The relationship between obstructive sleep apnea and insomnia:

A population-based cross-sectional polysomnographic study

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Abstract

Background: The relationship between insomnia and objectively measured obstructive sleep apnea (OSA) severity has not previously been investigated in the general population of both genders. The main aim of this population-based polysomnography (PSG) study was to evaluate the cross-sectional association between severity of OSA and DSM-V insomnia and insomnia severity.

Methods: A random sample of 1200 participants in the third Nord-Trøndelag Health Study (HUNT3) was invited and 213 (18%) aged between 21-82 years underwent an ambulatory PSG, a semi-structured interview, and a sleep-specific questionnaire. A proxy DSM-V insomnia diagnosis and an Insomnia Symptom Score (ISS, range 0-12) was calculated from three insomnia questions and one daytime sleepiness symptom question. Participants were divided into three groups according to their apnea-hypopnea index (AHI): AHI <5 (without OSA), AHI 5-14.9 (mild OSA), and AHI ≥15 (moderate-to-severe OSA). Associations between prevalence of insomnia and OSA groups were assessed by logistic regression models adjusted for age and gender. Associations between ISS and OSA were assessed in a general linear model with contrasts.

Results: A total of 25.2% (29.1% women, 12.5% men) had insomnia. Insomnia prevalence did not differ between subjects with and without OSA, but ISS differed significantly between OSA categories (ANCOVA df 2, F=6.73, p=0.001). ISS was lower in the moderate-to-severe OSA-group compared to those without OSA (mean difference -2.68; 95% [CI -4.33, -1.04]; p = 0.002). In subjects with moderate-to-severe OSA, ISS correlated negatively with age (Pearson r= -0.66, p=0.015).

Conclusion: In this population-based PSG study, no overall statistical association between OSA and insomnia prevalence was found. However, participants with moderate-to-severe

OSA reported less insomnia symptoms than subjects without OSA, in particular in older individuals.

Keywords: Insomnia – OSA – AHI - Polysomnography - Cross-sectional - Epidemiology

Introduction

Symptoms of insomnia are frequent and reported in 39-58% of individuals with obstructive sleep apnea (OSA) [1]. The majority of studies of insomnia among subjects with OSA has been clinical-based [2-10] and often without a relevant or comparable control group [3, 7, 9, 10].

In population-based studies of OSA, higher insomnia prevalence has been reported among individuals with OSA-related symptoms, compared to those without such symptoms [11-14], while one follow-up study did not report on this association [15]. In contrast, lower insomnia prevalence was found in subjects with OSA compared to those without OSA in some clinical studies, where OSA is diagnosed by polysomnography (PSG) or respiratory polygraphy (PG) [2, 3]. Inconsistent results have also been found regarding the relationship between insomnia severity and OSA. Both a positive association between insomnia severity and OSA [4, 5], and a negative or lack of association is reported [6, 7, 16, 17]. It is intriguing that the majority of population-based studies report more insomnia in subjects with OSA-suggestive symptoms, while clinical-based studies report diverging associations between insomnia and PSG-proven OSA. Our population-based study, using PSG to diagnose OSA and DSM-V criteria for insomnia intends to shed light on this discrepancy in findings.

Insomnia can be subtyped based on difficulties of initiating sleep (early insomnia) or maintaining sleep (middle insomnia), and early morning awakenings (late insomnia) [3, 8, 18,

19]. Interestingly, OSA-treatment response on insomnia symptoms might depend on early, middle or late insomnia subtype [20], suggesting that insomnia subtypes should also be investigated separately. In addition, how age may interact with insomnia in individuals with OSA has rarely been investigated. One study has reported less insomnia symptoms in older adults compared to younger persons [5], but no age difference was found in a recent study [7]. Another study found an age difference for difficulty maintaining, but not for initiating sleep among individuals with OSA [10].

Clinical-based studies on OSA have some obvious bias because they select only those with obvious OSA-symptoms [21], whereas population-based studies also include persons who are unaware of their OSA. On the other hand, most population-based studies reporting on the relationship between insomnia and OSA have used a symptom-based OSA diagnosis only [11-13]. However, PSG or PG is necessary to diagnose OSA [22]. Regarding the insomnia diagnosis, varying diagnostic criteria of insomnia have been used in previous studies. To the best of our knowledge, only one population-based [13] and one clinical-based study [2] have diagnosed insomnia with current DSM-V/ICSD-3 criteria.

In this cross-sectional population-based study, the primary aim was to evaluate the relationship between a proxy DSM-V diagnosis of insomnia and insomnia severity among subjects with OSA diagnosed by PSG. Secondary aims were to estimate the association between OSA and early, middle and late insomnia symptoms, and to evaluate how the OSA-insomnia relationship varied with age and gender.

Methods

The Nord-Trøndelag Health Study

The third Nord-Trøndelag Health Study (HUNT3) was performed between October 2006 and June 2008. All inhabitants of Nord-Trøndelag County 20 years and older were invited to participate. Details of this comprehensive health study are described elsewhere [23]. Of 94,194 invited adults, 50,807 individuals (54%) answered the initial questionnaire (Q1 and participated in a clinical consultation including measurements of height and weight, and 40,535 (43%) answered the second questionnaire (Q2), which included sleep-related questions.

HUNT3 polysomnography (PSG) Study

"The HUNT3 PSG study" was a sub-project of HUNT3 performed in Trondheim between October 2008 and June 2010. Invitation was made by telephone calls to 1200 randomly selected HUNT3 participants living in the town Stjørdal. This location was selected for its proximity to St. Olavs hospital in Trondheim (less than 45 minutes travel-time). Thirty-one of those who responded "yes", did not show up for the PSG. Twenty-nine subjects initially agreed to participate but later declined. Five participants were deceased upon invitation. Finally, a total of 213 (18%) (163 women and 50 men) participated in the PSG study with an age range of 21-82 years between 2008 and 2011. Besides costs to and from the hospital (up to 400 NOK), participants were not compensated economically.

Semi-structured interview

Upon arrival at St. Olavs hospital a semi-structured interview was carried out. The interview included a validated Norwegian versions of Karolinska Sleep Questionnaire (KSQ) [24], which assesses insomnia symptoms. Furthermore, questions regarding sleepiness, fatigue, headache and musculoskeletal complaints were also included.

Questionnaires filled out at home

Subjects completed a questionnaire and a sleep diary for one week before and 6 days after the PSG, at home. The questionnaire included questions regarding height, weight, gender, age and a Norwegian version of Hospital Anxiety and Depression Scale (HADS) [25].

PSG

Participants were told to refrain from resting after dinner (unless this was routine for them) and abstain from alcohol or sleep medicine. The PSG equipment was mounted at the hospital at 12:00 p.m., and participants had a full night of unattended ambulatory PSG at home. They were told to go to sleep between 10:00 p.m. and 12:00 a.m. under conditions where they probably would not be disturbed, e.g. sleeping in a room alone. The exact times of turning of the lights and going to sleep ("lights off"), of events during the night (such as visiting the restroom) and of final awakening ("lights on") was written down by the participant. The dismantling of the equipment was carried out the following morning at 08:00 a.m.

PSG-technical setup

The PSG system and setup has been described by Engstrøm et al. [26]. PSG was recorded by a Notta recorder (EEG Technology Int.bv, 6092 NM Leveroy, The Netherlands) and analyzed with Stellate Harmonie software (Stellate, Montreal, Quebec, Canada). Eight EEG electrodes were placed according to the International (10–20) system [27] (F3, F4, C3, C4, P3, P4, O1, O2 plus Pz reference and Cz ground); two electrooculographic electrodes (EOG) applied two cm laterally and, respectively, two cm above and below the right and left lateral eye cantus. EOG-reference electrodes were applied to the left (A1) and the right (A2) mastoids. Surface electromyography (EMG) was recorded from the submental and left anterior tibial muscle.

The following sensors were also applied for respiration and circulation measurements: a three-point oronasal airflow thermistor, a snore microphone, bands around thorax and abdomen to measure respiratory movements (Ultima Respiratory Effort Sensor™, piezo-electric crystals, Breabon Medical Corporation, Carp, Ontario, Canada), a body position sensor, (Ultima Body Position Sensor™, Breabon Medical Corporation, Carp, Ontario, Canada), an infrared index finger oximeter, and two ECG electrodes. The participants were instructed to go to bed, sleep as normal and write down lights-off and lights-on time from a synchronized watch.

PSG-analysis

PSG was analyzed from "lights off" in the evening to "lights on" in the morning. Sleep stage time and percentages of N1, N2, N3 and REM, and respiratory events, were scored according to "The AASM Manual for the scoring of sleep and associated events" from 2007 [28]. Scoring of respiratory events and desaturations was first done automatically by the Stellate Harmonie software (Stellate, Montreal, Quebec, Canada). An experienced certified specialist in clinical neurophysiology later performed manual sleep scoring and manual respiratory event editing. We calculated the apnea-hypopnea index (AHI) on the AASM 2007 "1a-rule"; a 4% fall in SaO2 with a 30% drop in airflow amplitude. Indexes were calculated as events per hour of sleep. Individuals with AHI less than 5 were defined as being without OSA. Participants were categorized as being without OSA (AHI<5), mild OSA (AHI 5-14.9), moderate-to-severe OSA (AHI ≥15).

Out of 213 participants, four individuals were excluded for technical reasons such as battery error or lost electrodes, one participant forgot to apply the thermistor, and two were excluded because of unusual road construction noise, leaving 206 subjects for statistical analysis.

Questionnaire-based diagnosis of Insomnia

A proxy insomnia diagnosis was given in accordance with the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) [29] with minor modification, through the semi-structured interview. We used a similar diagnostic algorithm (although with slightly different wording of questions) in a previous HUNT3 study on insomnia [30]. Subjects were diagnosed with insomnia if answering 'several times a week' or 'always' on at least one of the three questions: 'had difficulties falling asleep at night' (early insomnia), 'woke up repeatedly during the night' (middle insomnia), and 'woke up too early and couldn't get back to sleep (late insomnia).' In addition, all had to answer 'several times a week' on the question 'felt sleepy during the day' to get the diagnosis of insomnia. The latter question correlated well with Fatigue Severity Scale (r=0.52) and poorly with Epworth Sleepiness scale (r=0.21) in the present sample. Insomnia subtypes (early, middle and late) was defined accordingly, hence one subject could qualify for more than one subtype.

An Insomnia Symptom Score (ISS) was calculated as the summed response from the four questions regarding insomnia. The response 'never' was scored as 0, 'rarely' as 1, 'sometimes' as 2, 'several times a week' or 'always' as 3, with a maximum ISS of 12. In preliminary data from a sub-study of HUNT4 [31] including 152 women and 80 men (mean age 58 years), a total of 33% had interview-verified DSM-V insomnia. ISS correlated well with the insomnia severity index (ISI) [32] (r=0.81), and with cut-offs >8 for ISS and >12 for ISI, the chance-corrected agreement (Cohen's kappa) was good (0.65, 95% CI 0.55-0.76).

Categorization of health-related information

The HUNT3 study and the HUNT3 PSG study included many similar health-related-questions and measurements. This included body mass index (BMI) which was categorized according to WHO-criteria, with ≥25 as cutoff for overweight [33]. The screening question of headache was "Have you suffered from headache during the last 12 months?" (yes/no). The screening

question for chronic musculoskeletal complaints (CMSC) asked for pain and/or stiffness for at least three consecutive months during the past year (yes, no). For Hospital Anxiety and Depression Scale (HADS), a total sum score was used.

Data analysis and statistics

In this study, we aimed to include 200 participants since we then would, with acceptable precision, be able to estimate 95% confidence limits less than ±7% for an expected insomnia prevalence of 10%. For a main OSA vs. non-OSA comparison with 0.05 confidence level, the power to detect a moderate difference equal to 0.5 standard deviations would be 86%, comparing 150 subjects without and 50 subjects with OSA. Post-hoc contrasts with a Bonferroni corrected confidence level of 0.0167, would have a power equal to 81% to detect a slightly larger, still moderate-sized, group difference equal to 0.78 standard deviations for expected subgroup counts of 150 without, and 20 with moderate-to-severe OSA.

One participant had a missing response on the repeated-awakenings-at-night question, which was coded as 0 when calculating the ISS. Another participant answered two options on the early awakenings-question, of which the average was used. We carried out a linear regression model adjusted for gender and age in the SPSS GLM (general linear model)-module to determine if ISS differed across OSA groups and to estimate the interaction effects of gender and age by OSA on ISS. We also measured the ISS-difference between group pairs of OSA with the contrast option in the GLM-module.

We assessed the association between DSM-V-insomnia and OSA by logistic regression, presenting odds ratios (OR) with 95% confidence intervals (CI) adjusted for gender and age. We also compared crude prevalence of insomnia in OSA-groups and prevalence of AHI-groups within insomnia subtypes with chi-square tests. IBM SPSS statistics version 24

(Chicago, IL, USA) was used. Pearson correlation coefficients for age and ISS were calculated. The level of significance was set to 0.05, but the level was reduced to 0.0167 for the three post-hoc OSA group comparisons (Bonferroni correction).

Results

Comparison between participants in HUNT3 and the PSG study

The final sample in the PSG study included 206 persons (77% women), i.e. 18% of all invited to participate. The HUNT3 participants who answered ≥1 insomnia question included 40,535 persons with 22,728 (56%) women and 17,807 (44%) men (Table 1). We present characteristics of participants in the PSG Study and the HUNT3 study separated by gender in Table 1. As demonstrated, a much higher prevalence of insomnia was found in the PSG study (29.1% in women and 12.5% in men) compared to the HUNT3 study (8.4% in women and 5.5% men). In contrast, only a slightly higher headache prevalence was found in the PSG study compared to the HUNT3 study (Table 1).

Insomnia prevalence related to gender and OSA severity

Overall, 25.2% fulfilled the DSM-V criteria of insomnia. Crude prevalence of insomnia was not significantly different in the three AHI-groups (all participants, women and men separately; chi-square tests (df 2) <1.5, p<0.38; Table 2). Also in the multivariate logistic regression analyses, adjusting for age and gender, there was no significant association between DSM-V diagnosis of insomnia and AHI groups (Table 3).

In the group with moderate-to-severe OSA (AHI ≥15), the crude insomnia prevalence was 40.0% for women and 0.0% for men (Table 2). Thus, for participants with moderate-to-severe OSA, men tended to have less insomnia than women (post-hoc chi-square test, p=0.052).

The association between Insomnia Symptom Score (ISS), OSA severity, age and gender.

ISS differed between OSA-groups (ANCOVA df 2, F=6.73, p=0.001). Mean ISS was significantly lower in the moderate-to-severe OSA group compared to those without OSA (AHI <5) and mild OSA groups (Table 4; GLM-contrast p-values: p=0.002 and p=0.001, respectively).

ISS-score differed by gender, adjusted for age and OSA-group (ANCOVA df 1, F=6.8, p=0.01). There was no interaction of gender on the association between ISS and groups of OSA-severity (ANCOVA (df 2), F=0.68, $p_{interaction}$=0.51). However, there was a significant interaction for age on the association between ISS and groups of OSA-severity (ANCOVA df 2, F=3.1, $p_{interaction}$=0.048). In supplementary analyses, ISS correlated negatively with age in subjects with moderate-to-severe OSA (Figure 1; Pearson r=-0.66, p=0.015).

The association between early, middle and late insomnia subtype and OSA severity

We found no significant association between AHI groups and early, middle and late insomnia (Table 5). None of the 27 participants with late insomnia had AHI ≥15 (moderate-to-severe OSA).

Discussion

To the best of our knowledge, this is the first population-based PSG study including all adult age groups and both genders, evaluating the association between PSG-diagnosed OSA and DSM-V insomnia prevalence and severity. Individuals with moderate-to-severe OSA had a lower insomnia symptom score compared to those with mild OSA and being without OSA. However, despite a tendency towards a negative correlation among men, we did not find a definite association between overall prevalence of insomnia and OSA.

The association between OSA and insomnia has been evaluated in several clinical-based and population-based studies. Among studies using a symptom-based OSA diagnosis, results from population-based studies are summarized in Table 6, finding high insomnia prevalence (31-57%) among individuals with OSA-related symptoms in Norway, Australia, and the United States of America (USA) [11, 13, 14]. A clinical-based study found a prevalence of 20.5% [34]. Only one study, including sleep-related work problems in the insomnia-definition, reported a particularly low prevalence of 7% among those with OSA-symptoms [12]. However, OSA diagnoses based on symptoms instead of PSG cannot be directly compared to our study. Tiredness and fatigue, included in two Berlin questionnaire (BQ)-items [35], a questionnaire intended for OSA-screening, are for instance commonly reported in both OSA and insomnia, partly explaining why these questionnaires may have a low predictive value. We report a moderate prevalence equal to 15%.

As reviewed in our Table 6, the design and applied diagnostic criteria of insomnia and OSA differ widely between studies, and comparison should be done with caution. Even though PSG or PG is needed to diagnose OSA [22], it should be highlighted that there is still no consensus about hypopnea-definitions and AHI score and prevalence of OSA will vary with the applied definition [36]. E.g., studies using a 3% saturation cutoff for AHI would likely have higher AHI-scores (and define more subjects as OSA-patients), compared to studies using a 4% cutoff. So far only two studies have used the 3% rule, reporting lower insomnia prevalence in OSA of 29% [7] and 12.7% (in men) [37], compared to higher estimates (50-61%) from earlier clinical-based studies [3, 6, 9, 10].

Opposing the results from the OSA-symptom-based studies, one other population-based study on men, used PSG for the OSA diagnosis, finding 12.7% among persons with previously undiagnosed OSA. Furthermore, a lower prevalence of insomnia has been associated with AHI ≥5 in a case-control study of elderly [19] and with AHI ≥15 among patients referred to a university hospital on suspicion of OSA [2]. In accordance, insomnia was less frequent among those with AHI ≥10 vs. AHI <10 in a retrospective study of patients referred for sleep disordered breathing [3].

Consistent with two clinical-based studies [2, 16] and one case-control study [19], we found that individuals with moderate-to-severe OSA (AHI ≥15) had lower insomnia severity compared to those with mild or no OSA. In contrast, a positive correlation between symptom based diagnosis of OSA and the “insomnia severity index” (ISI) was found in clinical-based studies from Australia and the USA [4, 5]. Finally, ISI was found to be independent of OSA severity among patients in sleep clinics in the USA [6] and in South-Korea [7] (Table 6).

These inconsistent findings for ISI suggest that some other insomnia severity score (or index) like BIS [38] or ISS possibly may be more sensitive than ISI to reveal the "true" association between insomnia and moderate-to-severe OSA. ISI is based on how severe each symptom is felt. ISS however is based on symptom frequency per week, Bergen Insomnia Scale (BIS) also uses a frequency-based approach [11, 38] while USI (Uppsala Sleep Inventory) [39] has both severity- and frequency-based questions. Because DSM-V, ICSD-3 and ICD-10 [40] insomnia diagnostics have a frequency criterion, we believe that frequency-based symptom-scores should be adequate measures of insomnia severity, to be used and compared to ISI in future studies.

A negative association between insomnia and OSA, as we found, could be a consequence of sleepiness subsequent to obstructed breathing during sleep [2]. The lack of association between insomnia and OSA among individuals with AHI <15, and the inverse 'dose-response relationship' for AHI ≥15, suggests that there is no constant association between OSA and insomnia diagnoses. The relation may not be linear, and it seems to differ with the severity of OSA and other subject-related factors.

We also found a strong negative association between ISS and age in the moderate-to severe OSA group. Also, no men in the moderate-to-severe-group had insomnia. Such gender and age-related differences have only occasionally been reported before [3, 14, 16, 41]. Speculatively, gender and age-related differences in the relationship between OSA and insomnia may indeed explain part of the variability between studies. A likely reason for this is inclusion bias, in part by design, as clinical-based OSA studies naturally include more men. These factors should receive more attention in future studies.

We found no significant association was found between AHI groups and early, middle and late insomnia, in accordance with a clinical-based study from USA [8], and we could not confirm the previously reported association to middle insomnia [10]. However, another population-based study from USA reported higher frequencies of early, middle and late insomnia among those with self-reported sleep apnea [14]. Early and middle insomnia symptoms were also found to be more common among those with PSG diagnosed OSA compared to a control group from the general population [20].

Important strengths of this study include the population-based design and objective measurement of AHI by PSG. Furthermore, information about insomnia symptoms was assessed by a semi-structured interview. To our knowledge, this is the first population-based

study to evaluate the association between OSA status and prevalence of insomnia as well as insomnia symptom score.

Some limitations should be considered. The participation of 18% was low. At least partly, this can be explained by lack of time for many potential participants, because they needed to travel to Trondheim for two consecutive days. The sample was also enriched with insomniacs compared to the main HUNT3-survey, increasing statistical power but reducing representativeness. Women were much more likely to participate than men, indicating a self-selection bias regarding gender distribution. For this reason, summary statistics and statistical models were adjusted for gender. In addition, both genders were self-selected towards lower BMI in the PSG-sample compared to the HUNT3 population, although the mean group differences were small; 0.9 kg/m^2 in both genders. Accordingly, generalization should be done with caution. Although our sample of 206 participants ensured satisfactory precision and power regarding moderate and large effect sizes, the study was not powered to give precise prevalence estimates in small subgroups. For instance, the majority of participants were women and confidence intervals were accordingly wider for men. The lack of significance for insomnia in AHI ≥15 vs. AHI <5 subgroups (15% vs. 25%, respectively), potentially could be a type-II statistical error.

While ISS is an intuitive way of measuring insomnia symptom load, and our preliminary data indicate good correlation between ISI and ISS, it is not a fully validated instrument. However, as mentioned above, a frequency-based summed score like ISS may reflect insomnia, as defined in DSM-V and ICSD-3 in a good way. In the present study subjects were diagnosed with insomnia if answering 'several times a week', while the recent DSM-V (and ICSD-3) classifications now uses ≥3 times per week. Finally, we used *feeling of sleepiness* as a proxy for the daytime consequence insomnia criterion. We have also shown that this proxy question

correlates much better with fatigue than with sleepiness, probably because the words "sleepiness" and "tiredness" are used more interchangeably in the Norwegian language. Hence, this question, although a proxy compared to the actual DSM-V wording, seems to be a reasonable reflection of daytime fatigue.

Conclusion

In this population-based cross-sectional PSG study insomnia symptom score was lower in individuals with moderate-to-severe OSA compared to those with mild OSA or being without OSA. However, we did not find a definite statistical association between OSA and prevalence of insomnia or early, middle and late insomnia symptoms. The association between the two sleep disorders seems to be complex, being modified by OSA-severity, age and gender.

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