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RESEARCH LETTER

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Urticaria and angioedema in Estonia, Iceland and Sweden

To the Editor,

Urticaria and angioedema often appear together and impact the quality of life. Mast-cell activation and release of histamine and other mediators cause the typical hives of urticaria and are a major cause of the tissue swelling of angioedema.[1] The reported lifetime prevalence of urticaria has varied between 10 and 25%,[1] while the lifetime incidence of angioedema is 10–15%.[2] Among those with chronic urticaria, approximately 40% also have angioedema.[3]

There is a lack of studies on the concurrence of urticaria and angioedema in the general population, and little is known about geographical differences regarding the prevalence of the two disorders. The aim of this study was to analyse the prevalence of, and associated factors to, urticaria and angioedema in Sweden, Estonia and Iceland.

Data was collected in 2004–2009 by the Burden of Obstructive Lung Disease (BOLD) initiative.[4] Participants ≥ 40 years of age randomly selected from the general population answered questions on respiratory symptoms and cardiometabolic disorders, were assessed with spirometry and sampled blood to quantify inflammatory markers. Urticaria was defined as an affirmative answer to the question, 'Have you ever had urticaria—itchy, bright red, raised rash on the body?' Angioedema was defined as an affirmative answer to the question, 'Have you ever had Quincke oedema/angioedema—sudden swelling of the face, neck or extremities?'

Sleep disturbances and gastroesophageal reflux were assessed using a scale of 1–5. Epworth sleepiness scale (ESS) was used to estimate daytime sleepiness. SF-12 Health Survey was used to calculate mental (MCS) and physical component summary (PCS).

Forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) were measured seated before and 15 min after bronchodilatation with 200 μg inhaled salbutamol.

Interleukin 6 (IL-6) and C-reactive protein (CRP) were measured in all centres. Serum eosinophilic cationic protein ECP, eosinophil-derived neurotoxin (EDN), myeloperoxidase (MPO), and neutrophil gelatinase-associated lipocalin (NGAL) and IgE-sensitisation using were measured in Uppsala.

A detailed description of the methods is available as an online repository: https://osf.io/cpswa/files/osfstorage?view_only=3d50d04bac49476ca2032bbb9f401254.

This study included 1941 participants (response rate 66%). Of these, 23.9% reported having had urticaria, 9.1% angioedema and 5.5% both. The prevalence was higher in Sweden compared to Iceland and Estonia (Table 1). Women had a higher prevalence of urticaria (30.5 vs. 18.2%), angioedema (11.4 vs. 7.1%) and the combination of urticaria and angioedema (6.9 vs. 3.7%) than men ($p < .001$). Female sex, nasal allergies, IgE sensitisation, nocturnal gastroesophageal reflux, difficulties initiating sleep, excessive daytime sleepiness and lower physical health status (SF12 physical component score) were associated with a higher prevalence of urticaria and angioedema (Table 1). There was no difference between the groups regarding cardiometabolic comorbidities, lung function and inflammation biomarkers.

In the present population survey of subjects 40 years and older from three countries, almost one in four and one in ten reported having had urticaria and angioedema, respectively, with considerable overlap between the two disorders. The prevalence of ever urticaria and angioedema was on the same level as in some previous reports.[1] However, the magnitude of overlap between angioedema and urticaria was higher in our study than in previous investigations.[5]

There were geographical differences in the prevalence of urticaria and angioedema, with a higher prevalence in Sweden that may partly be connected to a lower prevalence of atopy in Estonia and Iceland than in Sweden and a lower prevalence of IgG antibodies against various microorganisms in Uppsala compared with the other two centres.[6] The possible explanation for the differences might be related to environmental factors, in line with the hygiene hypothesis, and the lower prevalence of allergy-related diseases in Estonia remains—at least in adults—despite the westernisation of Estonia in the last decades.[7]

The prevalence of urticaria alone and urticaria with angioedema was higher in women than men. One explanation could be that sex hormones impact immune response by affecting inflammation cells, such as mast cells, which have receptors for sex hormones.

Having urticaria without angioedema was associated with lower age and RLS, while having angioedema without urticaria was associated with RLS and reported COPD, but not with having a postbronchodilatory FEV1/FVC-ratio below 0.70.

Subjects with both urticaria and angioedema had a higher prevalence of IgE sensitisation to common inhalant allergens and reported nasal allergy, wheezing and current asthma. Nocturnal gastroesophageal reflux was associated with a higher likelihood of

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urticaria and angioedema. Aitella et al. reported similar results and found higher IgE antibodies and eosinophil blood count levels in those with gastroesophageal reflux and urticaria than those with only reflux.[8]

Urticaria and angioedema were associated with a poorer quality of sleep and lower physical health status. This is in accordance with Maurer et al., who reported that approximately 30% of patients with chronic urticaria had decreased quality of life and commonly reported poor sleep.[9]

One strength of our study is the large number and the geographical spread of participants. A weakness is that the data is self-reported and that the participants only reported whether they had ever had urticaria or angioedema and not if they are still having episodes of any of the diseases. We also cannot distinguish between acute and chronic urticaria and angioedema.

Summary box

- One in four and one in ten have had urticaria and angioedema, with considerable overlap.
- Those with urticaria and angioedema urticaria had lower quality of sleep and physical health status.

In conclusion, geographical differences in the prevalence of urticaria and angioedema were found, indicating that country-specific factors could influence the development of the diseases. Moreover, associations were found between urticaria and angioedema and nocturnal gastroesophageal reflux, female sex, allergies, sleep disturbances and low physical health status.

TABLE 1 Prevalence (*n* (%)) and variables independently associated with urticaria and angioedema.

	Only urticaria	Only angioedema	Both
Prevalence			
Tartu	112 (17.7)	15 (2.4)	16 (2.5)
Reykjavik	113 (15.7)	29 (4.0)	26 (5.0)
Uppsala	**137 (23.3)**	**32 (5.4)**	**49 (8.4)**
All centres	362 (18.7)	76 (3.9)	101 (5.2)
	RRR[a] (95% CI)	**RRR[a] (95% CI)**	**RRR[a] (95% CI)**
Tartu	1	1	1
Reykjavik	0.87 (0.65–1.17)	1.65 (0.87–3.13)	**2.15 (1.17–3.96)**
Uppsala	**1.62 (1.21–2.16)**	**2.79 (1.48–5.24)**	**4.28 (2.39–7.69)**
Women	**2.05 (1.62–2.60)**	1.59 (1.00–2.54)	**2.33 (1.53–3.55)**
Age (per 10 years)	**0.86 (0.78–0.95)**	0.85 (0.69–1.05)	1.06 (0.89–1.26)
Nasal allergy	**1.53 (1.15–2.04)**	**3.13 (1.93–5.09)**	**4.03 (2.64–6.16)**
Allergic reaction to food	**1.87 (1.32–2.64)**	**4.19 (2.45–7.16)**	**3.90 (2.42–6.28)**
Wheeze	**1.82 (1.40–2.37)**	1.12 (0.64–1.96)	**2.63 (1.71–4.03)**
Chronic bronchitis	**1.82 (1.08–3.06)**	2.02 (0.77–5.27)	**4.18 (2.15–8.16)**
Chronic obstructive pulmonary disease	1.63 (0.62–4.30)	**8.24 (3.01–22.58)**	1.56 (0.34–7.11)
Chronic cough	**1.60 (1.08–2.36)**	0.87 (0.34–2.21)	**2.97 (1.72–5.10)**
Chronic phlegm	1.25 (0.85–1.85)	1.60 (0.80–3.21)	**2.48 (1.45–4.24)**
Current asthma	**2.56 (1.66–3.93)**	2.02 (0.88–4.62)	**6.46 (3.81–10.96)**
Difficulties inducing sleep	0.98 (0.70–1.40)	**1.99 (1.11–3.59)**	**2.03 (1.24–3.34)**
Excessive daytime sleepiness	**1.36 (1.01–1.82)**	1.67 (0.98–2.87)	**2.38 (1.52–3.71)**
Nocturnal gastroesophageal	**2.36 (1.35–4.12)**	**3.32 (1.32–8.32)**	**3.51 (1.60–7.72)**
Epworth sleepiness scale (ESS) >10	1.42 (0.97–2.07)	1.17 (0.56–2.44)	**1.98 (1.13–3.47)**
Restless legs syndrome	**1.41 (1.02–1.96)**	**2.30 (1.30–4.05)**	1.59 (0.93–2.72)
Mental component score SF 12	0.95 (0.90–1.01)	0.97 (0.87–1.09)	1.00 (0.91–1.10)
Physical component score SF 12	**0.90 (0.86–0.95)**	0.88 (0.80–0.96)	**0.87 (0.80–0.94)**
IgE sensitisation[b]	1.10 (0.67–1.81)	1.82 (0.77–4.32)	**2.89 (1.48–5.65)**

Note: Statistically significant results ($p < .05$) are marked as bold. The group without urticaria and angioedema was the reference group.

[a]RRR = relative risk ratio adjusted for sex, age and centre.

[b]IgE data were only available in Uppsala.

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KEYWORDS

angioedema, epidemiology, inflammation, sleep, urticaria

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AUTHOR CONTRIBUTIONS

JHe and CJ drafted the manuscript, CJ, BB, TG and RJ collected the data, RM and MM analysed the biomarkers and AM, SAH and JHa contributed to the interpretation of the result. All authors contributed to and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Robert Movérare and Magnus Molin are affiliated with Thermo Fisher Scientific (Sweden). No other author has reported any conflict of interest.

DATA AVAILABILITY STATEMENT

The dataset is still subject to further analyses but will continue to be held and managed by the Department of Medical Sciences, Uppsala University, Uppsala, Sweden. Relevant anonymised data are available on reasonable request from the authors.

Johanna Heldin[1]
Andrei Malinovschi[2]
Shadi Amid Hägg[1]
Thorarinn Gíslason[3,4]
Bryndís Benediktsdóttir[3,4]
Robert Movérare[1,5]
Jenny Hallgren[6]
Magnus Molin[5,7]
Rain Jogi[8]
Christer Janson[1]

[1]*Department of Medical Sciences, Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden*
[2]*Department of Medical Sciences, Clinical Physiology, Uppsala Universitet, Uppsala, Sweden*
[3]*The Medical Faculty, University of Iceland, Reykjavik, Iceland*
[4]*Department of Sleep, Landspitali University Hospital Reykjavik, Reykjavik, Iceland*
[5]*Thermo Fisher Scientific, Uppsala, Sweden*
[6]*Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden*
[7]*Readily Diagnostics, Uppsala, Sweden*
[8]*Lung Clinic, Tartu University Hospital, Tartu, Estonia*

Correspondence
Christer Janson, Department of Medical Sciences, Respiratory, Allergy and Sleep Research, Uppsala University, 751 85 Uppsala, Sweden.
Email: christer.janson@medsci.uu.se

ORCID

Andrei Malinovschi https://orcid.org/0000-0002-4098-7765
Jenny Hallgren https://orcid.org/0000-0002-3685-5364
Christer Janson https://orcid.org/0000-0001-5093-6980

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