

## Sleep Disorder Screening: Integration of Subjective and Objective Measures

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### Abstract

**Purpose:** Comparing the output of two subjective self-evaluation sleep questionnaires commonly used in adult populations at-risk for sleep disorders, focusing on sleepiness and insomnia symptoms, to automated analysis of electrocardiography (ECG) data collected during sleep, to measure sleep quality.

**Method:** Output of two sleep questionnaires; the Epworth Sleepiness Scale (ESS) and the Bergen Insomnia Scale (BIS) were compared to the primary data signal, ECG, collected during sleep with a simple wearable device and analyzed with the Cardiopulmonary Coupling (CPC) algorithm. Based on the objective Sleep Quality Index (SQI), and the sleep pathology markers, Elevated Low Frequency Coupling Broad-Band (eLFC<sub>BB</sub>) and Narrow-Band (eLFC<sub>NB</sub>), participants were divided into healthy and unhealthy sleepers, and the output of each subjective questionnaire and the combination of both questionnaires statistically analyzed and compared to the CPC-output.

**Results:** Data collected from 57 obese individuals, when starting a lifestyle program supervised by a primary care physician, was retrospectively analyzed. Of the 57 individuals, 50 recorded two consecutive nights. When compared to the objective CPC-output the questionnaires had low sensitivity, specificity and agreement: (1) ESS; sensitivity 23%, specificity 69% and agreement 51%. (2) BIS; 73%, specificity 43% and agreement 54%. Combining the questionnaires ESS/BIS had sensitivity 73%, specificity 29% and agreement 46%.

**Conclusion:** Wearable devices offer a convenient and cost-effective alternative for more accurate evaluations of sleep quality complaints than methods previously available. Our results strongly suggest that in populations at high risk of sleep disorders, questionnaires and objective measurements are likely required to provide complementary and more comprehensive sleep quality assessments.

### Introduction

The National Health and Nutrition Examination Survey (NHANES) reported that in 2013-2014 that 32.7% of adult Americans were overweight ((Body Mass Index (BMI) of 25.0-29.9 kg/m<sup>2</sup>) and 37.9% were obese (BMI > 30.0 kg/m<sup>2</sup>), compared with 1960-1962 when a similar percentage of overweight Americans was 31%, but only 13% were obese, demonstrating a vast increase in obesity [1]. Obesity leads to significant health problems impacting nearly every organ system, including coronary heart disease, hypertension, dyslipidemia and type 2 diabetes [2].

In parallel to the obesity epidemic, society has become increasingly fast-paced, presenting us with numerous stressors including lack of sleep duration and impaired sleep quality [3]. Sleep is increasingly recognized as being important to public health, with sleep insufficiency linked to motor vehicle accidents, industrial disasters, occupational errors, and medical comorbidities. Having difficulties performing daily tasks, unintentionally falling asleep or nodding off while driving because of sleepiness may contribute to these hazardous outcomes [4-6]. Insufficient sleep is associated with a number of chronic diseases such as cardiovascular disease, [7,8] obesity, [9,10] type 2 diabetes, [11] as well as a reduced quality of life and increased mortality [12]. This underscores the importance of sleep problems as health indicators, emphasizing the need for sleep disorders to be placed in a broader health context [13-15].

Insomnia and Sleep Apnea (SA) are the two most common sleep disorders. Insomnia is commonly encountered in medical practices, and occurs in approximately 33-50% of the adult population and chronic insomnia in approximately 10-15% [16,17] It is estimated that 12% of adults suffer from the more common form of sleep apnea, Obstructive Sleep Apnea (OSA) that is characterized by repeated partial, or complete obstruction of the upper airway during sleep, resulting in intermittent hypoxia and transient repetitive sympathetic arousals from sleep, and that 80% of the patient population is undiagnosed [4,18,19]. A recent European study looking at the prevalence of Sleep Disorder Breathing (SDB) in the a general population found that the disease is highly prevalent: 23.4% in women and 49.7% in men [19] and a recent Icelandic study found the prevalence in a middle-aged general population of mild, moderate and severe OSA at 43.1%, or 19% when looking at only moderate and severe OSA [20]. The Center for Disease Control and Prevention (CDC) has stated that getting sufficient sleep is not a luxury – it is something people

need for good health [14] emphasizing the importance of sleep as an important part of health and wellbeing.

Accepted clinical methods used to screen for sleep disorders have mostly been limited to subjective questionnaires for convenience, effort and cost reasons. Questionnaires are based on respondents' own subjective evaluation of their sleep rather than objective data and even though they have been validated, when compared to objective measures, their results have shown to be inconsistent and unreliable [21-25]. Though subjective estimates undoubtedly can be useful to a degree, sleepiness and daytime functioning varies widely between patients, some report excessive daytime sleepiness while others do not [20,26]. People with sleep complaints and sleep disorders may not accurately estimate sleep as their perception depends heavily on extraneous factors including demographics and comorbidities, and they often tend to underestimate sleep time and quality. Conversely, individuals without sleep complaints, tend to over-estimate sleep duration [27]. A reasonable question is, what is the preferred standard? In many disease conditions, e.g., cardiovascular diseases or diabetes, subjective symptoms are not considered adequate. Generally, if a questionnaire has a high sensitivity, it is at the expense of poor specificity, and vice versa, deeming them inaccurate tools relying on in isolation, and likely that most of the questionnaires will inaccurately-classify a significant proportion of patients suffering from sleep disorders [21-25].

For patients identified to have insomnia based on a questionnaire, a diagnostic test such as a Polysomnography (PSG) is not used for routine evaluation, unless the screening test is inconclusive, or behavioral or pharmacologic treatment fails [28,29]. However, emerging evidence suggests that sleep-related breathing disorders in particular, may be an under-recognized causes of insomnia complaints, even among individuals who deny symptoms of SDB at initial presentation [30-32]. It is recommended that positive results for identifying SA based on sleep questionnaires be followed up with a diagnostic test for SA. PSG is the reference standard for diagnosis of SA before treatment is initiated, and attended study is the recommended testing method with the recording of Electro-Encephalography (EEG), Electrooculography (EOG), Electromyography (EMG), Electrocardiography (ECG), oronasal airflow, respiratory effort and oxygen saturation, presenting an index, the Apnea Hypopnea Index (AHI), subject to human interpretation of the data output [33,34]. PSG tests can be challenging to obtain, as the procedure is time-consuming, labor intensive, costly and not available to all at-risk patients. Home Sleep Testing (HST) is less expensive and can be somewhat less challenging to obtain, but lacks the sensitivity to rule out SA diagnosis as it does not record sleep onset, sleep duration, sleep efficiency or wakefulness. HST is not recommended to screen for Insomnia. If a patient suspected of having SA has a negative HST, the recommendation is to follow up with a PSG test [35]. This process is costly, time consuming and impractical in the population of at-risk patients.

The clinical settings that are best suited to play the role of screening patients with sleep complaints are in primary care settings [4,36-38]. In order to make that practical, an efficient screening method that analyses objective data, that is simple to collect and has automated output that is easy to interpret, is necessary for evidence-driven clinical assessment and clinical management.

The primary objective of this study is to compare the outcome of two subjective questionnaires, the Epworth Sleepiness Scale (ESS) [39] and Bergen Insomnia Scale (BIS) [40], to output of an ambulatory sleep screening system, SleepImage<sup>®</sup> (Figure 1), that objectively measures patients sleep in their home, to assess their sleep quality and identify the presence of sleep disorders to guide clinical decisions, and therapy management if needed. The second objective, to identify night-to-night sleep variability, since only measuring objective data for one night might falsely identify individuals as healthy. The SleepImage<sup>®</sup> system ([www.sleepimage.com](http://www.sleepimage.com)) is FDA approved and CE marked for sleep disorder screening based on patented and clinically validated algorithm analyzing a single lead ECG-signal and is a Health Insurance Portability and Accountability Act (HIPAA)-compatible Cloud Computing system. The method to characterize sleep based on the interaction of autonomic and respiratory oscillations (CPC), termed the Electrocardiogram (ECG) derived spectrogram and to provide an objective measure of sleep duration, sleep quality and sleep pathology has been performed as described in detail [41,42].

Sleep spectrogram analysis reveals that NREM sleep has a distinct bimodal-type structure marked by distinct alternating and abruptly varying periods of strong high and low frequency cardiopulmonary coupling intensity (High Frequency Coupling (HFC) and Low Frequency Coupling (LFC)), respectively. Much of HFC, which is associated with non-cyclic alternating pattern (non-CAP) EEG, occurs during part of stage N2 and all of stage N3 and is associated with periods of stable breathing, a paucity of phasic EEG transients, physiologic blood pressure dipping. Conversely, LFC is characterized by temporal variability of tidal volumes, Cyclic Alternating Pattern (CAP) EEG morphology, non-dipping of blood pressure and lower frequency cyclic variation in heart rate. The amount of HFC is reduced by processes that fragment sleep such as sleep apnea and fibromyalgia [43,44]. The ECG-CPC technique has been shown to accurately identify sleep apnea, and capture treatment effects in sleep apnea [46-50] and insomnia [51,52]. In this way, the NREM sleep phenotype extends beyond conventional scoring of AHI and its reliability on absolute delta power. These disparities are especially apparent in individuals over the age of 40-50 years, for whom stage N3 makes up less than 20% of the sleep period [53].

## Materials and Methods

### Design and setting

Retrospective analysis of data collected at Heilsborg, Bildshöði 9, 108 Reykjavik, Iceland, Tel: +1 354 560 1010, (<https://heilsborg.is>). The Institute Ethics Committee approved the study protocol and waived of requirement for consent.

### Study participants

Individuals attending a weight loss and lifestyle program, under the supervision of a physician, with the aim to improve their health. All participants completed both Epworth Sleepiness Scale (ESS) and Bergen Insomnia Scale (BIS) and applied the SleepImage<sup>®</sup> sleep data recorder for two consecutive nights.

### Data collection

SleepImage<sup>®</sup> sleep data recorder - CardioPulmonary Coupling analysis: The SleepImage<sup>®</sup> wearable recorder (Figure 1) collects

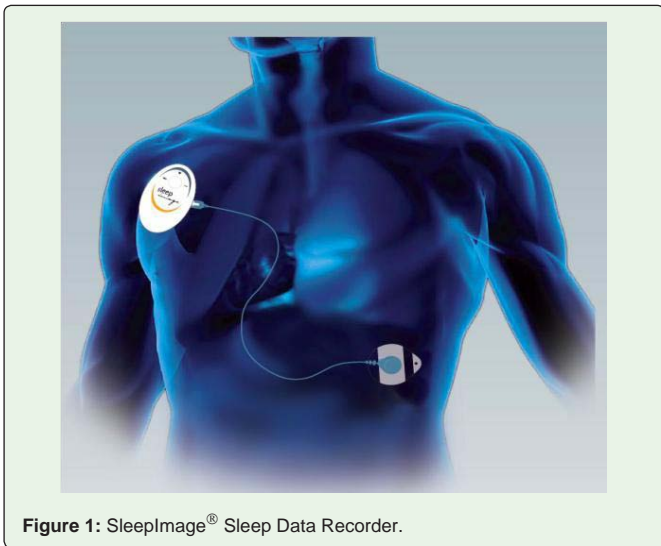


Figure 1: SleepImage® Sleep Data Recorder.

continuous ECG signal. One adhesive pad is attached under the device and connected with a thin wire across the chest to a second adhesive pad. Activity and body position is measured by internal accelerometers and gyroscopes and snoring is detected by vibration.

Collected-data is uploaded to the SleepImage® website and CPC algorithm automatically generates the CPC-variables and the sleep spectrogram graphs (Figure 2).

The SleepImage® system is FDA approved to aid in the evaluation of sleep disorders based on an objective measure of sleep duration, sleep quality and sleep pathology, it can inform or drive clinical management for sleep disorder patients. Collected data is uploaded to the SleepImage®secure, cloud-based system for automatic analysis. The system analyses the ECG signal with the CPC-algorithm,

based on coupling interactions between two physiological streams, respiratory (ECG-derived respiration, EDR) and autonomic (heart rate variability, HRV), both of which are strongly modulated by sleep and the outputs are automatically presented in a sleep spectrogram and CPC-parameters. The CPC analysis of the ECG signal was performed as described in detail [41,42]. The CPC-technique, while providing very rich output, is also meant to be a simple and efficient screener for sleep disorders. While the spectrogram is easy to interpret (Figure 2), data are automatically presented as sleep time, Sleep Quality Index (SQI), stable sleep (HFC) and unstable sleep (LFC). A subset of the low frequency band of the spectrogram called Elevated-Low Frequency Coupling (e-LFC) are the sleep pathology markers Elevated Low Frequency Broad Band (eLFC<sub>BB</sub>), that detects apnea-hypopnea or sleep fragmentation and Elevated Low Frequency Narrow Band (eLFC<sub>NB</sub>) detecting sustained periods of metronomic oscillatory characteristics is of central apnea or periodic breathing [41, 45,54].

Sleep Quality Index (SQI) is a summary index of an automated measure of sleep duration, sleep stability, sleep fragmentation, and sleep pathology. The SQI equation seeks to balance sleep duration, sleep quality, sleep stability, sleep fragmentation, and sleep pathology. The SQI uses these variables to generate a number between 0 and 100. This score is meant to serve as a summary of the CPC results [45].

The ECG-derived sleep spectrogram (Figure 2), reveals that Non Rapid Eye Movement Sleep (NREM) has a distinct bimodal-type structure marked by distinct alternating and abruptly varying periods of high and low frequency CardioPulmonary Coupling (CPC). Most of stable sleep (HFC) occurs during stage N2 and N3 and is associated with periods of stable breathing, Non-Cyclic Alternating Pattern (non-CAP), Electroencephalogram (EEG) morphology, increased absolute and relative delta power, strong sinus arrhythmia, and blood pressure dipping. Conversely, unstable sleep (LFC) is characterized

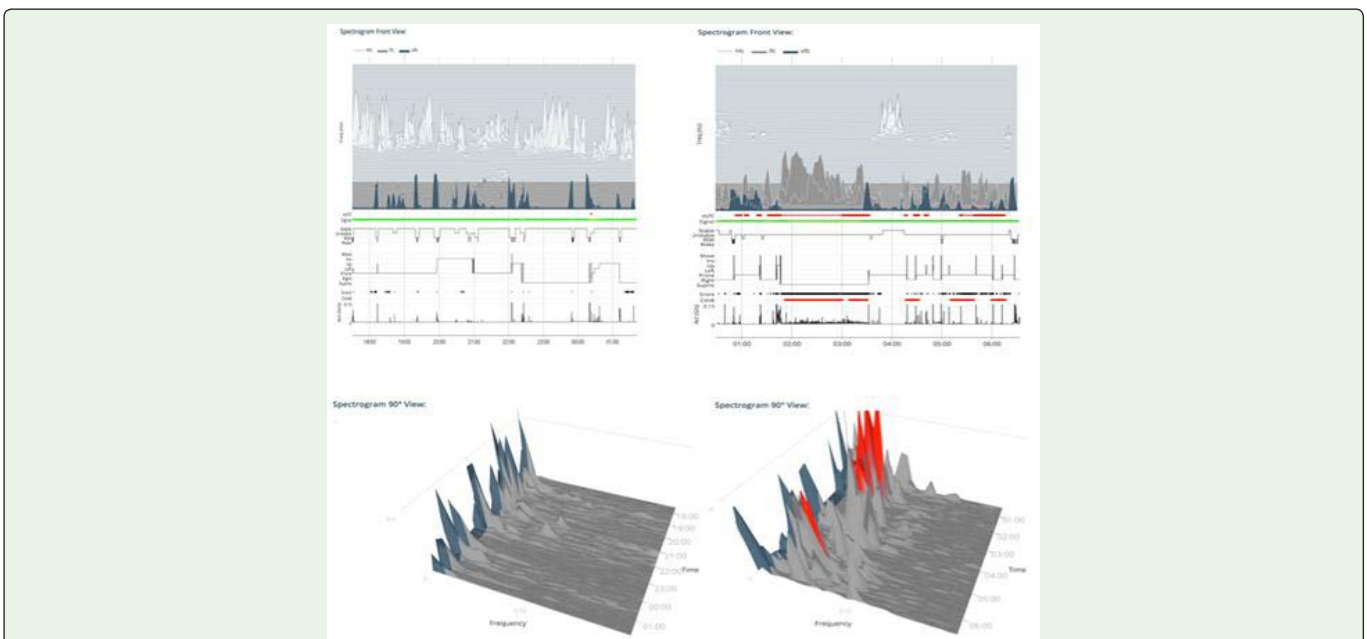


Figure 2: Sleep Spectrograms for a Healthy Sleeper (left) and Unhealthy Sleeper (right). Note the difference between the two with respect to the proportion of the recording spent in HFC and LFC, an increase in both eLFC<sub>BB</sub> and eLFC<sub>NB</sub> in the case of unhealthy sleep.

**Table 1:** Study Cohort by Gender.

	Females (n=54)	Males (n=3)	p-values
Age	41.9 (±18.5)	43.7 (±7.2)	0.87
BMI	36.7 (±6.3)	37.0 (±3.3)	0.93

Body Mass Index (BMI)

by temporal variability of tidal volumes, Cyclic Alternating Pattern (CAP) EEG morphology, non-dipping of blood pressure and lower frequency cyclic variation in heart rate. Fragmented Rapid Eye Movement Sleep (REM) has an LFC signature, while normal REM sleep and wake show very Low Frequency Coupling Signature (vLFC) [41]. ECG-derived CPC metrics show an independence of absolute EEG amplitudes and are thus not constrained by the “loss” of slow wave sleep with age [42]. Specific spectrographic signatures of fragmented sleep are biomarkers of strong chemo reflex effects on sleep-respiration [54].

**Epworth Sleepiness Scale (ESS):** Measures the level of daytime sleepiness and daytime functioning to identify patients with sleep apnea. The ESS is a simple, self-administered questionnaire based on retrospective reports of the likelihood of dozing off or falling asleep in a variety of different situations that provides a measurement of the subject’s general level of daytime sleepiness, or their average sleep propensity in daily life [39].

**Bergen Insomnia Scale (BIS):** Focuses on insomnia, looking at parameters of having difficulty falling asleep, staying asleep, waking up too early and feeling tired. The BIS is a simple self-administrated questionnaire consisting of six questions, of which the first three pertain to sleep onset, maintenance and early morning wakening. The last three questions refer to not feeling adequately rested, experiencing daytime impairment and being dissatisfied with sleep [40].

**Outcome measures**

Results between the objective sleep screening system and the two subjective questionnaires were compared and statistically analyzed. Data was summarized to evaluate the effectiveness of the questionnaires compared to objective ECG data collected during sleep and automatically analyzed by the CPC algorithm. Statistical comparison was conducted based on the following parameters: The presence of sleep disorder are identified as “unhealthy sleepers” and

is defined based on the automated CPC output, based on normative thresholds of the CPC biomarkers;  $SQI \leq 55$ , Stable sleep  $< 50\%$ , Unstable sleep  $> 30\%$ ,  $eLFC_{BB} > 15\%$  and/or  $eLFC_{NB} > 2\%$ . The absence of sleep disorder are called “healthy sleepers” and is defined based on the automated CPC output, based on normative thresholds of CPC biomarkers of  $SQI > 55$ , Stable sleep  $> 50\%$ , Unstable sleep  $< 30\%$ ,  $eLFC_{BB} < 15\%$  and/or  $eLFC_{NB} < 2\%$ .

**Statistical analysis**

Descriptive data are presented as number and percentage or mean ± Standard Deviation (SD), unless otherwise stated. An independent t-test (unpaired) was used to determine group differences when subjective measures (questionnaires) are utilized to categorize healthy and unhealthy sleepers. Rater reliability, subjective outcomes(questionnaires) vs objective outcomes (CPC), was analyzed using Receiver Operating Characteristics (ROC) to determine the level of agreement in binary outcomes (health vs unhealthy sleepers). The following parameters were calculated for each questionnaire: sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), likelihood ratio for a positive result (LR+), likelihood ratio for a negative test result (LR-) and agreement. A paired t-test was used to determine the presence of intra-night effect between adaptation night and baseline night within each group. The output from the analysis is summarized in tables below. Stata 12.0 was used for the analysis [55].

**Results**

Out of 60 individuals included in the program, 57 individuals were included in the study, having completed both questionnaires and recorded their sleep successfully for one night (95%). All participants were white, 54 women (94.7%), average age 41.9 (± 18.5), average BMI 36.7 (±6.3) and 3 men (5.3%), average age 43.7 (±7.2), average BMI 37.0 (±3.3) (Table 1). Seventeen (29.8%) were hypertensive, 5 (8.0%) with depression, 8 (14.0%) hypothyroid and one diabetic (1.8%).

Based on the ECG data collected and analyzed by the CPC algorithms, participants were assigned to two groups; healthy sleepers n=36 (63.2%) and unhealthy sleepers n=21 (36.8%). The average ESS score among healthy sleepers was 8.5 (±4.3) and among unhealthy sleepers 7.2 (±4.7). The average BIS score among healthy sleepers was 15.9 (±9.8) and among unhealthy sleepers was 17.2 (±7.8) (Table 2).

**Table 2:** The Combined Results, CPC Biomarkers, Epworth Sleepiness Score (ESS) and Bergen Insomnia Score (BIS), for the two groups, healthy sleepers and unhealthy sleepers.

	Cardio Pulmonary Coupling (CPC)		
	Healthy Sleepers (n=35)	Unhealthy Sleepers (n=22)	p-value
Sleep Time (min)	454.4 (±89.5)	436.9 (±106.3)	0.42
SQI	71.7 (±11.1)	49.1 (±16.3)	0
Stable Sleep (HFC%)	68.7 (±10.0)	45.5 (±14.9)	0
Unstable Sleep (LFC%)	17.4 (±7.7)	34.5 (±16.3)	0
eLFC <sub>BB</sub> (%)	6.1 (±3.8)	17.7 (±11.4)	0
eLFC <sub>NB</sub> (%)	0.3 (±0.9)	1.2 (±1.7)	0.01
Sleep Int.	33.6 (±19.5)	41.3 (±26.3)	0.21
ESS	8.5 (±4.3)	7.2 (±4.7)	0.33
BSI	15.9 (±9.8)	17.2 (±7.8)	0.79

Cardio Pulmonary Coupling (CPC) Sleep Quality Index (SQI), Elevated Low Frequency Coupling Broad Band (eLFCBB), Elevated Low Frequency Coupling Narrow Band (eLFCNB), Sleep Interruptions (Sleep Int.)

**Table 3:** Receiving Operating Characteristics (ROC) results. Comparison of objective sleep measurement (CPC) vs. subjective output (ESS and BIS Questionnaires).

	ESS (pos=16)	BIS (pos=36)	ESS + BIS (pos=41)
Sensitivity	23%	73%	73%
Specificity	69%	43%	29%
PPV	31%	44%	39%
NPV	59%	71%	63%
Agreement	51%	54%	46%
LR+	0.72	1.27	1.02
LR-	1.13	0.64	0.95

Receiver Operating Characteristics (ROC), Epworth Sleepiness Scale (ESS), Bergen Insomnia Scale (BIS), Positive Predictive Value (PPV), Negative Predictive Value (NPV), Positive Likelihood Ratio (LR+), Negative Likelihood Ratio (LR-).

Table 3 summarizes the binary outcomes of the questionnaires (healthy or unhealthy sleepers) when tested against the CPC binary outcome using ROC to validate their performance.

When compared to the objective CPC-output the questionnaires had low sensitivity, specificity and agreement: (1) ESS; sensitivity 23%, specificity 69% and agreement 51%. (2) BIS; 73%, specificity 43% and agreement 54%. Combining the questionnaires ESS/BIS had sensitivity 73%, specificity 29% and agreement 46%. The results demonstrate poor agreement with both questionnaires although the BIS performs slightly better than ESS with lower False Positive (FP) and False Negative (FN) rates. Combining the questionnaires did increase the positive identification rate but also increased FP and FN rates and decreased agreement.

Fifty individuals recorded their sleep for two consecutive nights (87.7%); 33 (66%) of those were in the healthy sleeper group and 17 (34%) in the unhealthy sleeper group (Table 4).

In the group of healthy sleepers, all were identified to be healthy sleepers on both nights recorded (adaption night and baseline night). In the group of unhealthy sleepers, 7 (41%) had different output when the adoption night is compared with the baseline night, with healthy sleep on adaption night and identified to have

sleep disorder on the baseline night. The Intra-Class Correlation Coefficient (ICC) was calculated separately for healthy and unhealthy sleepers, with the objective to further investigate any agreement in CPC output on adaption night and baseline night, suggesting sleep quality stability within a group. In the group of healthy sleepers ICC qualitative ratings ranged from fair ( $eLFC_{BB}$ ,  $eLFC_{NB}$ ), good (Sleep Interruptions), and excellent (SQI, Stable Sleep, Unstable Sleep). Sleep Time was the only variable demonstrating poor agreement and no statistical significance among healthy sleepers. Among unhealthy sleepers, Sleep Interruptions was the only variable demonstrating good agreement of statistical significance.

Lastly, to further investigate the performance of these questionnaires, the Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI) were calculated to determine the degree of correct reclassification when introducing the outcome of a questionnaire into a baseline binary logistic model predicting disease based on gender, age, and BMI. The results from introducing the results from each questionnaire are presented in Table 5.

In summary, both questionnaires, ESS and BIS, had poor sensitivity, specificity and agreement when compared to objective data; 23%, 69%, 51% and 73%, 43%, 54%, respectively. Comparing ICC, healthy sleepers had fair and statistically significant ICC indicating some correlation between nights; unhealthy sleepers did not demonstrate a statistically significant correlation. There were no statistically significant differences in the means of CPC output variables in healthy and unhealthy sleepers from adaptation night to baseline night (Table 4). Based on NRI and IDI, including the outcome of a questionnaire did not result in a statistically significant increase in risk prediction of our model. On the topic of power, because of the relationship between p-values and post-hoc (observed) power, such analysis is not meaningful since the failure to reject the null hypothesis because of high p-values always implies low observed power [56]. However, because post-hoc sample size calculation is a common inquiry, based on the averages, standard deviations, and the healthy/unhealthy ratio ( $n_1/n_2=1.6$ ) in Table 3, the two-sample comparison of means sample size estimate, for  $\Delta = 0.05$  and power = 0.8, the required sample size is 390 ( $n_1=150$ ,  $n_2=240$ ) and 1620 ( $n_1=623$ ,  $n_2=997$ ) for BIS and ESS, respectively.

**Table 4:** Mean Comparison Test (paired t-test) and Intra-class Correlation (ICC) Between Adaptation Night and Baseline Night.

	Healthy Sleepers (n=33)			Unhealthy Sleepers (n=17)		
	Adaptation Night	Baseline Night	p-value   ICC	Adaptation Night	Baseline Night	p-value   ICC
Sleep Time (min)	453.4 (±91.6)	466.6 (±76.7)	0.50   0.27	426.8 (±111.1)	436.6 (±114.5)	0.79   0.25
SQI	71.3 (±11.1)	71.2 (±11.4)	0.95   0.81**	49.7 (±16.8)	49 (±12.7)	0.88   0.34
Stable Sleep (%)	68.3 (±10.1)	68.1 (±10.3)	0.89   0.76**	45.6 (±16.6)	43.7 (±11.7)	0.69   0.20
Unstable Sleep (%)	17.6 (±7.7)	18.6 (±7.6)	0.37   0.79**	35.2 (±15.2)	35 (±10.6)	0.96   0.30
$eLFC_{BB}$ (%)	6.1 (±3.7)	6.5 (±4.1)	0.64   0.58**	18.5 (±11.9)	17.1 (±7.9)	0.60   0.56
$eLFC_{NB}$ (%)	0.3 (±0.9)	0.2 (±0.8)	0.83   0.48*	1.1 (±1.6)	1.7 (±2.2)	0.40   n/a
Sleep Int.	33.8 (±20.1)	33.4 (±24.7)	0.92   0.72**	39.5 (±24.3)	44.2 (±39.6)	0.59   0.60*

Sleep Quality Index (SQI), Elevated Low Frequency Coupling Narrow Band ( $eLFC_{BB}$ ), Elevated Low Frequency Narrow Band ( $eLFC_{NB}$ ), Sleep Interruptions (Sleep Int.).

\*\* p < 0.01, \* p < 0.05

**Table 5:** Net Reclassification Improvement (NRI), Integrated Discrimination Improvement (IDI), and Area Under the Curve (AUC).

	Epworth Sleepiness Scale		Bergen Insomnia Scale	
	Value	95% CI	Value	95% CI
<b>NRI</b>	0.259	(-0.447, 0.660)	0.215	(-0.457, 0.581)
event	0.436	(-0.350, 0.703)	0.538	(-0.494, 0.818)
non-event	-0.176	(-0.378, 0.168)	-0.324	(-0.507, 0.409)
<b>IDI</b>	0.022	(-0.013, 0.113)	0.01	(-0.013, 0.077)
event	0.013	(-0.010, 0.079)	0.007	(-0.010, 0.051)
non-event	0.009	(-0.005, 0.038)	0.002	(-0.005, 0.026)
<b>Δ AUC</b>	0.011	(-0.068, 0.091)	-0.008	(-0.072, 0.055)
Baseline	0.664	(0.529, 0.798)	0.66	(0.527, 0.792)
Enhanced	0.675	(0.553, 0.797)	0.651	(0.520, 0.782)

## Discussions

We compared the output of previously validated sleep questionnaires by utilizing a simple, sleep-screening system (SleepImage™) based on analyzing single lead ECG recorded during sleep, to objectively identify sleep disorders in a group of middle-aged obese patients.

Key findings of our analysis are: (1) The method had a low failure rate (3.5%), the group was instructed to measure their sleep for two nights; 88% of participants successfully finished recording both nights and 97% finished successfully recording their sleep for one night; (2) in a group of obese individuals (BMI=36.7 ±6.3 95% females, BMI=37.0 ±3.3 5% males), the prevalence of sleep disorders was 37% based on CPC analysis; 28% based on ESS and 37% based on BIS. Even though the BIS identified the same number of patients as the objective measurement it only had sensitivity of 73%, specificity of 43% and agreement of 54% and is therefore not statistically agreeable; (3) The questionnaires had rather low sensitivity (23%-73%) and specificity (29%-69%), and little agreement (46%-55%) with the objective data output, demonstrating the importance of objective data analysis for accurate identification of presence or absence of sleep disorders in a group of obese individuals as obesity is a risk factor for developing OSA and OSA is a risk factor of developing hypertension and other cardiovascular disorders [57]; (4) All metrics from ROC (Receiving Operating Characteristics) indicated that ESS, BIS, or combined ESS & BIS, do not provide adequate performance to screen for sleep disorders when compared to objective data collected in home settings in obese individuals; (5) Our results conclude what other studies have also concluded, that subjective questionnaires have a low sensitivity and low specificity when compared to objective output data and that subjective-objective mismatch is common, where patients overestimate sleep latency and underestimate sleep time and sleep quality [27,30-32].

Systematic screening for a disease represents an effort to identify subjects at risk of a disease, using a cost effective, simple and accurate test method. The decision to do a systematic screening for sleep disorders in this group of middle-aged obese individuals was motivated by high prevalence of SA in this population and its association with increased risk cardiovascular diseases. That OSA diagnosis is often delayed, negatively effects cardiovascular risk profile

of these patients as both duration and severity are important factors affecting arterial endothelial damage and elevating atherosclerosis risk and as early diagnosis and CPAP treatment slows progression of cardiovascular risk in these patients, prompt and accurate diagnosis of OSA is of high importance [58,59]. OSA in subjects <50 years of age may also have more deleterious cardiovascular consequences than in older patients and may be more likely to have hypertension and suffer greater morbidity and mortality [60]. These data may argue in favor of a more aggressively screening younger and middle-aged subjects with sleep complaints to improve diagnosis, therapeutic strategy and overall morbidity and mortality [61,62]. As sensitivity and specificity of questionnaires have not been well documented in screening for sleep disorders and delayed diagnosis of OSA that affects the morbidity and mortality of these patient a more accurate screening tool to improve clinical assessment of these patients is needed [63]. Neither of the two questionnaires (ESS and BIS) tested had adequate sensitivity or specificity although BIS performed slightly better with a lower False Positive (FP) and False Negative (FN) rates. Combining the questionnaires increased the positive identification rate but also increased FP and FN rates and decreased agreement rendering them unreliable tools to accurately screen for sleep disorders in this at risk patient population.

The cardiopulmonary coupling technique has been shown to have a high degree of concordance when compared to AHI-scoring of PSG studies to identify SA and capture treatment effects in both sleep apnea [46-50] and insomnia [51,52]. The method has been proven to yield reliable results that can be readily repeated and as data collection is markedly simplified and in-person visits are not required, the method has been proven to be feasible and cost-effective [64]. As the data collection is simple, this method can also more closely reflect real-life heterogeneity of factors influencing sleep from night to night allowing physicians to track dynamics of sleep over prolonged periods of time that should provide unique insights into sleep regulations in health and disease [65].

Although this study was focused on identifying sleep disorders in general, the literature shows that the AHI as an indicator of sleep disorder breathing as a sub-set of the domain of all sleep disorders can vary substantially between different nights in approximately 30% of patients. Single night testing can result in misleading clinical interpretation of sleep apnea and is more likely to be correctly detected through multiple nights of objective testing. The night to night variability caused by sleep architecture, sleep position, medication and fluid retention in patients with a high pre-test probability of the disease will benefit from recording sleep for more than one night, to improve accuracy in ruling out the presence of a sleep disorder [66-68]. In our study the group of healthy sleepers demonstrated healthy CPC biomarkers on both nights (adaption night and baseline night). In the group of unhealthy sleepers seven (41%) had discrepancy in the output, when comparing adaption night with baseline night, with healthy sleep on adaption night but identified to have sleep disorder on the second night (baseline night). This indicates more night-to-night variability in the group of unhealthy sleepers than in the group of healthy sleepers, with worse sleep on the baseline night, confirming what other studies have found in groups of individuals with high risk of SA. This emphasizes the importance of testing multiple nights to get accurate results before clinical assessment is made and is in line with inter-night changes that have been documented in other clinical

studies [66-68]. If only one night had been tested in this study, 41% of the poor sleepers would likely been identified as healthy and not been referred for further sleep disorder evaluation, confirming there may be benefit from acquisition of multiple nights of data in order to improve accuracy of the assessment and reduce the effect of night-to-night variability in SA patients. In conclusion, the SleepImage<sup>®</sup> system is a practical approach to improve screening for sleep disorders and improve clinical decision-making. Correct identification of the nature of a sleep complaint is the first step that can take place in primary care practices to triage patients. Those identified to have SA, should be provided a path to get treatment as needed through a multi-disciplinary approach involving a sleep medicine specialist. Equally important to accurately identifying the presence of a sleep disorder is tracking treatment efficacy that will start an interactive cycle between the patient and the provider. That methodology would follow commonly used practices for other chronic diseases such as diabetes, chronic heart failure and other chronic diseases. Collecting data over more than one night has shown to improve accuracy of screening for sleep disorders and tracking the dynamics of sleep physiology and pathology over prolonged periods of time is likely to provide unique insights into sleep regulation in health and disease.

Although questionnaires are widely used for purposes of evaluating what is being asked, sensitivity and specificity of questionnaires when compared to an objective measure of physiology has not been well documented in screening for sleep disorders, particularly in cardiovascular patients. As our result demonstrates, ESS and BIS have low sensitivity and low specificity when compared against an objective measurement of physiology. Relying on questionnaire output can therefore negatively affect clinical evaluation of sleep disorders [63].

There are limitations to this study based on its retrospective design, the small sample size and as that, it did not come from a community-based random sample and as such, our result may not represent the general population. Further research would be required to determine whether or not the sensitivity and specificity demonstrated in this study of obese individuals would be maintained when testing more heterogeneous groups. This study doesn't try to demonstrate that the objective measurements of the CPC technology correspond with a PSG test. Authors refer to other published studies [41,42,45-49,54] regarding the correlation between objective measures of sleep physiology using CPC vs PSG.

## Conclusion

Our findings support the need to add an objective measure of sleep physiology and pathology to subjective patient self-evaluation of sleep quality when screening for sleep disorders. Concordance of abnormality could reasonably trigger a low-cost approach to confirm or exclude sleep disorders including sleep apnea, and proceed to appropriate therapy. Discordant responses in a high-risk population could benefit from a full polysomnography test to confirm the screening outcome before making a definitive diagnosis.

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