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Insomnia symptoms and asthma control – interrelations and importance of comorbidities

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Abstract

Background

Insomnia symptoms are common with asthma. The aim of the study was to analyze the associations between insomnia symptoms and asthma control, asthma severity, and asthma-related comorbidity in a community-based population.

Methods

Adults (n=23,875, ages 18-45) from the community-based LifeGene study answered a questionnaire on insomnia symptoms, airway symptoms, asthma diagnosis, asthma medication, and asthma-related comorbidities (chronic rhinosinusitis, gastro-esophageal reflux, anxiety, depression, or obesity).

Results

Of the participants, 1,272 (5.3%) had asthma. The prevalence of any insomnia symptom was higher in participants with uncontrolled asthma (n=201) than with controlled or partially controlled asthma (32.2% vs. 19.9% and 20.1%, respectively, $p<0.01$). There was no significant difference in the prevalence of insomnia symptoms between subjects with controlled asthma and subjects without asthma.

Subjects with asthma and any asthma-related comorbidity reported more insomnia symptoms (29.0% vs. 22.4%, $p<0.01$) compared to asthmatics without comorbidity.

Moreover, the prevalence was highest among subjects reporting both uncontrolled asthma and any asthma-related comorbidity (45.1%, $p<0.01$).

Uncontrolled asthma remained significantly associated with insomnia symptoms (OR 1.72 (1.15-2.56)) after adjusting for age, sex, BMI, smoking history, comorbidities, physical activity, and educational level, while medication level was not. Among asthma-related comorbidities, chronic rhinosinusitis (OR 1.62 (1.20-2.19)), obesity (1.87 (1.07-3.25)), and depression (OR 1.85 (1.34-2.55)) were independently associated with insomnia symptoms.

Conclusion

Uncontrolled asthma was significantly associated with insomnia symptoms, while controlled or partially controlled asthma was not. Asthma-related comorbidity is of great importance, and asthma control seems to be more important than asthma severity for insomnia symptoms.

Introduction

Insomnia symptoms are common in asthma.¹ One common explanation for the higher prevalence of insomnia symptoms in asthma is poor asthma control.^{2,3} However, it is not fully known if this is an independent association, as several risk factors are common for insomnia and poor asthma control, and sleep quality is worse in more severe asthma.²

Another potential risk factor for insomnia in asthma is asthma-related comorbidity, which is common especially in difficult-to-treat asthma.⁴ Several common asthma-related comorbidities are associated with insomnia symptoms. Rhinitis and chronic rhinosinusitis are common with asthma and have adverse effects on sleep.⁵ Obesity and obstructive sleep apnea (OSA) are more commonly seen in asthma.⁶ Depression and anxiety are overrepresented with asthma,⁷ and are strongly associated with insomnia symptoms. Gastro-esophageal reflux may also worsen asthma control as well as sleep quality.⁸ Taken together, asthma-related comorbidity may explain a considerable part of the sleep impairment in asthma, beyond asthma control and asthma severity.

Uniform definitions of asthma control and asthma severity have not been available until recent years.⁹ Many of the epidemiological studies of insomnia symptoms in asthma were published much earlier, and several of the more recent studies on sleep in asthma are mainly focused on severe asthma. Large population-based studies, on the other hand, often lack information either on comorbidities or asthma medication.

The aim of the present study was to analyze the associations between insomnia symptoms, asthma control, asthma severity, and asthma-related comorbidities, using a large population-based material. A secondary aim was to study the possible similarities between variables associated with both insomnia symptoms and asthma control.

Material and methods

Study population

LifeGene is a cohort study in Sweden.¹⁰ Index persons (aged 18-45 years) were randomly selected from the government's Person Address Register (Statens personadressregister, SPAR). The index persons were invited to include household members to the study, and it was also possible to register for participation at the LifeGene website. The study included a questionnaire and a visit to a test center, where several tests were done, including blood sampling and measurements of height and weight. Questionnaire data on insomnia symptoms, airway symptoms, asthma diagnosis, asthma medication, and comorbidities were available from 23,875 participants aged 18-45 years. Informed consent was obtained by all participants, and the present analysis was approved by the Regional Ethics Review Board in Uppsala (Dnr 2014/265).

Definitions

Asthma was defined following positive answers to both the questions "Have you ever been diagnosed with asthma?" and "Are you currently taking any medication, including inhalers, aerosols, or tablets, for asthma?"¹¹

Asthma control, as defined by GINA,¹² was estimated based on four questions: (1) limitation of activity (where the answer "some of the time" was considered significant), (2) shortness of breath (more than once a week), (3) waking up due to asthma symptoms (more than twice a month), and (4) use of short-acting beta-agonist (more than two times a week). Uncontrolled asthma was defined following positive answers to three or four of these questions, while one or two positive answers were considered as partial asthma control.¹²

The level of asthma medication was defined based on a modification of the GINA guidelines:¹²

Step 1: as-needed short-acting beta-agonist (SABA)

Step 2: as above, plus an inhaled corticosteroid (ICS), continuously or for periods

Step 3: as above, plus either a long-acting beta-agonist (LABA) or a leukotriene receptor antagonist (LTRA)

Step 4: ICS + LABA + LTRA

Step 5: Oral corticosteroids (OCS) continuously

An exacerbation was defined as an impairment in asthma, requiring an emergency department visit or hospitalization during the last 12 months.

Insomnia symptoms analyzed in the study were: difficulty initiating sleep (DIS): “difficulty in falling asleep at night,” difficulty maintaining sleep (DMS): “waking up repeatedly during the night,” and early morning awakenings (EMA): “waking up too early and having difficulty in getting back to sleep again” at least 4 times a week.^{1,3}

Rhinitis was defined following a positive answer to the question “Have you had any nasal allergy or hay fever during the last 12 months?”¹¹

Chronic rhinosinusitis (CRS) was defined as having at least two of the following symptoms: nasal blockage/congestion, nasal discharge, facial pain or pressure, or reduction of smell. At least one symptom should be nasal blockage or nasal discharge, and a minimum of 4 weeks was needed for the symptom duration.¹³

Depression, anxiety, and gastro-esophageal reflux (GERD) were self-reported diagnoses, “Do you suffer from any of the following conditions?”

Obesity was defined as a body mass index (BMI) of $>30 \text{ kg/m}^2$ based on height and weight measured at the test center.³

Any asthma-related comorbidity was defined as having CRS, gastro-esophageal reflux, anxiety, depression, or obesity.

Participants who had smoked less than 100 cigarettes ever were defined as never-smokers. Current smoking was defined as current daily smoking. Participants who did not smoke daily but previously had smoked >1 cigarette/day were defined as ex-smokers.³

Physical exercise was defined following a positive answer to the question “Do you exercise regularly?”

Educational level was categorized according to the following levels: 9-year compulsory school, high school graduation, or academic degree.³

Statistical analyses

All the statistical analyses were conducted using STATA 12 (STATA Corp, Texas, U.S.A.). Univariate analyses were performed with the chi-square test and unpaired t-test. ANOVA with Bonferroni correction was calculated for the p-values. Multiple logistic regression analysis was used to calculate the adjusted odds ratios. Direct acyclic graphs (DAGs) were used for identifying the confounding factors. DAGs were created using the browser-based environment DAGitty (www.dagitty.net).¹⁴ The smallest set of co-variates necessary to control for bias was calculated and extracted from DAGitty. A p-value of <0.05 was considered significant.

Results

Of the total study population, 1,272 (5.3%) had asthma. Characteristics of the participants with and without asthma are presented in Table 1. The prevalence of difficulties inducing sleep, difficulties maintaining sleep, and all comorbidities was higher among participants with asthma than those without asthma.

Univariate analyses

Insomnia symptoms were more common in those with uncontrolled asthma than in those without asthma, whereas the prevalence of insomnia symptoms in the groups with controlled or partially controlled asthma was on the same level as in the non-asthmatic participants (Figure 1).

In subjects with asthma, insomnia symptoms were more common with poor asthma control (Table 2, Figure 1), while no significant association was found between the level of asthma treatment and insomnia symptoms (Table 2, Figure 2). The prevalence of insomnia symptoms was also higher among asthmatics reporting any comorbidity (Table 2, Figure 3), and highest among those with obesity (34.2%) or chronic rhinosinusitis (36.7%). Subjects that had both uncontrolled asthma and comorbidities had a high prevalence of all insomnia symptoms. Snoring was more common with asthma but was not associated with any insomnia symptoms.

Multivariable analyses

Having uncontrolled asthma remained a significant risk factor for difficulties initiating sleep, difficulties maintaining sleep, and early morning awakenings also after adjusting for age, sex, comorbidity, smoking, educational level, and physical activity (Table 3). Other risk factors for insomnia symptoms in the entire population were being of female sex, BMI 25-30 kg/m², chronic rhinosinusitis, gastro-esophageal reflux, depression, and anxiety.

When only analyzing the group with asthma, we found that uncontrolled asthma was a significant risk factor for any insomnia symptom, difficulties initiating sleep, difficulties maintaining sleep, and early morning awakenings (Table 4). Asthma control, chronic rhinosinusitis, obesity, and depression were the most important risk factors for insomnia symptoms among subjects with asthma (Table 4, Figures 4 and 5). When treatment level and exacerbation history were included in the analyses, all associations remained significant, except the associations between difficulties maintaining sleep and uncontrolled asthma (OR 1.51 (0.95-2.42)) and CRS (OR 1.38 (0.97-1.95)). No significant associations between insomnia symptoms and treatment level were seen. Gastro-esophageal reflux did not reach significance after adjusting for asthma control and obesity.

Discussion

Uncontrolled asthma was a risk factor for all insomnia symptoms, whereas having controlled asthma was not associated with insomnia. Asthma-related comorbidity had a great impact on insomnia symptoms; in particular, the combination of uncontrolled asthma and any comorbidity was unfavorable.

Asthma control

Uncontrolled asthma was a risk factor for all insomnia symptoms, and asthma control remained associated with all insomnia symptoms after adjusting for comorbidities. This underlines the importance of asthma control for sleep quality and corresponds to earlier findings. Specifically, a randomized control trial has previously demonstrated that sleep quality improves with better asthma control in mild to moderate asthma.¹⁵ Another study showed a higher prevalence of insomnia with uncontrolled asthma than with controlled asthma or no asthma.¹⁶ However, these studies did not focus on comorbidity. Luyster et al. controlled for comorbidity and found a higher prevalence of insomnia in severe asthma than in non-severe asthma,² and higher risk for uncontrolled asthma with insomnia.¹⁷

Asthma severity

The level of treatment was not associated with any insomnia symptom after adjusting for asthma control and asthma-related comorbidity. As the level of treatment may be considered a marker of asthma severity,⁹ this suggests that asthma control seems to be more important than asthma severity for insomnia symptoms. It has previously been demonstrated that the prevalence of insomnia symptoms is very high in severe asthma. This has in part been explained by poor asthma control and prevalent comorbidity,¹⁸ but it has also been proposed that asthma severity in itself affects sleep quality.² However, in accordance with our findings, a recent study showed that asthma control was a determinant for sleep disturbance, while asthma severity was not.¹⁹ Poor asthma control and undertreated asthma-related comorbidities are more widespread conditions than severe asthma, and may thus have a greater impact on the population level.^{20,21}

Asthma-related comorbidity

The additive effect of uncontrolled asthma and any comorbidity was very high. The prevalence of insomnia symptoms was high in the presence of any comorbidity, also with controlled asthma.

Allergic rhinitis was very common and may be considered as a marker of allergic asthma.

Allergic rhinitis was not associated with any insomnia symptoms. The smaller group reporting chronic rhinosinusitis had significantly worse symptoms, and chronic rhinosinusitis remained a risk factor for all insomnia symptoms also in multivariate analyses, which corresponds to previous findings.⁵ Chronic rhinosinusitis in asthma may represent nasal polyps and is more common with more severe asthma;²² accordingly, chronic rhinosinusitis was also associated with worse asthma control.

The prevalence of insomnia symptoms was higher with obesity, and obesity was also a risk factor for insomnia symptoms in multivariate analyses. Obesity is a known risk factor for developing asthma,^{23,24} and obese asthmatics report more severe asthma.^{25,26} This may in part be explained by the increased levels of pro-inflammatory adipokines, less response to treatment with inhaled corticosteroids, and reduced lung function secondary to excess abdominal and thoracic fat tissue, but obesity is also associated with a higher prevalence of other comorbidities.²⁷⁻³⁰ Of these, anxiety, depression, and gastro-esophageal reflux were analyzed separately in this study. However, obesity is also highly correlated to obstructive sleep apnea (OSA), which is a common condition with great adverse effects on sleep quality.³¹ Further, there is a direct association between OSA and asthma,³² where OSA is highly prevalent with severe asthma, and poor asthma control is a risk factor for OSA.³³ Hence, it is possible that OSA explains a part of the shown association between obesity and insomnia symptoms in the present study. However, there was no association between insomnia symptoms and snoring.

Gastro-esophageal reflux was a risk factor for insomnia symptoms, but the association did not reach significance after adjusting for asthma control and obesity. As gastro-esophageal reflux has a negative effect on asthma control, its effect on sleep in asthma may be mediated

through asthma symptoms.⁸ Depression was a risk factor for insomnia symptoms. This was expected, since depressive symptoms have an independent effect on sleep quality and also co-varies with asthma control.³⁴ Anxiety was a risk factor for insomnia symptoms in the entire population, but did not reach significance in the subgroup with asthma. Anxiety symptoms are associated with subjective asthma symptoms, which may result in worse reported asthma control.³⁵

Both smoking and anxiety were associated with uncontrolled asthma, while obesity and depression were associated directly with insomnia symptoms. Smokers had a higher prevalence of difficulties inducing sleep than non-smokers, but the overall effect of smoking was low in comparison to previous studies.³ It is possible that insomnia symptoms in smokers are mediated by poor asthma control and comorbidity.

The present study is based on a large amount of survey data, with more than 23,000 participants in total. However, the study is not without limitations. As the association between insomnia symptoms and asthma control may be bi-directional, and the present study is based on cross-sectional data, no conclusions on causality can be made. Conversely designed studies have shown that asthma control is worse among patients with insomnia.¹⁷ It has even been proposed that insomnia symptoms may precede an asthma diagnosis, and that insomnia is a risk factor for asthma.³⁶ Hence, an alternative implication is that treatment of insomnia may improve asthma control. The relationship between asthma control, asthma-related comorbidity, and insomnia symptoms is complex; thus, further longitudinal studies are needed to fully describe these associations. As only adults 18-45 years were included in the study, the results may not be generalized to apply to other age groups.

Our findings have high clinical relevance, as insomnia symptoms affect quality of life. The present study confirms that insomnia symptoms are very common in asthma, and that asthma control, especially when combined with asthma-related comorbidities, is an important risk factor for insomnia symptoms. Chronic rhinosinusitis was independently associated with insomnia symptoms and worse asthma control. Structured evaluation of asthma control and attention to unrecognized or undertreated comorbidities may improve sleep quality in asthma patients.

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Table 1: Characteristics of participants with and without asthma

	No asthma n=22,603	Asthma n=1,272	p
Female (%)	62.6	69.6	<0.01
Age, mean $\pm$ SD	31.2 $\pm$7.0	30.6 $\pm$7.3	<0.01
BMI, mean $\pm$ SD	23.9 $\pm$3.5	24.3 $\pm$4.1	<0.01
Never-smokers (%)	58.2	59.8	0.25
Ex-smokers (%)	22.7	23.4	0.56
Smokers (%)	7.3	7.7	0.60
Difficulty initiating sleep (%)	6.6	10.1	<0.01
Difficulty maintaining sleep (%)	13.0	15.7	<0.01
Early morning awakenings (%)	4.7	5.5	0.19
Any insomnia symptom (%)	18.1	22.4	<0.01
Rhinitis (%)	25.9	66.2	<0.01
CRS (%)	2.6	11.8	<0.01
GERD (%)	14.0	19.5	<0.01
Obesity (%)	3.9	6.2	<0.01
Anxiety (%)	8.5	11.4	<0.01
Depression (%)	16.5	25.9	<0.01
Any comorbidity (%)	32.2	49.1	<0.01
Physical activity (%)	59.1	60.0	0.53

Table 2: Prevalence of insomnia symptoms in asthma, depending on asthma control and asthma-related comorbidity

		Any insomnia symptom			Difficulty initiating sleep			Difficulty maintaining sleep			Early morning awakenings		
	n	n	(%)	p	n	(%)	p	n	(%)	p	n	(%)	p
<i>Asthma control</i>													
Shortness of breath	260	73	28.1	0.01	38	14.6	0.01	56	21.5	<0.01	24	9.2	<0.01
Waking up due to asthma symptoms	333	97	29.1	<0.01	50	15.0	<0.01	69	20.7	<0.01	30	9.0	<0.01
Short-acting beta agonist use	509	125	24.6	0.13	66	13.0	<0.01	89	17.5	0.16	36	7.1	0.05
Limitation of activity	307	86	28.0	0.01	46	15.0	<0.01	63	20.5	<0.01	31	10.1	<0.01
Uncontrolled asthma	201	65	32.3	<0.01	35	17.4	<0.01	47	23.4	<0.01	22	11.0	<0.01
Exacerbations	81	26	32.1	0.03	14	17.3	0.03	20	24.7	0.02	8	9.9	0.07
Treatment step 4 or 5	126	32	25.4	0.39	15	11.9	0.48	27	21.4	0.06	11	8.7	0.09
Current smoking	98	24	24.5	0.61	19	19.4	<0.01	19	19.4	0.30	7	7.1	0.46
<i>Comorbidity</i>													
Rhinitis	842	198	23.5	0.18	94	11.2	0.09	139	16.5	0.28	45	5.3	0.73
CRS	150	55	36.7	<0.01	33	22.0	<0.01	37	24.7	<0.01	17	11.3	<0.01
GERD	248	74	29.8	<0.01	37	14.9	<0.01	60	24.2	<0.01	21	8.5	0.02
Obesity	79	27	34.2	0.01	10	12.7	0.44	21	26.6	<0.01	8	10.1	0.06
Depression	330	108	32.7	<0.01	60	18.2	<0.01	80	24.2	<0.01	33	10.0	<0.01
Anxiety	145	41	28.3	0.07	24	16.6	<0.01	28	14.0	0.21	13	9.0	0.05
Any comorbidity*	624	181	29.0	<0.01	91	14.6	<0.01	133	21.3	<0.01	47	7.5	<0.01
Uncontrolled asthma and any comorbidity	111	50	45.1	<0.01	32	28.8	<0.01	38	34.2	<0.01	15	13.5	<0.01

p-values represent the comparison between asthmatic subjects reporting a symptom or comorbidity and asthmatic subjects not reporting it.

*: Any comorbidity = CRS, GERD, obesity, depression or anxiety

Figure 1: Prevalence of insomnia symptoms, depending on asthma control

The higher prevalence of difficulties initiating sleep (DIS), difficulties maintaining sleep (DMS), and early morning awakenings (EMA) with uncontrolled asthma was significant compared to all other groups (p-values ≤ 0.01). None of the insomnia symptoms were more common with controlled asthma compared to without asthma (DIS 7.0% vs. 6.6% $p > 0.99$, DMS 13.9% vs. 13.0% $p = 1.00$, EMA 3.6% vs. 4.7% $p > 0.99$).

Figure 2: Prevalence of insomnia symptoms, depending on level of asthma treatment

No differences between treatment groups were significant (all p-values > 0.05).

Step 1: SABA

Step 2: SABA+ICS

Step 3: SABA+ICS+LABA/LTRA

Step 4: SABA+ICS+LABA+LTRA

Step 5: OCS

Figure 3: Prevalence of insomnia symptoms, depending on asthma control and asthma-related comorbidity (CRS, GERD, obesity, depression or anxiety)

Table 3: Risk factors for insomnia symptoms in the study population

	Any insomnia symptom		DIS		DMS		EMA	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age (by year)	1.03	1.03-1.04	0.97	0.96-0.98	1.06	1.06-1.07	1.04	1.03-1.05
Female	1.47	1.36-1.58	0.99	0.89-1.11	1.85	1.69-2.02	1.27	1.11-1.46
<i>Smoking history</i>								
Never-smoker	1		1		1		1	
Ex-smoker	1.10	1.02-1.20	1.37	1.20-1.56	1.01	0.92-1.11	0.92	0.79-1.07
Smoker	1.07	0.94-1.22	2.20	1.88-2.58	0.77	0.66-0.90	0.87	0.75-1.14
<i>Educational level</i>								
9 year compulsory school	1.83	1.43-2.35	1.97	1.44-2.69	1.97	1.50-2.59	1.36	0.88-2.09
High school	1		1		1		1	
University	1.14	1.05-1.23	1.27	1.13-1.43	1.14	1.04-1.25	1.22	1.06-1.40
Physical activity	0.68	0.64-0.73	0.67	0.60-0.75	0.68	0.63-0.73	0.91	0.80-1.03
No asthma	1		1		1		1	
Controlled asthma	0.99	0.79-1.25	0.87	0.61-1.25	0.98	0.76-1.28	0.66	0.41-1.06
Partially controlled asthma	0.96	0.79-1.16	1.18	0.91-1.41	0.93	0.74-1.16	1.02	0.74-1.41
Uncontrolled asthma	1.59	1.16-2.18	1.73	1.15-2.60	1.55	1.09-2.21	1.77	1.12-2.82
BMI <20	1.04	0.90-1.20	1.13	0.91-1.41	0.91	0.76-1.07	1.16	0.90-1.49
BMI 20-25	1		1		1		1	
BMI 25-30	1.11	1.00-1.22	1.28	1.10-1.49	1.06	0.95-1.18	1.08	0.91-1.28
BMI >30	1.09	0.92-1.29	1.19	0.92-1.54	0.97	0.80-1.17	1.22	0.92-1.60
Rhinitis	1.03	0.95-1.11	1.08	0.96-1.22	0.99	0.91-1.08	1.04	0.91-1.19
CRS	1.40	1.27-1.53	1.73	1.52-1.97	1.30	1.17-1.45	1.64	1.41-1.92
GERD	1.33	1.21-1.45	1.35	1.18-1.53	1.39	1.26-1.54	1.24	1.06-1.45
Depression	1.73	1.58-1.89	2.29	2.02-2.60	1.67	1.51-1.84	1.70	1.46-1.99
Anxiety	1.45	1.29-1.62	1.70	1.46-1.97	1.44	1.27-1.64	1.54	1.28-1.87

Adjusted for all variables in the table

Table 4: Exposure, asthma control, and comorbidities as risk factors for insomnia symptoms in participants with asthma

	Any sleep disturbance		DIS		DMS		EMA	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Never-smoker	1		1		1		1	
Ex-smoker	1.20	0.87-1.67	1.22	0.77-1.95	1.20	0.83-1.73	0.92	0.50-1.69
Smoker	0.68	0.39-1.18	1.21	0.63-2.31	0.89	0.49-1.62	0.80	0.32-2.01
Controlled asthma	1		1		1		1	
Partially controlled asthma	0.97	0.72-1.33	1.38	0.87-2.17	0.96	0.67-1.37	1.36	0.74-2.52
Uncontrolled asthma	1.72	1.15-2.56	2.16	1.25-3.74	1.68	1.07-2.64	3.05	1.53-6.10
BMI <20	1.00	0.53-1.87	1.37	0.61-3.07	0.98	0.45-2.11	0.27	0.03-2.08
BMI 20-25	1		1		1		1	
BMI 25-30	1.53	1.02-2.31	1.94	1.10-3.43	1.34	0.83-2.18	2.49	1.25-4.94
BMI >30	1.87	1.07-3.25	1.51	0.67-3.38	1.89	1.02-3.50	1.91	0.76-4.81
Rhinitis	1.10	0.81-1.49	1.36	0.88-2.11	1.03	0.73-1.46	0.73	0.42-1.25
CRS	1.62	1.20-2.19	2.02	1.36-3.00	1.42	1.00-1.99	2.18	1.29-3.69
GERD	1.30	0.93-1.81	1.28	0.82-2.00	1.62	1.13-2.33	1.34	0.76-2.38
Depression	1.85	1.34-2.55	2.23	1.45-3.42	1.93	1.35-2.77	2.50	1.43-4.36
Anxiety	0.82	0.52-1.29	0.88	0.50-1.55	0.73	0.44-1.21	1.11	0.53-2.31

Adjusted for sex, age, educational level, physical activity, and all variables in the table

Figure 4: Risk factors for insomnia among participants with asthma. Adjusted for age, sex, educational level, and physical activity

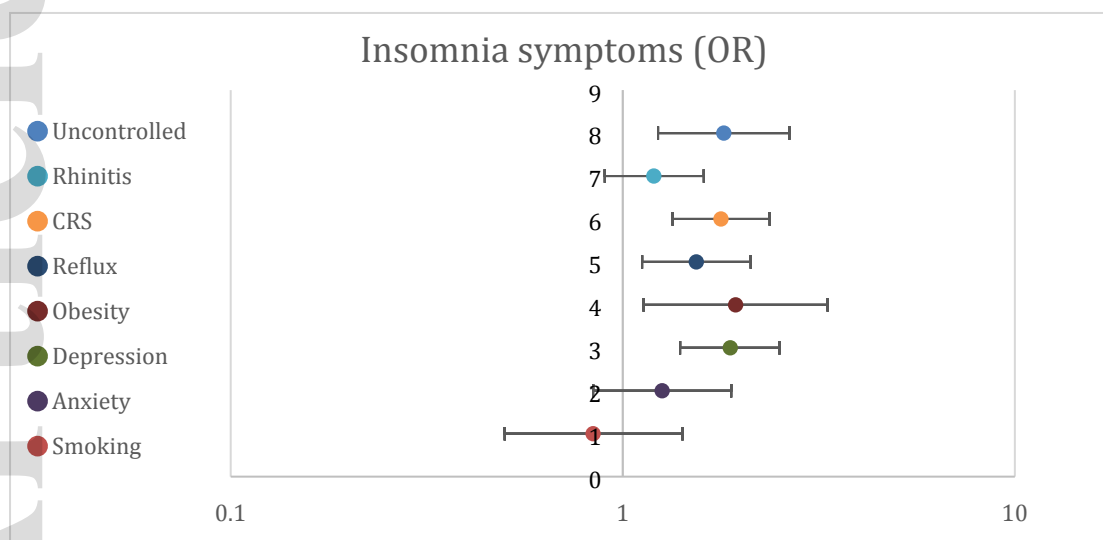
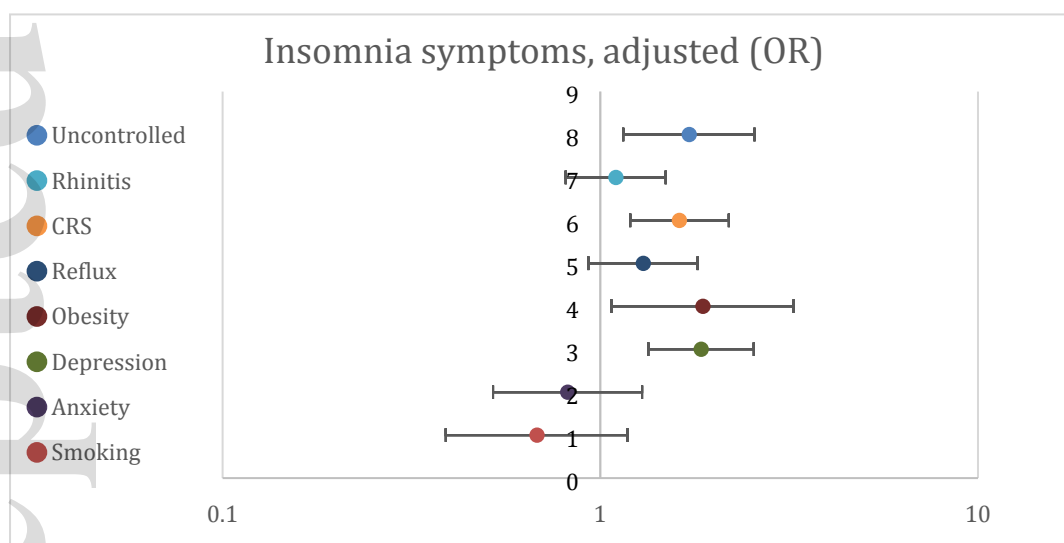
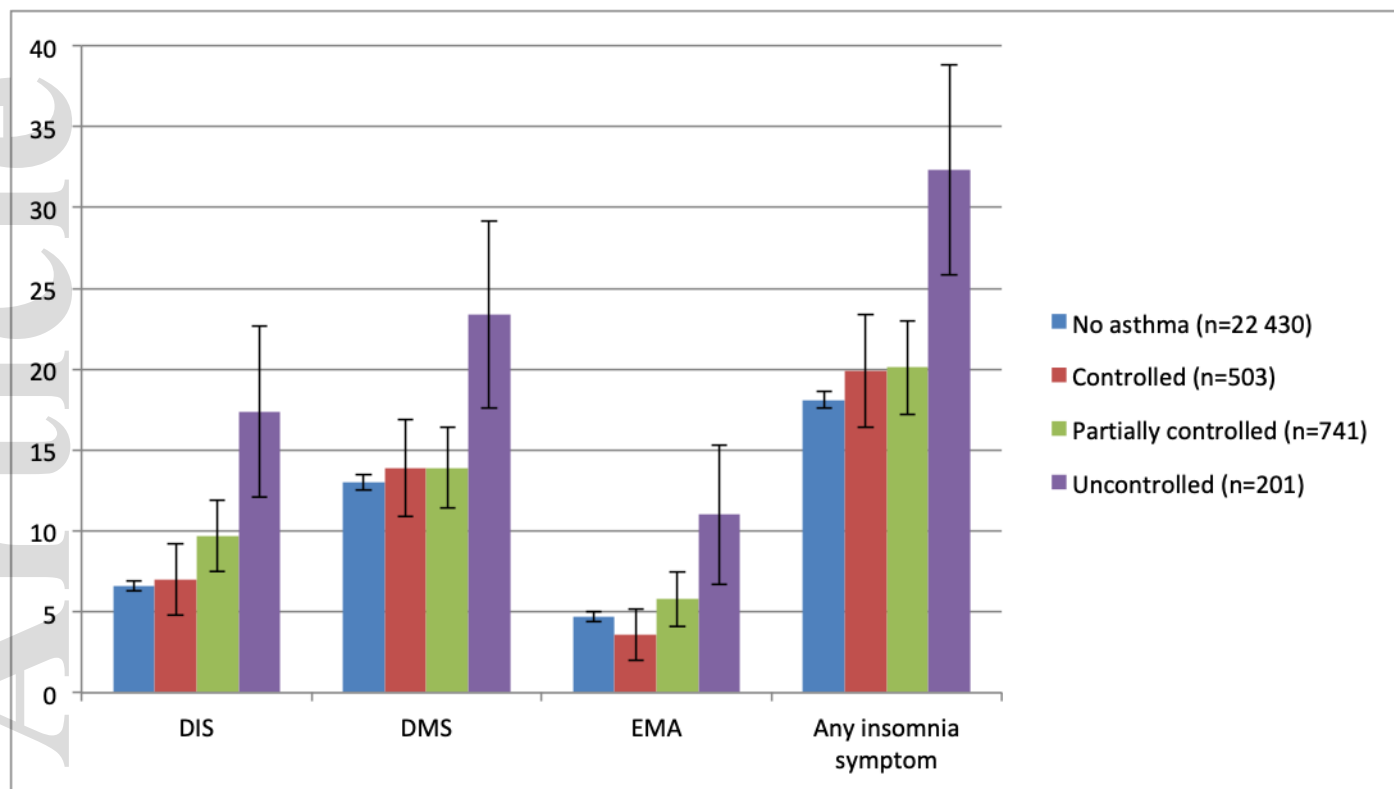
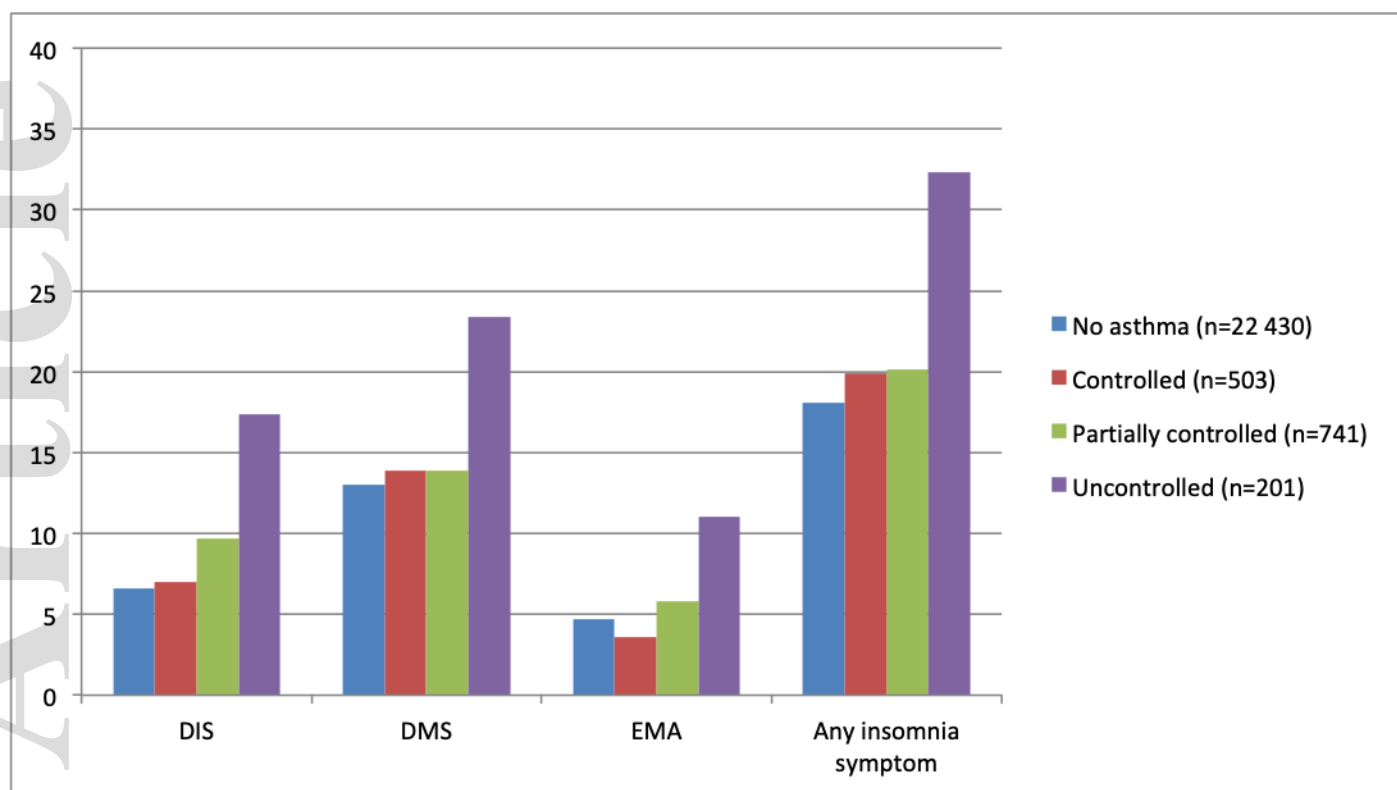


Figure 5: Risk factors for insomnia among participants with asthma. Adjusted for age, sex, educational level, physical activity, and all variables in the figure

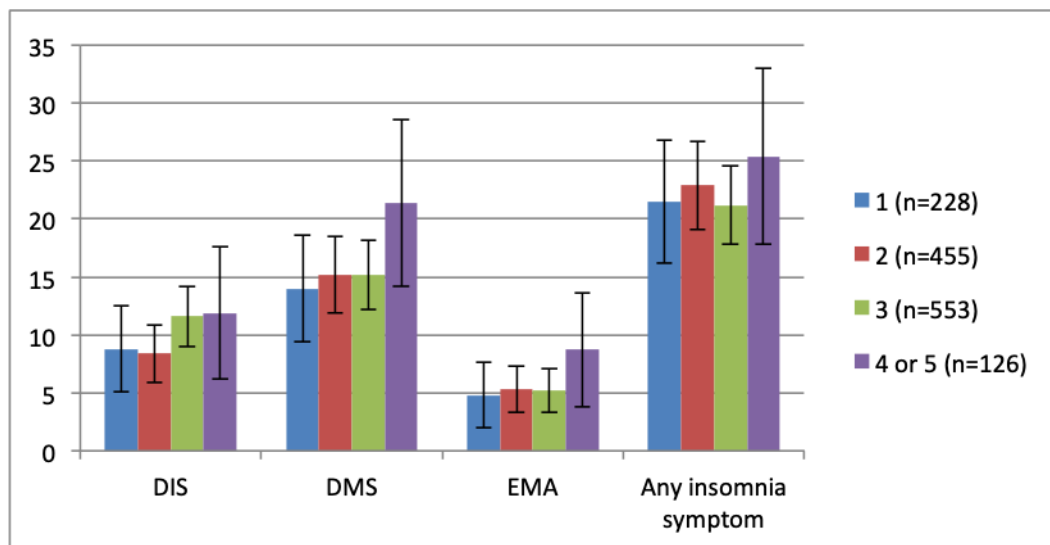




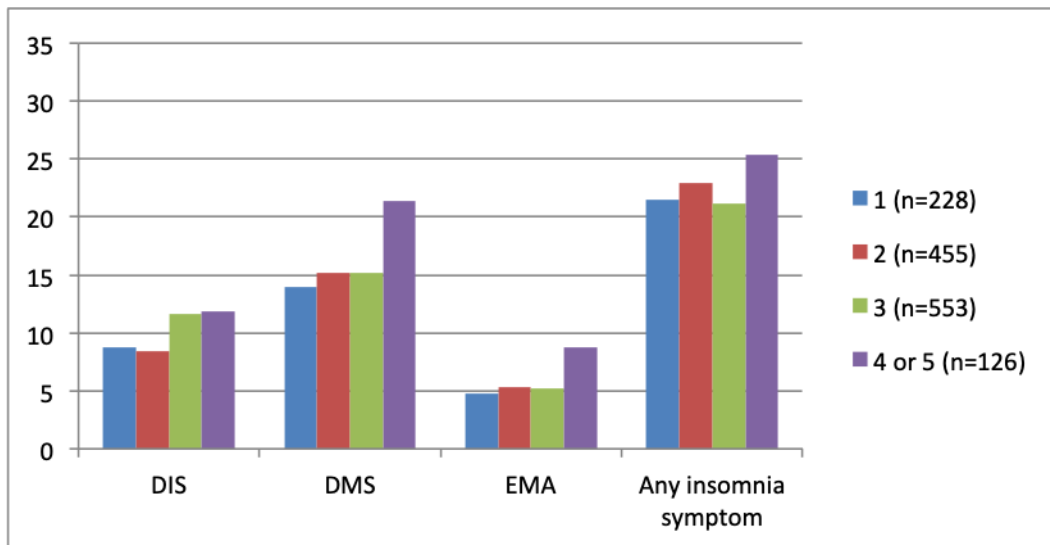
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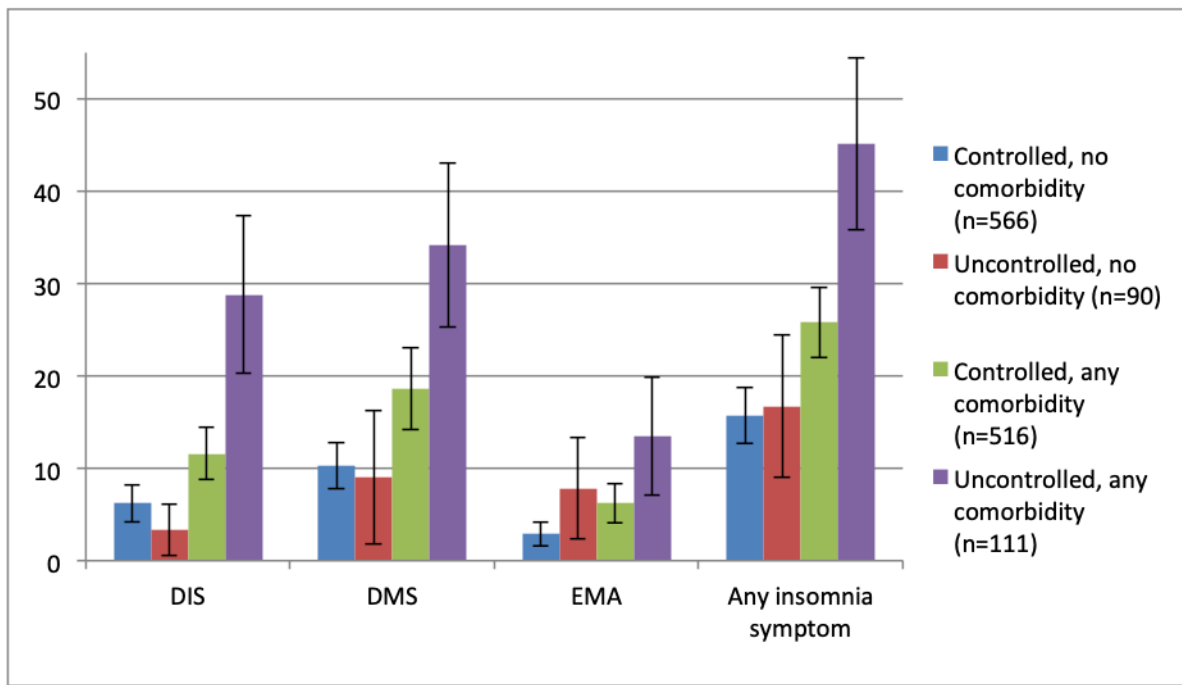
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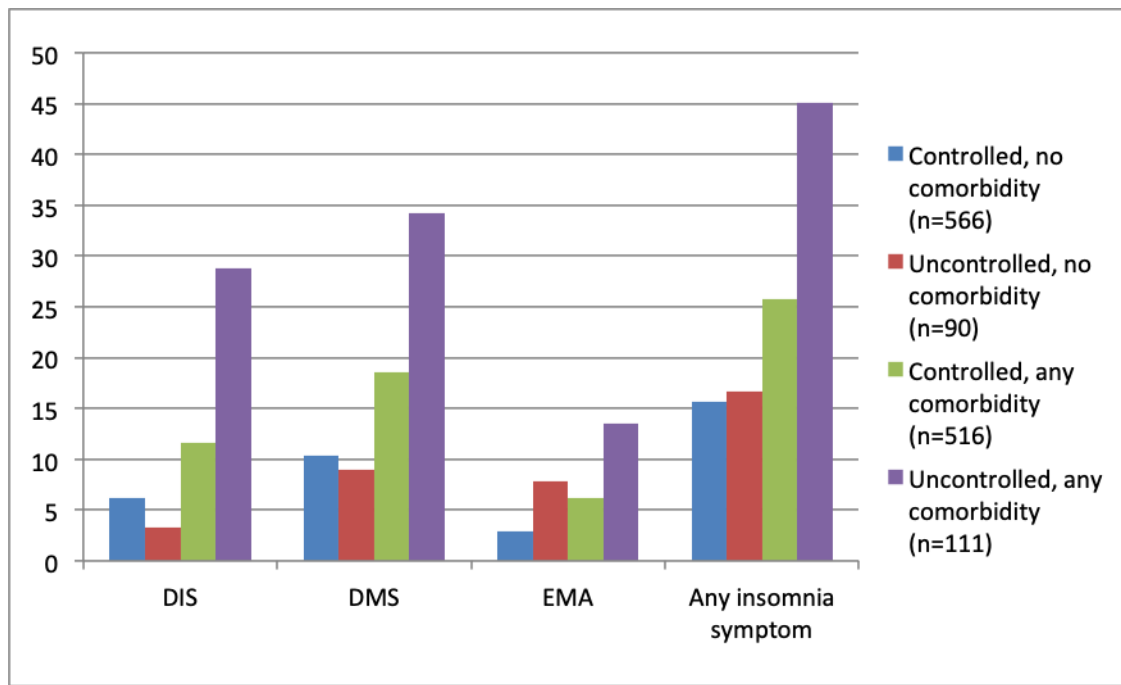
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