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The Association Between High Risk of Sleep Apnea, Comorbidities, and Risk of COVID-19: A Population Based International Harmonized Study

Frances Chung[1,2] MBBS, MD, Rida Waseem[1] MA, Chi Pham[1,2] BSc, Thomas Penzel[3] PhD, Fang Han[4] MD , Bjørn Bjorvatn[5] MD, PhD, Charles M. Morin[6] PhD, Brigitte Holzinger[7] PhD, Colin A. Espie[8] PhD, DSc, Christian Benedict[9] PhD, Jonathan Cedernaes[9,10] MD, PhD, Tarja Saaresranta[11] MD, PhD, Yun Kwok Wing[12] MBChB, Michael R. Nadorff[13,14] PhD, Yves Dauvilliers[15] MD, PhD, Luigi De Gennaro[16] PhD, Guiseppe Plazzi[17,18] MD, PhD, Ilona Merikanto[19] PhD, Kentaro Matsui[20] MD, PhD, Damien Leger[21] MD, PhD, Mariusz Sieminski[22] MD, PhD, Sergio Mota-Rolim[23] MD, PhD, Yuichi Inoue[24] MD, PhD, Markku Partinen[25] MD PhD, for the International COVID Sleep Study (ICOSS) group

1. Department of Anesthesia and Pain Medicine, Toronto Western Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada
2. Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, Ontario, Canada
3. Sleep Medicine Center, Charite Universitätsmedizin Berlin, Berlin, Germany
4. Department of Respiratory Medicine, Peking University People's Hospital, China
5. Department of Global Public Health and Primary Care, University of Bergen, and Norwegian Competence Center for Sleep Disorders, Haukeland University Hospital, Bergen, Norway
6. École de Psychologie, Centre d'étude des troubles du sommeil, Centre de recherche CERVO/Brain Research Center, Université Laval, Québec, Canada
7. Institute for Dream and Consciousness Research; Medical University of Vienna, Austria
8. Sleep and Circadian Neuroscience Institute, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK
9. Department of Neuroscience, Sleep Science (BMC), Uppsala University, Uppsala, Sweden
10. Department of Medicine, Division of Endocrinology, Metabolism, and Molecular Medicine, Northwestern University, Chicago, IL, USA
11. Division of Medicine, Department of Pulmonary Diseases, Turku University Hospital,

Finland

12. Li Chiu Kong Family Sleep Assessment Unit, Departments of Psychiatry, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China
13. Department of Psychology, Mississippi State University
14. Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine
15. Sleep-Wake Disorders Center, Department of Neurology, Gui-de-Chauliac Hospital, Institute for Neurosciences of Montpellier INM, INSERM, University of Montpellier, France
16. Department of Psychology, Sapienza University of Rome, Rome, Italy, and IRCCS Fondazione Santa Lucia, Rome, Italy
17. IRCCS, Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy
18. Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy
19. Department of Psychology and Logopedics and SleepWell Research Program, Faculty of Medicine, University of Helsinki, Helsinki, Finland
20. National Center of Neurology and Psychiatry National Institute of Mental Health, Department of Clinical Laboratory and Department of Sleep-Wake Disorders; Tokyo Women's Medical University, Department of Psychiatry
21. Hopital Hotel-Dieu de Paris, Sleep and Vigilance Center; Universite de Paris, VIFASOM (EA 7331 Vigilance Fatigue Sommeil et Santé Publique)
22. Department of Emergency Medicine, Medical University of Gdansk, Gdansk, Poland.
23. Brain Institute, Onofre Lopes University Hospital, and Physiology and Behavior Department – Federal University of Rio Grande do Norte, Brazil

24. Department of Somnology, Tokyo Medical University, Tokyo, and Japan Somnology Center, Neuropsychiatric Research Institute, Tokyo, Japan
25. Helsinki Sleep Clinic, Vitalmed Research Center, and Department of Neurosciences, Clinicum, University of Helsinki, Helsinki, Finland

Short title: High risk of sleep apnea and increased hospitalization with COVID-19

Address correspondence: Frances Chung, Department of Anesthesia and Pain Medicine, Toronto Western Hospital, University Health Network, Toronto, Ontario, Canada, M5T2S8

Frances.chung@uhn.ca

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ABSTRACT (250)

Purpose: Although obstructive sleep apnea (OSA) increases the risk of COVID-19, the risk modulation by being at risk of OSA has not been established. The objective of the study is to determine the association between high risk of OSA, comorbidities, and increased risk for COVID-19, hospitalization, and intensive care unit (ICU) treatment.

Methods: We conducted a cross-sectional population-based web survey in adults in 14 countries/regions. The survey included sociodemographic variables and comorbidities. Participants were asked questions about COVID-19, hospitalization, and ICU treatment. Standardized questionnaires (STOP questionnaire for high risk of OSA and Patient Health Questionnaire-4 for anxiety and depression) were included. Multivariable logistic regression was conducted adjusting for various factors.

Results: Out of 26,539 respondents, 20,598 (35.4% male) completed the survey. Mean age and BMI of participants were 41.5 ± 16.0 years and 24.0 ± 5.0 kg/m^2. The prevalence of physician diagnosed OSA and high risk of OSA was 4.1% and 9.5%, respectively. We found that high risk of OSA (adjusted odds ratio [aOR] 1.72, 95% confidence interval [CI]: 1.20, 2.47), and diabetes (aOR 2.07, 95%CI: 1.23, 3.48) were associated with the risk of COVID-19. High risk for OSA (aOR 2.11, 95% CI: 1.10-4.01), male sex (aOR: 2.82, 95% CI: 1.55-5.12), diabetes (aOR: 3.93, 95% CI: 1.70-9.12), and depression (aOR: 2.33, 95% CI: 1.15-4.77) were associated with increased risk of hospitalization or ICU treatment.

Conclusions: Participants at high risk of OSA had increased odds of having COVID-19 and were two times more likely to be hospitalized or treated in ICU.

Keywords: obstructive sleep apnea, COVID-19, STOP questionnaire, diabetes, depression

Abbreviations: OSA: obstructive sleep apnea; COVID-19: coronavirus disease 2019 (caused by severe acute respiratory syndrome coronavirus-2); ICU: intensive care unit; BMI: body mass index; ACE: angiotensin converting enzyme

INTRODUCTION

Globally, it is estimated that nearly one billion adults have obstructive sleep apnea (OSA), with the highest prevalence in China, followed by the USA, Brazil, and India.[1] OSA is characterized by collapse of the upper airway during sleep, which leads to interruption in breathing, intermittent hypoxemia, and frequent arousals. It is estimated that 82% of men and 93% of women with moderate to severe sleep apnea are undiagnosed in the general population.[2] A simple screening tool such as the STOP questionnaire (snoring, tiredness, observed apnea, blood pressure) is useful to identify individuals at risk of sleep apnea before laboratory polysomnography or home sleep apnea testing.[3,4]

Since January 2020, the Coronavirus disease 2019 (COVID-19) pandemic has significantly impacted global health and individual well-being. The Severe Acute Respiratory Syndrome Coronavirus-2 virus is highly contagious and causes fever, cough, fatigue, respiratory distress, and death. Patients with OSA have a significantly increased risk of severe COVID-19, as well as hospitalization and mortality due to COVID-19.[5-9] OSA have been hypothesized to increase COVID-19 severity and risk of death through proinflammatory pathways.[10,11] A low number of diagnosed OSA in an obese population with COVID-19 could reflect under-diagnosis of the disorder.[12] Since OSA is an emerging key risk factor for increased severity of COVID-19, screening for OSA may optimize the triage process in COVID-19 patients.[5]

Previous studies on the association between diagnosed OSA and COVID-19 have so far only included small sample sizes, and have examined hospitalized patients in a single country [8,13] or retrospectively examined electronic medical records of COVID-19 hospitalized patients with OSA.[5,7,14] To our knowledge, there has been no study on OSA, or at high risk of OSA, and COVID-19 in the general population. Although OSA increases the risk of severe COVID-19, [5-9] the risk modulation by being at

risk of OSA has not been established. The objective of our study was to examine the associations between high risk of OSA, comorbidities, and increased risk of being afflicted by COVID-19, as well as the risk of hospitalization or intensive care unit (ICU) treatment in a large sample of participants from 14 different countries/regions. We hypothesized that there would be associations between those at high risk of OSA – as well as its comorbidities – with greater risk of being diagnosed with COVID-19, and increased risk of hospitalization or requiring ICU treatment.

METHODS

Global survey during the COVID-19 pandemic

The research protocol and the final standardized survey questionnaire have been published previously.[15] All countries/regions obtained ethical approval or exemptions in keeping with national research governance and regulations. The cross-sectional survey data were collected online in each country/region in their native language between May and August 2020. It was administered in 14 countries/regions (Austria, Brazil, Canada, China/Hong Kong, China/Jinlin, Finland, France, Germany, Italy, Japan, Norway, Sweden, UK, and USA).

The survey included sociodemographic variables (age, gender, body mass index (BMI), marital status, etc.) and comorbidities. Participants were asked questions about having been diagnosed with COVID-19, and whether they were hospitalized or treated in the ICU. To investigate sleep problems, standardized and validated questionnaires were included such as Basic Nordic Sleep Questionnaire and STOP questionnaire (snoring, tiredness, observed apnea, pressure) and Patient Health Questionnaire (PHQ)-4 for anxiety and depression.[3,16,17] The STOP and PHQ questionnaires have been validated to use in diverse geographical population [4,18,19]

The survey was administered online by sharing a link on national newspapers, social media sites, and university/hospital webpages. Participants aged 18 years or older, anonymously, and voluntarily took part in the self-administered online survey. The most commonly used survey platforms for administration were Redcap and Qualtrics.

High risk of OSA (STOP questionnaire) and comorbidities

The STOP questionnaire is a screening questionnaire that consists of four Yes/No questions on snoring, tiredness, observed apnea, and high blood pressure. Answering yes to at least two of these questions shown to be an effective screening tool for high risk OSA. It has been validated by lab-polysomnography.[3,4] All respondents included in the analysis completed the STOP questionnaire. In the International COVID-19 Sleep Study (ICOSS) survey, instead of answering yes or no, participants rated on 5-point Likert scale for **S**noring, **T**iredness, **O**bserved apnea (never, less than once per week, 1-2 days per week, 3-5 days per week, and daily or almost daily) and Blood **P**ressure (Yes/No).[3] The questions were as follows: 1) Do you **snore** loudly (louder than talking or loud enough to be heard through closed doors)? 2) Do you often feel **tired**, fatigued, or sleepy during daytime? 3) Has anyone **observed** you stop breathing or choking during your sleep? 4) Do you have or are you being treated for high blood **pressure**? The first three questions were dichotomized into 0 = less than three nights per week versus 1 = three or greater than three nights per week. The highest total STOP score is four. STOP scores of two or greater were classified as high risk and a score of zero to one as low-risk of OSA. [3] Participants were asked (yes or no questions) whether they suffered from any comorbidities eliciting reports of physician diagnosed diseases such as sleep apnea, cardiovascular disorder, hypertension, cerebrovascular disorder, diabetes, asthma, chronic obstructive lung diseases (COPD), depression,

anxiety, insomnia, other sleep disorder, rheumatic disorder, autoimmune disease, chronic fatigue syndrome, attention deficit hyperactivity disorder, cancer, allergy, and other neurological disorder.

Statistical Analysis

The analyses were performed using STATA/SE 14.2 and participants' characteristics were described using mean ± standard deviation or percentage (frequencies). An independent sample t-test or chi-square was conducted to examine the differences in the sociodemographic of participants with high risk of OSA vs low-risk of OSA and OSA vs no-OSA. Multivariable logistic regression analyses, with 95% confidence intervals (CI) were conducted to examine the association between high risk of OSA, and risk of COVID-19 and hospitalization and ICU treatment, adjusting for BMI, age, gender, marital status, education, ethnicity, financial suffering, confinement, and other comorbidities. We chose the variables for models based on clinical importance and its association with dependent variable in the unadjusted analysis. Some analyses were stratified and weighed by countries. A P-value less than 0.05 was considered statistically significant (2-sided).

RESULTS

A total of 26,539 participants responded to the survey; 20,598 participants had complete data on both STOP questionnaire and the presence of comorbidities and were included in the analysis. The mean age and BMI were 41.5 ± 16.0 years and 24.0 ± 5.0 kg/m^2 with 35% males. Fifty-five percent were cohabiting/married and 64% had bachelors or higher-level education. The most commonly reported comorbidities were hypertension (11%), cardiovascular diseases (CVD) (4%), diabetes (4%), OSA (4%), depression (8%), and insomnia (7%). (Table 1) In total, 9.5% had a STOP score two or greater and were deemed to be at high risk of OSA. Eight percent of participants reported to have high risk of OSA but did

not indicate having OSA. There was a significant difference in the socio-demographics in high risk vs low risk OSA groups, and OSA vs non-OSA.(Table 1) Three percent (622/20,598) reported having had COVID-19, of whom 56% were confirmed by laboratory testing.

Characteristics and risk factors of participants with COVID-19

To examine the association between being at high risk of OSA and a reported diagnosis of COVID-19, we adjusted for participants characteristics and comorbidities. Participants with higher BMI (>35 kg/m^2) (adjusted odds ratio [aOR] 1.91, 95% CI: 1.08, 3.40), Hispanics ethnicity (aOR 1.55, 95%CI: 1.05, 2.30), high risk of OSA (aOR 1.72, 95%CI: 1.20, 2.47), and diabetes (aOR 2.07, 95%CI: 1.23, 3.48) had higher odds of reporting a COVID-19 diagnosis.(Table 2) The unadjusted analyses are also shown in eTable 1.

Risk factors associated with increased hospitalization and ICU treatment

In total, 622 participants reported having had COVID-19 infection, of whom 536 reported the disease severity level as follows: 42% reported having mild, 43% moderate, 12.5% severe, and 1.9% life threatening COVID infection symptoms. Of 104 participants who were hospitalized, 86.5% were admitted to hospital ward while 13.5% were treated in ICU. Of 431 participants who were not hospitalized, 77.3% were treated at home while 22.7% required no treatment.

To examined if there was an association between high risk of OSA (based on STOP questionnaire) and increased hospitalization for COVID-19, we adjusted for BMI, age, gender, and comorbidities. This analysis was not weighted and stratified due to limited and inconsistent number of responses across countries/regions. Male sex, high risk of OSA, diabetes, and depression were associated with increased hospitalization and ICU treatment related to COVID-19. Male sex (aOR: 2.82, 95% CI: 1.55-5.12) and diabetes (aOR: 3.93, 95% CI: 1.70-9.12) had three times higher odds of being hospitalized and receiving

ICU care for COVID-19, compared with female and no diabetes. Similarly, participants at high risk of OSA (aOR 2.11, 95% CI: 1.10-4.01) and depression (aOR: 2.33, 95% CI: 1.15-4.77) were at two-fold increased odds of hospitalization and ICU treatment for COVID-19 versus low risk of OSA and no depression. (Table 3) Depression was significantly associated with PHQ-2 for depression. (chi^2 =1000, p<0.001) The unadjusted analyses are shown in eTable 2. Figure 1 shows the probability of the significant variables.

Sleep problems and OSA (high risk; reported)

During the time of confinement of COVID-19 pandemic, we found that the prevalence of queried sleep problems such as poor sleep quality; sleep onset, sleep maintenance, and early morning awakening problems; nightmares; hypnotic use; fatigue; and excessive sleepiness were significantly increased in participants with risk of OSA (high risk vs. low risk) and for OSA vs no-OSA. (Figure 2)

To examine the association between sleep problems during pandemic and high risk of OSA as well as OSA, we adjusted for gender, age, BMI, marital status, ethnicity, education, presence of sleep problem before COVID-19 pandemic, duration of COVID-19 confinement, financial suffering, comorbidities, and the severity of the COVID-19 epidemic in each country. Analyses were weighted and stratified by countries/regions. (eTable 3) There were a significant association between all sleep problems and risk of OSA. For instance, risk of OSA was associated with largest increase for excessive sleepiness. (aOR 2.42, 95% CI: 1.90-3.09) Additionally, there was an association between some sleep problems and OSA. (eTable 3)

DISCUSSION

We found that participants with high risk of OSA and diabetes had higher odds of becoming afflicted by COVID-19. Additionally, our study showed that participants with high risk of OSA, male, diabetes, and depression were two to three times more likely to have been hospitalized or require ICU treatment due to COVID-19. To the best of our knowledge, our study is the first in the literature focusing on undiagnosed OSA by using the STOP questionnaire and the risk of COVID-19 whereas previous studies examined COVID-19 hospitalized patients with physician diagnosed OSA. [5-8,13,14]

The common risk factors for poor outcomes of COVID-19 are older age, hypertension, and diabetes; [20,21] all of which are prevalent or associated with OSA. Clinical recognition of OSA is markedly underdiagnosed worldwide. Previous studies which reported OSA in COVID-19 patients had small number of hospitalized patients, usually from one area, with no comparison to participants who had not been afflicted by COVID-19.[8,12,13] A few retrospective studies, which examined the association between diagnosed OSA and COVID-19 in electronic medical database, identified OSA as a risk factor for COVID-19 severity with higher ICU admission and mortality.[5,7,14] Screening patients for OSA are being recommended to aid in decisions for COVID-19 treatment.[5,7] Our study is novel as we globally examined the risk of COVID-19 hospitalization and ICU treatment in individuals with high risk of OSA – using the STOP questionnaire, from a diverse general population of over 20,000 individuals.

The proinflammatory status of OSA may enhance the typical COVID-19 cytokine storm, thus worsening disease evolution.[12] Interestingly, we observed a significant association between high risk of OSA (STOP score 2 or higher) and increased COVID-19 hospitalization and ICU treatment, but not between OSA and worse outcomes. Many individuals at high risk of OSA are presumably undiagnosed and have

not received treatment, whereas we hypothesized that those who reported physician diagnosed OSA in our study might have received prehospital and/or in-hospital benefit of treatment such as continuous positive airway pressure (CPAP) possibly accounting for better outcomes. CPAP therapy decreases the underlying proinflammatory conditions which may help manage COVID-19 symptoms by reducing upper airway and systemic oxidative stress.[7,22] COVID-19 patients with OSA treated with CPAP prescription appeared to have better outcomes in a study from electronic health records of the New England Health Care System.[7]

However, among patients with acute respiratory distress syndrome (ARDS) due to COVID-19, undiagnosed SDB was independently associated with ARDS.[23] It is difficult to know the true prevalence of OSA among patients with COVID-19 as diagnostic sleep studies with polysomnography are not feasible at the time of COVID-19 infection. Since our study shows that participants at high risk of OSA are about two times more likely to need hospitalization or ICU care due to COVID-19, we recommend screening for OSA in order to enhance the COVID-19 triage process. The STOP questionnaire has been validated as an effective tool for OSA screening,[3,4] and its use could aid in predicting COVID-19 severity and the need for more intensive in-hospital treatment.

Consistent with the literature, we found that individuals with diabetes had an increased (three times) odds of being hospitalized for COVID-19. Two meta-analyses found that diabetes was the second most prevalent comorbidity in COVID-19 patients.[24,25] Patients with diabetes are often treated with angiotensin converting enzyme (ACE) inhibitors, which result in upregulation of the protein ACE2.[26] The SARS-CoV-2 virus uses the enzyme as its main receptor to gain entry into the host cells.[27] Individuals with high risk of diabetes are thus potentially more likely to experience COVID-19 severe symptoms due to the increased expression of ACE2.

We showed males were at three-fold increased odds of being hospitalized for COVID infection. Our findings are consistent with the previous studies which showed an increased risk of hospitalization and mortality in males compared to females.[20,21,28,29]

There are high rates of depression in individuals with OSA in both community and clinical populations.[30] Up to 20% of those presenting with a diagnosed depressive syndrome may have OSA, and vice versa.[31] In our survey, we asked participants whether they have a physician diagnosed depression. Importantly, we found that participants who reported depression had almost two-fold increased odds of hospitalization due to COVID-19. Our findings are supported by two recent studies. Wang et al. analyzed a nation-wide database of electronic health records of 61 million adult patients in the US. Patients with a recent diagnosis of depression had over 7-folds increased risk for COVID-19. Patients with both a recent diagnosis of a mental disorder such as depression and COVID-19 had a higher death rate and increased hospitalization rate than those without mental disorder.[32] Also, Atkins et al. reported that in 269,070 older adults, preexisting diagnoses of depression emerged as independent risk factors for COVID-19 hospitalization.[20] However, it is plausible that depression may be a consequence of COVID-19 as a result of having been ill, or critically ill for a substantial period. Further research is needed to validate if COVID-19 hospitalization is due to pre-existing depression itself or secondary to other conditions.

Previous studies found age, hypertension, and COPD to be risk factors for mortality and hospitalization in COVID-19 hospitalized patients,[20,21,28,33] but we did not find an association for these variables. However, our study involved general population using an online platform. The participants in our study

were younger, with fewer comorbidities, such as hypertension and COPD than previous studies on COVID-19 hospitalized patients.[20,21,28,33]

We found that all types of sleep problems were associated with high risk vs low risk of OSA. OSA is characterized by intermittent complete and partial airway collapse, which results in sleep problems including frequent arousals, disruptive snoring, breathing pauses and co-occurrence of insomnia.[34] Remarkably, more sleep problems were recorded in participants who were at high risk of OSA based on the STOP questionnaire, compared with those with OSA, which further implies that patients with OSA might have received treatment that were beneficial to their symptoms.

Limitations

There are several methodological limitations due to the nature of survey-based data collection. Potential inaccuracy from reported data means that we cannot be certain all participants answered each survey question to the best of their ability or knowledge. We conducted the survey using web applications, which only allowed individuals with access to the internet to participate, thus potentially limiting the generalizability of our results. Variations in sample sizes and frame of sampling posed as another limitation and was relative to each different country. These variations were addressed using weighting in some analyses.

Another major limitation is that we used the STOP questionnaire to screen participants for high-risk of OSA. Although the STOP questionnaire is a validated screening tool in the population with pulmonary diseases [35,36], it has not been validated to use in patients with COVID-19 diagnosis. It is possible that an inflammatory state such as COVID-19 may produce enough upper airway inflammation to provoke snoring. Dyspnea associated with bilateral COVID-19 pneumonia could be misinterpreted as choking

during sleep. These may affect the reliability of the STOP questionnaire in this setting. Hence, our results should be interpreted with caution. Nevertheless, our findings are important as we demonstrated the association between those at high risk of OSA and COVID-19 in the general public in a large dataset. Our results epitomize a large and diverse global population representing different ethnicities and a broad age range.

Conclusion

In summary, participants at high risk of OSA had higher odds of reporting having been diagnosed with COVID-19. Participants at high risk of OSA were two times more likely to being treated in the hospital or ICU. Male, diabetes, and depression were also associated with increased risk of hospitalization and ICU treatment. Our study used the STOP questionnaire as a screening tool in the general population to identify individuals with a high risk of OSA. Identifying those at high risk of OSA by screening can enhance the COVID-19 triage process to optimize treatment.

Figure Legends

Figure 1: Predicted probabilities of hospitalization/ICU related to COVID for gender (A), STOP (risk of OSA) (B), diabetes (C), and depression (D). Vertical lines show 95 % confidence interval.

Figure 2. Prevalence of sleep problems during COVID-19 pandemic for risk of OSA (A) and OSA (B). Vertical lines show standard error. High risk of OSA: STOP score 2 or greater. Low risk of OSA STOP score less than 2. Chi-square analyses showed that there was a significant difference in the prevalence of risk of OSA (high vs. low) and OSA (Yes vs. No) for all sleep problems during pandemic ($P<0.001$).

Abbreviations OSA: obstructive sleep apnea, ICU: intensive care unit

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Author Contributions: Chung and Partinen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Chung, Penzel, Han, Bjorvatn, Morin, Holzinger, Espie, Partinen.

Drafting of the manuscript: Chung, Waseem, Pham.

Statistical analysis: Chung, Waseem.

Acquisition of data: All authors.

Critical revision of the manuscript for important intellectual content: All authors.

Administrative, technical, or material support: Chung, Thomas, Han, Bjorvatn, Morin, Holzinger, Espie, Benedict, Cedernaes, Wing, Nadorff, Dauvilliers, De Gennaro, Plazzi, Matsui,

Leger, Sieminski, Mota-Rolim, Inoue, Partinen.

Supervision: Chung, Penzel, Han, Bjorvatn, Morin, Holzinger, Espie, Benedict, Cedernaes, Wing, Nadorff, Dauvilliers, De Gennaro, Plazzi, Matsui, Leger, Sieminski, Mota-Rolim, Inoue. Partinen.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research 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.

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Table 1. Socio-demographics characteristics of participants

Variables	**N= 20,598[a]**	**STOP<2**	**STOP ≥2**	**No-OSA**	**OSA**
		18,645 (90.5)	**1,953 (9.5)**	**19,758 (95.9)**	**840 (4.1)**
Age, years	41.5 ± 16.0	40.9 ± 16.0	47.1 ± 15.0**	41.1 ± 16.0	51.3 ± 14.9**
(n=20,243) Range	18-98	18-95	18-98	18-98	18-84
Gender					
Male	7,288 (35.4)	6,228 (33.4)	889 (45.5) **	12,916 (65.4)	370 (44.1) **
Female	13,286 (64.5)	12,397 (66.5)	1060 (54.3)	6,818 (34.5)	470 (56.0)
Other	9 (0.1)	8 (0.04)	1 (0.05)	9 (0.05)	0
Missing	15 (0.07)	12 (0.06)	3 (0.15)	15 (0.08)	0
Body mass index, kg/m^2	24.0 ± 5.0	23.7 ± 4.7	27.0 ± 6.4**	23.9 ± 4.8	27.7 ± 6.6**
(n=19,683) Range	15-60	15-60	15-60	15-60	16-59
Marital status					
Single	7,724 (37.5)	7,296 (39.1)	428 (21.8) **	7,531 (38.1)	193 (23.0)**
Cohabiting	11,303 (54.9)	9,997 (53.6)	1,306 (66.9)	10,778 (54.6)	525 (62.5)
Others	1,518 (7.4)	1,307 (7.0)	211 (10.8)	1,401 (7.1)	117 (13.9)
Missing	53 (0.26)	45 (0.24)	8 (0.4)	48 (0.2)	5 (0.6)
Education					
Less than Bachelors	7,104 (34.5)	6,470 (34.7)	634 (32.5)*	6,808 (34.5)	296 (35.2)
Bachelors or higher	13,210 (64.1)	11,914 (63.9)	1,296 (66.4)	12,676 (64.1)	534 (63.6)

Missing	284 (1.4)	261 (1.4)	3 (1.2)	274 (1.4)	10 (1.2)
Ethnicity					
Caucasian	8,417 (41.0)	7,655 (41.1)	762 (39.0)**	8,133 (41.2)	284(33.8)**
Asian	8,868 (43.1)	8,127 (43.6)	741 (37.9)	8,490 (43.0)	378 (45.0)
Black	429 (2.1)	276 (1.5)	153 (7.8)	405 (2.1)	24 (2.9)
Hispanic	782 (3.8)	680 (3.6)	102 (5.2)	754 (3.8)	28 (3.3)
Other	1,824 (9.0)	1,662 (8.9)	162 (8.3)	1,708(8.6)	116 (13.8)
Missing	278 (1.4)	245 (1.3)	33 (1.7)	268 (1.4)	10 (1.2)
COVID-19					
No	16,165 (78.5)	14,667 (78.7)	1,498 (76.7)**	15,488 (78.4)	677 (80.6)**
Yes	622 (3)	464 (2.5)	158 (8.1)	582 (3.0)	40 (4.8)
Do not know	3,792 (18.4)	3,496 (18.8)	296 (15.2)	3,669 (18.6)	123 (14.6)
Missing	19 (0.09)	18 (0.10)	1 (0.05)	19 (0.1)	0
Confinement					
None to 3 weeks	11,955 (58.0)	10,911(58.5	1,044 (53.5)**	11,451 (58.0)	504 (60)
4 weeks or less	2,800 (13.6)	2,461 (13.2)	339 (17.4)	2,676 (13.5)	124 (14.8)
More than 4 weeks	5,647 (27.4)	5,093 (27.3)	554 (28.4)	5,445 (27.6)	202 (24.0)
Missing	196 (0.95)	180 (1.0)	16 (0.8)	186 (0.94)	10 (1.2)
Financial suffering					
None to little	14,799 (71.8)	13,577 (72.8)	1,222 (62.6)**	14,244	555 (66.1) **
Somewhat	3,155 (15.3)	2,814(15.1)	341(17.5)	3,023 (15.3)	132 (132)
Much to severely	2,616 (12.7)	2,320 (12.4)	386 (19.8)	2,463	153 (18.2)
Missing	28 (0.14)	24 (0.13)	4 (0.20)	28 (0.14)	0
Comorbidities					
STOP ≥ 2		-	-	1,561 (7.9)	392 (46.7) **
OSA (n=20,598)	840 (4.1)	448 (2.4)	392 (20.1) **	-	-
Insomnia (n=19,828)	1,346 (6.8)	1,099 (6.1)	247 (13.1) **	1,147 (6.0)	199 (25.1) **
Excessive daytime sleepiness (n=20,577)	3,380 (16.4)	2,700 (14.5)	680 (34.9) **	3,157 (16.0)	223 (26.6) **
Hypertension (n=19,828)	2,269 (11.4)	1,530 (8.5)	739 (39.2) **	1,939 (10.2)	330 (41.2) **
Cardiovascular disease (n=20,598)	766 (3.7)	575 (3.1)	191 (9.8) **	610 (3.1)	156 (18.6) **
Cerebrovascular disease (n=19,828)	297 (1.5)	198 (1.1)	99 (5.3) **	213 (1.1)	84 (10.6) **
Variables	**N= 20,598[a]**	**STOP<2 18,645 (90.5)**	**STOP ≥2 1,953 (9.5)**	**No-OSA 19,758 (95.9)**	**OSA 840 (4.1)**
Diabetes (n=20,598)	891 (4.3)	594 (3.2)	297 (15.2) **	706 (3.6)	185 (22.0) **
Autoimmune disease (n=19,828)	880 (4.4)	750 (4.2)	130 (6.9) **	757 (4.0)	123 (15.5) **
Neurological disorder (n=20,598)	589 (2.9)	457 (2.5)	132 (6.8) **	465 (2.4)	124 (14.8) **
Asthma (n=6,811)[b]	587 (8.6)	502 (7.9)	86 (20.1) **	537 (8.3)	50 (16.5) **
COPD (n=19,828)	267 (1.4)	185 (1.0)	82 (4.4) **	168 (0.9)	99 (12.5) **
Allergy (n=20,598)	5,558 (27.0)	5,025 (27.0)	533 (27.3)	5,217 (26.4)	341 (40.6) **
Neoplasm/Cancer (n=20,598)	588 (2.7)	474 (2.5)	84 (4.3) **	474 (2.5)	84 (4.3) **
Anxiety (n=19,828)	2,071 (10.4)	1,810 (10.1)	261 (13.8) **	1,871 (9.8)	200 (25.2) **
Depression (n=19,828)	1,682 (8.5)	1,359 (7.6)	323 (17.1) **	1,462 (7.7)	220 (27.7) **
Chronic fatigue (n=19,828)	444 (2.2)	328 (1.8)	116 (6.2) **	307 (1.6)	137 (17.3) **

Independent sample t-test or chi-square test was conducted to test the difference for high risk of OSA vs low-risk of OSA(using STOP questionnaire); and OSA (reported) vs No-OSA. **P<0.001, * P<0.05. OSA= obstructive sleep apnea, COPD= chronic obstructive pulmonary disease.

[a] Total number of participants were 20,598 but n varied for some variables.

[b] Due to low number of responses, asthma was not analysed in the multivariable analysis.

Table 2. Characteristics and risk factors of participants with COVID-19 infection

COVID19 Infection	**No COVID 19,957 N (%)**	**COVID 622 N (%)**	**Model odds ratio [95% CI]**
Age, years			
< 26	3,614 (18.1)	89 (14.3)	1 [reference]
26-45	8,423 (42.2)	339 (54.5)	1.41 (0.92-2.16)
46-65	5,616 (28.1)	158 (25.4)	1.03 (0.59-1.81)
>65	1,958 (9.8)	29 (4.7)	1.20 (0.49-2.94)
Gender			
Female	12,897	376 (60.4)	1 [reference]
Male	7,038 (35.3)	245 (39.3)	1.19 (0.88 -1.60)
Body mass index, kg/m^2			
< 25	12,905 (64.7)	292 (46.9)	1 [reference]
25-35	5,570 (27.9)	221 (35.5)	1.27 (0.95-1.70)
>35	641 (3.2)	38 (6.1)	1.91 (1.08-3.40)*
Ethnicity			
Caucasian	8,030 (40.2)	373 (60)	1 [reference]
Asian	8,788 (44.0)	80 (12.9)	0.52 (0.26-1.04)

Black	365 (1.8)	63 (10.1)	1.25 (0.78-2.0)
Hispanic	719 (3.6)	62 (10)	1.55 (1.05-2.30)*
Others	1784 (8.9)	38 (6.1)	0.31 (0.18-0.56)*
Risk of OSA			
Low	18,163 (91.0)	464 (74.6)	1 [reference]
High	1,794 (9.0)	158 (25.4)	1.72 (1.20-2.47)*
Diabetes			
No	19133 (95.8)	556 (89.4)	1 [reference]
Yes	824 (4.1)	66 (10.6)	2.07 (1.23-3.48)*
Cardiovascular diseases			
No	19,239 (96.4)	574 (92.2)	1 [reference]
Yes	718 (3.6)	48 (7.7)	1.79 (0.99-3.25)
Depression			
No	17,613 (88.3)	515 (82.8)	1 [reference]
Yes	1,596 (8.0)	85 (13.7)	1.34 (0.92-1.95)

Model was adjusted for body mass index, age, gender, marital status (single, cohabiting, others), ethnicity (Caucasian, Asian, Black, Hispanic, others), education (less than university, university degree), presence of COVID-19, financial suffering (to some extent, somewhat, severely), confinement (< 2 weeks, 2-4 weeks, over 5 weeks) and the severity of the COVID-19 epidemic in each country measured by cumulative number of cases per 100000 at the median time of the survey in each country. All variables were categorized. Results are weighted and stratified by countries. CI= confidence interval, OSA= obstructive sleep apnea. *P<0.05, **p<0.001

Table 3. Risk factors of participants with increased hospitalization and ICU treatment

Treatment severity	**No treatment/at home 431 N (%)**	**Ward/ICU-Hospitalization 104 N (%)**	**Adjusted odds ratio [95% CI] Model**
Age, years			
< 26	68 (15.8)	9 (8.7)	1 [reference]
26-45	230 (53.4)	67 (64.4)	1.63 (0.64-4.13)
>45	126 (29.2)	28 (26.9)	0.96 (0.33-2.78)
Gender			
Female	284 (65.9)	39 (37.5)	1 [reference]
Male	146 (33.9)	65 (62.5)	2.82 (1.55- 5.12)**
Body mass index, kg/m^2			
< 25	202 (46.9)	46 (44.2)	1 [reference]
25-35	164 (38.1)	30 (28.8)	0.71 (0.39-1.29)
>35	32 (7.4)	1 (1.0)	0.15 (0.02-1.22)
Risk of OSA			

Low	347 (80.5)	52 (50)	1 [reference]
High	84 (19.5)	52 (50)	2.11(1.10-4.01)*
Diabetes			
No	403 (93.5)	79 (76.0)	1 [reference]
Yes	28 (6.4)	25 (24.0)	3.93 (1.70-9.12)*
Cardiovascular diseases			
No	406 (94.2)	88 (84.6)	1 [reference]
Yes	25 (5.8)	16 (15.4)	1.62 (0.59-4.45)
COPD			
No	407 (94.4)	87 (83.7)	1 [reference]
Yes	11 (2.6)	8 (7.7)	0.85 (0.14-5.29)
Depression			
No	370 (85.8)	68 (65.4)	1 [reference]
Yes	48 (11.1)	27 (26.0)	2.33 (1.15-4.77)*

Model was adjusted for body mass index , age, gender, and comorbidities. All variables were categorized. ICU= intensive care unit, CI= confidence interval, OSA= obstructive sleep apnea, COPD = chronic obstructive pulmonary disease. *P<0.05, **p<0.001