Co-occurring insomnia and obstructive sleep apnea

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Abstract

Study objectives: Prior research investigating co-occurring insomnia/obstructive sleep apnea (CIO) has mainly focused on comparing comorbid patients, obstructive sleep apnea (OSA), and insomnia (INS) to those with OSA alone. This approach is informative but omits the potentially interesting comparison of comorbid patients to those with INS alone. Our study used an incomplete factorial design, crossing OSA (present or absent) with INS (present or absent) to more clearly focus on the question, is comorbid INS an epiphenomenon of OSA or an independent disorder?

Methods: Our study was an archival analysis from the database of a sleep center comparing consecutively diagnosed patients characterized as OSA or INS. A third group, CIO, was derived from the OSA group. Our study was conducted at an American Academy of Sleep Medicine–accredited sleep disorders center. We studied 299 patients, including 94 OSA, 97 INS, and 108 CIO. Patients ranged from ages 15 to 86 years.

Results: Groups were compared on polysomnography (PSG), sleep pattern, sleep stages, sleep pathology, self-reported sleep concerns, and self-reported daytime functioning. From a consecutive group of OSA patients, we estimate the prevalence of CIO at 67.4%. Based mainly on multivariate analysis of covariance (MANCOVA) controlling for demographic differences between groups, we found few if any significant differences between CIO and INS alone or between CIO and OSA alone.

Conclusions: The clinical presentation of CIO is indistinguishable from INS alone, both with respect to PSG findings and to self-reported sleep onset and sleep maintenance disturbance. We observed a weak relation between OSA severity and co-occurring INS. These data are consistent with the view that INS with co-occurring OSA is an independent, self-sustaining disorder. We hypothesized that in some unknown proportion of cases, OSA initially instigated the INS, but the INS was then perpetuated and reshaped by sleep concerns and self-defeating compensatory behaviors.

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1. Introduction

Insomnia (INS) and obstructive sleep apnea (OSA) are among the most prevalent sleep disorders and are both associated with considerable healthcare costs [1,2]. However, research studying their co-occurrence has rapidly started to accumulate only in the past decade, as evidenced by three recent reviews [3–5]. Interest in co-occurring insomnia/obstructive sleep apnea (CIO) comorbidity is spurred by both clinical and research concerns. For example, the presence of INS may hamper continuous positive pressure (CPAP) adherence [6], and undiagnosed OSA may contaminate INS clinical trials [7]. Research also may shed light on the feasibility of treating this type of comorbid INS as an independent disorder.

Reviews consistently find that the prevalence of INS among patients diagnosed with OSA ranges from 40% to 50% [3–5]. Although it has attracted less research interest, the inverse also is true. Individuals whose primary concern is INS often have [7] or at least report concerns of [8] OSA.

When INS and OSA co-occur (e.g., CIO), various mechanisms by which OSA actuates INS have received the most attention. Beginning with the initial report of this comorbid phenomenon [9] and continuing to the present [10,11], it has been assumed that sleep disruption from apneic events instigates sleep-maintenance INS, though this process has never been empirically demonstrated. Sleep-maintenance INS also may be induced by nocturia accompanying OSA [3]. In theory excessive sleepiness associated with OSA would render sleep-onset INS unlikely. Data suggest the possibility that psychiatric comorbidity accompanying OSA provokes INS [10–12]. In some cases, hyperarousal may contribute to the sleep-onset component in CIO [13]. Alternatively some have hypothesized that INS instigates or exacerbates OSA, possibly through the mechanism of weakened pharyngeal muscle tone [3,14].

Our study further investigates CIO. The body of evidence unambiguously shows that CIO is common. However, inconsistencies and gaps on the nature of the relation between these F disorders persist. Most of the studies in this area began by identifying their
OSA sample and then targeting the INS subgroup. This approach affords a CIO prevalence estimate. It is important and permits study of CIO compared to OSA alone, which also is a useful research goal. However, this design obscures investigation of the characteristics of INS when linked with OSA vs INS alone, and this comparison may be instructive.

Our study evaluated the sleep and daytime functioning characteristics of INS and OSA, separately and combined. We used conservative INS criteria to estimate the prevalence of CIO. We took an atypical methodologic approach in studying CIO, an incomplete factorial design. OSA (present or absent) was crossed with INS (present or absent) to create three arms: OSA/INS, INS only, and OSA only. The fourth arm, which would have completed the fully crossed factorial design of INS and OSA both absent, was omitted. These three groups will enable us to clarify the independent and joint characteristics of INS and OSA and perhaps shed light on the question—when INS occurs in the presence of OSA, is it an epiphenomenon or an independent disorder?

2. Methods

2.1. Subjects

Our study was an archival analysis of the electronic medical records (EMR) of a population of patients who presented to an American Academy of Sleep Medicine–accredited sleep disorders center from January 2007 to March 2011. Patients who present to this sleep disorders center undergo an initial clinical interview conducted by a board-certified sleep physician. If indicated, patients undergo a PSG study. Based on the clinical interview and PSG results, a final diagnosis is made. All patients included in our analysis had received a clinical interview, a PSG, a final diagnosis, and had begun treatment. The study was approved by the University and Hospital institutional review boards.

A total of 299 subjects were included in the analysis and were assigned to groups based on their final diagnosis of OSA, INS, or CIO. Selection of subjects for our study proceeded in two phases. In phase one, the OSA and CIO subjects were selected from consecutive patients who presented to the sleep center between January 2010 and March 2010, but the INS subjects with a PSG were far less plentiful. For phase two, we had to extend our timeframe (January 2007–March 2011) to accumulate our sample of insomniacs who had sleep studies. PSG was conducted in subjects in the INS group, 2007–March 2011) to accumulate our sample of insomniacs who had sleep studies. PSG was conducted in subjects in the INS group, as these individuals had symptoms suggestive of other sleep disorders in addition to their INS concern. If the PSG confirmed the presence of another sleep disorder, these individuals were excluded from the INS group.

Altogether from January 2007 to March 2011, approximately 13,000 patients presented to the sleep center. Of these 13,000 patients, 6300 were new patients and 6700 were follow-up patients. Of the 6300 new patients seen during this time, 4100 (65%) were patients, 6300 were new patients and 6700 were follow-up patients. Of the 13,000 patients, 299 were included in the analysis and were assigned to groups based on their final diagnosis of OSA, INS, or CIO. Selection of subjects for our study proceeded in two phases. In phase one, the OSA and CIO subjects were selected from consecutive patients who presented to the sleep center between January 2010 and March 2010, but the INS subjects with a PSG were far less plentiful. For phase two, we had to extend our timeframe (January 2007–March 2011) to accumulate our sample of insomniacs who had sleep studies. PSG was conducted in subjects in the INS group, as these individuals had symptoms suggestive of other sleep disorders in addition to their INS concern. If the PSG confirmed the presence of another sleep disorder, these individuals were excluded from the INS group.

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Diagnostics were rendered by a board-certified sleep physician and satisfied International Classification of Sleep Disorders, second edition, criteria [15]. Briefly an apnea–hypopnea index (AHI) of five or higher was required for OSA. As determined by clinical interview, the diagnosis of INS was based on a subject-initiated report of difficulty falling or staying asleep, impaired daytime functioning associated with poor sleep, adequate opportunity for sleep, and at least 1 month's duration of concerns.

2.2. Materials and procedure

Our study primarily focused on demographic, diagnostic, and sleep–wake data provided by subjects during their initial sleep clinic appointment and subsequent PSG. The PSG usually was performed within a month of the initial clinical appointment.

2.2.1. Intake questionnaire

Subjects provided a wide range of data including demographics, medical history, and description of sleep. Specific information derived from this questionnaire for our study included the recording of age, gender, and education level. We also computed body mass index (BMI) from weight and height. A count of the number of all-purpose medications was used as a crude measure of general health. If the questionnaire registered an INS concern, the subject also was asked: was this primarily difficulty falling asleep, staying asleep, or both? We recorded if the patient had received a psychiatric diagnosis. We inquired as to the presence or absence (binary measures) of sleep-quality concern, impaired work or school performance, and issues with daytime sleepiness or fatigue.

2.2.2. Polysomnography

Grass Telefactor digital PSG equipment using standard recording and scoring procedures was used for overnight PSG [16]. Physiologic measures included an electrooculogram; an electroencephalogram utilizing electrodes C3, C4, O1, O2, M1, and M2; an electrocardiogram; airflow by nasal–oral thermocouples; nasal pressure; respiratory effort by chest and abdominal respiratory inductance plethysmography; and submental and anterior tibialis electromyograms.

PSG variables of interest were sleep-onset latency (SOL), wake after sleep onset (WASO), number of awakenings (NWAK), total sleep time (TST), sleep efficiency (SE), sleep stage percentages (N1, N2, N3, and R), AHI utilizing the 2007 scoring guidelines rule B alternative method, respiratory distress index (RDI), which is defined as the AHI plus respiratory effort related arousals ([RERA]/h), minimum oxygen desaturation (OX), total arousal index (AR), and periodic limb movement index (PLM). PSG studies were scored by a registered polysomnographic technologist and were interpreted by a board-certified sleep physician.

2.2.3. Beck Depression Inventory, second edition

The Beck Depression Inventory, second edition (BDI-II), is a 21-item self-report questionnaire that assesses symptoms and severity of depression. Each item is scored from 0 to 3, with a total score range from 0 to 62. Higher scores are indicative of greater depressive symptoms. The BDI-II has adequate reliability and validity [17]. The BDI-II was obtained during the initial clinical appointment.

2.2.4. State-Trait Anxiety Inventory, trait scale, form Y

The State-Trait Anxiety Inventory, trait scale, form Y (STAI), is a 20-item self-report measure of cognitive and physical symptoms of anxiety. Each item is scored on a 4-point scale from one (never) to four (always). Total scores range from 20 to 80, with higher scores indicative of greater anxiety. The STAI has an adequate overall reliability [18]. The STAI was obtained during the initial clinical appointment.

2.2.5. Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) is an 8-item self-report questionnaire that assesses trait sleepiness in routine situations (e.g., watching television, riding in a car). Each item is scored from zero (would never doze) to three (high chance of dozing). Total scores range from 0 to 24, with higher scores indicative of greater sleepiness. The ESS has acceptable reliability and adequate internal consistency and correlates well with the multiple sleep latency test [19,20]. The ESS was obtained during the initial clinical appointment.
2.3. Procedure

An advanced graduate student reviewed the EMR database to identify subjects. Undergraduate and graduate psychology students reviewed the EMR of each subject and completed a data extraction sheet. Data were entered, checked, and analyzed in SPSS.

3. Results

3.1. Subject characteristics

In our final sample subjects ranged from ages 15 to 86 years. There were 175 women and 124 men. There were 94 individuals in the OSA group, 97 individuals in the INS group, and 108 individuals in the CIO group. The three groups were compared on five characteristics plausibly related to sleep and daytime functioning (Table 1). To summarize the findings, all but education showed significant differences between groups. The INS group was younger and had fewer men than the other two groups, the CIO and INS groups differed on BMI, and the CIO group was taking more medication than the other two groups. We considered these four measures as covariates in subsequent analyses dependent on the strength of their relation with the dependent variable.

3.2. Comorbidity prevalence

During a 4-month span, consecutive patient diagnoses were analyzed to determine diagnostic prevalence of CIO. Of 89 subjects who received a diagnosis of OSA between January 2010 and March 2010, 60 (67.4%) also satisfied International Classification of Sleep Disorders, second edition, criteria for INS.

3.3. Sleep

We used multivariate analysis of variance or MANCOVA to compare the sleep of the three groups in four clusters, including PSG sleep pattern, PSG sleep architecture, PSG sleep disturbance indices, and self-report binary sleep concerns. We used Bonferroni adjusted multivariate t tests with the same covariables used in the initial analyses to clarify pairwise group differences following significant MANCOVAs. Group mean scores are presented in Table 2.

3.3.1. PSG sleep pattern

Groups were compared on SOL, WASO, NWAK, TST, and SE, controlling for age. In our set of potential covariables, age significantly correlated with all of these sleep outcomes and the other measures correlated with none or few. The assumption of homogeneity of regression slopes was confirmed for age.

There was a significant difference between groups in this cluster (Wilks’ Λ = .93; F = 2.04; p < .05). Univariate follow-up found that only SOL significantly differed between groups. INS was significantly greater than OSA but CIO fell midway and did not differ from the other two groups. However, all pairwise multivariate T tests were not significant, even without Bonferroni adjustment tests.

3.3.2. PSG sleep architecture

Groups were compared on SOL, WASO, NWAK, TST, and SE, controlling for age. BMI, and gender correlated with very few outcomes. The assumption of homogeneity of regression slopes was confirmed for BMI and gender. However, we disqualified age and just used the other two covariables.

There was a significant difference between groups in this cluster (Wilks’ Λ = .81; F = 6.57; p < .01). Pairwise multivariate T tests found that CIO and OSA did not significantly differ, but INS was significantly different from both CIO and OSA. Univariate results in these two comparisons were identical. Compared to CIO and OSA, INS was significantly less disturbed on all three measures compared to the other 2 groups.

3.3.3. PSG sleep disturbance indices

Groups were compared on RDI, OX, AR, and PLM. Our intent was to control for age, BMI, and gender, as these three covariables significantly correlated with all or most of these sleep outcomes, and BMI and gender correlated with very few outcomes. The assumption of homogeneity of regression slopes was confirmed for both covariables. There was no significant difference between groups in this cluster (Wilks’ Λ = .98; F = .54).

3.3.4. Self-report sleep concerns

Groups were compared on presence or absence of concerns of falling asleep, staying asleep, and experiencing poor sleep quality.
We analyzed proportion of reporting a sleep concern. The potential covariables significantly correlated with only one or none of the dependent variables. No covariables were included in this analysis.

There was a significant difference between groups in this cluster (Wilks’ \( \Lambda = .53; F = 3.21; p < .001 \)). Univariate follow-up found that all three measures significantly differed between groups. Pairwise multivariate \( T \) tests found that CIO and INS did not significantly differ, but OSA was significantly different from both CIO and INS. Univariate results in these two comparisons were identical. Compared to CIO and INS, the OSA group registered significantly fewer reports of sleep concerns on all measures (i.e., falling asleep, staying asleep, sleep quality).

### 3.4. Daytime functioning

We used MANCOVA to compare the daytime functioning of three groups in two clusters, including self-report binary daytime functioning impairment and standard questionnaires. We used Bonferroni adjusted multivariate \( T \) tests with the same covariables used in the initial analyses to clarify pairwise group differences following significant MANCOVAs. Group mean scores are presented in Table 3.

#### 3.4.1. Self-report daytime functioning impairment

Groups were compared on presence or absence of concerns of work or school performance, reports of sleepiness or fatigue and presence of a psychiatric diagnosis, controlling for age. We analyzed proportion of having impairment. In our set of potential covariables, age significantly correlated with all of these outcomes and the other measures correlated with none or one. The assumption of homogeneity of regression slopes was confirmed for age.

There was a significant difference between groups in this cluster (Wilks’ \( \Lambda = .92; F = 3.18; p < .01 \)). Univariate follow-up found that only psychiatric diagnosis significantly differed between groups. Pairwise multivariate \( T \) tests found that CIO and INS did not significantly differ, but OSA was significantly different from both CIO and INS. Univariate results in these two comparisons were identical. Compared to CIO and INS, there was a significantly lower proportion of patients with a psychiatric diagnosis in the OSA group.

#### 3.4.2. Standard questionnaires

Groups were compared on the ESS, BDI, and STAI controlling for age and gender. These two covariables significantly correlated with all or most of these outcomes, and BMI and number of medications correlated with none or one. The assumption of homogeneity of regression slopes was confirmed for age and gender.

There was a significant difference between groups in this cluster (Wilks’ \( \Lambda = .91; F = 3.10; p < .01 \)). Univariate follow-ups found that BDI and STAI significantly differed between groups, but ESS did not. Pairwise multivariate \( T \) tests found that CIO vs INS and OSA did not significantly differ, but OSA was significantly different from INS. Univariate results revealed that there was significantly higher depression (BDI-II) and anxiety (STAI) in the INS group compared to the OSA group.

### 3.5. Types of comorbid INS

#### 3.5.1. Frequency distribution

We were interested in learning more about self-reported types of insomnia: sleep onset, sleep maintenance, and both in the CIO group compared to the INS group. The distribution of these concerns is shown in Fig. 1. The occurrence of onset concerns was low and was virtually identical in these two groups. Maintenance concerns were a little higher in the CIO group. The most common concern endorsing both onset and maintenance concerns was a little higher in the INS group. Overall, there was no significant difference in the distribution of concerns when comparing these two groups (\( \chi^2 [2] = 1.97 \)).

#### 3.5.2. Onset vs maintenance

To further study INS-type characteristics, we compared the maintenance group with the both group in a series of MANCOVAs, evaluating dimensions of sleep experience. The onset group was too small to study so we folded it into the both group. The following tests were compared between all individuals who experienced onset concerns (and many who also experienced maintenance concerns designated the onset/maintenance group) with a group reporting maintenance concerns only.

We performed a factorial MANCOVA comparing groups (CIO vs INS) \( \times \) INS types (onset/maintenance vs maintenance) with age as a covariable on the set of PSG sleep pattern measures. There were significant differences in sleep for the main effect of INS types, onset/maintenance compared to maintenance (Wilks’ \( \Lambda = .90; F = 3.52; p < .01 \)). Sleep in the onset/maintenance group was worse. However, there were no significant differences for the main effect of groups or the groups \( \times \) INS types interaction.

The same factorial MANCOVA was performed on PSG sleep architecture with age and number of medications as covariables.

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### Table 3

Adjusted mean (SE) daytime functioning by group.

<table>
<thead>
<tr>
<th></th>
<th>CIO</th>
<th>OSA</th>
<th>INS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-report daytime functioning impairment&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor performance at work or school</td>
<td>.28 (.05)</td>
<td>.25 (.05)</td>
<td>.39 (.05)</td>
</tr>
<tr>
<td>Concern of sleepiness or fatigue</td>
<td>.89 (.04)</td>
<td>.81 (.04)</td>
<td>.91 (.04)</td>
</tr>
<tr>
<td>Psychiatric diagnosis</td>
<td>.29 (.04)</td>
<td>.11 (.05)</td>
<td>.34 (.05)</td>
</tr>
<tr>
<td>Standard questionnaires&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epworth Sleepiness Scale</td>
<td>10.7 (0.6)</td>
<td>11.3 (0.6)</td>
<td>9.9 (0.6)</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>14.2 (1.1)</td>
<td>9.8 (1.2)</td>
<td>16.7 (1.2)</td>
</tr>
<tr>
<td>State-Trait Anxiety Inventory</td>
<td>40.1 (1.3)</td>
<td>36.1 (1.4)</td>
<td>42.9 (1.4)</td>
</tr>
</tbody>
</table>

**Abbreviations:** CIO, co-occurring insomnia/obstructive sleep apnea; OSA, obstructive sleep apnea; INS, insomnia.

<sup>a</sup> These are binary variables. Means are the proportion of patients who are positive for the measure.

<sup>b</sup> The only significant finding in this cluster was a lower proportion of psychiatric diagnoses in the OSA group compared to the other 2 groups.

<sup>c</sup> The only significant findings in this cluster were higher Beck Depression Inventory and State-Trait Anxiety Inventory scores in the INS group compared to the OSA group.

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**Fig. 1.** Percent distribution of types of insomnia in the comorbid and insomnia groups. There was no significant difference in the distribution of types of sleep concerns in the 2 groups.
There were no significant differences for either main effect or for their interaction.

The same factorial MANCOVA was performed on PSG sleep disturbance indices (RDI, OX, AR, and PLM) with gender and BMI as covariables. As expected there were significant differences in sleep disturbance for the main effect of groups, CIO compared to INS (Wilks’ Λ = .75; F = 11.29; p < .001). Sleep disturbance in the CIO group was worse. However, there were no significant differences for the main effect of INS types or the groups × INS types interaction.

3.5.3. INS and apnea severity

Within the CIO group, we wanted to investigate if INS severity was related to apnea severity. We performed two stepwise multiple regression analyses relating apnea severity indices (RDI, OX, and respiratory arousal index) to PSG SOL and WASO. We found no significant relation in the first regression for SOL. In the second regression, only RDI was significantly related to WASO (F(1,105) = 15.58; p < .001). This association explained 15.0% of the variability in WASO and the relationship was positive; higher RDI was associated with worse sleep and higher WASO.

4. Discussion

CIO is common. We observed that 67% of OSA cases present with clinically significant diagnosable INS. CIO was twice as prevalent as OSA alone. The rate of CIO we obtained was somewhat higher than typically is reported as stated in the introduction, even though we used more conservative criteria in diagnosing INS in comparison to several past studies. We cannot account for this discrepancy.

CIO is indistinguishable from INS alone. Examination of a wide range of INS characteristics—PSG sleep pattern, sleep stages, self-reported sleep concerns, self-reported daytime functioning, standardized questionnaires of sleepiness, depression, and anxiety, as well as sleep onset vs sleep maintenance INS patterns—consistently found no significant differences between INS comorbid with OSA (CIO) and INS alone. This remarkably consistent pattern of conformity between comorbid INS vs INS challenges entrenched views that INS in the presence of OSA functions differently and should be treated differently than INS alone.

Similarly, the incomplete factorial design allowed us to compare CIO and INS alone. One could reason that if comorbid OSA is more severe than OSA alone, it would explain the presence of INS and would imply that INS is an OSA epiphenomenon. With nearly the same degree of consistency seen with the insomnias, comorbid OSA and INS alone closely conformed. Neither PSG sleep pattern, sleep stages, sleep disturbance indices of RDI, OX, AR, and PLM, as well as most measures of self-reported daytime functioning, nor standardized questionnaires of sleepiness, depression, and anxiety, distinguished these two groups. Self-reported sleep concerns did separate these groups, but this finding is considered an additive effect of INS presence.

If INS is a byproduct of OSA, several OSA/INS associations should follow. OSA interrupts sleep and bestows sleepiness. We should expect the OSA phenotype to conceive a comorbid INS form heavy on sleep maintenance difficulties and light on sleep-onset disturbance compared to INS alone, but we did not observe this distinction. There was no significant difference in SOL and WASO concerns comparing CIO and INS. Others also have failed to observe an association between OSA and type of INS [10,21]. Perhaps the severity of PSG sleep disturbance, particularly with respect to WASO, would be more pronounced in comorbid INS than INS alone. It was not. Perhaps apnea severity would be related to INS severity. Neither RDI, OX, nor respiratory arousal index predicted PSG SOL. Only RDI predicted PSG WASO, and this explained only 15.0% of WASO variability. Absence of a relationship between apnea severity and INS frequently has been reported [10,12,21–23].

Separately treating the INS or the OSA in CIO patients would inform the issues under consideration, but such treatment data on CIO do not exist except in one complex study [24]. CIO patients received cognitive behavior therapy (CBT) for INS or multiple component surgery for OSA before administration of crossover treatment. INS resolved in five of 15 postsurgery patients, and the 10 residual cases derived additional INS benefits from subsequent CBT. Patients given CBT first achieved considerable improvement in INS symptoms SOL and WASO. Subsequent OSA treatment afforded additional sleep benefits. These data are supportive of the position that INS is an independent disorder in the majority of CIO cases. The authors recommended dual treatment for CIO.

We would like to acknowledge two limitations of our findings. First, self-reported sleep was based on single-point estimates at the time of the clinical interview. No study of CIO collected 2 weeks of sleep diaries, a critical measure when studying INS [25]. Two weeks of sleep diaries (or actigraphy) in the natural environment would have provided a meaningful increment to our circumstantial knowledge of our participants’ customary sleep. They would have allowed comparison between our two INS groups in the natural environment with a stable, high-quality, self-reported assessment. Second, in our INS group, individuals presenting to a sleep center with INS concerns and signs of other sleep disorders (mostly OSA), may not be representative of the population of insomnias to which we wish to generalize. The transient dip in blood oxygenation (OX of 87.7%) in Table 2 might be indicative of skewed composition in this group. Similarly between-group differences on demographics (age, gender, BMI, and medication) were statistically controlled for, but their presence implies that other distinctive variables, not monitored, may have differed between groups. Our study is not immune to the risk for elevated taint that may afflict convenience samples compared to sampling the population of interest.

Future research in this area should consider a more robust assessment of INS to more clearly illuminate similarities and differences between INS with and without accompanying OSA. For example, primary INS has been associated with objective performance decrements in a series of reaction time tasks [26] and elevated biomarkers such as cortisol, revealing 24-hour hyperarousal [27]. It would be instructive to know if INS comorbid with OSA exhibits characteristic behavioral or biologic patterns associated with primary INS.

Without considering cost, there are a number of additional future research possibilities that should incorporate a design shift and intervention focus. Existing descriptive studies of CIO including our own comprise archival or cross-sectional research. These studies are informative but also are an important next step in longitudinal research. Periodic assessment with an intact cohort would clarify the sequential relationship between INS and OSA, would shed light on causal mechanisms, and would isolate subgroups such as premorbid vs new-onset INS. The longitudinal design is critical for identifying the time of OSA onset if periodic monitoring could be extended over a long period of time. Introducing OSA or INS treatment to this design would be the most fruitful way of evaluating separate and combined therapeutic benefits to CIO subgroups.

With consistency spanning measures and replicating across methodologic angles, the results of our study dispute the conclusion that INS occurring with OSA corresponds to processes of secondary INS. However, we do not believe it is a coincidence that the rate of INS with OSA is many times greater than the population prevalence of INS, using the same criterion we used (6% diagnosable INS) [28]. In accordance with Spielman’s [29,30] model, we suppose the INS was precipitated by the apnea and was primarily
of the sleep maintenance type in its original form; however, soon thereafter worry about sleep and self-defeating compensatory behaviors reshaped and perpetuated the INS. Our data presume INS independence from a consistent presentation across INS types and weaken association with OSA severity, but our study cannot confirm this inference. Furthermore, research cited above suggests that two-thirds of CIO patients have primary INS.

The domain of secondary INS has evolved over the past several decades, and its most recent iteration was punctuated by the National Institutes of Health State-of-the-Science Panel [31] questioning the relation between INS and the presumed primary agent. As data continue to accumulate and our understanding of CIO fills out, we and others [11] anticipate that this comorbidity will be viewed much the same as others, and in many cases INS in the presence of OSA will be considered an independent self-sustaining disorder.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2013.02.008.

References