Sleep quality deterioration in middle-aged and older adults living in a rural Ecuadorian village severely struck by the SARS-CoV-2 pandemic. A population-based longitudinal prospective study.

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ABSTRACT

Study objectives: This study assessed changes in sleep quality before and after the peak of the SARS-CoV-2 pandemic in community-dwellers enrolled in the Atahualpa Project.

Methods: Atahualpa residents aged ≥40 were eligible if they had a Pittsburgh Sleep Quality Index (PSQI) nine months before the pandemic and a lateral flow-based test for identification of SARS-CoV-2 antibodies during the peak of the pandemic. Six months later, individuals completed a follow-up PSQI. The independent relationship between SARS-CoV-2 infection and deterioration in sleep quality was assessed by fitting logistic mixed models for longitudinal data.

Results: Of 639 participants (mean age at baseline: 59±12.8 years), 325 (51%) had SARS-CoV-2 antibodies. A total of 185 (29%) individuals at baseline and 311 (49%) at follow-up were poor sleepers (p<0.001). Mixed logistic regression models demonstrated a significant increase in poor sleepers at follow-up (OR: 2.85; 95% C.I.: 2.16 – 3.75), which was more marked among SARS-CoV-2 seropositive subjects (OR: 3.8; 95% C.I.: 2.48 – 5.81). The adjusted proportion of poor sleepers increased from 29% to 56.2% (95% C.I.: 50.9 – 61.6%) among SARS-CoV-2 seropositive individuals, but only to 40.7% (95% C.I.: 35.3 – 46.1%) in their seronegative counterparts (p<0.001). Likewise, progression from a good to a poor sleeper status was higher among seropositive individuals than in their seronegative counterparts (38.1% *versus* 22.3%; p<0.001), after adjusting for relevant covariates.

Conclusions: This study shows a deleterious effect of SARS-CoV-2 in sleep quality. An effect of SARS-CoV-2 in disrupting sleep-related pathways cannot be ruled out.

Key Words: Sleep quality; Pittsburgh Sleep Quality Index; SARS-CoV-2; COVID-19; Coronavirus-19.

Trial registration: The Atahualpa Project has been registered at ClinicalTrials.gov; the identifier number is NCT01627600, and the date was: 10/02/2012 (https://clinicaltrials.gov/ct2/show/NCT01627600?cond=Atahualpa&draw=2&rank=1). The Sleep Disorders substudy has been registered at ClinicalTrials.gov; the identifier number is NCT01877616, and the date was: 06/13/2013 (https://clinicaltrials.gov/ct2/show/NCT01877616?cond=Atahualpa&draw=2&rank=4).

STATEMENT OF SIGNIFICANCE

A longitudinal prospective study in 639 community-dwelling middle-aged and older adults living in rural Ecuador, demonstrated the impact of the SARS-CoV-2 pandemic on sleep quality as assessed by the Pittsburgh Sleep Quality Index (PSQI) before and after the start of the pandemic. Antibodies to SARS-CoV-2 were detected in 325 (51%) individuals. Multivariate adjusted logistic mixed models for longitudinal data disclosed an overall significant increase in the categorized PSQI score at the follow-up, which was more important among SARS-CoV-2 infected individuals. A potential effect of SARS-CoV-2 in disrupting sleep-related pathways within the CNS cannot be ruled out.

INTRODUCTION

The SARS-CoV-2 pandemic has been associated with the occurrence of sleep-related disorders, not only in subjects affected by the virus but in the population at large [1-3]. Lockdowns, loss of social and support networks, unemployment and fear to acquire this infection or to develop permanent sequelae, range top among psychological consequences of this pandemic. All these factors may contribute to a detriment in sleep quality, as suggested by the literature [4-9]. However, most information came from studies using unstructured questionnaires applied online or through phone interviews, asking people about sleep problems during the lockdown or in patients evaluated at specialized clinics. A meta-analysis of published data on sleep disorders in COVID-19 patients up to August, 2020, disclosed that only a few studies used validated questionnaires, such as the Pittsburgh Sleep Quality Index (PSQI), yielding a pooled prevalence of poor sleep quality that ranged from 19% and 43% [10]. None of the studies included in that meta-analysis assessed the demonstration of changes (deterioration) of sleep quality before and after the start of the SARS-CoV-2 pandemic in both infected and non-infected individuals.

The Atahualpa Project is an ongoing population-based prospective cohort study aimed to assess the burden of sleep disorders and cerebrovascular diseases among community dwellers living in rural Ecuador [11]. During the past nine years, the adult population of Atahualpa has undergone several interviews and procedures for assessing breathing and non-breathing sleep-related disorders, cardiovascular risk factors and other conditions of interest [12-15]. Atahualpa was severely struck by the SARS-CoV-2 pandemic from March to May 2020, with a mortality rate of 21.6 per 1,000 population [16], a seroprevalence of 45% among survivors [17], and an incidence rate ratio of 7.4 per 100 person months of potential virus exposure [18]. Taking the unique opportunity of this well-established cohort, the present longitudinal

prospective study aimed to assess changes in sleep quality (before and after the peak of the pandemic) among individuals with and without evidence of SARS-CoV-2 infection.

METHODS

Study population: Atahualpa residents are homogeneous in terms of race/ethnicity, dietary habits, socioeconomic status and lifestyles, as detailed elsewhere [19]. Minimal migration rate of the population together with the high adherence to the project, make this village an optimal setting for the conduction of cohort studies [20]. In addition, these individuals share important characteristics for the study of sleep-related symptoms that reduce the chance of unexpected confounders. These include exposure to 12 daily hours of sunlight all over the year, hot and dry weather, virtually no shift working, and limited nighttime light pollution.

Atahualpa residents aged ≥40, previously identified by means of door-to-door surveys, were eligible for the present study if they have had assessment of sleep quality in the year before the start of the pandemic (by the use of the PSQI), and a serological test for identification of SARS-CoV-2 IgM and IgG by the use of a lateral flow-based SARS-CoV-2 antibody testing (BIOHIT Health Care Ltd., Cheshire, UK) in two rounds performed on May and June, 2020 [17,18]. Candidates were identified by a new door-to-door survey conducted on October, 2020. In this new visit, a repeated PSQI was completed by the same trained field personnel that performed previous tests. In addition, individuals who were seronegative for SARS-CoV-2 in the previous two surveys were specifically asked for the occurrence of clinical manifestations suggestive of COVID-19 (World Health Organization operational definitions of suspected cases were used [21]), and those who gave a positive answer underwent a repeated lateral flow-based antibody testing to assess for more recent infections. Those who only had IgM antibodies (associated or not with a weak IgG response) were excluded from

the study because this meant a recent infection, and those who only had IgG antibodies were added to the previous list of seropositives assuming an infection of at least one month before the current study.

Study design: Following a population-based longitudinal prospective design, this study investigated the presence of changes in sleep quality before and after the peak of the SARS-CoV-2 pandemic in the village. We took into account the serological status of individuals as well as the presence of covariates that may influence changes in sleep quality. The study was approved by the I.R.B. of Universidad Espíritu Santo - Ecuador (FWA: 00028878). Signed informed consent was waived because all these individuals had already signed a comprehensive form for assessment of sleep-related symptoms and SARS-CoV-2 antibodies determinations. Nevertheless, individuals were free to decline further participation in this new study.

Sleep Quality Assessment: We used a validated Spanish version of the PSQI [22]. The questionnaire consists of a combination of open-ended and Likert-type questions assessing sleep duration (total amount of sleep obtained during the nocturnal sleep episode), sleep disturbances (symptoms that change sleeping habits), sleep latency (length of time that it takes to slept), day dysfunction due to sleepiness (daytime somnolence), sleep efficiency (ratio of time spent asleep to the amount of time in bed), overall sleep quality (self-perceived satisfaction with sleep), and use of medications needed to sleep (sedatives, sleep inductors, etc) [23]. The maximum score is 21 points, and the cutoff value for defining poor sleep quality is >5 points. For this study, we used for analysis the cutoff stratifying subjects as good and poor sleepers.

Clinical covariates: Demographics (age, sex, level of education), traditional cardiovascular risk factors (obesity, poor physical activity, high blood pressure,) assessed according to criteria proposed by the American Heart Association [24]) and symptoms of depression – assessed by the depression axis of the depression-anxiety-stress scale-21 (DASS-21) [15] – were selected as confounding variables, as they have shown to influence sleep quality in the study population. All the above-mentioned covariates had been updated during a survey conducted three months before the start of the pandemic in the village (December, 2019). Social factors inherent to the pandemic itself were also included as covariates. These included home confinement, social isolation (living alone), and having a bed partner with SARS-CoV-2 infection (irrespective of the serological status of the index bed partner). All the above-mentioned covariates had been updated during the surveys assessing SARS-CoV-2 seropositivity in villagers (two-to-three months after the start of the pandemic) [17,18]. Therefore, we used those measures and determinations for analyses as they represented a midpoint between retrospective and prospective PSQI evaluations of this study (coinciding with the exposure).

Statistical analyses: Data analyses were carried out using STATA version 16 (College Station, TX, USA). In univariate analyses, continuous variables were compared by linear models and categorical variables by x^2 or the Fisher exact test as appropriate. Multivariate logistic mixed models adjusted first for baseline covariates, and then, for covariates associated with the SARS-CoV-2 pandemic, were fitted to assess changes in the sleep status (good sleepers *versus* poor sleepers) at the follow-up. In addition, a logistic regression model calculated the rate of progression for being a good sleeper at baseline to a poor sleeper at follow-up (as the dependent variable). Marginal means were used to estimate the size of the difference of having a poor sleep quality in SARS-CoV-2 seropositive subjects when compared with seronegative ones, after adjusting for relevant covariates.

RESULTS

Of 730 individuals aged ≥40 years that were actively enrolled in the Atahualpa Project as of June, 2019, 673 (92%) underwent a PSQI on June, 2019, and a lateral flow-based assay for identification of SARS-CoV-2 antibodies on May and June, 2020. Of the 57 non-participants, 24 had died and 15 emigrated between the PSQI interview and the determination of SARS-CoV-2 antibodies, and the remaining 18 declined consent for participation in the current survey. Of the 673 initially enrolled individuals, 639 had a follow-up PSQI (October, 2020) and were included in this study (95% coverage). These individuals contributed 850.1 person-years of follow-up (mean: 1.33±0.03 years; SD: 0.28 years; range: 1.25 – 1.41 years). Of the 34 subjects not participating in this study, seven had died between July and September (three of them from COVID-19), eight could not complete the PSQI (due to a stroke causing aphasia or a degenerative disorder of the CNS appearing after the pre-pandemic PSQI), six had moved out of the village, seven had a recent (less than one month) SARS-CoV-2 infection, and six declined participation to the second sleep quality survey.

The mean (±SD) age of the 639 participants at the time of pre-pandemic PSQI (June 2019) was 59±12.8 years (median age: 58 years), and that at follow-up PSQI (October, 2020) was 60±12.8 years (median age: 59 years). A total of 361 (56%) individuals were women, and 335 (52%) had primary school education only. Obesity (body mass index ≥30 kg/m^2) was noticed in 179 (28%) individuals, a poor physical activity in 44 (7%), and high blood pressure (≥140/≥90 mmHg) in 184 (29%). The mean score in the depression axis of the DASS-21 was 1.7±2.2 (68 subjects had >4 points and were considered to be depressed), and 29 (5%) lived alone. A total of 325 (51%) had SARS-CoV-2 antibodies in blood, 222 (35%)

were confined to home during the peak of the pandemic (April to June), and 202 (32%) had a bed-partner with SARS-CoV-2 infection.

Using the PSQI cutoff of >5 points for defining poor sleep quality, 185 (29%) individuals at baseline, and 311 (49%) at the time of the follow-up PSQI, were "poor sleepers" (p<0.001). In univariate analysis, individuals who remained in the category of "good sleepers" across baseline and follow-up PSQI were more commonly SARS-CoV-2 seronegative (47% *versus* 35%; p=0.001). On the other hand, individuals who moved from the category of "good sleeper" to that of "poor sleeper" in the follow-up, were more often SARS-CoV-2 seropositive (38% *versus* 22%; p<0.001). Table 1 is a description of changes across categories of stratified PSQI scores between baseline and follow-up assessments according to whether individuals were SARS-CoV-2 positive or negative (univariate analysis).

A multivariate logistic mixed model adjusted for baseline covariates (demographics, cardiovascular risk factors and symptoms of depression) disclosed a significant increase in poor sleepers at the follow-up (OR: 2.85; 95% C.I.: 2.16 – 3.75; p<0.001). In this model, being hypertensive (p=0.049), and having higher scores in the depression axis of the DASS-21 (p=0.002) remained independently significant; the adjusted proportion of poor sleepers before the pandemic was 29%, and at the follow-up it was 48.6% (predictive marginal model). When the model was also adjusted for SARS-CoV-2 serological status, the odds for having a poor sleep quality in the follow-up among seropositive subjects was 3.8 (95% C.I.: 2.48 – 5.81; p<0.001); having higher scores in the depression axis of the DASS-21 (p=0.003) was the single covariate remaining independently significant. The proportion of poor sleepers increased from 29% to 56.2% (95% C.I.: 50.9 – 61.6%) among SARS-CoV-2 seropositive individuals, but only to 40.7% (95% C.I.: 35.3 – 46.1%) in their seronegative counterparts (p<0.001).

Then, a logistic regression model was fitted to assess the rate of progression for being a good sleeper at baseline to a poor sleeper at follow-up (as the dependent variable). In this model, there was a significant relationship between worsening of sleep quality and being SARS-CoV-2 seropositive (OR: 2.19; 95% C.I.: 1.54 – 3.12; $p<0.001$). In this model, being male ($p=0.028$) and obesity ($p=0.027$) remained as independent significant covariates. Overall, the progression was noticed in 194/639 individuals (30.4%; 95% C.I.: 26.8 – 34.1%). This proportion was higher among SARS-CoV-2 seropositive subjects (38.1%; 95% C.I.: 32.9 – 43.3%). Table 2 depicts a summary of multivariate models fitted for assessing changes in sleep quality between baseline and follow-up evaluations.

DISCUSSION

This longitudinal prospective study in community-dwelling middle-aged and older adults living in rural Ecuador, demonstrated a robust impact of the SARS-CoV-2 pandemic on sleep quality. Sleep quality deterioration mainly involves SARS-CoV-2 seropositive individuals. Progression from good to poor sleep quality as well as increases in the PSQI in the follow-up are higher among seropositive individuals than in their seronegative counterparts.

As previously mentioned, no single study has prospectively evaluated changes in sleep quality before and after the start of the SARS-CoV-2 pandemic in community-dwellers according to whether or not they were infected with the virus. Therefore, our results are not comparable to previous works. Nevertheless, some pieces of information can be extracted from published data. A Chinese study investigated the frequency of poor sleep quality and its stressors in apparently healthy subjects during the peak of the SARS-CoV-2 pandemic (assessment was conducted by means of an online survey only); about one third of participants had a poor sleep quality that was mediated by perceived stress, anxiety levels,

and low self-esteem [25]. Another online study conducted in China, also during the peak of the pandemic, disclosed sleep disturbances in about 18% of respondents. However, participants were not specifically inquired on whether they had SARS-CoV-2 infection or not. In that study, self-perceived health conditions were major factors favoring a poor sleep quality [9]. A Norwegian online survey, involving healthy subjects from a fitness center disclosed sleep disturbances in about 22% of individuals, which was significantly associated with decreased physical activity and psychological distress [26]. In general, those – and other – studies focused on the decreased sleep quality observed in populations under the threat of SARS-CoV-2 infection, as well as on the importance of a good mental health for reducing the risk of sleep-related symptoms. None of them attempted to assess whether there has been a measured change in sleep quality before and after the peak of the SARS-CoV-2 pandemic. To our knowledge, only one study from Nepal suggested that sleep disorders – mostly insomnia – were more frequently reported after the start than before the pandemic; however, such study collected data by means of an online cross-sectional survey asking about sleep symptoms occurring in the past, and such design could be flawed by a recall bias [27].

Our findings disclose a potentially important, yet non-explored, aspect of the relationship between sleep quality and SARS-CoV-2 infection. While the population at large experience a small degree of sleep quality deterioration during the pandemic (likely related to the above-mentioned psychological consequences), individuals infected by the virus have a more severe deterioration in sleep quality than their non-infected counterparts (after adjusting for stressors and risk factors).

The above-mentioned results suggest a direct (and late) effect of the virus itself on the anatomical pathways related to sleep. In this view, direct invasion of the central nervous system by SARS-CoV-2 is plausible since the receptor used by the virus for cell entry – angiotensin-converting enzyme-2 – is expressed in neurons and glial cells [28]. This

neurotropism may be the cause of sleep-related symptoms as well as other neurological complications that, according to a recent comprehensive review include – but are not limited to – stroke, encephalitis (or diffuse encephalopathy), myelitis, and peripheral or cranial neuropathies [29]. In addition, many patients develop anosmia-ageusia or non-specific headaches. However, knowledge on these complications is still limited and pathogenetic mechanisms involved in the development of COVID-19-related neurological complications are complex and not fully-understood thus far [29-31].

Entry of SARS-CoV-2 into the CNS through the nasal olfactory epithelium and, from then, to the olfactory bulb, facilitates further spread of the virus by trans-synaptic transfer to limbic structures and subsequently to deeper parts of the brain. An alternative theory proposes entrances of the virus to the CNS directly from the bloodstream through the blood brain barrier [32]. In any case, presence of the virus within the CNS may explain the disruption of structures involved in the anatomy of sleep, such as periventricular fibers connecting the frontal lobes with nuclei deep in the brain (basal ganglia, thalamus and hypothalamus) [33]. Studies using Positron Emission Tomography CT support this possibility by showing abnormal fluorine-18 Fluorodeoxyglucose uptake (hypometabolism) in limbic structures, frontal and orbito-frontal cortex, the cingulate gyrus, and the thalamus/hypothalamus among COVID-19 survivors [34].

The present study provides the unique opportunity to prospectively evaluate sleep quality – by means of an internationally accepted field instrument – in an unbiased population of middle-aged and older adults that have such evaluation before and several months after the establishment of the SARS-CoV-2 pandemic in the village. Another strength of this study includes the high coverage of long-term participants in the Atahualpa Project cohort, in whom several risk factors have been well characterized. Nevertheless, the study has limitations. The lateral flow-based antibody test we used is reported to have high sensitivity

and specificity, but we cannot rule out a small degree of misclassification due to false positive or false negative results [17,18]. In addition, assessment of SARS-CoV-2 status at the time of the follow-up PSQI was only investigated in individuals with symptoms of recent onset, and there is the possibility that some seropositive-asymptomatic individuals may had escaped detection. The PSQI is reliable and has been widely validated, but it is mostly based on the subjective assessment of sleep quality and the time-frame of such evaluation is in the month before the test. Despite the above-mentioned limitations, this is the single study proving information on sleep quality before and after the peak of the pandemic in a population highly endemic for SARS-CoV-2. The use of actigraphy, for a more objective evaluation of non-breathing sleep-related manifestations (sleep hours and sleep efficiency), is strongly recommended. In addition, other well-established population-based cohorts in whom participants have had sleep quality assessments before the SARS-CoV-2 pandemic, should be encouraged to obtain data after the start of the pandemic in their given populations to confirm our findings by assessing potential detriments in sleep quality among those who were infected.

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Data availability and sharing: Raw data will be available from the corresponding author upon reasonable request.

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Table 1 – Changes across categories of stratified Pittsburgh Sleep Quality Index scores (good sleepers *versus* poor sleepers) across baseline and follow-up assessments according to whether individuals were SARS-CoV-2 positive or negative (univariate analyses).

Pittsburgh Sleep Quality Index		**Total series (n=639)**	**SARS-CoV-2 status**		**Significance (*p* value)**
Baseline	**Follow-up**		**Negative (n=314)**	**Positive (n=325)**	
Good sleepers	Good sleepers	260	148 (47%)	112 (35%)	0.001
Good sleepers	Poor sleepers	194	70 (22%)	124 (38%)	<0.001
Poor sleepers	Good sleepers	68	39 (13%)	29 (9%)	0.152
Poor sleepers	Poor sleepers	117	57 (18%)	60 (18%)	0.920

Table 2 – Summary of multivariate models used to assess differences across good and poor sleepers at follow-up.

Model	Outcome	Results	Significant covariates
Multivariate logistic mixed, adjusted for baseline covariates	Increase in the odds of poor sleepers at follow-up	OR: 2.85; 95% C.I.: 2.16 – 3.75; p<0.001	Hypertension (p=0.049) Depression (p=0.002)
	Adjusted proportion of poor sleepers at baseline	29%; 95% C.I.: 24.48 – 32.45%	
	Adjusted proportion of poor sleepers at follow-up	48.6%; 95% C.I.: 44.8 – 52.47%	
Multivariate logistic mixed, adjusted for baseline and SARS-CoV-2-related covariates	Increase in the odds of poor sleepers among seropositive individuals at the follow-up	OR: 3.8; 95% C.I.: 2.48 – 5.81; p<0.001	Depression (p=0.003)
	Adjusted proportion of poor sleepers at follow-up among seronegative individuals	40.7%; 95% C.I.: 35.3 – 46.1%	
	Adjusted proportion of poor sleepers at follow-up among seropositive individuals	56.2%; 95% C.I.: 50.9 – 61.6%	
Logistic regression, adjusted for baseline and SARS-CoV-2-related covariates	Odds for progression from good sleeper to poor sleeper among seropositive individuals at follow-up	OR: 2.19; 95% C.I.: 1.54 – 3.12; p<0.001	Being male (p=0.028) Obesity (p=0.027)
	Adjusted proportion of progression among seronegative individuals	22.3%; 95% C.I.: 17.8 – 26.9%	
	Adjusted proportion of progression among seropositive individuals	38.1%; 95% C.I.: 32.9 – 43.3%	