

# Risk factors of chronic urticaria among nurses with insomnia

## A nationwide population-based study

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### Abstract

Chronic urticaria has a high economic burden and reduces patient's quality of life. Nurses experience insomnia because of their shifting work, especially if they work night shifts and 3-shift rotational schedules. This study aimed to examine whether insomnia is a risk factor of chronic urticaria in nurses.

Data were obtained from the Registry for Medical Personnel, which contains all registered medical staff between 2007 and 2008. All study subjects were divided into those with insomnia and without insomnia. The primary exposure of interest was chronic urticaria. In addition, potential comorbidities including diabetes mellitus, hypertension, hyperlipidemia, anxiety, and depression were estimated.

A total of 103,242 registered nurses between 2007 and 2008 were enrolled. Around 97,899 (94.8%) nurses did not have insomnia, and 5343 (5.2%) had insomnia. The proportion of chronic urticaria in nurses with insomnia was significantly higher than those without (0.92% vs 0.50%,  $P < .0001$ ). The odds ratio of chronic urticaria in nurses with insomnia was 1.67 (95% confidence interval: 1.22–2.29,  $P = 0.0014$ ) compared to those without insomnia after adjusting for age, sex, hospital level, and comorbidities.

The risk of chronic urticaria was higher in nurses with insomnia than in those without insomnia. The relationship between insomnia and chronic urticaria might not be a direct causal association. Other contributing factors of insomnia include different perceptions of stress from night shift work, stress coping and adaptation, positive self-image, and emotional equilibrium related to person's capacity to adapt to change. The same situation may have different effects on different individuals.

**Abbreviations:** CI = confidence interval, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, NHIRD = National Health Insurance Research Database, OR = odds ratio, SD = standard deviation.

**Keywords:** chronic urticaria, insomnia, nurse, quality of life

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## 1. Introduction

Urticaria is one of the common dermatoses and presented with wheals and angioedema.<sup>[1]</sup> Urticaria has a chronic course, difficult treatment, and complex etiopathogeny.<sup>[2]</sup> Urticaria also has a high economic burden and reduces patient quality of life.<sup>[3]</sup> It is a heterogeneous group of disease with different underlying causes, evoked by various factors, and manifest clinically differently.

The diagnosis of urticaria was made according to disease duration and etiology,<sup>[4]</sup> although >2 types of urticaria may coexist in the same person. Acute urticaria is designated as the presence of spontaneous wheals or angioedema for <6 weeks, and chronic urticaria is defined as wheals or angioedema lasting for >6 weeks.<sup>[5]</sup> Some chronic urticaria can be induced and triggered by obviously identifiable external factors, but some chronic urticaria has no definite cause.<sup>[6]</sup>

Patients with chronic urticaria may have difficulty sleeping because of persistent and severe skin itching.<sup>[7]</sup> A case-control study examined the association between chronic idiopathic urticaria and stress and found that insomnia may be the important psychosomatic symptom that induces the onset of urticaria.<sup>[8]</sup> Another study using a population-based database in Taiwan showed that sleep disorder will increase the risk of chronic urticaria.<sup>[9]</sup>

Previous population-based studies also indicated that insomnia was a potential risk factor for ill health, including depression, anxiety, fibromyalgia, rheumatoid arthritis, cervical trauma, osteoarthritis, osteoporosis, headache, asthma, and myocardial

infarction.<sup>[10–13]</sup> In addition, insomnia is associated with increased mortality, especially in those patients with stroke.<sup>[14]</sup> The impact of job category on insomnia may differ relying on the social and occupational characteristics.<sup>[15,16]</sup> Shift work was the leading factor of insomnia due to the alterations of circadian rhythm.<sup>[17,18]</sup>

Nurses are the largest group of health care professionals, and around 70% of nurses are working in hospitals in Taiwan. Nurses experience sleep problems such as insomnia because of their shifting work, especially if they work night shifts and 3-shift rotational schedules. To our knowledge, studies on the association of chronic urticaria with insomnia in nurses and the risk factors of urticaria in nurse are lacking, and there are limited studies about the association between insomnia and chronic urticaria. Therefore, this study aimed to examine whether insomnia is the risk factor of chronic urticaria in a nurse cohort.

## 2. Material and methods

### 2.1. Data sources

This was a nationwide cross-sectional study of data retrieved from the Taiwan National Health Insurance Research Database (NHIRD), which contains all claims data from the Taiwan National Health Insurance program. The NHIRD contains nearly 99% of patients' medical benefit claims of the 23 million residents of Taiwan and has been used extensively in various studies.<sup>[19–22]</sup> This database contains personal information, clinical diagnoses, prescribed drugs, medical treatment, medical history, and basic sociodemographic information such as birthday, working area, and employment types. The *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code was adopted for clinical diagnoses.

### 2.2. Cases selection

After obtaining the approval of the ethics review board of Chi Mei Medical Center (IRB: 10302-E01), we used encrypted personal identification to protect individuals' confidentiality. The requirement for written informed consent was waived due to the retrospective study design. In this study, data on nurses aged 20 to 50 years were obtained from the Registry for Medical Personnel, which contains data of all registered medical staff between 2007 and 2008. Nurses aged <20 or >50 were excluded in the study. All study subjects included were those with a diagnosis of insomnia and without insomnia. Nurses in the insomnia group (ICD-9-CM codes 307.41, 307.42, and 780.52) were diagnosed with insomnia at least 2 times during outpatient clinic visits within the study periods. Insomnia was defined as a transient disorder of initiating or maintaining sleep (ICD-9-CM code: 307.41), persistent disorder of initiating or maintaining sleep (ICD-9-CM code: 307.42), and unspecified insomnia (ICD-9-CM code: 780.52). Figure 1 presents a flowchart of the study subject selection process.

### 2.3. Exposure assessment

In this study, the primary exposure of interest was chronic urticaria. Chronic urticaria was defined as other specified urticaria (ICD-9-CM code: 708.8) that claimed at least 2 outpatient clinic visits. In addition, potential comorbidities including diabetes mellitus (ICD-9-CM code: 250), hypertension (ICD-9-CM: 401–405), hyperlipidemia (ICD-9-CM code: 272),

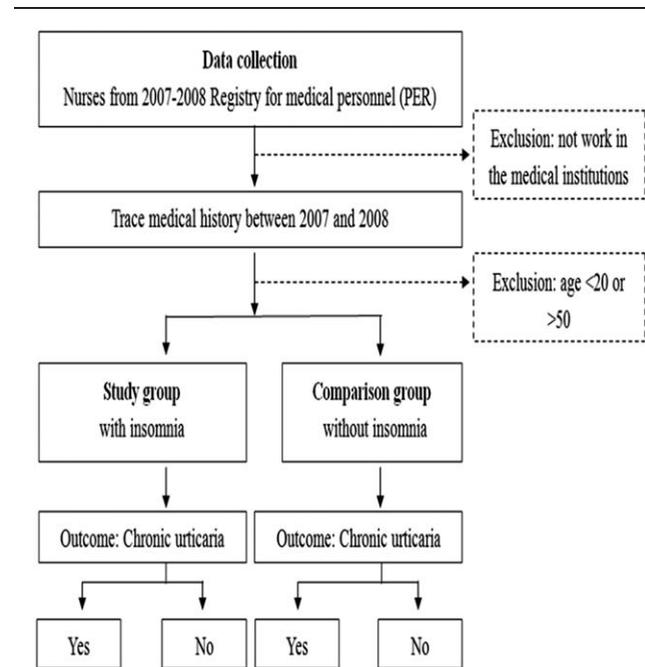


Figure 1. Flow chart of study subject selection.

anxiety (ICD-9-CM code: 300 [but not 300.4] and 309.24), and depression (ICD-9-CM code: 311, 296.2, 296.3, 296.5, 296.82, 300.4, 309.0, 309.1) were estimated in this study.

### 2.4. Statistical analyses

Student *t* test for continuous variables and Pearson  $\chi^2$  test for categorical variables were used to compare differences between cases and controls. The logistic regression was used to obtain the odds ratios (ORs) for chronic urticaria between nurses with and without insomnia. SAS 9.4 for Windows (SAS Institute, Inc., Cary, NC) was used for all statistical analyses. A 2-tailed *P* value <0.05 was considered statistically significant.

## 3. Results

A total of 103,242 registered nurses between 2007 and 2008 were enrolled in this study. Around 97,899 (94.8%) nurses have insomnia, and 5343 (5.2%) do not have insomnia. Baseline information of nurses showed significant difference between those with and without insomnia (Table 1).

For the outcome of interest, nurses with insomnia had significantly higher incidence of chronic urticaria than those without insomnia (0.92% vs 0.50%,  $P < .0001$ ). The OR of chronic urticaria in nurses was also explored. After adjustments for age, sex, hospital level, and comorbidities, nurses with insomnia had an adjusted OR 1.67 (95% confidence interval, CI: 1.22–2.29,  $P = .0014$ ) times higher occurrence of chronic urticaria than did nurses without insomnia (Table 2).

A stratified analysis is shown in Table 3. Demographic variables such as age group, sex, and working hospital level were stratified to examine the difference between nurses with and without insomnia who experienced chronic urticaria. After controlling for age, sex, hospital level, and comorbidities, the adjusted ORs of chronic urticaria were 1.77 (95% CI: 1.7–2.66,

**Table 1****Baseline information of nurses with and without insomnia in Taiwan during 2007 to 2008.**

	Without insomnia	With insomnia	<i>P</i>
	N=97899	N=5343	
	N (%)	N (%)	
Age, mean±SD	30.81±7.15	31.81±7.19	<.0001*
Age group, y			
<25	20180 (20.61)	695 (13.01)	<.0001*
25-35	50718 (51.81)	3060 (57.27)	
>35	27001 (27.58)	1588 (29.72)	
Sex			
Female	96912 (98.99)	5308 (99.34)	.0011*
Male	987 (1.01)	35 (0.66)	
Working hospital level			
Medical center	29072 (29.70)	1094 (20.48)	<.0001*
Regional hospital	32225 (32.92)	1467 (27.46)	
Local hospital	19618 (20.04)	1352 (25.30)	
Physician clinics	16984 (17.35)	1430 (26.76)	
Chronic urticaria			
Yes	485 (0.50)	49 (0.92)	<.0001*
No	97414 (99.50)	5294 (99.08)	
Comorbidity			
Diabetes mellitus	670 (0.68)	56 (1.05)	.0019*
Hypertension	1520 (1.55)	179 (3.35)	<.0001*
Hyperlipidemia	1553 (1.59)	173 (3.24)	<.0001*
Anxiety	1612 (1.65)	1105 (20.68)	<.0001*
Depression	498 (0.51)	283 (5.30)	<.0001*

The *P* value for continuous variable was derived from Student *t* test and the categorical variables were calculated from Pearson  $\chi^2$  test. SD=standard deviation.

\**P*<.05.

*P*=.0066), 1.60 (95% CI: 1.16–2.20, *P*=.0043), and 2.66 (95% CI: 1.43–4.93, *P*=.0020) for the 25- to 35-year age group, female nurses, and working at a medical center, respectively (Table 3).

**Table 2****Odds ratio for chronic urticaria between nurses with and without insomnia by logistic regression.**

	Crude odds ratio (95% CI)	<i>P</i>	Adjusted odds ratio (95% CI)	<i>P</i>
Insomnia				
Yes	1.86 (1.38–2.50)	<.0001*	1.67 (1.22–2.29)	.0014*
No	Reference		Reference	
Age group, y				
<25	Reference		Reference	
25–35	1.07 (0.86–1.34)	.5468	1.02 (0.81–1.28)	.8653
>35	1.00 (0.78–1.29)	.9753	0.92 (0.71–1.19)	.5426
Sex				
Female	1.33 (0.63–2.81)	.4541	1.44 (0.68–3.05)	.3410
Male	Reference		Reference	
Working hospital level				
Medical center	Reference		Reference	
Regional hospital	1.02 (0.82–1.28)	.8422	1.01 (0.80–1.27)	.9350
Local hospital	1.01 (0.78–1.30)	.9578	0.98 (0.76–1.27)	.8839
Physician clinics	1.60 (1.26–2.02)	.0001*	1.56 (1.23–1.98)	.0003*
Comorbidities				
Diabetes mellitus	1.37 (0.55–3.24)	.5195	1.49 (0.59–3.80)	.3983
Hypertension	1.02 (0.53–1.98)	.9423	0.99 (0.50–1.97)	.9787
Hyperlipidemia	0.78 (0.37–1.65)	.5153	0.69 (0.31–1.52)	.3526
Anxiety	1.59 (1.04–2.45)	.0328*	1.17 (0.73–1.86)	.5166
Depression	2.26 (1.17–4.39)	.0157*	1.75 (0.88–3.49)	.1128

CI=confidence interval, SD=standard deviation.

\**P*<.05.

#### 4. Discussion

Our findings suggest that the relationship between insomnia and chronic urticaria is not a direct causal association. Studies about the association between insomnia and chronic urticaria are limited. To the best of our knowledge, this study is the first to examine the association of chronic urticaria and insomnia in nurse and risk factors of urticaria in nurse. Sleep disorder such as insomnia can be a stress for our body and can induce chronic urticaria. Therefore, insomnia may play an important role in patients with chronic urticaria and sleep disorder. From our study, we found that insomnia is the risk factor of chronic urticaria in nurses with adjusted OR of 1.67 (95% CI=1.22–2.29). Nurses with insomnia had more comorbidities including diabetes, hypertension, hyperlipidemia, anxiety, and depression. Among nurses with chronic urticaria, we found that nurses aged 25 to 35 years and worked in medical center are at risk of insomnia.

A Norway's population study indicated that insomnia was a potential risk factor for several diseases, including depression (OR: 2.38, 95% CI: 1.91–2.98), anxiety (OR: 2.08, 95% CI: 1.63–2.64), fibromyalgia (OR: 2.05, 95% CI: 1.51–2.79), rheumatoid arthritis (OR: 1.87, 95% CI: 1.29–2.52), cervical trauma (OR: 1.71, 95% CI: 1.21–2.41), osteoarthritis (OR: 1.68, 95% CI: 1.43–1.98), osteoporosis (OR: 1.52, 95% CI: 1.14–2.01), headache (OR: 1.50, 95% CI: 1.16–1.95), asthma (OR: 1.47, 95% CI: 1.16–1.86), and myocardial infarction (OR: 1.46, 95% CI: 1.06–2.00).<sup>[10]</sup> A population-based cohort study also found that insomnia patients had significantly higher risks of developing anxiety only (hazard ratio, HR: 8.83, 95% CI: 7.59–10.27), depression only (HR: 8.48, 95% CI: 6.92–10.39), and both anxiety and depression (HR: 17.98, 95% CI: 12.65–25.56).<sup>[12]</sup> In addition, considering of the occupational effects, the higher insomnia risk had been found among nurses.<sup>[13,23,24]</sup>

Chronic urticaria and insomnia show a bidirectional relationship. Chronic urticaria as a result of pruritus induces insomnia,

**Table 3**  
Odds ratio for chronic urticaria between nurses with and without insomnia in different stratum.

	Number of chronic urticaria in nurses without insomnia, N (%)	Number of chronic urticaria in nurses with insomnia, N (%)	Adjusted odds ratio <sup>†</sup> (95% CI)	P
Age group, y				
<25	99 (0.49)	5 (0.72)	1.32 (0.51–3.39)	.5681
25–35	258 (0.51)	29 (0.95)	1.77 (1.17–2.66)	.0066*
>35	128 (0.47)	15 (0.94)	1.70 (0.95–3.02)	.0734
Sex				
Female	480 (0.50)	47 (0.89)	1.60 (1.16–2.20)	.0043*
Male	5 (0.51)	2 (5.71)	—	
Working hospital level				
Medical center	128 (0.44)	12 (1.10)	2.66 (1.43–4.93)	.0020*
Regional hospital	148 (0.46)	12 (0.82)	1.84 (0.99–3.41)	.0538
Local hospital	86 (0.44)	12 (0.89)	1.71 (0.88–3.32)	.1146
Physician clinics	123 (0.72)	13 (0.91)	1.07 (0.58–1.97)	.8386

CI = confidence interval.

\*  $P < 0.05$ .

<sup>†</sup> Adjusted by age, sex, hospital level, and comorbidities.

reduces quality of life, and even progresses to serious psychopathology, including risk of suicide. With regard to the normal sleep physiology, the skin has a role in thermoregulation and sleep onset.<sup>[25]</sup> Skin disorders disrupt temperature regulation, disturb heat dissipated through the peripherals, and lead to difficulties with sleep onset. Human skin cells express 2 circadian clock genes, *clock* and *period1*, and the skin play a role in systemic and cutaneous circadian rhythms.<sup>[26]</sup> Skin symptoms are associated with peripheral circadian oscillator. Temperature, barrier function, and itch mediators with circadian rhythms are impaired in the skin, which led to patients increase pruritus at night.<sup>[27]</sup>

A German study investigated the impact of chronic urticaria on patient's sleep. They found that most patients with chronic urticaria has somewhat impaired sleep pattern, and when their sleep was affected, >50% of the patients need taking prescription medication and 57% of the patients are using anti-itch lotion to relieve the itching symptom. Itching remained an unresolved problem for 69% of chronic urticaria patients, and 48% of patients with sleep disturbances.<sup>[28]</sup>

On the contrary, insomnia will exacerbate the skin inflammation and increase inflammatory cytokines involved in the vicious cycle of chronic urticaria. Sleep deprivation can impair skin barrier function recovery, aggravate allergic and irritant contact dermatitis, and increase inflammatory cytokine in women such as interleukin-1 $\beta$ , tumor necrosis factor- $\alpha$ , and natural killer cell activity.<sup>[29]</sup> Interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$  are important in the regulation of sleep rhythm. Besides the adverse effects of psychological stress, insomnia may exacerbate chronic urticaria by altering the circadian rhythm of the cortisol level and reduced cortisol level.

He et al<sup>[9]</sup> also used the Taiwan NHIRD to investigate the risk of chronic spontaneous urticaria in patients with preceding sleep disorders. Compared to our study, we focus on nurses with insomnia, but their study enrolled general population with sleep disorder, including sleep apnea and nonapnea sleep disorder. In the present study, the outcome of interest was chronic urticaria, and chronic urticaria was defined as other specified urticaria (ICD-9-CM code: 708.8) claimed at least 2 times in outpatient clinic visits. However, in He et al's study, the outcome of interest was chronic spontaneous urticaria, which was defined as having a

diagnosis of ICD-9-CM 708.1 (idiopathic urticaria), 708.8 (other specified urticaria), or 708.9 (urticaria, unspecified) at least 3 times in inpatient visits or at least 4 times in outpatient visits.

Defining chronic spontaneous urticaria using the claims database is difficult because there is no specific ICD-9-CM diagnosis code. In He et al's study, the subjects' mean age was 47.7 years and 60% patients were women. Our cohort has a mean age of 31 years, and 99% of the patients were women. Moreover, their adjusted HRs for sleep disorder in subjects with chronic spontaneous urticaria ranged from 1.64 to 1.82 compared with the control population. Our study found that chronic urticaria in nurses with insomnia had an adjusted OR of 1.67 compared with those without insomnia. Our cohort results are consistent with a previous study in which the reported mean age of patients was 30 to 40 years,<sup>[30]</sup> and we found that patients with chronic urticaria aged 25 to 35 years had significant risk of insomnia.

This study has some limitations. First, the number of patients with insomnia and chronic urticaria might have been underestimated because some of them may have self-medication practices using over-the-counter drugs.<sup>[31]</sup> Second, as our result were obtained from a claims database, we cannot delineate patients' history of chronic urticaria and investigate factors eliciting chronic urticaria, such as infections, specific stimulus, drugs, food, and psychological factors.

## 5. Conclusions

The relationship between insomnia and chronic urticaria might be not a direct causal association. Other contributing factors of insomnia include different perceptions of stress from night shift work, stress coping and adaptation, positive self-image, and emotional equilibrium related to person's capacity to adapt to change. The same situation may have different effects on different individuals. Prospective studies should be performed to clarify thoroughly the underlying mechanism linking insomnia and chronic urticaria.

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