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Original Research

Feasibility of Using a Wearable Biosensor Device in Patients at Risk for Alzheimer's Disease Dementia

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Abstract

BACKGROUND: Alzheimer's disease (AD) is the most common and most costly chronic neurodegenerative disease globally. AD develops over an extended period prior to cognitive symptoms, leaving a "window of opportunity" for targeted risk-reduction interventions. Further, this pre-dementia phase includes early physiological changes in sleep and autonomic regulation, for which wearable biosensor devices may offer a convenient and cost-effective method to assess AD-risk.

METHODS: Patients with a family history of AD and no or minimal cognitive complaints were recruited from the Alzheimer's Prevention Clinic at Weill Cornell Medicine & New York-Presbyterian. Of the 40 consecutive patients screened, 34 (85%) agreed to wear a wearable biosensor device (WHOOP). One subject (2.5%) lost the device prior to data collection. Of the remaining subjects, 24 were classified as normal cognition and were asymptomatic, 6 were classified as subjective cognitive decline, and 3 were amyloid-positive (one with pre-clinical AD, one with pre-clinical Lewy-Body Dementia, and one with mild cognitive impairment due to AD). Sleep-cycle, autonomic (heart rate variability [HRV]) and activity measures were collected via WHOOP. Blood biomarkers and neuropsychological testing sensitive to cognitive changes in pre-clinical AD were obtained. Participants completed surveys assessing their sleep-patterns, exercise habits, and attitudes towards WHOOP. The goal of this prospective observational study was to determine the feasibility of using a wrist-worn biosensor device in patients at-risk for AD dementia. Unsupervised machine learning was performed to first separate participants into distinct phenotypic groups using the multivariate biometric data. Additional statistical analyses were conducted to examine correlations between individual biometric measures and cognitive performance.

RESULTS: 27 (81.8%) participants completed the follow-up surveys. Twenty-four participants (88.9%) were satisfied with WHOOP after six months, and twenty-three (85.2%) wanted to continue wearing WHOOP. K-means clustering separated participants into two groups. Group 1 was older, had lower HRV, and spent more time in slow-wave sleep (SWS) than Group 2. Group 1 performed better on two cognitive tests assessing executive function: Flanker Inhibitory Attention/Control (FIAC) ($p=.031$), and Dimensional Change Card Sort (DCCS) ($p=.061$). In Group 1, DCCS was correlated with SWS ($\varrho=.68$, $p=0.024$) and HRV ($\varrho=.6$, $p=0.019$). In Group 2, DCCS was correlated with HRV ($\varrho=.55$, $p=0.018$). There were no significant differences in blood biomarkers between the two groups.

CONCLUSIONS: Wearable biosensor devices may be a feasible tool to assess AD-related physiological changes. Longitudinal collection of sleep and HRV data may potentially be a non-invasive method for monitoring cognitive changes related to pre-clinical AD. Further study is warranted in larger populations.

Key words: Alzheimer's disease, actinography, unsupervised machine learning, early detection, biosensor devices.

Introduction

Alzheimer's disease (AD) is the most common and most costly chronic neurodegenerative disease in the world, with over 47 million people affected by dementia globally (1, 2). Considering that the worldwide costs of dementia were estimated at US $1 trillion dollars in 2018, AD has quickly become one of the most prominent public health burdens (1).

AD develops over an extended period of time prior to the presence of cognitive symptoms, and this pre-dementia period offers a window of opportunity for early intervention targeting modifiable AD risk factors (3). Furthermore, early physiological changes in sleep and autonomic regulation have been found in patients before the onset of AD dementia (4). Multiple studies suggest that irregularities in cardiac rhythm associated with autonomic dysfunction may be related to cognitive impairment and AD (5-8). Additionally, a bidirectional relationship may link sleep and AD, as sleep disturbances caused by AD pathology can increase risk of cognitive impairment and beta-amyloid protein (Aβ) deposition (9). Therefore, objective measurements of sleep and autonomic regulation may be useful in assessing AD risk and tailoring targeted interventions aimed to delay cognitive decline (10, 11).

While sleep patterns change with age, specific sleep-pattern changes and comorbid sleep disorders

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have been established in AD (4, 12). More importantly, certain changes are detectable before the onset of AD dementia, such as decreases in both rapid eye movement sleep (REM) and slow wave sleep (SWS) (13, 14). Decreases in SWS are partly due to the degradation of cholinergic neurons in the basal forebrain and can diminish glymphatic clearance of Aβ (15, 16). SWS has also been shown to preferentially benefit the prefrontal cortex (PFC), which substantially contributes to executive function (17). Considering this, along with the fact that executive function impairments are seen in early AD, sleep-cycle measurements may be an effective way for clinicians to monitor pathological changes in patients at risk for AD (18).

Polysomnograms (PSGs), or sleep studies, are considered the "gold standard" for assessment of neurophysiological function during sleep. However, even considering the high prevalence of sleep disorders, many patients defer PSG evaluation, mainly due to its high financial cost, long waiting lists, and burdensome protocol that can limit comfort (19). Furthermore, PSG administration typically involves an overnight stay in a specialized facility, which may be less accessible to certain patient populations (20). While there has been an emergence of at-home sleep assessment tools, most of these instruments are focused on sleep apnea assessment rather than broad neurophysiological function (21). Thus, using PSGs to longitudinally track sleep in patients remains impractical, and this can limit a clinician's access to useful data for designing interventions to reduce AD risk.

With the proliferation of wearable biometric devices, longitudinal collection of sleep and autonomic biometrics has become possible in a real-world clinical setting. These newer wearables use an accelerometer to monitor sleep, a validated method used in traditional actinography devices (22), and demonstrate sleep tracking performance comparable to their actinographic predecessors (23). Additionally, many devices record heart rate variability (HRV), commonly measured as the root mean square (RMS) of successive differences between beats in a given time interval. The RMS HRV is a validated metric for autonomic function, where higher HRV generally reflects more robust autonomic regulation (24, 25).

One device that tracks both sleep patterns and HRV is the WHOOP strap, a wearable wrist device developed for athletes (26). Like many other commercial sleep tracking devices, WHOOP uses an accelerometer to monitor sleep. Additionally, the WHOOP device internally computes the RMS HRV metric using the wearer's heart rate via an optical sensor.

It is currently unknown whether using a wearable biosensor device to detect changes in sleep and autonomic regulation may be a cost-effective and convenient way to broadly screen patients for AD risk. It is also unclear whether the use of these tools may hold promise in clinical research settings to monitor longitudinal changes over time in patients at risk for cognitive decline. Our study's objective was to prospectively examine the feasibility of using a wearable biosensor device to collect sleep and HRV data longitudinally in patients at risk for AD, and investigate whether these physiological data may be related to cognitive performance.

Methods

Study Overview

Beginning August 1, 2017, patients from the Alzheimer's Prevention Clinic (APC) at Weill Cornell Medicine and New York-Presbyterian were recruited to wear the WHOOP biosensor. Prior to wearing the WHOOP, participants completed a comprehensive survey assessing user attitudes, and included validated sleep and exercise scales. Participants were also given written instructions on how to use the WHOOP device. After one month and six months of wearing the WHOOP, participants were again asked to complete surveys assessing their satisfaction. Throughout the study duration, sleep and HRV data were acquired and aggregated for each patient. Additionally, participants underwent neuropsychological testing and blood biomarker evaluation during the initial and 6-month follow-up visit to the APC. A combination of machine learning and traditional statistical techniques was used to examine the physiological data in relation to performance on neuropsychological testing sensitive to changes in pre-clinical AD (27).

Institutional Review Board approval was obtained, and patients were consented to participation in the Comparative Effectiveness Alzheimer's and Dementia Registry (Protocol # 1408015423).

Participants

Forty consecutive APC patients were asked to participate in the study. Thirty-four patients (85%) agreed to wear the WHOOP device. However, one patient (2.5%) lost the device prior to data collection. All 33 patients had a family history of AD and were given an extensive clinical evaluation which included neuropsychological testing, anthropometric measurements, serum biomarkers, and AD biomarker assessment (via amyloid positron emission tomography [PET] or cerebrospinal fluid). Upon clinical assessment, 24 patients (72.7%) were classified as normal cognition and were asymptomatic, 6 patients (18.2%) had subjective cognitive decline (SCD), and 3 patients (9.1%) were found to be amyloid-positive (one with pre-clinical AD, one with pre-clinical Lewy-Body Dementia [LBD], and one diagnosed with MCI due to AD). Five patients took prescription medications for sleep (trazodone x3, zolpidem x1, mirtazapine x1) and these medications remained unchanged throughout the study duration.

Procedures

Biometrics

Metrics collected from the WHOOP were total sleep time (TST), proportion and hours spent in REM, non-REM (NREM), and SWS, as well as daily RMS HRV. The metrics were averaged over all days that the patient wore the WHOOP. Participants were instructed to wear the WHOOP device at all times, except when showering/bathing.

User Surveys

Participants were asked to complete surveys at baseline, after one month, and after six months. The initial survey contained 17 questions assessing a host of behaviors and attitudes toward exercise and sleep, and also included a validated scale regarding participants' exercise habits (28). The one month and six month surveys repeated all questions asked on the initial survey, as well as 4 additional questions regarding their experience with the WHOOP and its influence on their sleep and exercise habits (Appendix A).

Neuropsychological Testing

Neuropsychological testing involved a combination of validated computerized and pen-and-paper tests that assess cognitive domains sensitive to early signs of cognitive decline (27). These domains include memory, attention, executive function, language and lexical access, visuospatial function, and processing speed. The tests were selected from the National Institutes of Health Toolbox Cognition Battery (NIHTB-CB) (29), including the Rey Auditory Verbal Learning Test, Dimensional Change Card Sort, the Flanker Inhibitory Control/Attention, Pattern Comparison Processing Speed and Oral Symbol Digit tasks. Additional validated tests included the Face-Name Associative Memory Task, the Mini-Mental State Examination, Logical Memory Immediate and Delayed Recall & Oral Word Production (under both phonemic and categorical constraint). To assess crystallized intelligence, Picture Vocabulary and Oral Reading Recognition were used (30).

Statistical Analysis

User Surveys

Differences among ordinal variables within the baseline, one month, and six month surveys were compared using the Friedman test, with post hoc Wilcoxon Rank Sum tests. Repeated measures ANOVA was used to compare differences in means of numeric variables, with post hoc paired t-tests. Differences in categorical variables within each group were compared using multivariate McNemar's Chi-Squared test.

K-means Clustering

Unsupervised machine learning [K-means clustering (K=2, cosine similarity, 50 iterations)] was performed to separate patients into two groups that shared similar biometrics (31). Daily RMS HRV, TST, hours spent in NREM, REM, and SWS, proportion of time spent in NREM, REM, and SWS were standardized and then used as clustering variables. Because results of studies reporting age related sleep changes have been highly variable and inconsistent, the sleep metrics were not age-adjusted, but rather age itself was included as an additional clustering variable (32, 33).

Participants were clustered along nine variables (dimensions; d). The optimal d for a given sample size (n) is typically n-1 for uncorrelated variables and $\sqrt{n}$ for highly correlated variables (34). Based on this, the optimal d would be between 6 and 32. In this study, some variables had known correlation with one another (e.g., age and total sleep time), while some were expected to be closely correlated (e.g., hours slept in SWS and proportion slept in SWS). Thus, the d=9 used in this study, at the lower range of 6-32, was a reasonable parameter.

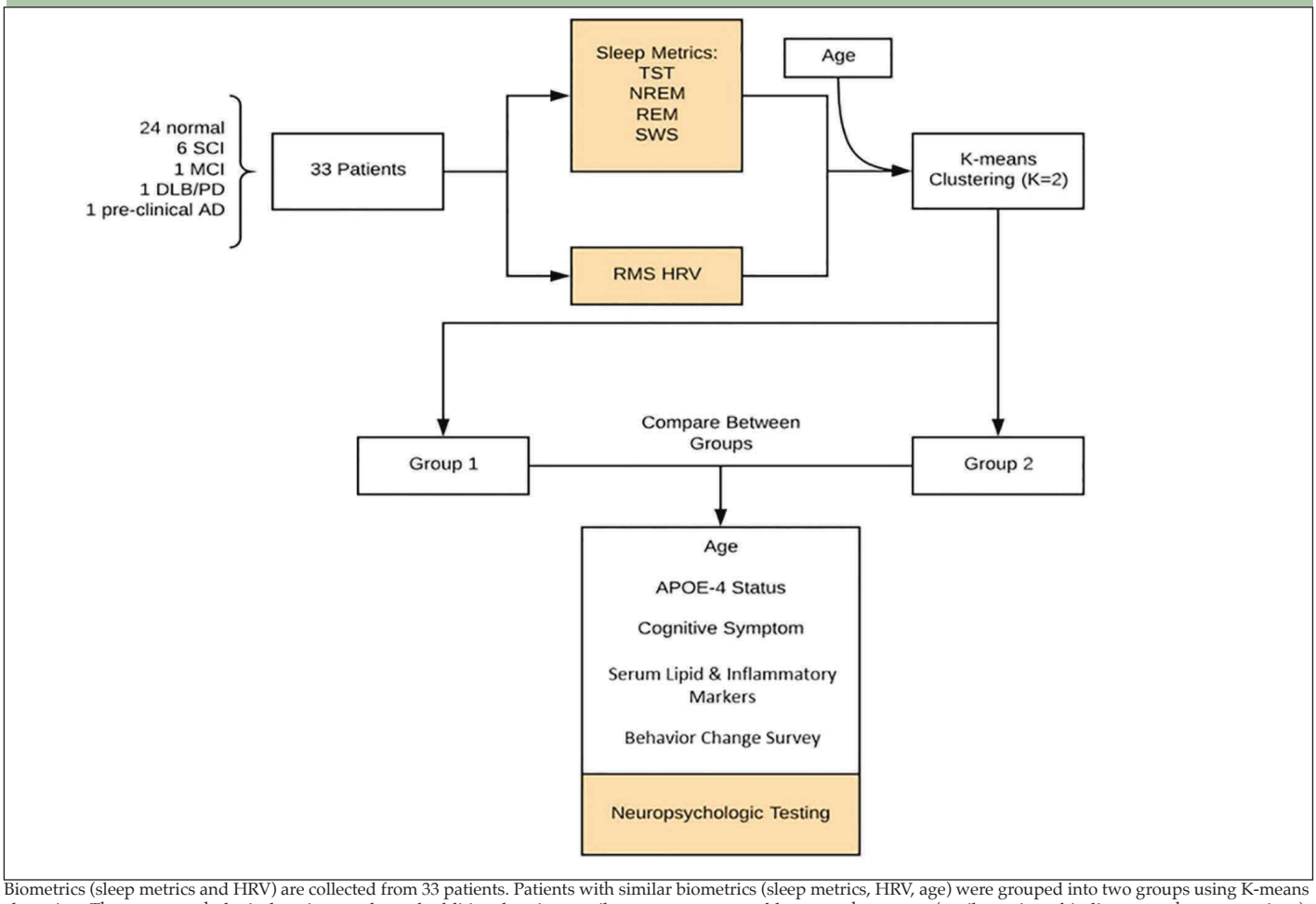
We used K-means clustering, a parametric clustering technique where the number of clusters (k) must be specified a priori. We selected k=2 because of our relatively low sample size (n=33) compared to the number of clustering variables (d=9). As the number of dimensions increases, points in a d-dimensional space spread out in a roughly exponential manner (35). This spread can produce an 'artificial' separation that obscures the underlying true separation among clusters. This can be especially problematic when n and k are similar. Thus, we selected the smallest possible k (k=2) to maximize the difference between n and k.

Group Comparison

To determine if biometric differences were associated with cognitive differences, performance on the neuropsychological tests was compared between the two groups. This was followed by a comparison of serum lipid and inflammatory markers between the two groups (Appendix B). Finally, potential correlations among biometrics and the neuropsychological test results were examined within each group. (Figure 1)

Differences in continuous variables (e.g., time spent in SWS, REM, NREM) between groups were compared using the Wilcoxon Sum Ranked test. Differences in categorical variables (e.g. amyloid-positive PET) were compared with the Chi-squared test. P-values were

Figure 1. Study design overview



Biometrics (sleep metrics and HRV) are collected from 33 patients. Patients with similar biometrics (sleep metrics, HRV, age) were grouped into two groups using K-means clustering. The neuropsychological testing results and additional patient attributes were compared between the groups (attributes in red indicate post-hoc comparison). Potential correlation between biometrics and neuropsychological test performance (orange boxes) were correlated within each group.

adjusted for multiple comparisons using the Benjamini-Hochberg method. Potential correlation of cognitive scores to biometrics within each group was assessed using Spearman's correlation.

Results

User Satisfaction

There were 34 participants who completed the baseline questionnaire, one of which lost the WHOOP. 31 participants (91.2%) completed the one month follow up questionnaire and 29 participants (85.3%) completed the six month follow up questionnaire. 27 participants (79.4%) completed both the one month and six month follow-up questionnaires and were included in the analyses. Of these 27 participants, 22 (81.5%) were satisfied with WHOOP after one month and 24 (88.9%) were satisfied after six months (satisfied = Strongly Agree + Agree). There was no significant difference in satisfaction with WHOOP between these two time points (p=0.31). At six months, 23 participants (85.2%) responded that they wanted to continue wearing the WHOOP while 2 participants (8.4%) responded that they were not sure.

K-Means Clustering

The 33 participants were clustered into two well-demarcated groups consisting of 14 and 19 participants (Figure 2). The mean biometric values of the two groups are shown in Table 1. On average, Group 1 was older (59.3y vs 43.4y), had lower HRV (26.5 vs 47.7), and had less total sleep time (6.74h vs 6.96h) than Group 2. However, Group 1 spent more total and proportion of time in SWS than Group 2 (.25 vs .15).

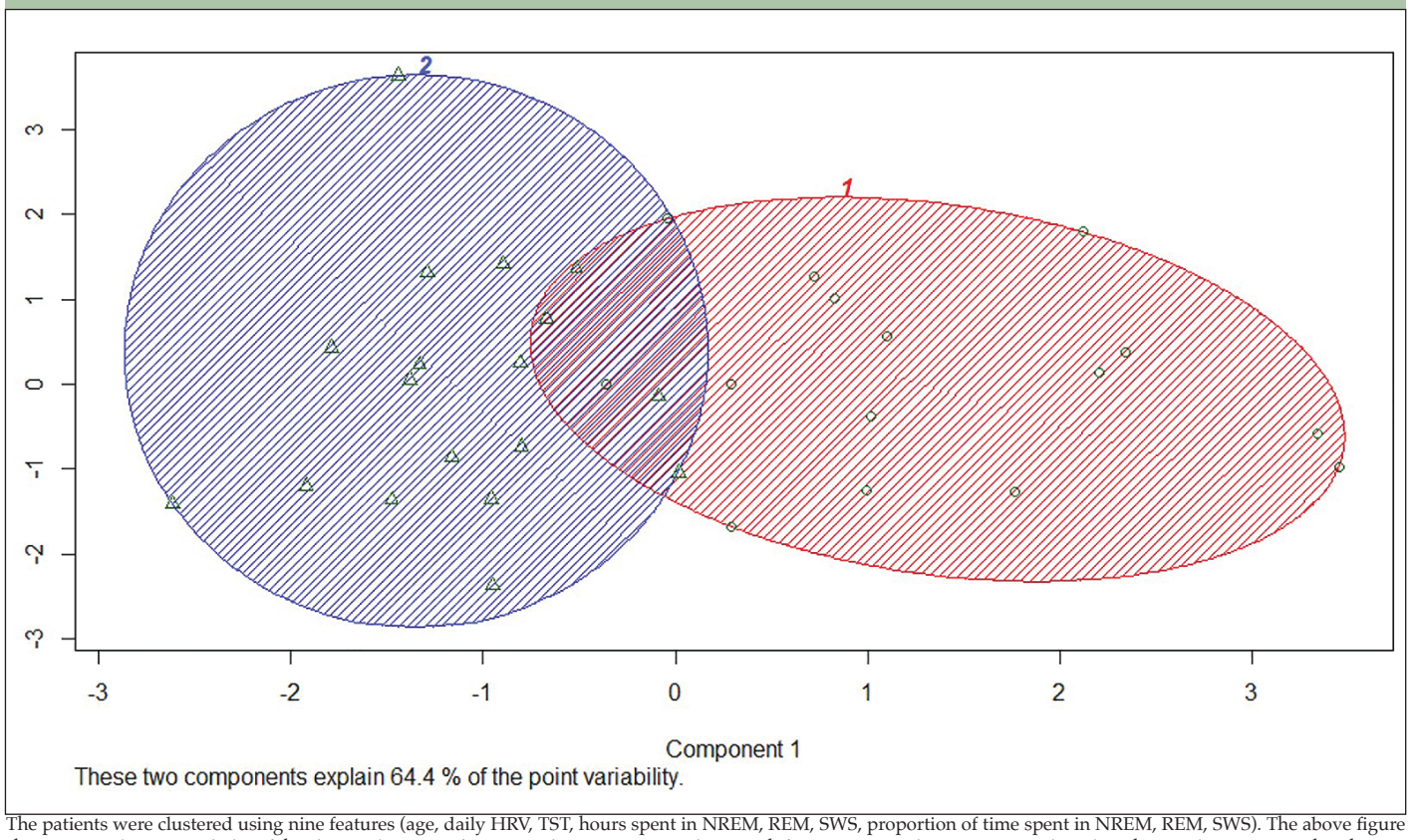
A comparison of the neuropsychological testing performance between the two groups is shown in Table 2. Performance on the Flanker Inhibitory Attention and Control (FIAC) was higher in Group 1 than in Group 2 (p=.031). Performance on the Dimensional Change Card Sort (DCCS) was also higher in Group 1, and this was marginally significant (p=.061). None of the other neuropsychological test results approached a statistically significant difference between the two groups.

Table 1. Mean biometrics of the patients in the two clustered groups

Biometrics	Group 1		Group 2	
	mean	95% CI	mean	95% CI
Age	59.27	53.27 - 65.26	43.44	37.02 - 49.87
HRV	26.5	22.39 - 30.62	47.72	41.44 - 54.01
Hours Slept	6.74	6.44 - 7.04	6.96	6.7 - 7.22
REM Sleep Hours	0.94	0.67 - 1.22	1.39	1.15 - 1.63
Light Sleep Hours	4.1	3.8 - 4.4	4.43	4.19 - 4.66
Deep Sleep Hours	1.69	1.5 - 1.87	1.05	0.86 - 1.25
Proportion REM	0.14	0.1 - 0.17	0.2	0.16 - 0.24
Proportion Light	0.61	0.58 - 0.64	0.65	0.62 - 0.67
Proportion SWS	0.25	0.22 - 0.29	0.15	0.13 - 0.18

For all biometrics between the groups, the 95% confidence interval (CI) are non-overlapping.

Figure 2. K-means clustering resulting in two distinct groups



The patients were clustered using nine features (age, daily HRV, TST, hours spent in NREM, REM, SWS, proportion of time spent in NREM, REM, SWS). The above figure shows a two-dimensional plot of the clustered groups after principle component analysis, with first two principle components plotted on the x and y axis. Note that the two groups (red and blue shaded regions) are already well separated along the first principle components.

Within each group, statistically significant correlations between the neuropsychological test results and WHOOP data are shown in Figure 3. Performance on DCCS demonstrated a strong positive correlation with total time spent in SWS (ϱ=0.68, p=0.024) and proportion SWS in Group 1 (ϱ= 0.58, p= 0.0054), but not in Group 2. Performance on DCCS also demonstrated a positive correlation with HRV in both Group 1 (ϱ=.6, p=0.019) and Group 2 (ϱ=.55, p=0.018). Performance on the FIAC did not have a significant correlation to any biometrics in either group.

There was no significant difference between the two groups in any of the lipid and inflammatory markers, as well as the patient behavior surveys.

Discussion

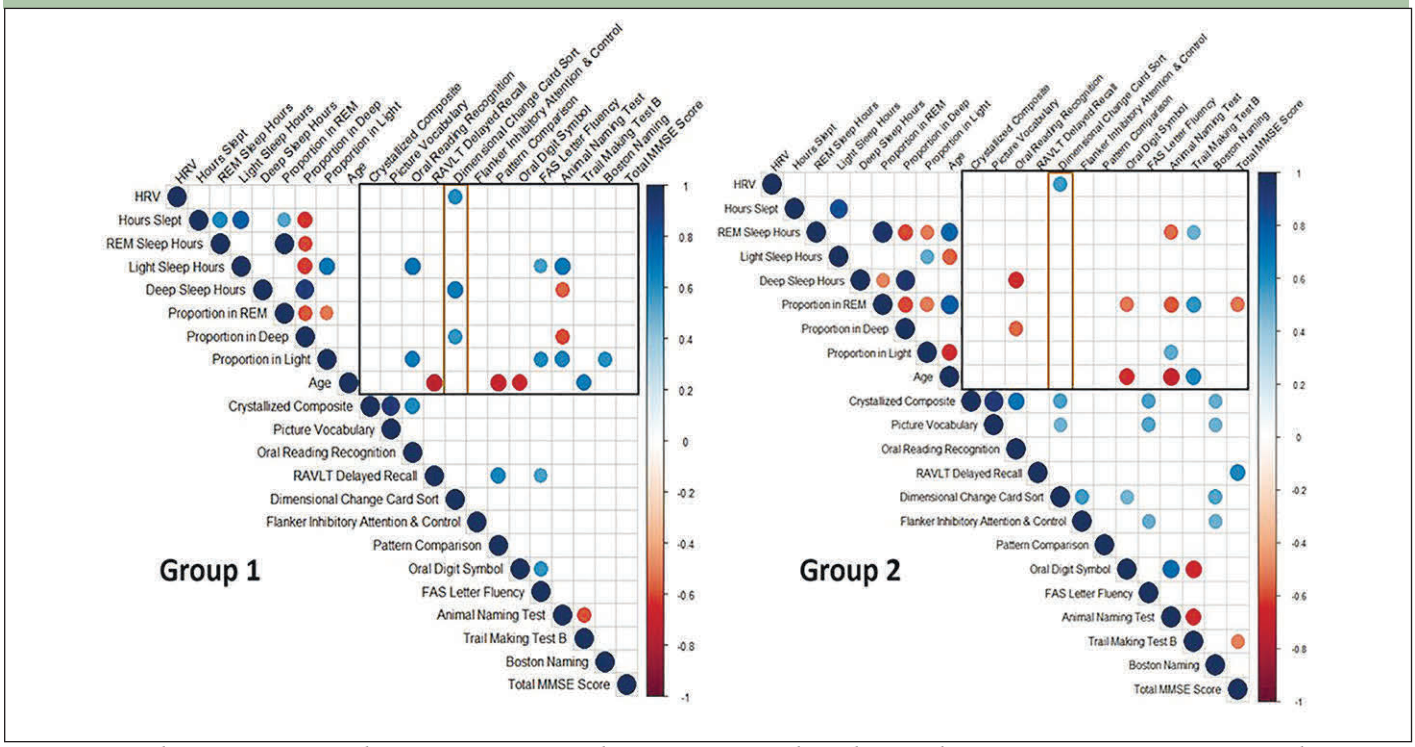
Our study demonstrated that participants were highly satisfied with the WHOOP device, and the vast majority planned to continue wearing the device past the study

Table 2. Comparison of neuropsychological testing performance between groups

Cognitive Assessment	Group 1		Group 2		
	mean	95% CI	mean	95% CI	p-value
Crystallized Composite	130.47	124.12 - 136.82	121.59	113.13 - 130.05	0.261
Picture Vocab	129.84	122.69 - 136.99	120.03	111.81 - 128.25	0.261
Oral Reading Recognition	117.77	114.38 - 121.17	114.1	108.77 - 119.44	0.584
RAVLT Delayed Recall	10.13	7.94 - 12.33	10.61	9 - 12.22	0.944
Dimensional Change Card Sort	113.14	108.71 - 117.57	104.99	100.92 - 109.05	0.061
Flanker Inhibitory Attention & Control	111.86	109.49 - 114.23	103.96	100.25 - 107.67	0.031
Pattern Comparison Scale Score	128.17	119.51 - 136.82	118.88	110.83 - 126.93	0.261
Oral Digit Symbol	80.87	72.14 - 89.59	88.83	80.67 - 96.99	0.459
FAS Letter Fluency	53.33	46.85 - 59.82	50.28	43.33 - 57.23	0.584
Animal Naming Test	27.8	24.58 - 31.02	26.22	23.54 - 28.9	0.584
Trail Making Test B	45.33	36.61 - 54.06	44.17	37.89 - 50.44	0.957
Boston Naming	14.67	14.32 - 15.01	14.28	13.41 - 15.14	0.943
Total MMSE score	29.13	28.38 - 29.88	29.5	29.19 - 29.81	0.843

The Flanker Inhibitory Attention & Control scores were significantly different between the two groups. The Dimensional Change Card Sort score approached significant difference. P-values were adjusted for multiple comparisons (Benjamini-Hochberg method).

Figure 3. Correlogram plots



A visualization of the correlation matrix of the biometrics and neuropsychological test scores within each group. The black boxes outline correlation between the biometrics and neuropsychological test scores, with blue indicating positive and red indicating negative correlation. Of the two cognitive tests that approached significant difference between the two groups, only the Dimensional Change Card Sort had a significant positive correlation with the biometric markers (red rectangle). Only correlations with $p<0.050$ are shown.

period. The convenient nature of the WHOOP device allowed us to collect an average of 149 days of sleep and HRV data for each participant. To our knowledge, this is the first study to demonstrate the feasibility of using a wearable biosensor device to collect sleep and HRV measures in effort to assess and longitudinally monitor physiological changes in at-risk AD patients. Our study applied unsupervised machine learning to cluster patients based on differences in multivariate physiological data, which allowed for identification of potential patterns in these data and cognitive performance related to pre-clinical AD.

Overall, Group 1 patients were older and had lower HRV, which reflects the decline of autonomic robustness with age (32). Interestingly, while SWS generally decreases with age, the time and proportion spent in SWS was higher in Group 1. Five of the 14 patients in Group 1 took a prescription sleep medication, which likely affected their sleep cycles. These medications include trazodone and mirtazapine, both of which affect serotonin uptake, are minimally anti-cholinergic, and have been reported to increase SWS (36, 37). Other potential contributing factors to the difference seen in SWS include patient sleep and exercise habits. To assess their contributions, we compared the patient sleep and exercise experiences recorded in the baseline and follow up surveys, and no significant differences were found between the two groups.

The FIAC and DCCS tests assess executive function, and both were of significant or nearly significant difference between Groups 1 and 2. While the FIAC did not show significant correlation to any biometric in Group 1 or 2, the DCCS did show a significant positive correlation with SWS in Group 1. Performance on the DCCS has been associated with functional connectivity in the PFC (38). Given that reduced SWS is associated with PFC atrophy, therapeutic intervention targeting SWS may have led to improved PFC function, resulting in Group 1's improved performance on the DCCS (39). Further research exploring the use of SWS-preserving interventions to improve cognition in older adults is needed.

Additionally, we found a significant positive correlation between HRV and DCCS scores in both groups. This suggests that HRV may also be a potentially useful marker for executive function, though it was unable to differentiate the relative differences in DCCS performance between the two groups. Since there is no established standard in calculating the HRV or delineation of which HRV calculation method best suits a specific purpose, HRV may be better compared within an individual rather across groups of individuals. Future research consisting of multiple cognitive tests over time would be required to examine how changes in an individual's HRV compare to cognitive change and AD risk.

There are several limitations within this study. The study population was obtained by recruitment of consecutive clinic patients. While this led to a study sample that included a majority of asymptomatic, generally healthy patients at risk for AD, patients with SCD, MCI due to AD, pre-clinical AD, and pre-clinical LBD were also included. Additionally, while ~75% of patients enrolled in the APC clinical research registry are over age 50, the cohort recruited in this study was younger (with only ~65% of participants above the age of 50). Our clinic cohort includes a broad range of ages, as patient demand for risk reduction care spanned across younger, middle-aged, and older populations. Despite the limitation of a broad age range, and heterogeneous study population, this patient sample is generally representative of the patient population visiting the Weill Cornell APC. Nevertheless, random sampling would be ideal for analysis to provide more definitive conclusions.

While clustering followed by correlation analysis allowed for grouping of patients based multivariate biometrics, and identified both between group differences and within group similarities, the small sample size significantly constrained these analytical techniques. A larger sample would allow us to produce more than two clusters, or enable non-parametric clustering with self-organizing maps (40). Additionally, a larger sample would enable cross-validation of our clustering method as well as better define the correlations among biometrics and cognitive performance in the grouped patients.

A large portion of our biometrics were sleep-related, and multiple extrinsic factors can affect sleep, such as changes in the home environment, travel, and other psychosocial stressors which were not explicitly controlled in our study. Controlling for these factors would not have represented how patients usually behave, which would limit our feasibility assessment of the device's usefulness in a clinical research setting and/or real-world clinical practice. However, controlling for these factors this may provide more definitive conclusions regarding the WHOOP data's effectiveness. Furthermore, conducting the study in larger samples and for longer periods of time may mitigate the effects of any transient outliers.

Additionally, while several wearable biosensor devices have demonstrated high sensitivity for measuring total sleep time and wake after sleep onset, these devices may not be as accurate for SWS and REM sleep when compared to the gold standard PSGs and may not be an optimal alternative for sleep-stage measurement (41). However, wearable biosensors may be more practical and, despite the potentially decreased accuracy, we were able to identify correlates between these collected measurements and cognitive function. Further research is warranted to better understand the potential utility of these wearable biosensor-collected metrics in assessing and reducing AD risk.

Conclusion

Our study demonstrates the initial feasibility of using a wearable biosensor device for assessment and monitoring of sleep and HRV measures in patients at risk for AD dementia. Using wearable devices may help to eventually enable clinician researchers to non-invasively and cost-effectively, detect sleep disturbances and autonomic dysregulation related to early AD pathology, in a possible effort to tailor risk reduction interventions that may help delay cognitive decline (11, 30, 42). Through unsupervised machine learning techniques, we demonstrated that physiological data collected via a biosensor device may be a potentially

useful method for monitoring cognitive changes related to preclinical AD. Future studies with larger sample sizes, different biosensor devices, and more robust analytical methods are warranted to expand upon these preliminary findings, and may help to elucidate the potential of wearable biometric devices in AD risk assessment and individualized AD risk reduction.

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Declaration of interests: Dr. Isaacson has served as a scientific advisor for Eisai. The remaining authors report no conflicts of interest or other relevant disclosures.

Ethical standards: The study procedures followed were in accordance with the ethical standards of the Institutional Review Board and the Principles of the Declaration of Helsinki (revised version of 2013).

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