial patients who underwent preoperative assessments and had intraoperative electroencephalogram recordings were analyzed. All participants provided written informed consent.

**Study Population.** Study details for the MINDDDS trial, including inclusion and exclusion criteria, have previously been published.<sup>22</sup> Study eligibility criteria were age at or above 60 years, scheduled for a cardiac surgical procedure with CPB, planned postoperative admission to the intensive care unit for at least 24h, and scheduled same-day surgical admission. Study exclusion criteria were blindness, deafness, inability to speak English, more than 2 days of ICU admission in the month preceding the current surgical procedure, renal and liver failure requiring dialysis or Child-Pugh score greater than 5, anticipated follow-up difficulties, previous cardiac surgery within 1 yr of surgical procedure, allergy to dexmedetomidine, chronic therapy with benzodiazepines or antipsychotics, severe neurologic deficit, and surgical procedure requiring total circulatory arrest. Patients scheduled for a second surgical procedure during their hospital stay or postoperative intubation more than 12h were dropped from the study. Data from 159 patients were analyzed in this prespecified substudy: 117 patients were followed up in the MINDDDS trial, 7 patients withdrew consent for MINDDDS trial long-term follow-up after surgery, 18 patients met objective drop criteria for MINDDDS trial long-term follow-up, and 17 patients did not consent to be randomized into the MINDDDS trial.

**Data Collection.** Patients underwent a baseline prerandomization assessment for study inclusion and exclusion criteria. Subjects were recruited and data collected between March 2017 and February 2019. We evaluated baseline cognitive function using the abbreviated Montreal Cognitive Assessment, physical function with the Patient-Reported Outcomes Measurement Information System SF v2.0-Physical function 8b, general health with the Patient-Reported Outcomes Measurement Information System SF v1.2-Global Health, pain with the Patient-Reported Outcomes Measurement Information System SF v1.0-Pain Interference 8a, applied cognition with the Patient-Reported Outcomes Measurement Information System v2.0-Applied Cognition Abilities 8a, and sleep quality with the Patient-Reported Outcomes Measurement Information System v1.0-Sleep Disturbance 4A. We also screened for delirium during the prerandomization assessment using the 3-min Confusion Assessment Method.

Patient-Reported Outcomes Measurement Information System measures were normalized to a standardized

T-distribution ([https://www.assessmentcenter.net/ac\\_scoringservice](https://www.assessmentcenter.net/ac_scoringservice); accessed March 31, 2019). The T-score mean for Patient-Reported Outcomes Measurement Information System questionnaires is 50 for the population, with SD of 10. Higher scores indicate more of the concept being measured. This could be a desirable or undesirable outcome, depending on the concept being measured (*i.e.*, higher scores for physical function is desirable while higher scores for pain or sleep disturbance is undesirable). None of the study patients screened positive for delirium during the baseline assessments. Comorbid conditions were extracted from the history and physical notes that were documented during the presurgical planning visit.

We recorded electroencephalogram data using Sedline monitor (Masimo Inc, USA). Sedtrace electrode arrays were placed on the forehead at approximately Fp1, Fp2, F7, and F8, the ground electrode at approximately Fpz, and the reference electrode approximately 1 cm above Fpz. Data were recorded with a preamplifier bandwidth of 0.5 to 92 Hertz, a sampling rate of 250 Hertz, with 16-bit, 29 nano Volts resolution. Electrode impedance was maintained at less than 5k $\Omega$  in each channel. General anesthesia was induced with an intravenous induction agent, followed by maintenance with isoflurane. We selected electroencephalogram data segments using information from the electronic medical record and spectral analysis of the electroencephalogram. For each patient, we carefully selected 2-min electroencephalogram segments that represented the maintenance phase of general anesthesia during surgery. The data were selected from a period at least 15 min after the initial induction bolus of the intravenous hypnotic, while the expired concentration of isoflurane was stable and before the onset of CPB. We visually inspected the selected segments in both the time and spectral domains to ensure data quality. These data have not been reported in any previous publication.

**Burst-suppression Analysis.** We manually identified patients who exhibited burst-suppression during CPB by analyzing electroencephalogram data in the spectral and time-series domain. Two independent anesthesiologists (J.P., O.A.) identified periods of burst-suppression defined as the presence of at least three consecutive suppression events within 60-s periods during CPB. Only cases that both evaluators agreed upon were formally coded as burst suppression events. We used complete cases analysis ( $n = 141$ ).

**Postoperative Delirium Analysis.** Patients were screened for postoperative delirium twice daily (before midday and past midday with at least 6 h between tests) beginning on postoperative day 1 using the long version of the Confusion Assessment Method, until postoperative day 3. Delirium was also assessed with a structured chart review beginning on postoperative day 1 until postoperative day 3 by performing a text search for the diagnosis of *delirium* or *delirious* in the medical record.

**Spectral Analysis.** We computed multitaper spectral estimates using the Chronux Matlab toolbox with the

following parameters: window length  $T = 2$  s without overlap, time-bandwidth product  $TW = 3$ , number of tapers  $K = 5$ . We equally weighted the signals from Fp1, Fp2, F7, and F8 channels.

**Bias.** Selection bias was managed by analyzing data from all patients who were sequentially enrolled in the MINDDDS study until the sample size for this substudy was reached. Misclassification was reduced by clearly defining exposures (burst-suppression during CPB) and outcomes (delirium). Data collection with the aid of standardized clinical tools (abbreviated Montreal Cognitive Assessment, Patient-Reported Outcomes Measurement Information System Health Measures, and Confusion Assessment Method) helped to minimize recall bias. However, the nature of our investigation does not preclude bias introduced by unknown or unmeasured confounders.

## Statistical Methods

Data and statistical analyses plans were defined and written after the data were accessed. Continuous variables are presented as median [quartile 1 (25th percentile) to quartile 3 (75th percentile)] and categorical variables as frequency (percentage). We used the Mann-Whitney  $U$  test for associations between continuous and categorical variables, and the Fisher exact test for associations among categorical variables. All  $P$  values were computed based on the two-sided tests at significance level of 0.05. In some cases, multiple testing was corrected using false discovery rate. Significance was declared if false discovery rate  $< 0.05$ .

**Power Analysis.** A primary objective of this study was to detect a difference in mean preoperative cognitive scores between burst-suppression and no-burst-suppression patient groups. We assumed a sampling ratio (burst-suppression/no burst-suppression) during CPB in major cardiac surgery of 50%,<sup>18</sup> a reduction in abbreviated Montreal Cognitive Assessment score of 1.5 in the burst-suppression group, and an abbreviated Montreal Cognitive Assessment SD of 2.5. Based on type I error of 0.05, and power of 0.90, a total of 132 patients was expected to enable detection of this difference using a two-sample  $t$  test. We assumed approximately 20% data loss as a result of electroencephalogram poor quality and incomplete recordings and thus assumed our  $n$  of 159 to be adequate.

**Electroencephalogram Analysis.** We manually matched patients by actual age ( $\pm 2$  yr) and abbreviated Montreal Cognitive Assessment ( $\pm 3$  points) score using a one to one matching criteria. An empirical bootstrap approach was used to enable statistical inferences. First, we bootstrapped the estimates of each nonoverlapping window. Next, we computed a median of the bootstrapped estimates at the subject level and then computed the group median of this estimate. We computed the median difference between groups and then iterated the above procedure 5,000 times to obtain a distribution of the median difference between groups. We computed the 99% CI of this distribution. We

defined our threshold for statistical significance as when the upper and lower CI of the median difference distribution did not border zero over a contiguous frequency range greater than 2 bandwidths (2W).

**Univariate Linear Regression Analysis.** In separate linear regression analyses, we estimated the association between abbreviated Montreal Cognitive Assessment (using continuity correction) and the following delirium risk factors: age, American Society of Anesthesiologists (ASA) Physical Status (using continuity correction), education (more than high-school education categorized), applied cognition (Patient-Reported Outcomes Measurement Information System Cognition), physical function (Patient-Reported Outcomes Measurement Information System Physical Function), global health (Patient-Reported Outcomes Measurement Information System Global Health Physical and Mental), pain (Patient-Reported Outcomes Measurement Information System Pain), sleep (Patient-Reported Outcomes Measurement Information System Sleep), alpha power, and burst-suppression during CPB. Regression models were constructed in R (RStudio Inc, USA, version 1.1.453).

**Univariate Logistic Regression Analysis.** In separate logistic regression analyses, we estimated the association between burst-suppression during CPB and the following delirium risk factors: age, ASA Physical Status, abbreviated Montreal Cognitive Assessment, applied cognition (Patient-Reported Outcomes Measurement Information System Cognition), physical function (Patient-Reported Outcomes Measurement Information System Physical Function), global health (Patient-Reported Outcomes Measurement Information System Global Health Physical and Mental), pain (Patient-Reported Outcomes Measurement Information System Pain), sleep (Patient-Reported Outcomes Measurement Information System Sleep), alpha power, length of CPB, and lowest temperature during CPB. We also estimated the association between delirium and the same predictors as above including an analysis for the predictor burst-suppression during CPB. Regression models were constructed in R (RStudio Inc, version 1.1.453).

**Causal/Mediational Inference Analysis.** The analysis of potential underlying causal mechanisms suggested fitting separate multivariable logistic regression models for the dependent variables: burst-suppression during CPB and delirium. In the model for burst-suppression, the predictors were age, ASA Physical Status, abbreviated Montreal Cognitive Assessment, Patient-Reported Outcomes Measurement Information System Physical, Patient-Reported Outcomes Measurement Information System Global Mental Health, Patient-Reported Outcomes Measurement Information System Pain, Patient-Reported Outcomes Measurement Information System Cognition, Patient-Reported Outcomes Measurement Information System Sleep, alpha power, CPB length, and lowest

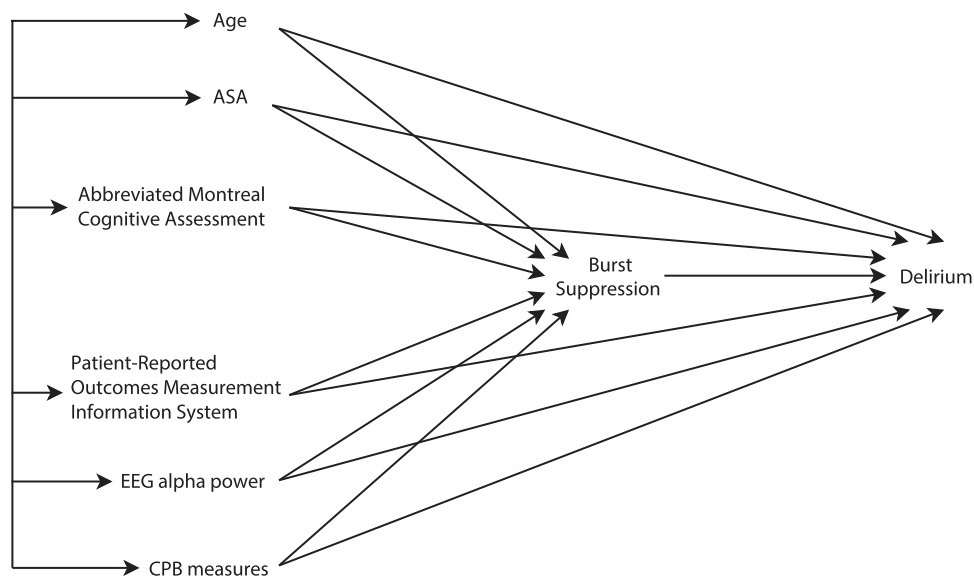
temperature during CPB. In the model for delirium, the same predictors were analyzed with the addition of burst-suppression. In both models, a backward elimination algorithm was applied to the predictors. Only predictor terms that remained after backward elimination using a  $P < 0.1$  significance threshold were included in the final model. These analyses were performed with SAS statistical software (SAS Institute Inc, USA, version 9.4). The hypothetical underlying causal model that guided our data analysis strategy is illustrated in figure 1. This figure makes clear that we are testing the hypothesis that burst-suppression partly mediates the hypothetical causal effects of the exogenous variables (age, ASA Physical Status, abbreviated Montreal Cognitive Assessment, Patient-Reported Outcomes Measurement Information System measures, alpha power, CPB measures) on delirium. However, we are also positing the possibility of additional direct effects of the exogenous variables on delirium additive to their indirect effects *via* burst-suppression, as indicated by the direct arrows from exogenous variables to delirium. The age variable was the only exogenous variable that had largely the role of a potential confounding covariate rather than being of direct substantive interest in this study as the other predictors were. No modifier effects were tested (*i.e.*, no interactions among predictors).

## Results

### Patient Characteristics Stratified by Burst-suppression and Delirium

Data from 159 patients were analyzed in this manuscript. Patient characteristics are summarized in supplementary material (Supplemental Digital Content, table 1, <http://links.lww.com/ALN/C365>). Electroencephalogram data of 18 subjects could not be analyzed for burst-suppression because of poor quality or incomplete data capture throughout CPB. There were 23 patients who screened positive for delirium in our study cohort: 18 of the 117 MINDDS trial patients (16 from assessments, 2 chart review), 1 of the 7 patients who withdrew consent for MINDDS trial long term follow-up (1 from assessments, none from chart review), 3 of the 18 patients who met objective drop criteria for MINDDS trial long-term follow-up (none from assessments, 3 from chart review), and 1 of the 17 patients who did not consent to be randomized into the MINDDS trial (none from assessments, 1 from chart review). These data are summarized in the Supplemental Digital Content, table 2 (<http://links.lww.com/ALN/C366>). The characteristics of patients with complete electroencephalogram data stratified by burst-suppression and delirium are summarized in table 1 and Supplemental Digital Content table 3 (<http://links.lww.com/ALN/C367>), respectively. Patient comorbidities are summarized in Supplemental Digital Content, tables 4 (<http://links.lww.com/ALN/C368>) and 5 (<http://links.lww.com/ALN/C369>).





**Fig. 1.** Initial hypothetical causal model. Burst-suppression during cardiopulmonary bypass was hypothesized to mediate the association between known delirium risk factors and delirium. However, the initial model also allowed for the possibility of direct effects of the risk factors on delirium, in addition to, or instead of, the indirect, mediational effect of burst-suppression. Patient-Reported Outcomes Measurement Information System measures included applied cognition, physical function, global health, pain, and sleep. Cardiopulmonary bypass (CPB) measures included duration of CPB and lowest temperature during CPB. *Straight arrows* indicate causal effects; *double-headed arrows* connecting exogenous variables on the left indicate correlations not explicated in the model. ASA, American Society of Anesthesiologists Physical Status; EEG, electroencephalogram.

**Univariate Analyses of Independent Associations**

*Age, Education, and Alpha Power Were Independently Associated with the Abbreviated Montreal Cognitive Assessment.* We found significant independent associations with abbreviated Montreal Cognitive Assessment for age, education, and intraoperative alpha power (Supplemental Digital Content, table 6, <http://links.lww.com/ALN/C370>). The patient’s predicted abbreviated Montreal Cognitive Assessment score decreased by 0.087 points for each year increase in age (false discovery rate  $P = 0.008$ ). Predicted abbreviated Montreal Cognitive Assessment score increased by 1.096 points if patients were formally educated beyond high school education (false discovery rate  $P = 0.014$ ). High school education was coded a 1 for at least a high school education and 0 for less than a high school education. Similarly, abbreviated Montreal Cognitive Assessment score increased 0.155 points for each decibel increase in intraoperative alpha power (false discovery rate  $P = 0.033$ ).

*Age, Physical Function Scores, Alpha Power, and Lowest Temperature during Cardiopulmonary Bypass Were Independently Associated with Burst-suppression during CPB.* We found significant independent associations with the incidence of intraoperative burst-suppression during CPB for age, Patient-Reported Outcomes Measurement Information System Physical Function, Patient-Reported Outcomes Measurement Information System Global

Health Physical, intraoperative alpha power, and lowest temperature during CPB. The odds of burst-suppression during CPB increased by 8% (odds ratio, 1.08 [95% CI, 1.03 to 1.14]; false discovery rate  $P = 0.006$ ) for each year increase in age. The odds of burst-suppression during CPB decreased by 5% (odds ratio, 0.95 [0.91 to 0.98]; false discovery rate  $P = 0.020$ ) for every T-score increase in Patient-Reported Outcomes Measurement Information System Physical Function. Similarly, the odds of burst-suppression during CPB decreased by 5% (odds ratio, 0.95 [0.92 to 0.99]; false discovery rate  $P = 0.021$ ) for every T-score increase in Patient-Reported Outcomes Measurement Information System Global Health Physical Function. The odds of burst-suppression during CPB decreased by 35% (odds ratio, 0.65 [0.54 to 0.80]; false discovery rate  $P < 0.001$ ) for each decibel increase in electroencephalogram alpha power. Finally, the odds of burst-suppression during CPB decreased by 21% (odds ratio, 0.79 [0.66 to 0.94]; false discovery rate  $P = 0.024$ ) for each degree increase in lowest temperature during CPB. These data are summarized in Supplemental Digital Content, table 7 (<http://links.lww.com/ALN/C371>).

*Age, Abbreviated Montreal Cognitive Assessment, Alpha Power, and Burst-suppression during Cardiopulmonary Bypass Were Independently Associated with Delirium.* We found significant independent associations for age, abbreviated Montreal

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**Table 1.** Patients Characteristics with Complete Electroencephalogram Data, Stratified by Burst Suppression

Burst Suppression	No Burst Suppression	Burst Suppression	False Discovery Rate	
	(n = 81)	(n = 60)	P Value	P Value
Age, median [quartile 1 to quartile 3]	67 [64 to 73]	73 [68 to 78]	0.001	0.007
ASA Physical Status, n/total (%)			0.667	0.788
II	4/81 (5)	2/60 (3)		
III	57/81 (70)	39/60 (65)		
IV	20/81 (25)	19/60 (32)		
Abbreviated Montreal Cognitive Assessment, median [quartile 1 to quartile 3]	19 [17 to 20]	19 [17 to 20]	0.965	0.965
Patient-Reported Outcomes Measurement Information System Physical, median [quartile 1 to quartile 3]	48 [41 to 60]	43 [39 to 49]	0.007	0.018
Patient-Reported Outcomes Measurement Information System Global Health Physical, median [quartile 1 to quartile 3]	50 [43 to 55]	46 [38 to 51]	0.009	0.020
Patient-Reported Outcomes Measurement Information System Global Health Mental, median [quartile 1 to quartile 3]	56 [50 to 62]	54 [49 to 61]	0.541	0.703
Patient-Reported Outcomes Measurement Information System Pain, median [quartile 1 to quartile 3]	41 [41 to 52]	41 [41 to 55]	0.158	0.228
Patient-Reported Outcomes Measurement Information System Cognition, median [quartile 1 to quartile 3]	61 [51 to 61]	51 [51 to 61]	0.120	0.195
Patient-Reported Outcomes Measurement Information System Sleep, median [quartile 1 to quartile 3]	50 [44 to 56]	50 [44 to 57]	0.750	0.813
Alpha power, median [quartile 1 to quartile 3]	2.84 [1.85 to 6.54]	1.06 [0.68 to 2.22]	< 0.001	< 0.001
CPB length, median [quartile 1 to quartile 3]	113 [93 to 148]	133 [105 to 188]	0.028	0.052
Lowest CPB temperature, median [quartile 1 to quartile 3]	34.1 [33.7 to 34.5]	33.8 [31.2 to 34.3]	0.005	0.016
Delirium, n/total (%)	5/81 (25)	15/60 (75)	0.003	0.013

ASA, American Society of Anesthesiologists; CPB, cardiopulmonary bypass.

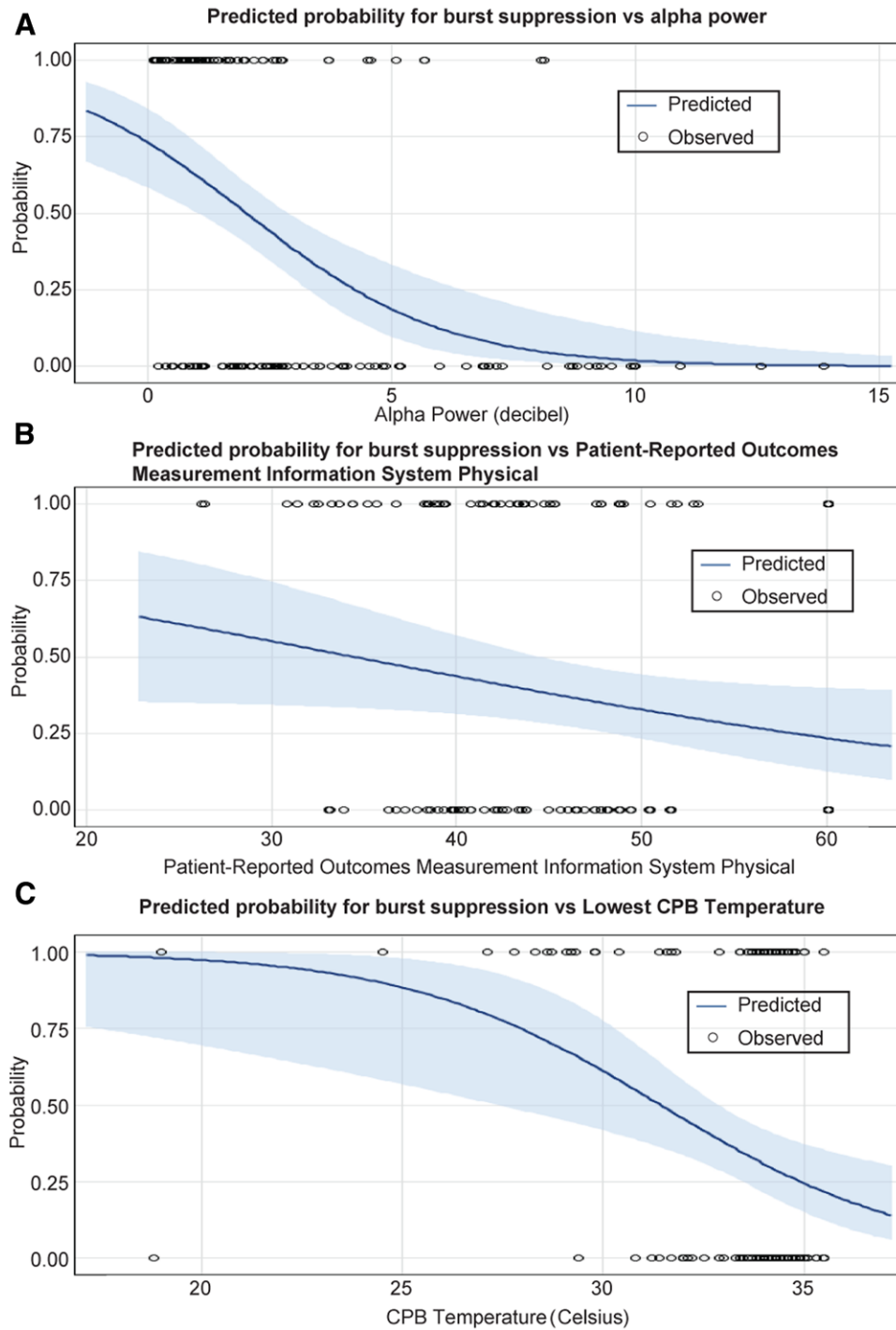
Cognitive Assessment, alpha power, and burst-suppression during CPB with delirium. The odds of delirium increased by 9% (odds ratio, 1.09 [1.02 to 1.16]; uncorrected  $P = 0.009$ ) for each year increase in age. The odds of delirium decreased by 20% (odds ratio, 0.80 [0.66 to 0.97]; uncorrected  $P = 0.024$ ) for each point increase in abbreviated Montreal Cognitive Assessment score. The odds of delirium decreased by 25% (odds ratio, 0.75 [0.59 to 0.96]; uncorrected  $P = 0.025$ ) for each decibel increase in electroencephalogram alpha power. The odds of delirium increased by 279% (odds ratio, 3.79 [1.50 to 9.60]; uncorrected  $P = 0.005$ ) in patients with burst-suppression during CPB. These findings did not meet our threshold for statistical significance after correction for multiple comparisons (Supplemental Digital Content, table 8, <http://links.lww.com/ALN/C372>).

### Multivariable Logistic Regression Models

**Alpha Power, Lowest Temperature during Cardiopulmonary Bypass, and Patient-reported Outcomes Measurement Information System Physical Scores Predicted Electroencephalogram Burst-suppression.** After backward elimination, only alpha power, lowest temperature during CPB, and Patient-Reported Outcomes Measurement Information System Physical were retained as significant predictors. (These predictors had near zero correlations with each other in our sample; thus, multicollinearity

was not of concern.) The overall model of all three was also significant (Likelihood Ratio: 46.4,  $P < 0.001$ ): alpha power (odds ratio, 0.61 [0.47 to 0.76];  $P < 0.001$ ), lowest temperature during CPB (odds ratio, 0.73 [0.58 to 0.88];  $P = 0.003$ ), and Patient-Reported Outcomes Measurement Information System Physical (odds ratio, 0.96 [0.91 to 0.99];  $P = 0.044$ ) were retained as significant predictors (fig. 2). The area under the receiver operating curve for this model was 0.84. Incidentally, the three significant predictors that we found after backward elimination were also individually significant, and no others were, in the initial model before backward elimination. Further, our finding was conserved when we ran a limited backward elimination using only predictors that were significant in univariate analyses (alpha power,  $P < 0.0001$ ; lowest temperature during CPB,  $P = 0.003$ ; Patient-Reported Outcomes Measurement Information System Physical,  $P = 0.044$ ). This suggests that our findings were not chance artifacts resulting from the iterative backward elimination procedure.

**Age and Burst-suppression during Cardiopulmonary Bypass Predicted Postoperative Delirium.** After backward elimination, only burst-suppression during CPB and age were retained as relevant predictors. The overall model of both predictors was also significant (Likelihood Ratio: 13.1,  $P = 0.002$ ): age (odds ratio, 1.07 [0.99 to 1.15];  $P = 0.090$ ), and burst-suppression (odds ratio, 4.1 [1.5 to 13.7];  $P = 0.012$ ; Supplemental Digital Content, fig. 1,



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**Fig. 2.** Predicted probability for burst-suppression during cardiopulmonary bypass (CPB) from multivariable backward logistic regression model. (A) Relationship between alpha power and probability of burst-suppression during CPB. Physical function and lowest temperature during CPB were held constant at their grand means of 46.5 and 33.2°C, respectively. (B) Relationship between physical function and probability of burst-suppression during CPB. Alpha power and lowest temperature during CPB were held constant at their grand means of 3.1 dB and 33.2°C, respectively. (C) Relationship between lowest temperature during CPB and probability of burst-suppression during CPB. Alpha power and physical function were held constant at their grand means of 3.1 dB and 46.5, respectively.

<http://links.lww.com/ALN/C389>). The area under the receiver operating curve for this model was 0.74. (The point biserial correlation of burst-suppression and age was  $r = 0.27$ ,  $P = 0.001$ , which was significant given the large sample size but well below the level of concerns associated with multicollinearity). As was the case for the retained predictors of burst-suppression, the significant predictor that we found after backward elimination was also individually significant, and no others were, in the initial model before backward elimination. This indicates that our findings were not chance artifacts resulting from the iterative backward elimination procedure. Further, our finding was conserved when we ran a limited backward elimination using only predictors that were significant in univariate analyses (burst-suppression,  $P = 0.0032$ ).

Based on our two-step multivariable logistic regression approach, our final estimated causal model is illustrated in figure 3.

### Electroencephalogram Analyses

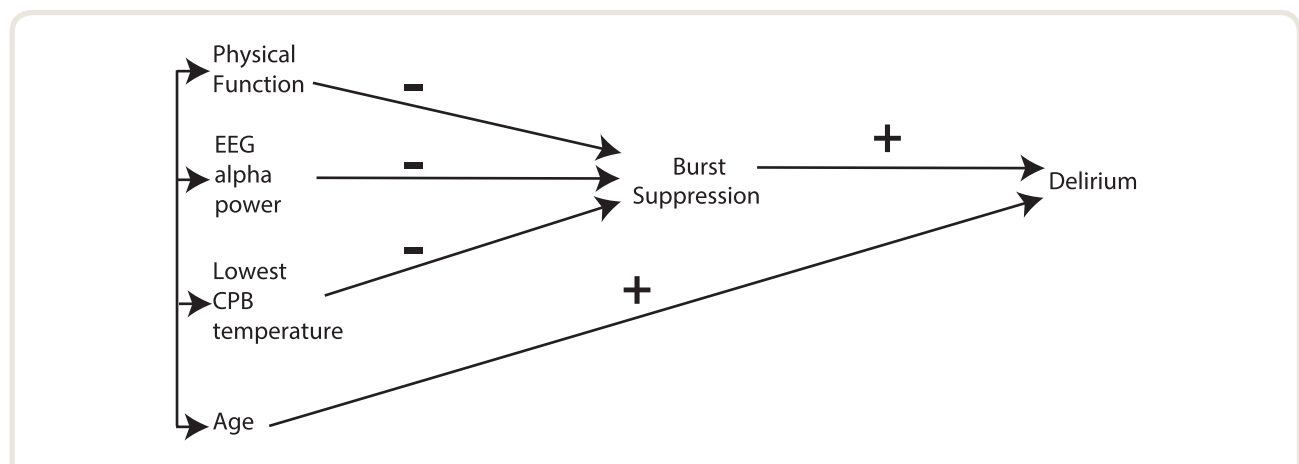
#### *Decreased but Distinct Patterns of Broadband Electroencephalogram Power Were Associated with Physical Function, Cognitive Status, and Delirium*

**Physical Function.** We compared electroencephalogram spectral estimates of age-matched patients ( $n = 34$  in each group) with low physical function scores (Patient-Reported Outcomes Measurement Information System Physical  $\leq 45$ ; Patient-Reported Outcomes Measurement Information System Global Health Physical  $\leq 45$ , mean age,  $71 \pm 6.4$ ) with patients with high physical function scores (Patient-Reported Outcomes Measurement Information System Physical  $> 45$ ; Patient-Reported Outcomes Measurement Information System Global Health Physical  $> 45$ ; mean age,

$70 \pm 6.1$ ). The isoflurane concentrations for the electroencephalogram epochs analyzed were  $0.8 \pm 0.14\%$  and  $0.8 \pm 0.11\%$  for the low physical function group and high physical function group, respectively ( $P = 0.849$ ). Representative spectrograms and time series data of two age-matched and abbreviated Montreal Cognitive Assessment-matched patients with high and low physical function are shown in Supplemental Digital Content, figure 2 (<http://links.lww.com/ALN/C373>). We observed decreased power in the low physical function group when compared with high physical function group. This difference met our threshold for statistical significance between 7.3 to 19.0 Hz (fig. 4A). **Delirium.** We compared electroencephalogram spectral estimates of age-matched patients ( $n = 23$  in each group) with no delirium (abbreviated Montreal Cognitive Assessment  $18 \pm 3$ , Patient-Reported Outcomes Measurement Information System Physical  $45 \pm 8$ , mean age  $74 \pm 6.8$ ) with patients with delirium (abbreviated Montreal Cognitive Assessment  $17 \pm 3$ , Patient-Reported Outcomes Measurement Information System Physical  $44 \pm 9$ , mean age  $74 \pm 6.7$ ). The isoflurane concentrations for the electroencephalogram epochs analyzed were  $0.8 \pm 0.12\%$  and  $0.8 \pm 0.15\%$  for the no delirium group and delirium group, respectively ( $P = 0.249$ ).

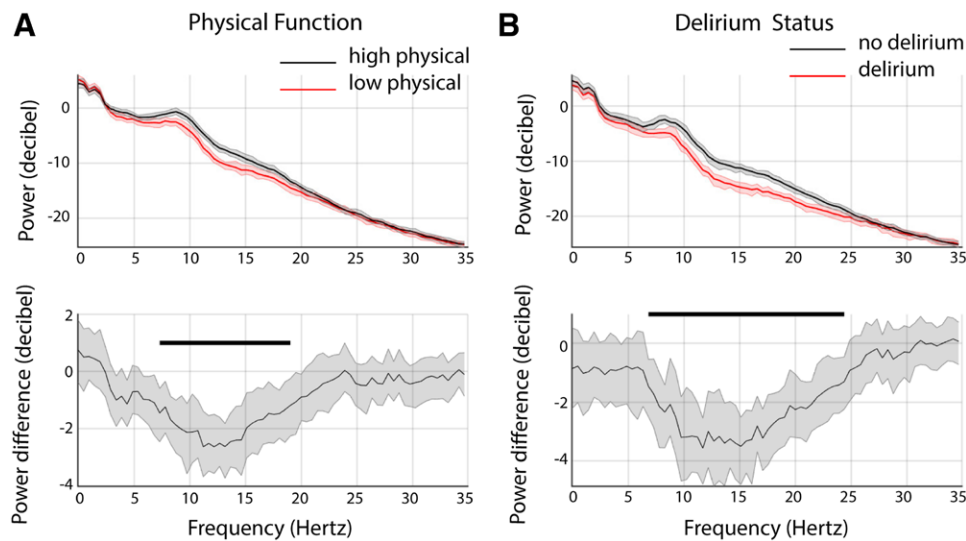
We observed decreased power in the delirium group when compared with no delirium group. This difference met our threshold for statistical significance between 6.84 to 24.41 Hz (fig. 4B).

**Cognitive Status.** The abbreviated Montreal Cognitive Assessment ranges from 0 to 22 points, and scores are categorized as positive for cognitive impairment if they are at or below 17 (mild cognitive impairment, 13 to 17; mild dementia, 7 to 12; moderate dementia, at or below 6).<sup>23</sup> We computed and compared electroencephalogram spectral



**Fig. 3.** Final estimated causal model. Physical function, electroencephalogram (EEG) alpha power, and lowest temperature during cardiopulmonary bypass (CPB) have effects on delirium mediated through their impact on burst-suppression during CPB. None of these predictors was found to have a separate direct effect on delirium outside of indirect effects through burst-suppression during CPB. Age had a direct positive effect on delirium. This model also suggests that the significant univariate association of age with burst-suppression during CPB (see Results) may partly be mediated through one or more of the exogenous predictors on the left.





**Fig. 4.** Group level spectra. (A) Power spectra of high physical function (*black*) versus low physical function (*red*) groups (*top*). Electroencephalogram power was significantly greater in the high physical function group between 7.3 to 19 Hz (*bottom*, bootstrap difference of mean). (B) Power spectra of no delirium (*black*) versus delirium (*red*) groups (*top*). Electroencephalogram power was significantly greater in the no delirium group between 6.8 to 24.4 Hz (*bottom*, bootstrap difference of mean). Median bootstrapped spectra presented with 99% CI. Horizontal solid black lines represent significantly different frequencies.

estimates of age matched patients ( $n = 48$  in each group) who screened positive for cognitive impairment (abbreviated Montreal Cognitive Assessment at or below 17; mean age,  $73 \pm 7.3$ ; mean abbreviated Montreal Cognitive Assessment,  $15.7 \pm 2.5$ ) with age-matched control patients (abbreviated Montreal Cognitive Assessment  $>18$ ; mean age,  $72 \pm 6.7$ ; mean abbreviated Montreal Cognitive Assessment,  $20.4 \pm 3.0$ ). The isoflurane concentrations for the electroencephalogram epochs analyzed were  $0.8 \pm 0.13\%$  and  $0.8 \pm 0.13\%$  for the cognitive impairment group and cognitively normal group, respectively ( $P = 0.310$ ). We observed decreased power in the cognitive impairment group (Low abbreviated Montreal Cognitive Assessment) when compared with control patients (High abbreviated Montreal Cognitive Assessment). This difference met our threshold for statistical significance between 4.88 to 9.77 Hz (Supplemental Digital Content, fig. 3, <http://links.lww.com/ALN/C374>).

## Discussion

In this study, we investigated whether burst-suppression during cardiopulmonary bypass mediates the effects of known delirium risk factors on postoperative delirium. Based on a two-step multivariable logistic regression approach, a causal model consistent with the results of our analyses is that burst-suppression during CPB mediates the effects of physical function, lowest temperature during CPB, and alpha power on delirium. Age exhibited a direct effect on delirium in our final estimated model. However, our

model also suggests that age may have an indirect effect on burst-suppression during CPB mediated through physical function and alpha power. This is because there was a significant univariate association between age and burst-suppression during CPB. Also, age was significantly correlated with physical function ( $r = -0.16$ ,  $P = 0.039$ ) and electroencephalogram alpha power ( $r = -0.33$ ,  $P < 0.001$ ). Thus, age has an additional indirect effect on delirium through burst-suppression (fig. 3). Taken together, our results suggest that electroencephalogram burst-suppression during cardiopulmonary bypass in elderly patients is a mediator of postoperative delirium.

Intraoperative burst-suppression has been associated with postoperative delirium.<sup>12–14</sup> Our finding that burst-suppression during cardiopulmonary bypass is associated with increased odds of delirium in our univariate analyses and our multivariable model is consistent with these reports.<sup>12–14</sup> However, we note that the probability of postoperative delirium in elderly patients with burst-suppression during cardiopulmonary bypass was less than 0.5 across a range of ages (Supplemental Digital Content, fig. 1, <http://links.lww.com/ALN/C389>). Thus, the sole use of burst-suppression during cardiopulmonary bypass for the identification of patients at high risk for postoperative delirium may not benefit clinical decision making. Future studies are necessary to make clear whether other electroencephalogram dynamics—from burst-suppression (*e.g.*, burst amplitude) and no burst-suppression epochs (*e.g.*, cross-frequency coupling)—may benefit delirium prediction models.

Although pathophysiologic mechanisms to explain delirium are not clear, there is strong biologic plausibility to suggest that burst-suppression mediates the association between physical function and delirium. Physical activity is associated with increased cerebral blood flow,<sup>24</sup> neurogenesis,<sup>25,26</sup> cell proliferation,<sup>27,28</sup> and synaptic plasticity<sup>29</sup> in laboratory models. In humans, physical activity is associated with increased hippocampal volume,<sup>30,31</sup> improved cognitive function,<sup>32,33</sup> and a decreased incidence of dementia.<sup>30,34,35</sup> These data are consistent with our finding that patients with low physical function scores exhibited a broadband decrease in power between 7.3 to 19 Hz. We note that poor physical function has been associated with delirium after major cardiac surgery.<sup>3</sup> Our finding that patients who subsequently developed postoperative delirium exhibited a broadband decrease in power between 6.8 to 24.4 Hz is consistent with this notion. Thus, decreased broadband electroencephalogram power during isoflurane general anesthesia may reflect delirigenic structural and perhaps functional brain dynamics.

The underlying mechanism underpinning the decreased broadband power in patients who subsequently screened for delirium is an open question. Anesthetic drugs that significantly modulate  $\gamma$ -aminobutyric acid type A receptors (*i.e.*, isoflurane, sevoflurane) are associated with highly structured oscillations.<sup>36,37</sup> The power of these oscillations exhibits a linear decrease as a function of age to suggest that they arise from intrinsic cellular properties such as synaptic integrity.<sup>38</sup> Holschneider *et al.*<sup>39</sup> demonstrated that a thio-pental challenge unmasked an abnormality (decreased beta power during sedation) in frontal electroencephalogram oscillations of patients with Alzheimer's disease that was not discernible at baseline. This abnormality was postulated to result from cortical deafferentation.<sup>39</sup>

Sun *et al.* recently conceptualized *brain age*—different from chronological age—from the electroencephalogram of sleep. They proposed the brain age index (brain age minus chronological age) to reflect the degree of deviation from normal aging.<sup>40</sup> Using an interpretable machine learning model based on spectral, entropy, time-series features, patients with neurologic or psychiatric diseases were found to exhibit increased brain age indices compared with healthy controls. Although the concept of brain age has not been applied to intraoperative electroencephalogram data, we conjecture that deviations from chronological aging may have perioperative clinical implications. This is because (1) anesthetic drugs may accentuate differences in electroencephalogram data from pathologic brain regions<sup>39</sup> and (2) we found significant differences in electroencephalogram power of patients with poor physical function and delirium.

Our study has several important limitations. First, we did not measure objective measures of physical function such as gait or grip strength. Second, we studied patients who presented for elective cardiac surgery without clinically diagnosed dementia. Thus, we cannot make inferences on

whether cognitive status is associated with intraoperative burst-suppression during CPB in other patient populations (*e.g.*, such as those with a clinical diagnosis of Alzheimer's disease). We note that the abbreviated Montreal Cognitive Assessment is not a substitute for a formal neuropsychologic battery. Third, this study was powered to analyze the association between abbreviated Montreal Cognitive Assessment scores and burst-suppression during CPB. Fourth, anesthetic adjuncts may affect electroencephalogram power. Fifth, we did not analyze spectral characteristics of bursts or the duration burst-suppression. Sixth, our sample size was modest relative to the number of predictors initially considered our multivariable models. Therefore, replication of our findings is recommended in future research. Finally, this was a prespecified substudy of the MINDDS trial where patients were randomized to placebo or dexmedetomidine intervention, an adrenergic sedative medication<sup>41,42</sup> that may affect the incidence of delirium. Thus, the incidence of delirium may have been underestimated in the MINDDS trial cohort.

In conclusion, the present study provides evidence that burst-suppression during CPB in patients older than 60 yr who present for elective cardiac surgery mediates the effect of physical function, alpha power, and lowest temperature during CPB on delirium. We also conclude that patients with postoperative delirium in this cohort possessed a preexisting susceptibility to delirium that was reflected in the intraoperative electroencephalogram as decreased broadband power. A clinical implication of our study is that physical function may be a modifiable risk factor for postoperative delirium. This concept is based on a growing body of evidence that has related cognitive,<sup>43,44</sup> morbidity,<sup>45–48</sup> and mortality<sup>49,50</sup> benefits to physical activity.

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## Competing Interests

Dr. Akeju has received speaker's honoraria from Masimo Corporation (Irvine, California) and is listed as an inventor on pending patents on EEG monitoring and sleep that are assigned to Massachusetts General Hospital (Boston, Massachusetts). Dr. Houle is a consultant for GlaxoSmithKline (Brentford, United Kingdom) and is the cofounder of StatReviewer (North Andover, Massachusetts). The other authors declare no competing interests.

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