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Previously diagnosed obstructive sleep apnea is not associated with increased risk of SARS-CoV-2 infection in community-dwelling older adults living in a highly endemic setting

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ABSTRACT

Objective: In view of the high prevalence of obstructive sleep apnea (OSA) and the increasing global pandemic of SARS-CoV-2 infection, it is likely that many patients with OSA get exposed to this virus. Besides theoretical assumptions, there is no evidence that OSA may favor SARS-CoV-2 acquisition or may lead to a more severe disease. Taking the opportunity of the Atahualpa Project cohort, we aimed to assess the relationship between previously diagnosed OSA and SARS-CoV-2 infection in older adults living in rural Ecuador.

Patients and methods: SARS-CoV-2 antibodies were determined in 180 individuals aged > 60 years that underwent polysomnography previously to this novel pandemic. Those with OSA remained untreated due to income limitations. Exposure-effect models were fitted with OSA as the exposure, SARS-CoV-2 seropositivity and symptomatology as the outcomes, and confounders – age, gender, obesity, arterial hypertension, diabetes mellitus, hypercholesterolemia, individuals per house, home confinement – as independent variables.

Results: A total of 87 (48%) individuals were seropositive to SARS-CoV-2, 77% of whom were symptomatic. The mean apnea/hypopnea index was 11.1 ± 11.7 episodes per hour, with 83 (46%) individuals having mild, and 38 (21%) moderate-to-severe OSA. Exposure-effect models demonstrated lack of relationship between OSA and SARS-CoV-2 seropositivity and symptomatology.

Conclusions: This study shows no relationship between history of OSA and SARS-CoV-2 seropositivity or symptomatology, opposing previous suggestions that persons with OSA are more prone to acquire the infection and have a more severe disease.

1. Introduction

Obstructive sleep apnea (OSA) affects more than 1 billion people worldwide, particularly older adults [1]. On the other hand, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) global pandemic has affected more than 100 million people [2]. It is likely that many people with OSA get exposed to this novel virus. Recent comments suggested that OSA may make individuals more prone to acquire SARS-CoV-2 infection, and that the course of the disease may be more severe, than in those without OSA [3–5]. However, there are no data supporting those assumptions, with the possible exception of a recent study that relied on administrative coding data to reveal that patients with OSA had more severe COVID-19 infections [6].

The Atahualpa Project is a population-based cohort study designed to assess factors influencing the burden of neurological and cardiovascular diseases in rural Ecuador [7]. As part of this project, we performed a single-night diagnostic polysomnography (PSG) in community-dwelling older adults (aged >60 years) [8–10]. These exams were performed several months before the onset of the SARS-CoV-2 pandemic, but these findings were not expected to have changed since no individual with OSA had received proper management during that time.

During April and May 2020, an abrupt increase in deaths was noticed

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in Atahualpa, which coincided with the peak of the SARS-CoV-2 pandemic in Ecuador. This suggested an outbreak of SARS-CoV-2 infection in the village. A door-to-door survey covering 97% of individuals enrolled in the Atahualpa Project demonstrated a SARS-CoV-2 seroprevalence of 45% and clinical manifestations consistent with COVID-19 in 77% of seropositive individuals (unpublished data). Taking the opportunity of the above-mentioned cohort, we aimed to assess the relationship between previously diagnosed OSA and SARS-CoV-2 infection in older adults enrolled in the Atahualpa Project.

2. Methods

2.1. Study population

Atahualpa is a rural Ecuadorian village with a low migration rate. Characteristics of its residents have been detailed elsewhere [11]. In brief, the population is homogeneous regarding race/ethnicity, living conditions, and dietary habits; most men belong to the blue collar class and most women are homemakers. There is only one health center of the Minister of Health, and the nearest hospital is about 10 miles away in a small city (Ancón).

2.2. Study design

Field personnel (including a medical doctor) visited all houses where Atahualpa Project individuals were actively enrolled. Demographic data and risk factors were extracted from the archives of the project and updated during the present survey. Individuals were interviewed and examined regarding previous (past two months) or current SARS-CoV-2-related symptomatology. In addition, SARS-CoV-2 antibodies were detected by an antibody test (see below). Exposure-effect models were fitted to assess the relationship between OSA and SARS-CoV-2 infection, after adjusting for relevant covariates. The Independent Review Board of Universidad Espiritu Santo (FWA: 00028878) approved the study protocol and informed consent forms.

2.3. Review of PSG data

We reviewed the results of PSG performed in individuals aged > 60 years enrolled in the Atahualpa Project, with attention to the apnea/hypopnea index (AHI), which calculates the number of apnea events by the number of sleep hours. PSGs were performed at the Sleep Unit of the Atahualpa Project Community Center, with the use of an Embletta® X100™ Comprehensive Portable PSG System (Embla Systems, Inc; Thornton, CO, USA). A sleep medicine neurologist – blinded to other information – reviewed raw data and interpreted all exams [8–10].

2.4. Assessment of SARS-CoV-2 antibodies

Detection of SARS-CoV-2 IgM and IgG antibodies was performed using the BIOHIT SARS-CoV-2 antibody test kit (BIOHIT Health Care Ltd., Cheshire, UK). Inasmuch as IgM and IgG responses in SARS-CoV-2 develop with only a few days of difference, seropositivity was defined as a positive response to any of them [12]. Results of those tests were independently reviewed by two readers blinded to clinical data, and discrepancies were resolved by consensus.

2.5. Clinical manifestations of SARS-CoV-2

We used the World Health Organization operational definitions of suspected cases, as follows: 1) acute respiratory illness (fever and at least one sign/symptom of respiratory disease) and a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset; 2) any acute respiratory illness and having been in contact with a confirmed or probable COVID-19 case in the last 14 days prior to symptom onset; and 3) severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease and requiring hospitalization) in the absence of an alternative diagnosis that fully explains the clinical presentation [13].

2.6. Covariates investigated

Clinical and epidemiological covariates were included if they have been associated with an increased risk of OSA or may play a role in SARS-CoV-2 acquisition and symptomatology. These included age, gender, obesity (body mass index $\geq$30 kg/m^2), arterial hypertension, diabetes mellitus, hypercholesterolemia, individuals per house, home confinement during the previous two months.

2.7. Statistical analysis

Data analyses were carried out by using STATA version 16 (College Station, TX, USA). In univariate analyses, continuous variables were compared by linear models and categorical variables by the x^2 or Fisher exact test, as appropriate. To evaluate the relationship of OSA categories (exposure) with SARS-CoV-2-related seropositivity and symptomatology (outcomes), we used treatment effects methodology computing inverse probability of treatment (exposure) weighting to minimize and adjust for the effect of confounders on OSA categories. Thereafter, we constructed exposure effect models, which fitted weighted logistic regression models for the outcomes.

3. Results

From 201 individuals aged > 60 years undergoing PSG up to December, 2018, 183 were actively enrolled in the Atahualpa Project as of May, 2020. The remaining 18 individuals had either died or emigrated during the past months. In addition, three declined participation to the present survey.

The mean age of the 180 participants was 71.8 $\pm$ 7.2 years and 116 (64%) were women. A body mass index $\geq$ 30 kg/m^2 was determined in 38 (21%) individuals, arterial hypertension in 83 (46%), diabetes mellitus in 51 (28%), and hypercholesterolemia in 30 (17%). The mean number of individuals per house was 4.8 $\pm$ 2.8, and 94 (52%) had been confined to home during the previous two months.

The mean AHI was 11.1 $\pm$ 11.7 episodes per hour; 59 persons (33%) had no OSA, 83 (47%) had mild OSA (5–15 episodes per hour), and 38 (21%) had moderate-to-severe OSA (>15 episodes per hour). A total of 87 (48%) individuals were seropositive to SARS-CoV-2 antibodies (including 71 who were reactive to both IgM and IgG, four to only IgM, and 12 to only IgG). The Kappa coefficient for interrater agreement for SARS-Cov-2 seropositivity was 0.91 (95% C.I.: 0.88 – 0.94).

SARS-CoV-2-related symptomatology was recalled by 78 (43%) individuals, most of whom (86%) were seropositive. Most symptomatic individuals presented symptoms during the past two months but were asymptomatic at the present survey.

There were no differences in univariate analyses across categories of OSA and the different covariates investigated, nor differences in the percentage of individuals with SARS-CoV-2 seropositivity or symptomatology (Table 1). To get more insights on the relationship between the AHI and the presence of SARS-CoV-2 seropositivity and symptomatology – irrespective of cutoffs assigned to designate the presence and severity of OSA – we fitted univariate linear models using the continuous AHI value and the number of individuals stratified according to whether they were seropositive or symptomatic. In such models, the mean AHI of 87 seronegative individuals was 10.2 $\pm$ 11.5 and that of 93 seropositive individuals was 12 $\pm$ 11.9 (p = 0.304). Likewise, the mean AHI of 102 asymptomatic and 78 symptomatic individuals were not different (10.6 $\pm$ 11.4 *versus* 11.8 $\pm$ 12.1; p = 0.496). Exposure-effect models demonstrated no significant relationship between OSA categories and SARS-CoV-2 seropositivity or symptomatology (Table 2).

Table 1
Characteristics of the study population across categories of obstructive sleep apnea (univariate analysis).

	Total series (n = 180)	No OSA (n = 59)	Mild OSA (n = 83)	Mod-Severe OSA (n = 38)	*p* value
Age, years (mean±SD)	71.8 ± 7.2	71.4 ± 7.5	72.2 ± 7.1	71.5 ± 7	0.632
Females, n (%)	116 (64)	43 (73)	54 (65)	19 (50)	0.070
Body mass index ≥ 30 kg/m^2, n (%)	38 (21)	8 (14)	22 (27)	8 (21)	0.176
Arterial hypertension, n (%)	83 (46)	23 (39)	42 (51)	18 (47)	0.386
Diabetes mellitus, n (%)	51 (28)	20 (34)	18 (22)	13 (34)	0.187
Hypercholesterolemia, n (%)	30 (17)	11 (19)	15 (18)	4 (11)	0.518
Persons per house (mean±SD)	4.8 ± 2.8	4.4 ± 2.4	5.3 ± 3.1	4.5 ± 2.4	0.112
Confined to home for 2 months, n (%)	94 (52)	34 (58)	44 (53)	16 (42)	0.321
Antibodies to SARS-CoV-2, n (%)	87 (48)	25 (42)	39 (47)	23 (60)	0.206
Symptoms of the disease, n (%)	78 (43)	23 (39)	34 (41)	21 (55)	0.241

OSA: Obstructive sleep apnea.

4. Discussion

This study shows no relationship between history of OSA and SARS-CoV-2 seropositivity or symptomatology, opposing previous assumptions that persons with OSA are more prone to acquire the infection and to have more severe disease [3–5]. Literature on this relationship is limited to editorial comments providing no data at all. Rationale for this hypothesis come from the finding that individuals with preexisting OSA are more predisposed to the development of cardiovascular diseases that, in turn, may facilitate the susceptibility to SARS-CoV-2 infection and increase the severity of this disease [3]. OSA is associated with intermittent episodes of hypoxia, which may further compromise the function of the pulmonary vascular endothelium and parenchyma (already compromised in SARS-CoV-2). It has also been said that concomitant obesity may favor the interaction between OSA and SARS-CoV2 infection [4]. This possibility is sound since obesity may upregulate the renin-angiotensin-aldosterone system and thus, the angiotensin-converting enzyme 2, which has been shown to be the portal of entry of this virus into the organism [14,15]. This was not the case in our series, where obesity was not relevant as a covariate in the aforementioned association. This was probably related to the phenotypic constitution of our population of Amerindian ancestry, where the neck circumference is more often associated with OSA than the body mass index [16].

The present study provides the unique opportunity to evaluate the role of OSA in the acquisition and severity of SARS-CoV-2 infection in an unbiased population of older adults that had PSG recordings before the establishment of this novel pandemic. A potential limitation is the racial homogeneity of the study population, which may not be representative of other races/ethnic groups. In addition, PSGs were performed several months before the SARS-CoV-2 pandemic, and it could be argued that OSA severity had improved during that time. However, none of our patients received proper management for this condition and this possibility seems unlikely. Further studies are needed to confirm our findings.

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Table 2
Exposure effect models constructed with obstructive sleep apnea categories as the exposure, SARS-CoV-2 seropositivity and symptomatology as the outcomes, and confounders as independent variables. The coefficients are the difference between the adjusted proportions.

Exposure	Independent variables	Outcomes	Exposure effect proportion (95% C.I.)[a]	Exposure effect coefficient (95% C.I.)[b]	*p* value
OSA categories	Age, gender, obesity, hypertension, diabetes, hypercholesterolemia, individuals per house, and home confinement.	SARS-CoV-2 seropositivity	46.3 (34–58.5)	OSA mild *vs* none: 0.009 (−0.15 to 0.17) OSA mod-severe *vs* none: 0.175 (−0.02 to 0.37)	0.915 0.084
		SARS-CoV-2 symptomatology	44.2 (31.2 – 57.1)	OSA mild *vs* none: − 0.032 (−0.20 to 0.14) OSA mod-severe *vs* none: 0.150 (−0.05 to 0.14)	0.708 0.141

[a] Exposure proportion is the proportion with a positive outcome at the referent obstructive sleep apnea category.
[b] Exposure effect coefficient is the difference between the referent category and obstructive sleep apnea level.

CRediT authorship contribution statement

Oscar H. Del Brutto: study conception and design, manuscript drafting. Robertino M. Mera: statistical analyses of data. Pablo R. Castillo: polysomnography readings, significant intellectual contribution to manuscript content. Bettsy Y. Recalde: data collection and analysis. Aldo F. Costa: data collection and interpretation, significant intellectual contribution to manuscript content.

Conflict of interest

The authors have nothing to disclose.

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