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Insomnia symptoms in primary care: A prospective study focusing on prevalence of undiagnosed co-morbid sleep disordered breathing

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ABSTRACT

Objective: To determine prevalence of comorbid undiagnosed sleep disordered breathing (SDB) in chronic insomnia patients, using two complementary methods, one standard and one novel.
Methods: Using prospective design, adult patients diagnosed with chronic insomnia, treated with prescription pharmacological agents for > 3 months without prior objective sleep evaluation or diagnosis of SDB were invited to participate. All patients recorded their sleep for two consecutive nights using level 3 home-sleep-apnea-test (HSAT) device to derive Respiratory Event Index (REI) for OSA diagnosis. The electrocardiogram-signal (ECG) recorded by the same device was analyzed using FDA cleared medical software, Cardiopulmonary Coupling (CPC) to quantify sleep time and identify sleep-quality and pathology.
Results: Of 110 chronic insomnia patients who volunteered between May 2017 and June 2018, 88% were women. Prevalence of moderate-severe SDB (REI > 15) was 25% based on REI-scoring. Surrogate markers of moderate-severe SDB detected by the novel method identified prevalence of 33%, with negative predictive value 96%, reclassifying 10 individuals that HSAT diagnosed with mild SDB with more advanced disease state. Agreement between the methods is 88%.
Conclusion: High prevalence and overlap in symptoms between insomnia and SDB warrants objective testing when evaluating sleep complaints before therapy is initiated. Diagnostic caution is even more importantly warranted for female patients presenting insomnia sleep complaints, as SDB may not be initially considered as a biological symptom driver. CPC-analysis can complement standard HSAT or serve as a standalone option to evaluate sleep complaints in individuals presenting insomnia symptoms before therapy is initiated.
Clinical trial registry name and number: Pilot study: Co-occurrence of Insomnia and Sleep Disordered Breathing (SDB) symptoms: Prospective study focusing on chronic insomnia patients treated with pharmacological agents. Approved by the Bioethics Committee on March 7th, 2017.
VSNb: 17- 047- S1/ ST - GRA - 17029 – PDX – SH http://vsn.is/is/content/17-047

1. Introduction

Sleep complaints are prevalent in primary care. The two most common sleep disorders in adults, insomnia and sleep disordered breathing (SDB) [1] have different etiology and are often thought of as opposing clinical conditions, while evidence suggests these two diseases often coexist [2–4]. Chronic insomnia is presented in approximately 10% of adults [5]. Pathophysiology of insomnia involves hyper-arousal in the form of cognitive arousal and/or physiologic arousal [6]. The most common form of SDB, Obstructive Sleep Apnea (OSA) is defined by repeated obstruction of the upper airway during sleep, irrespective of continued ventilation effort, causing decrease in blood oxygen

Abbreviation: AASM, American Academy of Sleep Medicine; CAP, Cyclic Alternating Pattern; CPC, Cardiopulmonary Coupling; CVHR, Cyclic Variation of Heart Rate; EDR, Electrocardiogram Derived Respiration; ECG, Electrocardiogram; EEG, Electroencephalogram; $eLFC_{BB}$, Elevated Low Frequency Broad-band; $eLFC_{NB}$, Elevated Low Frequency Narrow-band; FDA, Federal and Drug Administration; HRV, Heart Rate Variability; HIPPA, Health Insurance Portability and Accountability Act; HFC, High Frequency Coupling; LFC, Low Frequency Coupling; HSAT, Home Sleep Apnea Test; NREM, Non-Rapid Eye Movement Sleep; non-CAP, Non-Cyclic Alternating Pattern; OSA, Obstructive Sleep Apnea; PSG, Polysomnography; ROC, Receiver Operating Characteristics; REI, Respiratory Event Index; SAI, Sleep Apnea Indicator; SDB, Sleep Disordered Breathing; SQI, Sleep Quality Index; TST, Total Sleep Time; vLFC, Very Low Frequency Coupling; SaMD, Software as Medical Device

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saturation, increased autonomous sympathetic and reduced parasympathetic activity and at termination, often preceded by a cortical arousal and sleep fragmentation, that may cause excessive daytime sleepiness or fatigue [7]. OSA affects about 34% of adult men who are at twofold greater risk of OSA than premenopausal women. The genders are affected equally in the post-menopausal age range when some patient groups like those with resistant hypertension, type 2 diabetes and ischemic heart disease have higher prevalence [8–10]. Although etiology and treatment for Insomnia and OSA differ, both conditions are associated with a higher risk of accidents, absenteeism, and onset and progression of other health problems like depression, type 2 diabetes, hypertension and other cardiovascular and metabolic morbidity's and mortality [7,11–15]. This risk can be reduced in OSA patients with effective airway treatment [16–20].

Clinical identification of insomnia primarily relies on subjective evaluation and questionnaires and cause of nocturnal awakenings in patients with insomnia complaints are therefore rarely evaluated objectively [5]. Numerous publications have demonstrated a mismatch between subjective and objective sleep evaluation where cause for awakenings interpreted as insomnia are caused by airway obstruction, exposing the patient to therapy that could negatively affect their health, representing a clinical challenge [2–4,21–24]. Polysomnography (PSG) is the reference standard for diagnosis of OSA, recording respiratory, cardiovascular and neurologic parameters to produce comprehensive analysis of sleep, including sleep staging and the Apnea Hypopnea Index (AHI), the primary metric for therapeutic decision-making in patients with OSA [25]. PSG is not recommended for insomnia and not a feasible solution for large-scale use due to cost and inconvenience [26]. Commonly used alternative are Level 3 portable Home Sleep Apnea Tests (HSAT) recording minimum of oximetry, airflow and respiratory effort to evaluate breathing events, reported as Respiratory Event Index (REI). HSAT are not helpful to phenotype insomnia as they do not identify sleep-wake states, measure sleep time or sleep quality. Non-hypoxic arousals are missed by HSAT often underestimating presence and severity of OSA.

Our study evaluates prevalence of comorbid undiagnosed OSA, inviting chronic insomnia patients to volunteer to record their sleep for two consecutive nights with an HSAT device including electrocardiogram (ECG) recording. We hypothesize that [1] co-morbid OSA will be prevalent in chronic insomnia patients and [2] utilizing simple novel method analyzing ECG-signal, it is possible to identify OSA with the same degree of accuracy as commonly accepted based on the REI values [27–29]. The novel method, evidence-based medical software (SleepImage®) analyzes ECG-signal collected during sleep to present autonomic nervous system activity, calculating the degree of Cardiopulmonary Coupling (CPC) and cyclic variation of heart rate (CVHR) for characterization of sleep quality, quantity and to provide diagnostic assessment of sleep disordered breathing (SDB). The software is Health Insurance Portability and Accountability Act (HIPAA) compliant and U.S Food and Drug Administration (FDA) cleared to establish sleep quality and aid in evaluation of sleep disorders to inform and drive clinical management. Metrics automatically derived from the software analysis include the Sleep Quality Index (SQI), a summary index of sleep duration, stability, fragmentation and pathology, helpful when phenotyping insomnia and Sleep Apnea Indicator (SAI) a measure of respiratory disturbance during sleep which correlates with the apnea-hypopnea index (AHI) [27,28,31].

2. Methods

2.1. Study design

Prospective study focusing on comorbid OSA in chronic insomnia patients currently treated with pharmacological agents. Data was collected in the patients' homes, administered by a private primary care clinic, Heilsuborg, Bíldshöði 9, 110 Reykjavik, Iceland, phone +1 354 560 1010 (https://heilsuborg.is/). The National Institute of Bioethics Committee approved the study protocol (VSNb:17- 047-S1/ST-GRA-17029-PDX-SH http://vsn.is/is/content/17-047).

2.2. Study participants

Following the National Institute of Bioethics Committee approval (http://vsn.is/is/content/17-047) an invitation was posted in the clinic's reception to individuals diagnosed with chronic insomnia currently using pharmacological treatment visiting the clinic to volunteer to participate in the study during the recruitment period. No active recruitment was performed.

Recruitment goal of 110 patients recording their sleep for two consecutive nights, based on sample size considered appropriate for preliminary investigation and confidence level of 90% of estimated conservative population of 100,000, 5% margin of error and response distribution of 25%.

Inclusion criteria: 1) Chronic insomnia patients (age 20–70), using pharmacological agents based on subjective evaluation and not with delayed or advanced phase insomnia.

Exclusion criteria: 1) Individuals previously evaluated by a sleep specialist and tested with HSAT/PSG, or been diagnosed with OSA, 2) Chronic obstructive pulmonary disease (COPD) or severe Asthma and cardiac arrhythmias. All patients who met the criteria signed a written consent.

2.3. Study procedures/interventions

Study participants recorded their sleep for two consecutive nights in their home using level-3 unattended HSAT' (Alice PDx, Philips Respironics, PA, USA). Data was collected between May 2017 and June 2018. After visual inspection of recordings, REI was calculated both manually by registered polysomnographic technologist (RPSGT) according to AASM scoring guidelines [32] and using automated scoring software (Somnolyzer) [33]. The ECG data was analyzed using CPC [27,28,31,34–36].

2.4. Philips respironics Alice PDx and Somnolyzer

Alice PDx is FDA cleared level-3 portable HSAT, recording pulse oximetry, airflow (nasal thermistor and pressure), respiratory effort by abdominal and chest belts, snoring and ECG-data, intended for data collection to diagnose OSA. Somnolyzer is an FDA cleared automated scoring software to aid clinical diagnosis of SDB.

2.5. Cardiopulmonary Coupling (CPC), cyclic variation of heart rate (CVHR) and the spectrogram

The automated, FDA cleared and HIPAA compliant medical software (SaMD) (SleepImage®) analyzes continuous ECG-data collected during sleep, by extracting and coupling heart rate variability (HRV) and electrocardiogram derived respiration (EDR). Data provides information on sleep duration, sleep quality and sleep pathology and is visually displayed in the ECG-derived sleep spectrogram [27,28,34,35]. Detailed methodology on the basic algorithms has been published [34]. The sleep-spectrogram presents NREM sleep as bimodal, alternating between high and low frequency CPC. Stable sleep (high-frequency coupling, HFC) occurs during part of stage-N2 and all of stage-N3 NREM-sleep and is associated with periods of stable breathing, increased delta power, vagal dominance of heart rate variability and blood pressure dipping. Conversely, unstable sleep (low-frequency coupling, LFC) is characterized by variability of tidal volumes and non-dipping of blood pressure. A subset of low-frequency coupling, termed elevated low-frequency coupling broad-band ($eLFC_{BB}$) defines sleep fragmentation resulting from periods of apneas-hypopneas and arousals while elevated low-frequency coupling narrow band ($eLFC_{NB}$)

distinguishes between apneas caused by upper airway obstruction and respiratory dyscontrol [27,28,36].

The Sleep Quality Index (SQI) provides an automated summary measure of sleep quality incorporating sleep duration, sleep stability, sleep fragmentation, and sleep pathology, generating a number between 0 and 100. The Sleep Apnea Indicator (SAI) provides an automated summary of breathing events and correlates with AHI [27,28]. During apnea and hypopnea events, decrease in blood oxygen is accompanied by a physiological reaction of bradycardia and relative tachycardia when breathing resumes [30,31]. SAI detects these autonomic cardiac oscillations associated with prolonged respiratory perturbations, during unstable breathing (tidal volume fluctuations in breathing). The CPC-method accurately identifies sleep apnea [27,28], captures treatment efficacy in sleep apnea [37–39], and can objectively identify insomnia to guide therapy initiation and track therapy efficacy [37,40]. Using SAI together with SQI, $eLFC_{BB}$ and $eLFC_{NB}$ it is possible to identify the presence of SDB and categorize sleep apnea as obstructive, central or complex [28,36].

2.6. Data analysis and outcome measures

Prevalence and severity of OSA is based on REI scoring of the reference test, HSAT [32,33]. For output comparison, the ECG-signal recordings were analyzed using CPC with primary parameters of interest; SQI; $eLFC_{BB}$ which correlates with sleep fragmentation or OSA; $eLFC_{NB}$, which correlates with periodic breathing or central sleep apnea, and the SAI indicating SDB [27,28,36]. Scoring of the reference test was blinded to clinical information. Output of the novel method is fully automated. Output from the two systems were compared and statistically analyzed.

Data were categorized based on the REI output of HSAT utilizing the sleep time output of CPC. CPC results were presented as means with associated standard deviation and compared for each OSA category (no-, mild-, moderate- and severe) and are summarized in tables below, where statistical significance was rejected for p-values $\geq .05$. Prevalence of OSA was defined as REI > 15 (moderate OSA). Calculations were performed using Stata 15.0 (Stata version 15.0, StataCorp, College Station, TX) [41].

3. Result

3.1. Study sample allocation

HSAT data was grouped as patients having no OSA REI < 5, mild (REI 5–15), moderate (REI > 15–30) and severe (REI ≥ 30). The CPC outputs were compared between the groups.

3.2. Demographic characteristics

Flow of patients in the study is presented in Fig. 1 and Table 1 summarizes the cohort's characteristics of the 110 individuals included in the study, 97 females (F, 88%) and 13 males (M, 12%) with mean age of 49.9 ± 11.2 (F 49.9 ± 1.1 vs. M 49.7 ± 3.6) range 21–69 years and mean BMI of 32.0 ± 7.0 (F 32.5 ± 0.7 vs. M 28.2 ± 0.9).

3.3. Respiratory event index and cardiopulmonary coupling parameters

134 subjects signed informed consent, 6 subjects withdrew after signing, expressing the HSAT-equipment too difficult to use. In the group attempting HSAT recordings, 24 failed to produce successful studies, yielding 110 successful HSAT sleep recordings, with failure rate of 17.9%.

Based on REI scoring, Prevalence of moderate-severe OSA was 25% based on REI scoring and 33% based on the CPC-output. Results of both methods are summarized in Table 2. Comparison of baseline characteristics of individuals with moderate-severe OSA and those with no or mild disease are summarized in Table 3. Comparison of CPC and REI > 15, is summarized in Table 4. Agreement between the two methods was 88%, negative predictive value of CPC when compared to REI 96% and kappa 0.76. CPC did not identify 3 individuals that HSAT identified with moderate-severe SDB but reclassified 10 individuals to moderate-severe SDB that HSAT diagnosed as mild disease. CPC parameters for these participants are presented in Table 5.

4. Discussion

The study results report high prevalence of undiagnosed co-morbid moderate-severe OSA (25%) in a cohort previously diagnosed with chronic insomnia, predominantly consisting of women. We additionally confirmed and quantified that the CPC technique is a reliable alternative to drive appropriate clinical diagnosis, demonstrating negative predictive value of 96% and agreement of 88% when compared to HSAT.

This high prevalence of moderate-severe OSA in patients diagnosed with chronic insomnia is concerning but concurring with current literature that clinical examinations, interviews and subjective questionnaires currently recommended and used to evaluate sleep complaints, to identify insomnia and exclude co-morbid OSA are insufficient both for clinical management and in research [2–4,21–24,42]. As all patients included in the study were required to contact their healthcare provider the preceding 3 months for medication prescription, sleep complaints were either insufficiently described due to patients' misperception of cause of awakening's or incorrectly interpreted [5].

Our findings of observed HSAT-prevalence of moderate-severe OSA of 25% (n = 27) in chronic insomnia patients, predominantly consisting of women (88%) is supported by findings of Franklin et al. [43] observing prevalence of moderate-severe OSA among women in the general population of 26%. The CPC-method observed prevalence of 33% (n = 37) identifying 10 additional individuals, all women with clear evidence of OSA. All ten reported daytime sleepiness, five reported mood disorder often linked to undiagnosed OSA [44] and two were concurrently on hypertension therapy, comorbidity known to be associated with OSA [45].

Thomas et al. have previously shown the feasibility of using the CPC-method for tracking sleep both in health and disease, for better targeted therapies and feedback regarding effectiveness of therapy [37]. In individuals with insomnia complaints, objective sleep-monitoring is crucial for insomnia phenotyping as dissociation between self-reported and objective sleep-quality and quantity is documented [4,13,42]. Objective monitoring additionally may identify individuals with aberrant somnoperception that may offer new insights into insomnia and nonrestorative sleep.

Traditionally OSA has been seen as a disease in men, profiled over forty with a thick neck and prominent snoring. This though by no means represents a complete picture of the demographic of sleep apnea sufferers with growing evidence supporting that OSA in women is under-recognized with gender differences in symptom presentation documented. Women with OSA are less likely than men to report the classical symptoms of snoring, daytime sleepiness and witnessed apneas but more likely to report fatigue, mood disturbances and insomnia symptoms [43,46]. This may lead to misdiagnosis of other disorders and prescription of medications rather than a sleep study for further testing [47–50]. Gender-related differences in reporting and presentation of symptoms needs to be taken into clinical evaluations of women reporting sleep problems to avoid not recognizing OSA before any therapy is initiated [48,51,52]. Despite widespread use of the Epworth Sleepiness Scale (ESS) to screen for OSA, in population-based studies in women it has not been shown to strongly associate with daytime sleepiness [43]. Patient's misperceptions of cause of their awakening's and variance in their answers to questionnaires is presented in our study with 24% reporting snoring on the STOP-Bang and 57% on the Berlin questionnaire, respectively. Of those identified with moderate-severe

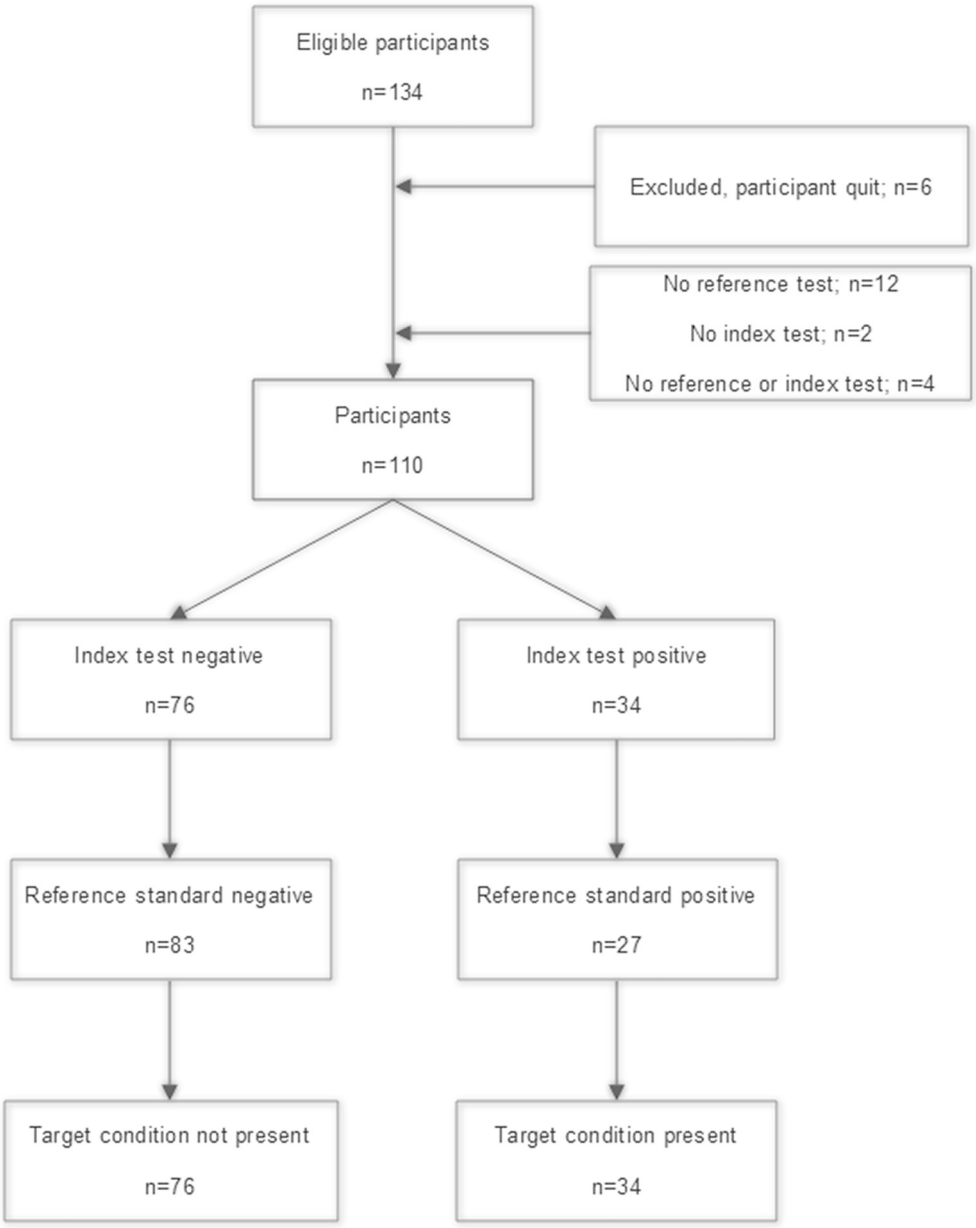

Fig. 1. STARD flow diagram, showing flow of participants in the trial.

OSA 26% did not report snoring.

Accurate measure of sleep time is vital and should be a requisite when generating sleep disorder diagnosis and HSAT accuracy is expected to be higher utilizing CPC-sleep duration than if estimates from monitoring sleep time are used [53–55]. As HSAT conventionally do not measure sleep from brain activity, apneas and hypopneas only associated with cortical arousals, and no drop-in oxygen-saturation are missed by HSAT, causing underestimation of OSA severity when compared to PSG. CPC sleep-quality is calculated based on autonomic activity at brainstem levels, correlating with slow wave sleep measured from the surface EEG, linking cortical activity and autonomic brain stem related cardiorespiratory signals [35]. Sleep fragmentation due to arousals is detected and presented as $eLFC_{BB}$ and oscillations associated with obstructive breathing and decreased oxygen levels as SAI [55]. Lower prevalence of SDB from HSAT when compared to CPC was expected as CPC has previously demonstrated high correlation to AHI output of PSG [27,28,53,54].

Delay in OSA diagnosis and therapy may eventually negatively affect both psychological and physical well-being of patients. Both objective short sleep duration and OSA severity are important factors in arterial endothelial damage causing and elevated cardiovascular risk with increased morbidity and mortality [11–13,56–58,60]. OSA in patients 50 years of age and younger may also have more deleterious cardiovascular consequences than in older patients, further affecting their morbidity and mortality [61]. Critical part of public health approach to cardiovascular disease (CVD) management should include timely identification of OSA as continuous positive airway pressure (CPAP) treatment may reduce mortality and other associated risks [19,20,58–60].

Observed misperception and high prevalence of co-morbid SDB among insomnia patients indicates that individuals with sleep complaints would benefit from sleep testing capturing both insomnia and SDB [30,46,48,53]. Part of public health approach to cardiovascular disease (CVD) management should include educating clinicians about effect of objective short sleep duration, comorbid SDB, the importance of timely identification of OSA before therapy is initiated,

Table 1
Characteristics of the Study's Cohort.

	All (n = 110)	Male (n = 13)	Female (n = 97)	p-Value
REI	13.7 (± 14.0)	23.6 (± 5.3)	12.3 (± 1.3)	0.01
Age	49.9(± 11.2)	49.7 (± 3.6)	49.9 (± 1.1)	0.88
Height (cm)	169.2 (± 7.7)	180.7 (± 2.4)	167.7 (± 0.6)	0.00
Weight (kg)	91.4 (± 21.1)	91.6 (± 4.1)	91.5 (± 2.2)	0.98
BMI (kg/m²)	31.9 (± 7.1)	28.2 (± 0.9)	32.5 (± 0.7)	0.04
Neck Circumference (cm)	37.4 (± 4.2)	40.9 (± 4.1)	36.9 (± 4.0)	0.00
Diabetes	6%	15%	5%	0.27
HT	38%	38%	38%	0.70
Insomnia Severity Index Total Score	16.5 (± 4.6)	15.6 (± 5.0)	16.6 (± 4.5)	0.47
Diff. Falling Asleep (ISI)	2.3 (± 1.2)	2.1 (± 1.2)	2.3 (± 1.1)	0.42
Diff. Staying Asleep (ISI)	2.3 (± 1.0)	2.1 (± 0.8)	2.3 (± 1.0)	0.68
Wake Up Early (ISI)	1.9 (± 1.2)	2.2 (± 1.2)	1.8 (± 1.2)	0.25
STOP-BANG Total Score	3.0 (± 1.6)	4.3 (± 2.0)	2.8 (± 1.4)	0.00
STOP-BANG Positive	62%	77%	60%	0.23
Berlin Positive	60%	46%	62%	0.28
Snoring (SB1)	24%	62%	19%	0.00
Snoring (BQ1)	57%	77%	55%	0.13
Daytime Sleepiness (SB2)	78%	69%	79%	0.41
Daytime Sleepiness (BQ2)	64%	46%	66%	0.16

BMI, Body Mass Index; HT, Hypertension; ISI, Insomnia Severity Index; questionnaire; REI, Respiratory Event Index; SB, Stop-BANG questionnaire; BQ, Berlin questionnaire.

pharmacological treatments that may adversely affect severity of OSA and mortality [47,56–58,61,62] and that continuous positive airway pressure (CPAP) treatment in OSA patients may reduce mortality and other associated risks [19,20,58–60]. Clinicians need to beware of available evidence-based methods that may offer improvements in clinical management of sleep disorders [48,63]. Furthermore, this overlap of insomnia and OSA identifies a subgroup with compromised quality of life [44], needing a more comprehensive and often complex treatment that may benefit from regular monitoring of therapy [37,63]. For HSAT-devices, additional ECG-signal could be collected and analyzed for improved diagnostic accuracy, sleep architecture and sleep quality or by utilizing simple compatible consumer wearable devices able to collect single-lead ECG-signal for automated CPC-analysis [30,64]. Innovations and improvements in sensor technology focused on consumers to collect data to be analyzed with HIPAA-compliant, evidence based medical software, offers tracking of sleep dynamics, collecting data over multiple nights and time points, in patients' natural sleep environment to optimize diagnostic accuracy and disease management [27,28,30,64]. Methods, simple both for patients and care providers, should improve both diagnostic accuracy and management of sleep disorders and should have meaningful and measurable positive impact on patient care. Finally, for research, evidence-based methods that are low-cost and scalable will be helpful in defining both cases and controls, offering more comprehensive phenotypic profiles contributing important information for design of research studies. Only with this kind of high quality, objective data will it be possible to have the potential of making useful mechanistic or actionable inferences from large studies [65,66].

Our study has several limitations as all our participants are Caucasian and majority of them female, therefore our results may not be generalizable to other ethnicities or males. Although the “gold standard” test for OSA is attended PSG, unattended HSAT are commonly used and is per se not a limitation. That our sample predominantly consisted of females (88%) could be seen as a limitation but reflects the typical gender disease presentation among insomnia patients and could therefore also be considered as strength [44,45] emphasizing that women with OSA report and experience symptoms differently compared to men and are more likely to discuss their symptoms

Table 2
Sleep apnea category determined by REI values. MANOVA analysis.

	Sleep Apnea category				p-value					
	(α) Normal (n = 22)	(β) Mild (n = 61)	(δ) Moderate (n = 18)	(γ) Severe (n = 9)	α vs β	α vs δ	α vs γ	β vs δ	β vs γ	δ vs γ
Respiratory Event Index	3.0 (± 1.6)	9.5 (± 1.9)	22.7 (± 2.7)	48.1 (± 3.0)	0.00	0.00	0.00	0.00	0.00	0.00
Snoring (SB)	5%	25%	28%	56%	0.04	0.04	0.00	0.78	0.05	0.16
Snoring (BQ)	32%	61%	67%	78%	0.02	0.03	0.02	0.64	0.32	0.55
Daytime Sleepiness (SB)	77%	82%	72%	67%	0.63	0.71	0.54	0.37	0.28	0.77
Daytime Sleepiness (BQ)	68%	64%	61%	56%	0.72	0.64	0.50	0.83	0.63	0.78
BMI (kg/m^2)	28.9 (± 1.5)	32.8 (± 1.8)	33.0 (± 2.3)	33.3 (± 2.8)	0.03	0.08	0.15	0.92	0.85	0.93
Neck Circumference (cm)	35.8 (± 0.9)	37.0 (± 1.0)	39.12 (± 1.3)	41.6 (± 1.6)	0.18	0.04	0.00	0.07	0.00	0.28
Sleep Time (Hrs)	8.3 (± 0.3)	7.6 (± 0.4)	7.6 (± 0.5)	7.4 (± 0.6)	0.07	0.11	0.09	0.83	0.59	0.73
SQI	63.1 (± 3.1)	63.6 (± 3.7)	54.0 (± 4.7)	46.6 (± 5.7)	0.88	0.04	0.01	0.02	0.00	0.28
SAI	7.0 (± 2.2)	8.4 (± 2.6)	17.7 (± 3.3)	33.3 (± 4.1)	0.46	0.00	0.00	0.00	0.00	0.03
CVHR (%)	16.5 (± 3.2)	17.3 (± 3.8)	32.1 (± 4.8)	47.0 (± 5.8)	0.81	0.00	0.00	0.00	0.00	0.07
HFC (%)	60.1 (± 3.8)	61.2 (± 4.4)	53.8 (± 5.6)	45.8 (± 6.9)	0.79	0.24	0.07	0.11	0.02	0.31
LFC (%)	23.5 (± 3.0)	23.0 (± 3.6)	29.2 (± 4.6)	45.2 (± 5.6)	0.89	0.17	0.00	0.08	0.00	0.03
vLFC (%)	15.6 (± 1.4)	15.2 (± 1.6)	16.12(± 2.1)	8.33(± 2.5)	0.80	0.80	0.00	0.59	0.00	0.01
$eLFC_{BB}$ (%)	9.9 (± 1.7)	9.1 (± 2.0)	11.9 (± 2.6)	14.0(± 3.1)	0.71	0.43	0.23	0.20	0.10	0.58
$eLFC_{NB}$ (%)	0.1 (± 1.1)	0.6 (± 1.3)	2.7 (± 1.6)	11.2 (± 2.0)	0.11	0.00	0.00	0.00	0.00	0.05

BMI, body mass index; SB, STOP-Bang questionnaire; BQ, Berlin sleep-questionnaire; SQI, sleep quality index; SAI, sleep apnea indicator; CVHR; cyclic variation of heart rate; HFC, high frequency coupling; LFC, low frequency coupling; vLFC, very low frequency coupling; $eLFC_{BB}$, elevated low frequency coupling broad band; $eLFC_{NB}$, elevated low frequency coupling narrow band.

Table 3
Comparison of baseline characteristics and output of the Insomnia Severity Index, STOP-Bang and Berlin questionnaires.

	No- Mild OSA (n = 83)	Moderate-Sever OSA (n = 27)	p-Value
Age	48.1 (± 1.2)	55.6 (± 2.5)	0.00
Height (cm)	168.8 (± 0.9)	170.3 (± 1.8)	0.38
Weight (kg)	90.3 (± 2.4)	95.9 (± 4.8)	0.25
BMI (kg/m²)	31.7 (± 0.8)	33.1 (± 1.6)	0.38
Neck Circ. (cm)	36.6 (± 0.4)	40.0 (± 0.9)	0.00
Insomnia Severity Index (ISI)	16.4 (± 0.5)	16.8 (± 1.0)	0.65
Diff. Falling Asleep (ISI1)	2.3 (± 0.1)	2.3 (± 0.2)	0.88
Diff. Staying Asleep (ISI2)	2.2 (± 0.1)	2.4 (± 0.2)	0.29
Wake Up Early (ISI3)	1.8 (± 0.1)	2.2 (± 0.3)	0.10
STOP-BANG	2.7 (± 0.2)	4.0 (± 0.3)	0.00
STOP-BANG Positive	53%	89%	0.00
Berlin Positive	55%	74%	0.09
Snoring (SB)	19%	37%	0.06
Snoring (BQ)	53%	70%	0.11
Daytime Sleepiness (SB)	81%	70%	0.26
Daytime Sleepiness (BQ)	65%	59%	0.59

BMI, Body Mass Index; ISI, Insomnia Severity Index; questionnaire; SB, Stop-BANG questionnaire; BQ, Berlin questionnaire.

Table 4
Receiver operating characteristics.

	Respiratory Event Index (REI)		
		Pos	Neg
CardioPuplmonary Coupling (CPC)	Pos	24	10
	Neg	3	73
	Prevalence*		25%
	FP		12%
	FN		11%
	Sensitivity		89%
	Specificity		88%
	PPV		0.71
	NPV		0.96
	Agreement		88%
	PABAK		0.76
	PLR		7.38
	NLR		0.13

Positive Predictive Value (PPV), Negative Predictive Value (NPV), Prevalence and Bias Adjusted Kappa (PABAK), Positive Likelihood Ratio (LR+), Negative Likelihood Ratio (LR-)

* REI ≥ 15 - > Positive Sleep Disorder Breathing (SDB).

SAI ≥ 15|eLFC$_{BB}$ > 20%|eLFC$_{NB}$ > 5% - > Positive Sleep Disorder Breathing (SDB).

with their primary care provider than a sleep specialist. This high proportion of undetected OSA found in these women, further underscores that diagnostic caution is warranted for female patients presenting insomnia related sleep complaints. Gender based pharmacokinetic differences exist with common medications used for treatment of insomnia [46] and the fact that sleep duration has been linked with mortality in postmenopausal women, further emphasizes importance of objective sleep testing before therapy is initiated in women [46,52,62]. Our data were derived from participants who had some interest in participating in a clinical trial for insomnia and may therefor differ from a cross section of clinical insomnia patients. We do though not believe that the population in Iceland is any different from what could be expected in other populations.

5. Conclusion

High prevalence of occult OSA among individuals previously diagnosed with insomnia based on subjective evaluation, suggests substantial overlap in symptoms between insomnia and OSA. This advances a need for a new perspective for more effective methods to evaluate sleep complaints objectively, methods capturing both insomnia and OSA before making diagnostic decisions and initiating therapy. Offering access to objective, medically validated test for patients with sleep complaints who currently are considered ineligible for PSG or HSAT test, could fill a void in clinical management of sleep disorders. Wearable devices that can expand data collection for clinical purposes and HIPAA-compliant, evidence-based methods analyzing collected data to identify sleep pathology for appropriate therapy initiation, should improve clinical management of sleep disorders. A change in clinical protocols to this extent could have meaningful and measurable positive impact on both disease management and public health.

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Conflict of interest

Erla Sveinsdottir, MD, MPH is Chief Medical Director at Heilsuborg and has partial ownership in the company.

Hugi Hilmisson, MA is a Data Analyst for MyCardio LLC. SleepImage is the brand name of MyCardio LLC, a privately held entity. MyCardio LLC is a licensee of the CPC technology, a method to use ECG to measure sleep and sleep apnea from the Beth Israel Deaconess Medical Center, Boston, MA, USA.

Neale Lange, MD is Assistant Clinical Professor of Medicine; University of Colorado Health Sciences Center, Denver, CO. Dr. Lange declares no conflict of interest.

Solveig Magnusdottir, MD, MBA is Medical Director at MyCardio LLC and has a partial ownership in the company. SleepImage is the brand name of MyCardio LLC, a privately held entity. MyCardio LLC is a licensee of the CPC technology, a method to use ECG to measure sleep and sleep apnea from the Beth Israel Deaconess Medical Center, Boston, MA, USA.

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Authors' contributions

ES: Principal investigator of the study with active participation in the encoding of the data, supervised the research work, interpretation of results and approval of the final manuscript. HH: Extraction of relevant data and analysis, statistical analysis and support in drafting the manuscript and approval of the final manuscript. SM: Initial drafting of

Table 5
Details on subjects with conflicting diagnoses comparing the two methods.

		REI positive – CPC negative for sleep disordered breathing												
CVD	Mood Disorder	Daytime Sleepiness	Gender	BMI	Age	REI	SQI	SAI	CVHR (%)	HFC (%)	LFC (%)	vLFC (%)	$eLFC_{BB}$ (%)	$eLFC_{NB}$ (%)
NONE	No	No	Male	29.0	48	25.5	59.7	7.9	14.4	58.3	15.9	24.2	11.9	0.0
HT	Yes	Yes	Female	30.9	48	21.5	84.3	2.3	5.8	83.0	12.4	4.6	2.8	0.0
HT	No	Yes	Female	30.5	67	32.6	82.7	0.6	9.0	81.0	9.6	8.9	1.4	0.0
		REI negative – CPC positive for sleep disordered breathing												
NONE	Yes	Yes	Female	21.8	52	7.3	52.3	26.1	54.0	53.1	30.93	12.4	11.7	0.0
HT, DLP	No	Yes	Female	32.7	66	14.3	64.3	23.9	45.7	67.9	22.73	9.3	2.5	2.5
NONE	Yes	Yes	Female	29.0	50	9.1	47.0	20.4	27.5	40.9	40.48	15.9	13.5	0.0
NONE	Yes	Yes	Female	19.4	48	6.1	33.5	31.9	39.7	25.1	60.08	14.8	20.9	1.9
NONE	Yes	Yes	Female	41.3	35	6.5	48.4	17.5	24.7	47.1	33.42	18.5	11.7	4.9
NONE	No	Yes	Female	26.3	45	8.5	56.0	23.5	26.0	54.7	39.18	6.4	7.0	3.2
HT, DLP	Yes	Yes	Female	27.4	50	5.7	27.7	16.7	19.2	13.4	67.60	19.0	40.3	4.6
NONE	No	Yes	Female	36.3	52	12.6	44.2	21.7	38.4	42.4	34.02	23.5	17.2	0.0
NONE	No	Yes	Female	35.3	64	4.2	54.1	27.9	41.7	52.9	32.43	12.6	9.8	0.0
NONE	No	No	Female	23.9	38	3.2	45.0	19.7	22.4	40.1	39.65	20.3	11.9	4.4

CVD, cardiovascular disease; HT, hypertension; DLP, dyslipidemia; BMI, body mass index; REI, respiratory event index; SQI, sleep quality index; SAI, sleep apnea indicator; CVHR, cyclic variation of heartrate; HFC, high frequency coupling; LFC, low frequency coupling; vLFC, very low frequency coupling; $eLFC_{BB}$, elevated low frequency coupling; $eLFC_{NB}$, elevated low frequency coupling narrow band; HT, hypertension; DLP, dyslipidemia.

the manuscript, approval of the final manuscript and guarantor of the overall content. NL: Review and interpretation of the raw HSAT data, statistical analysis review, critical edit and final approval of the manuscript.

Compliance with ethical standards

The Bioethics Committee approved the study protocol in Reykjavik, Iceland and recruitment procedures met local HIPAA rules. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2019.01.011.

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