



## The Association between Overweight/Obesity and Chronic Spontaneous Urticaria

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### Abstract

Chronic spontaneous urticaria (CSU) is characterized by transient pruritic wheals with or without angioedema, which have unidentified eliciting factors and persist for more than six weeks. However, there are few studies that investigate the relationship between overweight/obesity and CSU. This study aimed to investigate the relationship between overweight/obesity and CSU. This study was a retrospective case-control which included patients aged  $\geq 18$  recorded in the electronic medical record (EMR) at the outpatient department of the Institute of Dermatology in Thailand from 2018-2020. The study included 382 CSU patients and 382 non-CSU controls who were divided into two subgroups: Body mass index (BMI)  $< 23$  (reference) and BMI  $\geq 23$  (overweight/obesity). The logistic regression model showed no statistically significant association between the two subgroups (Odds ratio (OR) = 1.03, 95% confidence interval (CI) 0.78-1.37,  $p$ -value = 0.828). The Erythrocyte Sedimentation Rate (ESR) was the only significant abnormal laboratory investigation finding which was higher in the BMI  $\geq 23$  subgroup ( $p$ -value = 0.036) that supported CSU and overweight/obesity may be linked in a pathogenetic involvement in the inflammatory process. However, our result showed no statistically significant association between overweight/obesity and CSU among the adult Thai population which is different from many previous studies but compatible with a few studies in the past. Further studies are needed to confirm and clarify our results and the possible association between overweight/obesity and CSU.

**Keywords:** association, overweight, obesity, chronic spontaneous urticaria

### 1. Introduction

Urticaria is a heterogeneous group of diseases characterized by wheals and flares that sometimes concomitantly present with angioedema (Kulthanan et al., 2016). If the symptoms persist for more than six weeks, it is defined as chronic urticaria (CU). It is divided into two groups based on the role of definite triggers: a) chronic inducible urticaria (CIU), which has specific triggers for developing symptoms, and (b) chronic spontaneous urticaria (CSU), which has no definite triggers (Kulthanan et al., 2016; Zuberbier et al., 2022). In the updated International EAACI/GA<sup>2</sup>LEN/EuroGuiDerm/APAAACI guidelines, CSU is classified as type I [autoallergic, related to immunoglobulin E (IgE) to self-antigens] and type IIb (autoimmune, related to mast cell activating autoantibodies) (Oztop, Beyaz & Orcen, 2022; Zuberbier et al., 2022).

CSU is the most common type of non-acute urticaria. The estimated prevalence is 0.5-1% in the general population. It is twice more common in women than in men. Peak incidence ranges from 20-40 years, with an average duration of 3-5 years (Moestrup, Ghazanfar & Thomsen, 2017), although the pathogenesis of CSU remains unclear. However, the immune system (autoimmunity), inflammation (inflammation), blood clotting (Coagulation), and self-allergy (Autoallergy) may be involved (Matano et al., 2020). Mast cells were found to be responsible for the disease, and clinical manifestations were caused by several factors, from which mast cells are released, stimulated, and broken down. It was found that the number of mast cells tripled in patients with CSU, both showing skin rash and without skin area (Bansal & Bansal, 2019).

Obesity is chronic, systemic, and rarely asymptomatic and is an inflammatory process that causes a decrease in immunity to antigens (Zbiciak-Nylec et al., 2018). Therefore, it increases the risk of allergies and other immune-related diseases. It is also a most common element of metabolic syndromes, including abdominal obesity, abnormal fat in the blood, high blood pressure, and high blood sugar levels. In addition, it has been linked to inflammatory processes that increase risk factors for atherosclerosis and coronary heart disease (Chung, Wang, Tsai, Lin, & Chen, 2016; Engin, 2017). The prevalence of obesity has been increasing

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worldwide and has been a significant health issue associated with disability and mortality (Goda & Masuyama, 2016). In Thailand, in 2009, the prevalence of overweight (BMI 23 – 24.9 kg/m<sup>2</sup>) and obesity (BMI ≥25 kg/m<sup>2</sup>) among adults was 17.5% and 35%, respectively (Aekplakorn et al., 2014) and also has been increasing both among males and females. In 2014, the Thai National Health Examination Surveys V (NHES V) reported the prevalence of obesity (BMI ≥25 kg/m<sup>2</sup>) was 37.5, 32.9 and 41.8% overall and among males and females, respectively (Sakboonyarat et al., 2020).

Some studies reported that CSU, especially if it persists for an extended duration, may be associated with overweight and obesity, while increased body mass has also been linked to the later onset of urticaria symptoms (Zbiciak-Nylec et al., 2018). It was also found that increased body weight may be the leading risk factor for developing allergic diseases, including CSU and overweight or obesity. There may be a pathogenetic involvement in the inflammatory process (Zbiciak-Nylec et al., 2018; Zuberbier et al., 2022; Matano et al., 2020), but there are limited data supports the association between both diseases.

Despite the growing body of research on the association between overweight/obesity and Chronic Spontaneous Urticaria (CSU), there has been no investigation conducted in Thailand to date. Therefore, this study aimed to explore the relationship between overweight/obesity and CSU in Thai patients using non-CSU patients as a control group.

## 2. Objectives

To study the relationship between overweight/obesity and CSU in Thai patients.

## 3. Materials and Methods

This study was a retrospective case-control study of CSU and those over 18 years old. Demographic data were recorded in the EMR of all patients at the outpatient department of the Institute of Dermatology from 2018-2020 (1 January 2018 to 31 December 2020).

### 3.1 Population and samples

#### Case group

The data were collected and recorded in a case record form, including age, sex, weight, height, body mass index, underlying disease, current medications, symptoms, and laboratory results, including histopathological records (if any) of all patients on their first visit. The groups were divided by BMI (kg/m<sup>2</sup>) of the sample as follows: Group 1: BMI < 18.5 = Underweight & BMI 18.5 - 22.99 = Normal and Group 2: BMI ≥ 23 = Overweight & BMI >25 = Obesity. Out of 990 cases diagnosed with chronic urticaria in 2018-2020, 382 cases were selected using a computerized simple random method.

#### Inclusion Criteria (case)

- Patients diagnosed with chronic urticaria who were not previously received treatment at the outpatient department of the Institute of Dermatology (New cases).
- Age ≥18 years

#### Exclusion criteria (case)

- Patients with acute urticaria.
- Patients with urticaria caused by physical factors (inducible urticaria or physical urticaria) such as pressure urticaria, cold urticaria, heat urticaria, dermatographism urticaria, cholinergic urticaria, and contact urticaria.
- During follow-up, the patient was diagnosed with other diseases (non-chronic urticaria) again.
- In cases where there was incomplete information, such as age, weight, height, and clinical symptoms data, including symptoms and duration of the disease.

#### Control group

Select the control group according to the criteria for selecting the control group. Record the control group's data such as age, weight, height, and diagnosed disease at the time of the visit. From 90,621 new



patients in 2018-2020, the control group was randomly selected by a computerized simple random method (n = 382).

#### Inclusion Criteria (Control)

- A new patient who receives services at the outpatient department of the Institute of Dermatology (New hospital number) each year (2018-2020) with information recorded in the EMR
- Diagnosis of other diseases (non-chronic urticaria).
- Age  $\geq 18$  years

#### Exclusion criteria (Control)

- Patients in the category of skin diseases and autoimmune skin diseases associated with metabolic syndrome and chronic spontaneous urticaria, e.g., psoriasis, acne vulgaris, hidradenitis suppurativa, androgenetic alopecia, acanthosis nigricans, atopic dermatitis, lichen planus, autoimmune bullous disease, Sjogren syndrome, Bechet's disease, and vasculitis.
- Incomplete data, including age, weight, height, and diagnosed disease or either.

### 3.2 Data Analysis

Descriptive statistics was used to depict the characteristics of general information of the sample and control groups, such as frequency, percentage, mean, standard deviation or median, and quartile range. The relationship between overweight/obesity and CSU presented with an Odds ratio (OR) and 95% confidence interval (95% CI). Data were analyzed using IBM SPSS Statistics, Version 23.0 and set to statistically significant at 0.05.

## 4. Results and Discussion

### 4.1 Results

The researcher presented the study results as follows:

The demographic data for the cases (CSU) were female (75.7%), mean age  $39.51 \pm 13.51$ , mean weight  $61.19 \pm 12.06$ , mean height  $160.96 \pm 10.61$ , and BMI  $\geq 23$  (49.2%), while the majority of controls (non-CSU) also were female (64.9%), mean age  $43.24 \pm 16.56$ , mean weight  $62.00 \pm 13.20$ , mean height  $162.71 \pm 8.638$  and BMI  $\geq 23$  (48.4%). Gender, age, and height there were statistically significant differences between CSU and non-CSU ( $p$ -value  $< 0.05$ ).

**Table 1** Comparison of the clinical characteristics of CSU patients between BMI  $< 23$  and BMI  $\geq 23$

	BMI $< 23$ (kg/m <sup>2</sup> ) N=194	BMI $\geq 23$ (kg/m <sup>2</sup> ) N=188	<i>p</i> -value
<b>Age (year)</b>			
18-40	138 (72.2 %)	73 (42.0%)	$< 0.001^*$
41-64	50 (22.7%)	107 (53.7%)	$< 0.001^*$
$\geq 65$	6 (3.1%)	8 (4.3%)	0.546
<b>Gender</b>			
Female	157 (80.9%)	132 (70.2%)	0.015*
Male	37 (19.1%)	56 (29.8%)	
<b>Symptoms</b>			
Wheal	185 (95.4%)	179 (95.2%)	0.946
Both	9 (4.6%)	9 (4.8%)	
<b>Underlying diseases</b>			
Hypertension	4 (2.1%)	10 (5.3%)	0.090
Diabetes	2 (1.0%)	7 (3.7%)	0.083
Dyslipidemia	2 (1.0%)	5 (2.7%)	0.235
Thyroid disease	2 (1.0%)	7 (3.7%)	0.083
Allergic rhinitis	7 (3.6%)	7 (3.7%)	0.952
<b>Duration of symptoms</b>			

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	BMI < 23 (kg/m <sup>2</sup> ) N=194	BMI ≥ 23 (kg/m <sup>2</sup> ) N=188	p-value
≥ 6 months	86 (44.3%)	87 (46.5%)	0.627
< 6 months	108 (55.7%)	100 (53.5%)	

Independent t-test and Chi-square test

Table 1 shows a comparison of the clinical characteristics of CSU patients between BMI < 23 and BMI ≥ 23. It was found that age (18 – 40 and 41- 64 years) and gender exhibited statistically significant differences between two BMI groups (BMI < 23 and BMI ≥ 23). However, there were no statistically significant differences in other data, including symptoms, underlying diseases, and duration of symptoms.

**Table 2** Comparison of abnormal laboratory investigations of CSU patients between BMI < 23 and BMI ≥ 23

	Total (%)	BMI <23 (kg/m <sup>2</sup> )	BMI ≥ 23 (kg/m <sup>2</sup> )	p -value
<b>LAB</b>				
Complete blood count	35 (14.5)	21 (8.7%)	14 (5.8%)	0.219
Erythrocyte Sedimentation Rate	16 (17.6)	4 (4.4%)	12 (13.2%)	0.036*
Liver function test	2 (3.8)	0 (0.0%)	2 (3.8%)	0.153
Hepatitis profile	7 (4.4)	3 (1.9%)	4 (2.5%)	0.702
Antinuclear Antibody	59 (28.5)	30 (14.5)	29 (14.0%)	0.888
Urine analysis	0	0	0	N/A
Stool exam	0	0	0	N/A
Chest x-ray	0	0	0	N/A
Thyroid function	9 (4.6)	3 (1.5%)	6 (3.1%)	0.312
Thyroid antibody				
Antiperoxidase antibody	12 (9.2)	5 (3.8%)	7 (5.3%)	0.555
Antithyroglobulin antibody	19 (14.5)	9 (6.9%)	10 (7.6%)	0.812

Independent t-test and Chi-square test

Table 2 presents the results of abnormal laboratory investigations among CSU patients between BMI < 23 and BMI ≥ 23 with no generally significant differences. However, statistically significant differences were observed in Erythrocyte Sedimentation Rate (ESR) between those two BMI groups.

**Table 3** The association between overweight/obesity and CSU

	Odd Ratio (OR)	95% CI	p -value
<b>BMI (kg/m<sup>2</sup>)</b>			
< 18.5	0.61	0.37 – 1.01	0.053
18.5 - 22.99	Reference	N/A	N/A
23 - 24.99	0.82	0.54 – 1.23	0.325
> 25	1.01	0.72 – 1.41	0.962
<b>BMI (kg/m<sup>2</sup>)</b>			
BMI < 23	Reference	N/A	N/A
BMI ≥ 23	1.03	0.78 – 1.37	0.828

Logistic regression analysis

Table 3 shows the association between overweight/obesity and CSU, with BMI classified into four groups: BMI < 18.5 (OR = 0.61), BMI 18.5 - 22.99 (reference), BMI 23 - 24.99 (OR = 0.82), and BMI > 25 (OR= 1.01). The findings indicate that there were no statistically significant associations between classified BMI and CSU. Also, there were no statistically significant associations between BMI ≥ 23 (OR = 1.03) and CSU. In summary, the findings suggest that there is no statistically significant association between overweight/obesity and CSU.

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#### 4.2 Discussion

Our study represents a case-control study of CSU patients. We aimed to find a possible relationship between overweight/obesity and CSU among adults in our population. The findings showed that overweight and obese were not associated with CSU (OR= 1.03, 95% CI 0.78-1.37,  $p$ -value = 0.828), which was not consistent with many previous studies as in the literature review (Lapi et al., 2016; Zbiciak-Nylec et al., 2018; Shalom et al., 2018; Kim, Han, Lee, Lee, & Park, 2019; Choudhary & Shrestha, 2020). However, that was compatible with few studies in the past. Soria et al. (2018) studied a French cohort study of 278 patients with CU (CSU & CIU) using BMI and waist circumference as indicated for obesity. Their study reported only that obesity was not associated with severe chronic urticaria, which was similar to our study.

Basic demographic data of the normal population in Westerns were different from Orientals, that was one of the various results of our study. However, the main difference distinguishing our study from other studies, except for some studies in Asia (Kim et al., 2019), was the criteria for dividing BMI. For adults, two BMI classifications, the World Health Organization (WHO) standard and the World Health Organization, Regional Office for the Western Pacific (WPRO) standard, were used to categorize overweight and obesity. According to the WHO criteria, BMI is classified as normal 18.5 - 24.9, overweight 25 - 29.9, and obese  $\geq$  30. Although the WHO criteria have been well-accepted and widely used internationally, it has been documented that the WHO standard might not be appropriate for the classification of obesity in Asian populations due to different body fat percentages and body composition. The alternative weight status classification, or the WPRO standard, was proposed by the International Association for the Study of Obesity and the International Obesity Task Force (IOTF) in 2000 in order to have more applicable and appropriate BMI cut-off points for Asian populations. According to the WPRO criteria used in our study, BMI is classified as normal 18.5 - 22.9, overweight 23 - 24.9, and obese  $\geq$ 25 (Deurenberg, Deurenberg-Yap, & Guricci, 2002; Low, Chin, Ma, Heng, & Deurenberg-Yap, 2009; Jitnarin et al., 2011).

In our study, there were more women than men in CSU patients, and the peak incidence of CSU was 20 – 40 years (58.37%), which is in accordance with several studies (Lapi et al., 2016; Chu et al., 2017; Moestrup, Ghazanfar & Thomsen, 2017; Kim, Yang, Choi, Choi, & Youn, 2018; Ghazanfar, Kibsgaard, Thomsen, & Vestergaard, 2020). Furthermore, Ghazanfar et al. (2020) referred that it may reflect a gender-dependent distribution of CU because the data were based on hospital registries; the results may also reflect the fact that men were less likely to seek medical attention than women (Galdas, Cheater, F., & Marshall 2005), which similar to this study that the majority of the study population were women.

ESR was the only abnormal laboratory investigation among CSU patients that showed statistically significant differences between BMI < 23 and BMI  $\geq$  23. The ESR and C-reactive protein (CRP) were the most commonly used laboratory tests for detecting the acute phase response and, thus diagnosis and monitoring of inflammatory conditions. Despite the lack of disease specificity and influence by several disease factors, some studies provide valuable information to clinicians in terms of supporting clinical signs and symptoms of inflammation (Bray et al., 2016; Lapić, Padoan, Bozzato, & Plebani, 2020). Obesity is known to be associated with elevated levels of inflammatory markers, and Sharma, Kumar, Jha, Agarwal, & Misra (2020) reported that approximately one-fifth of patients with rheumatoid arthritis, who were actually in low disease activity, had elevated inflammatory markers, primarily due to obesity. This finding supported previous studies suggesting that CSU and overweight/obesity may be linked through pathogenetic involvement in the inflammatory process (Zbiciak-Nylec et al., 2018; Zuberbier et al., 2022; Matano et al., 2020).

Limitations of this study were 1) the lack of a specific ICD-10 code for CSU, and the absence of formal validation of the individual diagnoses, which might have resulted in misclassification of some cases of CSU as similar to other studies (Lapi et al., 2016). However, in this study, we used inclusion and exclusion criteria for selection and all the diagnoses were made by a specialized dermatologist at the Institute of Dermatology, which is a tertiary center. 2) Body weight, height, and BMI were measured using a consistent method in real-world clinical practice, validating the results. False diagnoses could be possible, and the effects of unidentified confounding factors could not be adjusted (Kim et al., 2019).





There have many studies explored the relationship between overweight/obesity and CSU, but the etiopathogenesis of CSU has not been completely understood. Even though, our study found no statistically significant association between overweight/obesity and CSU in Thai population, we suggest that larger population, prospective study, or multicenter population are necessary in the future to improve our understanding of this relationship and clarify our results. These studies would help to shed light on the possible association between overweight/obesity and CSU and could lead to the development of targeted interventions for patients with CSU.

## 5. Conclusion

Our study found that significantly higher ESR in the overweight/obesity group also supported CSU. The overweight/obesity may be linked through pathogenetic involvement in the inflammatory process. Although, there was no association between overweight/obesity and CSU in the adult Thai population, which was different from many previous studies. However, this finding was compatible with a few earlier reports. Therefore, further studies to confirm and clarify our results and the possible association between overweight/obesity and CSU are needed.

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