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Sleep quality and risk of recurrent aphthous ulcers: A Spanish cohort study

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Abstract

Objective: Recurrent aphthous stomatitis (RAS) is a condition that affects 20% of the world population and is characterized by painful ulcers in the oral mucosa. So far, the epidemiology and risk factors of RAS have been infrequently studied. Our objective was to determine whether sleep-related factors are related to the occurrence of RAS in the first prospective study carried out on this topic.

Methods: A cohort of 11210 Spanish students, 13–17 years old, was followed up for one year. Sleep disorders were assessed at baseline using a standard validated questionnaire.

Results: We detected 2655 new cases of RAS with a total of 287,262 person-week of follow-up. Subjects with high (4th quartile) Insomnia Index showed an incidence rate ratio (IRR) of RAS of 1.29 (95% confidence interval (CI) 1.15–1.45), while subjects with high Hypersomnia Index presented an IRR of 1.42 (95% CI 1.26–1.61). A high score of sleep-related phenomena was also associated with an increased IRR: 1.53 (95% CI 1.37–1.69). Adolescents with high level of sleep satisfaction were at lower risk of RAS: 0.88 (95% CI 0.77–1.01).

Conclusion: These findings suggest that sleep disorders are moderately associated with RAS in adolescents.

KEYWORDS
adolescents, aphthous stomatitis, hypersomnia, insomnia, oral mucosa, sleep

1 | INTRODUCTION

Recurrent aphthous stomatitis (RAS) is a common condition characterized by recurrent small ulcers with circumscribed margins in the oral mucosa (Jurge et al., 2006). Pain is the main symptom of the disease which may last between 3 and 4 days (Scully et al., 2003) and 10–14 days (Akintoye & Greenberg, 2014). It causes difficulties in eating, swallowing, and speaking (Scully et al., 2003), and as a result, it negatively affects the quality of life in the patients (Tabolli et al., 2009; Zwiri, 2015). It has been estimated that RAS affects 20% of the general population (Scully & Felix, 2005) and is the most frequent oral mucosal lesion in teenagers (Amadori et al., 2017).

RAS is a multifactorial disease that can be affected by several risk factors including trauma of the oral mucosa (Wray et al., 1981), family history of RAS (Koybasi et al., 2006), vitamin B12 deficiency (Koybasi et al., 2006; Sun et al., 2015), nonsmoking status (Koybasi et al., 2006; Ussher et al., 2003), psychiatric disorders (Gavic et al., 2014), hormonal imbalance (Balan et al., 2012), and food sensitivity (Wray et al., 1982).

A relation between sleep-related factors and RAS is biologically plausible as, on the one hand, sleep disturbance was linked in previous studies to psychological disorders such as stress among adolescents (Benca et al., 1992; Breslau et al., 1996) and, on the other hand, psychological stress was implicated in the occurrence of RAS (Akintoye & Greenberg, 2014; Keenan & Spivakovksy, 2013). These two relationships are mediated by immunological factors such as growth hormone (GH) and cortisol (Hatzinger et al., 2008; Vgontzas et al., 1999).

Epidemiologic studies on the role of sleep patterns in the occurrence of RAS are scarce. Apart from two recent cross-sectional studies that revealed a relation of late bedtime and excessive sleep with RAS (Ma et al., 2015; Webb et al., 2013), no prospective study is available. We, therefore, decided to fill the gap and carry out a study to assess the effect of insomnia, hypersomnia, sleep satisfaction, and presence of sleep-related phenomena on RAS among adolescents, using a prospective cohort design.

2 | MATERIAL AND METHODS

2.1 | Study population and data collection

We started the study with 11,210 students aged 13–17 years registered in 58 Spanish secondary schools in the region of Galicia (Northwest of Spain). Our study population was a random sample of the students' population of the same age in the Galician region. The number of selected students in each institute was proportional to the total number of students of each school. Upon selection, we obtained students' assent and the written informed consent from their parents to participate in the study.

Before starting the follow-up, each participant responded to a baseline questionnaire about RAS, quality and quantity of sleep and other lifestyle variables that could represent potential confounders of the relation between RAS and sleep. We evaluated four different aspects of sleep including insomnia, hypersomnia, and satisfaction with sleep, in addition to a score of sleep-related phenomena such as snoring or involuntary leg movements.

To increase the response rate, both initial and follow-up questionnaires were anonymous. To link each questionnaire with its corresponding follow-up, we asked the students to provide on each questionnaire a 12-digit code including the code of school (two digits), sex (one digit), and date of birth in the format of day/month/year (six digits) followed by the last three digits of their phone number. We excluded participants with duplicate codes from the study. We also excluded from the follow-up students who reported RAS at baseline.

Students filled in the questionnaires in the presence of professionals who helped them when needed and checked the completion of the questionnaires. The initial and follow-up questionnaires took 15 and 3 min on average to be filled in, respectively. We followed the students for 1 year.

The study was approved by the Regional Ethics Committee (reference 2004/130). The manuscript is in compliance with the STROBE statement as per its checklist.

2.2 | Exposure assessment

In the baseline evaluation, we assessed the quality of sleep during the last month using the Oviedo Sleep Questionnaire (OSQ) (García et al., 2000). This scale is a brief semi-structured questionnaire which consists of 15 items, 13 of which are grouped into three dimensions, including subjective satisfaction with sleep, insomnia, and hypersomnia. Two additional questions assess the existence of sleep-related phenomena including snoring, snoring with suffocation, involuntary leg movements and nightmares, and the intake of sleep pills or other remedies.

This questionnaire has the advantage of being developed in Spanish in a neighboring population of the Northwest of Spain, and thus did not need any translation or cultural adaptation. The validity and reliability have been evaluated in healthy people (Jiménez et al., 2017) and patients (García et al., 2000; Garcia-Portilla González et al., 2009). The questionnaire showed a Cronbach's alpha value of 0.83 for the total OSQ score in healthy people (Jiménez et al., 2017). It also showed a test–retest reliability of 0.87 and an internal consistency of 0.90, 0.88, and 0.91 for total score, hypersomnia, and insomnia, respectively. It demonstrated an acceptable convergent validity and discriminant validity and was able to differentiate between cases and non-cases, as well as distinct degrees of sleep disorder severity in patients (Garcia-Portilla González et al., 2009).

2.3 | Disease assessment

We determined cases of RAS on the basis of a short questionnaire that we administered to the participants every 12 weeks. We based our questionnaire on symptoms described in the literature (Bruce & Rogers, 2003; Scully et al., 2003). We further asked two questions to exclude traumatic wounds caused by dentistry interventions, or piercing. These questions, answered on a yes/no basis, were as follows: Did you have “aphthous ulcers” in your mouth, which are small and painful white sores? Do you associate their occurrence with the fact that you broke a tooth or bit your cheek? Do you associate their occurrence with the contact with your braces or your piercing?

We considered cases with two or more episodes of disease appearing on separate occasions during the follow-up as severe RAS.

2.4 | Validation substudy

To assess the validity and reproducibility of our diagnosis of RAS, based on self-examination, we compared this diagnosis with that established by nine different dentists on a random sample of 125 patients, 74 with RAS and 51 without RAS who attended to the dental clinics for a different motive than mouth ulcers. The diagnosis made by the dentists was considered as the gold standard. These dentists had previously received specific training with visual aids to enable them to make a differential diagnosis between RAS and

similar mouth lesions such as intraoral herpes ulcers or oral lichen planus. We asked the dentists to consider as a case of RAS the following clinical forms of the disease: (1) Minor or Mikulicz type: oval or round shape wounds smaller than 1 cm in diameter lasting for 1–2 weeks and which normally do not leave any scar after recovery, (2) major type (or Sutton ulcer): wounds that are larger than 1 cm of diameter and which may last more than one month and may leave a scar after recovery, and (3) Herpetiform type: very small (1–2 mm) but numerous and painful lesions.

2.5 | Data analysis

We calculated person-time for each participant, which started when the initial questionnaire was returned and ended with the onset of the disease, termination of the study, or loss to follow-up, whichever occurred first. For severe RAS, we considered the last episode of disease as the end of the follow-up. To calculate the person-time for each positive case of RAS, we summed all previous periods with a negative response and half of the last period (6 weeks), assuming constant incidence of RAS during the period.

Continuous variables such as score of hypersomnia, score of insomnia, and number of phenomena during sleep were introduced in the model as quartiles of distribution. Poisson regression model was used to calculate adjusted incidence rate ratios (IRRs) and their corresponding 95% confidence intervals (95% CIs).

To explore the shape of the curve relating the insomnia and hypersomnia scores to the onset of RAS, we fitted a cubic splines model adjusted for potential confounders. We set three knots (quartiles 1 to 3) at the boundaries of the exposure categories.

Variables that were considered in the analysis as potential confounders were age, sex, smoking, passive smoking, total alcohol intake, total caffeine intake, total physical activity, geographical area (coastal/inland), body mass index, and two uncorrelated dimensions of psychological stress: Negative Affect and Positive Affect (Watson et al., 1988).

Except for age and sex, which were introduced in all models, we introduced potential confounders in the final model if their inclusion modified the IRR of the main exposure variable by at least 10% (Greenland, 1995). Stata 12 (Stata Corp) was used for all statistical analyses.

2.6 | Sensitivity analysis

To assess the robustness of our results to misclassification bias, in a secondary analysis we corrected the relative risk estimates of the highest level of each sleep variable using the sensitivity and specificity of our diagnosis tool of mouth ulcers obtained from the concurrent validation substudy. We assumed that all subjects in the cohort were followed until the end of the study (Kleinbaum et al., 1982).

3 | RESULTS

A total of 9617 participants were analyzed (Figure 1). Five hundred forty-five out of 11,210 participants were excluded because

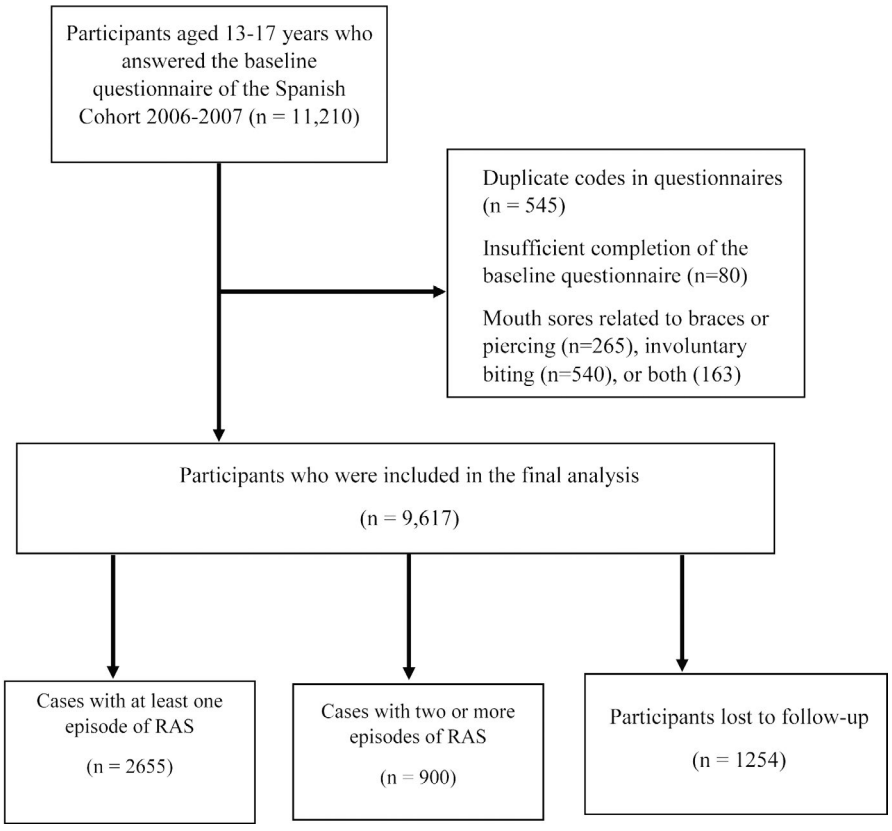

FIGURE 1 Flow chart of the cohort study on sleep and risk of recurrent aphthous ulcers

of duplicate codes in questionnaires, and 80 further cases were excluded due to insufficient completion of the baseline questionnaire (5.6%). We also excluded participants who had mouth sores related to braces or piercing ($n = 265$), sores related to involuntary biting ($n = 540$), or both ($n = 163$). Female participants represented 53% of the sample, and 68% of the participants were living in urban areas. The mean follow-up time was 29.9 ± 19.7 weeks. Students were between 13 and 17 years old [mean (SD): 16.2 (1.46) years].

We detected 2655 incident cases of RAS with a total of 287,262 person-weeks of follow-up. The overall incidence rate of RAS was 0.48 $year^{-1}$ (0.43 in men and 0.52 in women). The incidence rate of severe RAS was 0.19 $year^{-1}$ (0.16 in men and 0.21 in women).

The sensitivity and specificity of the questionnaire for diagnosis of RAS were 65% and 85%, respectively.

Absence or low level of satisfaction with sleep was reported by 13.6% of the study population. Mean age was similar in all subgroups of sleep-related variables. Table 1 represents the distribution of potential confounders in different categories of sleep-related variables. Table 2 shows the adjusted IRRs for RAS according to four sleep-related variables.

Both insomnia and hypersomnia scores were related in a monotonic fashion to increased RAS incidence rate. Compared to adolescents in the first quartile of the distribution, those of the 3rd and 4th quartiles of insomnia presented the following IRRs: 1.24 (95%CI: 1.10 to 1.38) and 1.29 (95%CI: 1.15 to 1.45). The trend was similar for hypersomnia with IRRs of 1.22 (95%CI: 1.09 to 1.36) and 1.42 (95%CI: 1.26 to 1.61) for 3rd and 4th quartiles, respectively. A similar trend was observed for the score of phenomena during sleep, the IRRs of which for 3rd and 4th quartiles were, respectively, 1.12 (95%CI: 1.01 to 1.26) and 1.53 (95%CI: 1.37 to 1.69). Sleep satisfaction was inversely associated with incidence of RAS, as subjects with sufficient and high sleep satisfaction showed IRRs of 0.87 (95%CI: 0.77 to 0.98) and 0.88 (95%CI: 0.77 to 1.01), respectively, when compared to subjects with low sleep satisfaction.

The exposure-effect curve in Figure 2 shows the relation between scores of hypersomnia and insomnia, and the adjusted incidence rate ratio of RAS. For both variables, there are steady increasing trends of IRRs with increasing scores of hypersomnia and insomnia.

Our results for severe aphthous ulcers were similar to those found for non-severe forms. According to Table 3, the increase in the score of insomnia, hypersomnia, and number of sleep-related phenomena was related in a dose-response fashion to the rate of severe aphthous ulcer. Adjusted IRR for 4th quartiles of insomnia and number of phenomena compared with their 1st quartiles were 1.26 (95%CI: 1.03 to 1.53) and 1.63 (95%CI: 1.36 to 1.95), respectively. Adjusted IRRs for 3rd and 4th quartile of hypersomnia compared with the 1st quartile were 1.39 (95%CI: 1.14 to 1.69) and 1.65 (95%CI: 1.33 to 2.04), respectively. However, we could not find any evidence of a significant relation between sleep satisfaction and severe aphthous ulcers.

In addition to sex and age, further adjustment for smoking, passive smoking, total alcohol intake, total caffeine intake, total physical activity, geographical area (coastal/inland), body mass index, and stress measured through Negative Affect and Positive Affect scales did not meaningfully change the results (data not shown).

A total of 1254 subjects (13.04%) of the cohort were lost to follow-up before the end of the study. To assess whether loss to follow-up was related to exposure and to potential confounders, we compared the distribution of the four sleep-related exposure variables, in addition to sex, age, smoking, passive smoking, total alcohol intake, total caffeine intake, total physical activity, geographical area, and body mass index among participants who were lost to follow-up to the distribution of those variables among subjects who completed the follow-up. The distribution of all variables, except smoking and alcohol consumption, was similar. On average, subjects with incomplete follow-up consumed more alcohol than those with complete follow-up [Mean (SD): 65.1 (3.2) vs. 46.8 (1.1) gr]. However, alcohol consumption did not show any relation with the incidence of RAS in our data, and the introduction of this variable in the model did not modify the results. Furthermore, smoking was more frequent among subjects with incomplete follow-up than among those with complete follow-up (29% vs. 19%). Separate analyses showed that, in our data, smoking was related to an increase in the rate of RAS but when this variable was introduced in the model, the results were not altered substantially, probably due to the fact that smoking is not related to the sleep-related exposure variables in our data and, hence, is not a confounder.

To assess further the possible effect of loss to follow-up, we recalculated the incidence rate ratios in two extreme situations. First, we assumed that all participants lost to follow-up developed RAS. Second, we assumed that none of them developed the disease. In both scenarios, our results were not meaningfully modified from the original one. The highest change was found in the point estimates of "hypersomnia" of 3rd and 4th quartiles which changed from 1.22 and 1.42 to 1.15 and 1.27, respectively, when we assumed that all participants lost to follow-up developed RAS. Furthermore, the IRR for 4th quartile of "score of sleep-related phenomena" was modified from 1.53 to 1.41 when we assumed that all censored participants developed RAS.

The secondary analysis aimed at assessing the robustness of the results to misclassification bias of the outcome yielded the following corrected crude relative risk estimate for the highest level of each sleep-related variable: insomnia: 1.44 (95%CI: 1.30 to 1.59), hypersomnia: 1.60 (95%CI: 1.44 to 1.79), satisfaction with sleep: 0.89 (95%CI: 0.79 to 1.00), and score of sleep-related phenomena: 1.87 (95%CI: 1.71 to 2.04). The observed (uncorrected) crude estimates were as follows: insomnia: 1.18 (95%CI: 1.07 to 1.30), hypersomnia: 1.24 (95%CI: 1.12 to 1.37), satisfaction with sleep: 0.95 (95%CI: 0.85 to 1.06), and score of sleep-related phenomena: 1.35 (95%CI: 1.24 to 1.47).

4 | DISCUSSION

Our findings indicated that high levels of insomnia and hypersomnia, and the existence of phenomena during sleep are moderately associated with a higher rate of RAS. On the other hand, high levels

TABLE 1 Distribution of potential risk factors for Recurrent Aphthous Stomatitis in students of 58 Spanish schools according to different aspects of sleep

Sleep-related variables	Age[a] (years)	Female[b]	Passive smoker[b]	Current smoker[b]	Living in coastal area[b]	Living in rural area[b]	BMI[a] (kg/m^2)	Alcohol intake[a] (g/week)	Caffeine intake[a] (mg/day)	Total physical activity[a] (score)	Negative Affect[a] (score)	Positive Affect[a] (score)
	Mean	N (%)	N (%)	N (%)	N (%)	N (%)	Mean	Mean	Mean	Mean	Mean	Mean
Insomnia score												
1st quartile	16.1	969 (41.7)	1624 (69.9)	371(15.7)	1187 (50.2)	776 (32.8)	21.0	40.7	70.5	21.9	21.8	10.7
2nd quartile	16.2	1122 (51.0)	1647 (75.1)	376 (16.8)	1098 (49.1)	716 (31.9)	21.1	44.1	70.1	21.2	24.2	10.4
3rd quartile	16.2	1235 (56.6)	1731 (79.5)	494 (22.3)	1178 (53.2)	716 (32.3)	21.1	50.2	81.8	21.0	26.8	10.3
4th quartile	16.3	1411 (65.0)	1841 (84.1)	632 (28.5)	1147 (51.8)	638 (28.8)	21.1	62.0	115.0	20.6	32.1	9.8
p-value	<0.001	<0.001	<0.001	<0.001	0.03	0.01	0.2	<0.001	<0.001	<0.001	<0.001	<0.001
Hypersomnia score												
1st quartile	15.9	904 (43.5)	1398 (67.6)	317 (15.0)	1083 (51.1)	727 (34.3)	20.9	34.4	68.4	22.1	22.0	10.4
2nd quartile	16.2	1473 (55.1)	1990 (74.7)	481 (17.7)	1396 (51.4)	846 (31.8)	21.1	40.9	72.3	21.2	24.5	10.4
3rd quartile	16.2	1468 (54.1)	2119 (80.5)	588 (21.3)	1429 (51.7)	901 (32.6)	21.2	53.3	91.0	20.8	27.5	10.2
4th quartile	16.5	1041 (61.1)	1496 (86.8)	551 (31.7)	875 (50.3)	465 (26.7)	21.0	72.9	110.2	20.6	31.5	10.1
p-value	<0.001	<0.001	<0.001	<0.001	0.8	<0.001	0.003	<0.001	<0.001	<0.001	<0.001	<0.001
Sleep satisfaction												
None or a little	16.3	727 (56.9)	1063 (82.9)	363 (27.9)	711 (54.6)	366 (28.1)	21.2	59.8	108.0	21.0	31.5	9.6
Regular	16.3	1394 (59.1)	1853 (78.9)	543 (22.7)	1290 (53.8)	742 (31.0)	21.1	50.9	86.1	20.3	28.4	9.8
Enough	16.2	2092 (53.1)	3008 (76.5)	745 (18.6)	1996 (49.8)	1303 (32.5)	21.0	45.7	75.3	21.2	24.5	10.5
High	16.1	795 (43.7)	1303 (71.1)	332 (17.8)	925 (49.6)	614 (32.9)	21.0	47.0	84.0	22.2	23.0	10.9
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	0.01	0.12	<0.001	<0.001	<0.001	<0.001	<0.001
Score of sleep-related phenomena												
1st quartile	16.2	1605 (47.2)	2414 (71.4)	534 (15.4)	1679 (48.5)	1091 (31.5)	20.9	40.8	72.3	21.4	23.5	10.4
2nd quartile	16.3	924 (56.1)	1295 (78.8)	314 (18.8)	795 (47.6)	530 (31.7)	21.1	44.8	77.2	20.8	25.2	10.3
3rd quartile	16.2	921 (59.5)	1263 (80.6)	359 (22.7)	809 (51.0)	492 (31.1)	21.0	50.7	79.0	21.0	27.3	10.3
4th quartile	16.2	994 (57.1)	1456 (83.4)	497 (28.1)	940 (53.2)	558 (31.6)	21.4	66.8	116.5	21.3	30.7	10.3
p-value	0.08	<0.001	<0.001	<0.001	0.002	0.9	<0.001	<0.001	<0.001	0.001	<0.001	0.2

[a]One-way ANOVA was used to compare groups.

[b]Chi-square test was used to compare groups.

TABLE 2 Incidence rate ratios of Recurrent Aphthous Stomatitis in students of 58 Spanish schools, according to different aspects of sleep

Sleep-related variables	Sample size	Crude IRR[a]	95% CI[a]	Adjusted IRR[a],[b]	95% CI[a]	No. of person-weeks	No. of cases
Insomnia score							
1st quartile (9 to 13)	2366	1.00	Reference	1.00	Reference	75,046	601
2nd quartile (14 to 16)	2238	1.07	0.95, 1.20	1.07	0.95, 1.20	69,1124	592
3rd quartile (17 to 20)	2216	1.25	1.12, 1.40	1.24	1.10, 1.38	64,304	646
4th quartile (21 to 45)	2216	1.33	1.19, 1.49	1.29	1.15, 1.45	62,172	664
Hypersomnia score							
1st quartile (2 to 3)	2118	1.00	Reference	1.00	Reference	67,130	527
2nd quartile (4 to 5)	2718	1.08	0.97, 1.21	1.06	0.95, 1.19	84,442	717
3rd quartile (6)	2763	1.26	1.12, 1.40	1.22	1.09, 1.36	80,912	798
4th quartile (7 to 10)	1739	1.47	1.30, 1.66	1.42	1.26, 1.61	46,554	537
Sleep satisfaction							
None or a little	1303	1.00	Reference	1.00	Reference	36,762	371
Regular	2395	1.01	0.88, 1.14	1.01	0.89, 1.14	68,844	698
Enough	4003	0.86	0.77, 0.97	0.87	0.77, 0.98	122,546	1067
High	1864	0.86	0.75, 0.98	0.88	0.77, 1.01	57,830	503
Score of sleep-related phenomena							
1st quartile (5)	3458	1.00	Reference	1.00	Reference	108,204	874
2nd quartile (6)	1670	1.03	0.92, 1.16	1.02	0.91, 1.15	51,050	457
3rd quartile (7 to 8)	1584	1.16	1.03, 1.30	1.12	1.01, 1.26	47,638	447
4th quartile (9 to 21)	1768	1.57	1.41, 1.74	1.53	1.37, 1.69	47,716	604

[a]IRR, Incidence Rate Ratio; CI, Confidence Interval.

[b]Adjusted for sex and age (continuous). Further adjustment for the following variables did not modify the results: smoking, passive smoking, total alcohol intake, total caffeine intake, total physical activity, geographical area (coastal/inland), body mass index, Negative Affect and Positive Affect.

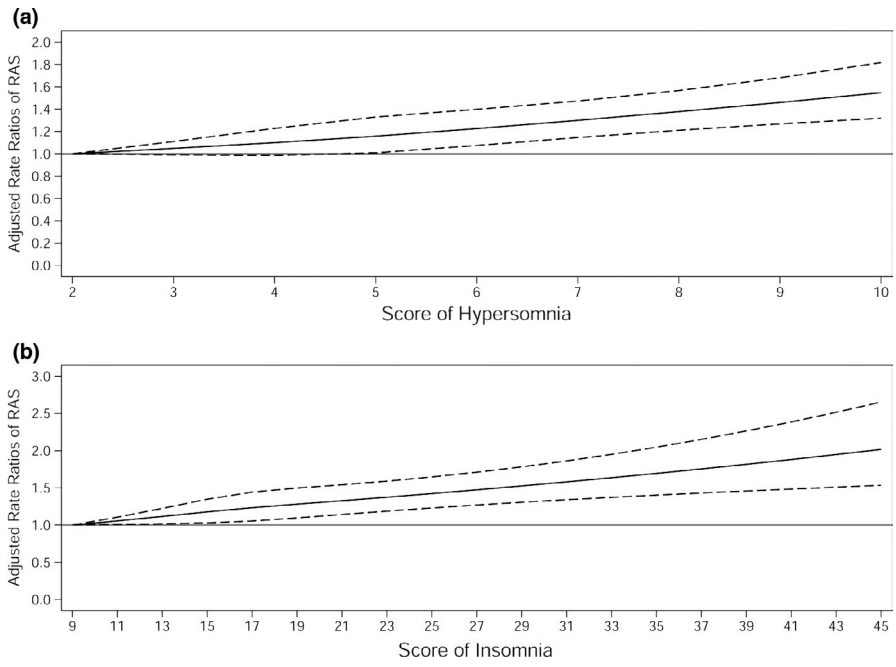

FIGURE 2 Incidence rate ratios of Recurrent Aphthous Stomatitis (RAS) in students of 58 Spanish schools, adjusted for sex and age (continuous), according to (a) hypersomnia and (b) insomnia; two-tail restricted cubic splines model. Solid line represents point estimates; dotted lines represent 95% confidence intervals

of satisfaction with sleep are inversely related to the rate of RAS. For severe forms of RAS, except for sleep satisfaction for which no effect was noticed, the findings were similar to those concerning non-severe forms.

These findings are biologically consistent. Indeed, sleep disorders may be associated with RAS through increased serum and salivary cortisol and decreased growth hormone levels as a consequence of psychological disorders such as stress and anxiety

TABLE 3 Incidence rate ratios of severe Recurrent Aphthous Stomatitis in students of 58 Spanish schools, according to different aspects of sleep

Sleep-related variables	Sample size	Crude IRR[a]	95% CI[a]	Adjusted IRR[a],[b]	95% CI[a]	No. of person-weeks	No. of cases
Insomnia score							
1st quartile (9 to 13)	1967	1.00	Reference	1.00	Reference	63,218	202
2nd quartile (14 to 16)	1869	1.18	0.97, 1.42	1.15	0.95, 1.39	59,211	223
3rd quartile (17 to 20)	1783	1.22	1.01, 1.49	1.18	0.97, 1.44	54,341	213
4th quartile (21 to 45)	1771	1.32	1.09, 1.60	1.26	1.03, 1.53	51,894	219
Hypersomnia score							
1st quartile (3)	1752	1.00	Reference	1.00	Reference	55,847	161
2nd quartile (4 to 5)	2246	1.19	0.98, 1.46	1.18	0.97, 1.45	71,109	245
3rd quartile (6)	2247	1.42	1.17, 1.72	1.39	1.14, 1.69	68,908	282
4th quartile (7 to 10)	1393	1.65	1.34, 2.04	1.65	1.33, 2.04	40,067	191
Sleep satisfaction							
None or a little	1052	1.00	Reference	1.00	Reference	30,693	120
Regular	1928	1.02	0.82, 1.27	1.04	0.83, 1.30	57,977	231
Enough	3299	0.89	0.73, 1.10	0.91	0.73, 1.12	103,811	363
High	1539	0.93	0.74, 1.17	0.97	0.77, 1.23	49,016	178
Score of sleep-related phenomena							
1st quartile (5)	2872	1.00	Reference	1.00	Reference	90,588	288
2nd quartile (6)	1391	1.08	0.89, 1.32	1.07	0.88, 1.31	42,979	148
3rd quartile (7 to 8)	1279	1.12	0.92, 1.37	1.10	0.90, 1.35	39,866	142
4th quartile (9 to 21)	1383	1.67	1.40, 1.99	1.63	1.36, 1.95	41,217	219

[a]IRR, Incidence Rate Ratio; CI, Confidence Interval.

[b]Adjusted for sex and age (continuous). Further adjustment for the following variables did not modify the results: smoking, passive smoking, total alcohol intake, total caffeine intake, total physical activity, geographical area (coastal/inland), body mass index, Negative Affect and Positive Affect.

(Albanidou-Farmaki et al., 2008; Bali & Jaggi, 2016). Cortisol is released as a response to acute psychological stress by the hypothalamic–pituitary–adrenocortical (HPA) system (Steiger, 2002). Hormones of the HPA system also regulate the sleep–wake cycle, while their dysfunction can disrupt sleep. In turn, sleep loss can hyper-activate the HPA system (Meerlo et al., 2008). It was also described that patients with insomnia present high levels of cortisol (Vgontzas et al., 2001), and that increased secretion of morning cortisol was associated with poor sleep quality in both children (Hatzinger et al., 2008) and adults (Bassett et al., 2015). Furthermore, the associations between stress and anxiety with RAS on the one hand (Albanidou-Farmaki et al., 2008; Gallo Cde et al., 2009), and between stress and sleep problems on the other hand (Hansen et al., 2018; LeBlanc et al., 2009), have been described before. This evidence could plausibly explain the association between sleep disorders and RAS found in our study.

The validity of the questionnaire for diagnosis of RAS was acceptable. In addition, previous studies confirmed the validity of the OSQ tool in the assessment of different aspects of sleep (García et al., 2000; Garcia-Portilla González et al., 2009). The prospective design of the study ensured that the quality of sleep was assessed before the diagnosis of RAS and, therefore, prevented the differential misclassification of exposures between RAS cases and non-cases.

Our study could be limited by the fact that the diagnosis of RAS was self-assessed and a certain amount of misclassification of the outcome could have been introduced. However, our secondary analysis, carried out to assess this effect of outcome misclassification due to an imperfect diagnosis tool, showed that our results were conservative and that the unknown true value of the risk increase was probably more extreme.

We also adjusted the associations for potential confounders and performed sensitivity analyses to assess the effect of loss to follow-up, but the results were not meaningfully modified. Therefore, the associations we found are unlikely to be due to confounding by measured variables, misclassification, or loss to follow-up. However, we cannot rule out a possible effect modification by a genetic factor. Indeed, previous studies showed that the HLA-B51 gene as well as genes that control heat shock proteins or cytokines may be implicated in the occurrence of RAS (Mizuki et al., 1995; Shohat-Zabarski et al., 1992). In our study, we did not measure those genetic factors. The effect of sleep disturbance on RAS may then be different depending on whether subjects harbor a polymorphism in those genes or not. Furthermore, we cannot exclude potential confounding by unmeasured factors either. The relation between psychological stress, sleep disorders, and RAS is not straightforward. Although we did not find sufficient evidence in our study of a potential role of

confounders of stress-related variables such as Negative Affect and Positive Affect, we cannot exclude that other dimensions of stress should be taken into account.

Our results were consistent with the study of Ma et al. which found a relation between late bedtime and RAS (Ma et al., 2015). In another cross-sectional study, Webb et al. revealed a possible association between RAS and increased sleep (Webb et al., 2013). However, both studies used a cross-sectional design, which makes it difficult to draw any causal inference.

In summary, our cohort study showed a moderate association between lack of satisfaction with sleep, insomnia, hypersomnia, and a high score of sleep-related phenomena; and the occurrence of RAS in adolescents. These findings are biologically plausible and unlikely to be due to confounding by measured variables or selection bias. However, residual confounding due to unmeasured variables, including stress-related variables, as well as some misclassification of the outcome due to the self-assessed diagnosis of RAS cannot be dismissed.

Sleep hygiene measures and observance of the amount of sleep recommended by experts to reach optimal health in adolescents should be promoted (Paruthi et al., 2016).

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CONFLICT OF INTEREST

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

AUTHOR CONTRIBUTIONS

Hamid Reza Tohidinik: Conceptualization; Formal analysis; Writing-original draft; Writing-review & editing. **Almudena Rodríguez:** Data curation; Formal analysis; Investigation; Writing-review & editing. **Carlos Regueira-Méndez:** Conceptualization; Investigation; Methodology; Writing-review & editing. **Bahi Takkouche:** Conceptualization; Methodology; Project administration; Supervision; Writing-review & editing.

ETHICAL APPROVAL

The authors certify that informed consent was obtained from patients and that the study was performed in accordance with the Declaration of Helsinki. IRB: Comité Ético de Investigación Clínica de Galicia. N° of approval: 2004/130 Date of approval: 7/7/2004.

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DATA AVAILABILITY STATEMENT

Anonymous data are available from the corresponding author upon reasonable request.

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