

# Risk Factors for the Absence of Diagnosis of Asthma Despite Disease Symptoms: Results from the Swedish GA2LEN Study

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**Background:** Asthma is a common chronic disease presenting with airway symptoms such as wheezing, chest tightness and attacks of breathlessness. Underdiagnosis of asthma is common and correlates to negative outcomes such as a lower quality of life and reduced work capacity.

**Purpose:** This study aims to identify factors for not being diagnosed with asthma if presenting with asthma symptoms.

**Patients and Methods:** A questionnaire was sent to 45,000 subjects (age 16–74 years) in Sweden. Subjects who reported both wheeze and breathlessness and wheeze when not having a cold were defined as having asthma-related symptoms. Data on demographics, educational level, smoking, physical activity, comorbidities, symptoms and asthma were collected. Logistic regression was used to identify risk factors for not being diagnosed with asthma.

**Results:** Of the 25,391 who responded to the survey, 6.2% reported asthma-related symptoms. Of these, 946 had been diagnosed with asthma previously, while 632 had not. Independent risk factors for not being diagnosed with asthma were higher age (OR (95% CI) (2.17 (1.39–3.40))), male sex (1.46 (1.17–1.81)), current smoking (2.92 (2.22–3.84)), low level of education (1.43 (1.01–2.01)), low physical activity (1.36 (1.06–1.74)), and hypertension (1.50 (1.06–2.12)).

**Conclusion:** Men, smokers, older subjects, and those with low educational level or low physical activity are less likely to be diagnosed with asthma despite presenting asthma-related symptoms.

**Keywords:** asthma symptoms, no diagnosis despite symptoms of asthma

## Introduction

Asthma is a common heterogeneous respiratory disease usually characterised by airway inflammation.<sup>1</sup> It is a major cause of disability and health resource utilisation worldwide.<sup>2</sup> The asthma diagnosis is most often based on a history of respiratory symptoms such as wheezing, chest tightness and shortness of breath, and a clinical examination showing reversible airflow limitation.<sup>3</sup>

Previous studies report that 19% to 73% of asthmatics are undiagnosed.<sup>3–5</sup> The large discrepancies in the prevalence of under-diagnosed asthma may be due to varied populations, definitions and approaches of asthma diagnosis.<sup>4,6</sup> The diagnosis may be missed due to inaccurate evaluation by health care practitioners or underreporting of symptoms by the patient.<sup>4,5,7,8</sup> Not having access to effective treatment is a major consequence of underdiagnosis. Insufficient treatment

might reduce physical activity, sleep quality and quality of life.<sup>3</sup> It may also aggravate symptoms, lead to frequent health care visits, hospitalisation and reduced work capacity.<sup>9</sup>

The underdiagnosis of asthma seems particularly common in older subjects due to reduced perception of symptoms or under-reporting of symptoms.<sup>10</sup> In this age group, it is difficult to differentiate asthma from other frequent conditions such as chronic obstructive pulmonary disease (COPD), cardiac failure and acute bronchitis.<sup>11</sup> Also, asthma may be underdiagnosed in children, leading to consequences in adult age.<sup>12</sup> For example, lack of treatment of asthma causes low physical activity and high body mass. The previous studies also revealed that asthma was more often unrecognised in girls and women compared to boys and men.<sup>11,13</sup>

This study aimed to identify factors related to the underdiagnosis of asthma by comparing subjects with asthma-related symptoms who had been diagnosed with asthma to those with symptoms but without an asthma diagnosis.

## Materials and Methods

### Study Design

This cross-sectional study was based on the Global Allergy and Asthma European Network (GA<sup>2</sup>LEN) Survey conducted in 2008. The GA<sup>2</sup>LEN-network was formed by researchers to collect information on the prevalence of respiratory and allergic diseases in Europe.<sup>14</sup> In 2008, as part of the European survey, the GA<sup>2</sup>LEN questionnaire was posted to 45,000 adults between 16 and 75 years of age, randomly identified through civil registries in four Swedish cities: Gothenburg, Stockholm, Uppsala and Umeå.<sup>15,16</sup> This analysis included 25,391 subjects with complete data for the relevant variables. Participants with diagnosed asthma but without asthma-related symptoms (n=2176) and subjects with diagnosed chronic obstructive pulmonary disease (COPD) or subjects that had not answered the questions on COPD (n=342) were excluded (Figure 1).

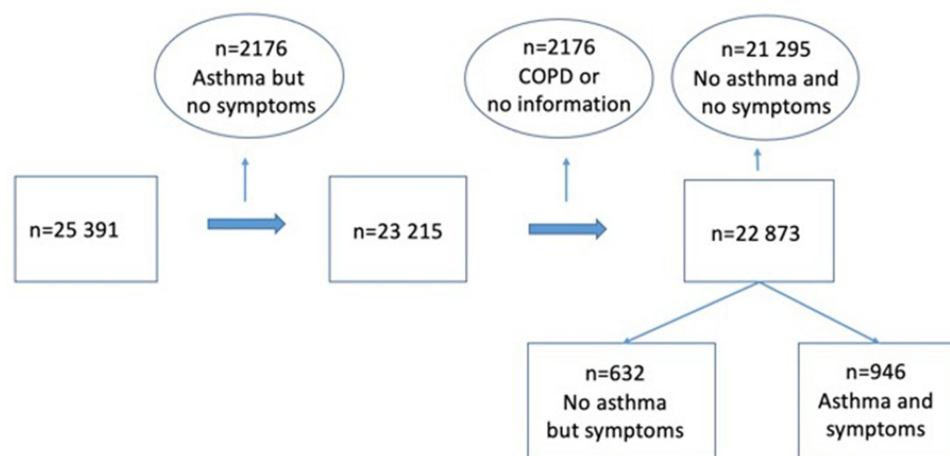
The Regional Ethical Review Board in Uppsala, Sweden approved the Swedish participation in the GA<sup>2</sup>LEN survey (Dnr 2008/014). All respondents gave written informed consent at the start of the questionnaire.

### Questionnaire

The GA<sup>2</sup>LEN questionnaire was based on the validated questions from the European Community Respiratory Health Survey.<sup>17</sup> The international questionnaire had 27 questions, but in Sweden, 13 further questions covered aspects such as educational level, physical activity and sleep disturbances were added.<sup>15</sup>

### Definitions

Asthma-related symptoms were defined as an affirmative response to all three following questions: “Have you had wheezing or whistling in your chest at any time in the last 12 months?”, “Have you been at all breathless when the



**Figure 1** Flow chart showing how the study groups were selected.

wheezing noise was present?”, and “Have you had this wheezing or whistling when you did not have a cold?”<sup>18</sup> Asthma was self-reported and defined as replying “yes” to the question “Have you ever had asthma?”.

Body mass index (BMI) in kg/m<sup>2</sup> was calculated by using self-reported height and weight and divided into the four groups <20, >20–25, >25–30, and >30 kg/m<sup>2</sup>. The level of physical activity, defined as exercise-induced sweating or shortness of breath, was divided into three categories: low, at least once a month; medium, up to three times a week; high, at least four times a week.<sup>18</sup> Smoking status was categorised into three groups; current smokers, former smokers, and never smokers. It was based on the questions: “Have you ever smoked for as long as a year? (‘Yes’ means at least one cigarette per day or one cigar per week for one year)” and “Have you smoked at all in the last month?”. Educational level was divided into three groups: elementary school (up to 9 years of education), high school graduation or University degree.

History of chronic disease included:

-Allergic rhinitis; affirmative answers to both of the following questions: “Do you have any nasal allergies including hay fever?” and “Have you been troubled by nasal allergies in the last 12 months?”

-Chronic rhinosinusitis; was defined according to the EP3OS diagnostic criteria<sup>19</sup> presence of at least two of the following symptoms for at least 12 weeks in the past year: (i) nasal blockage, (ii) nasal discharge, (iii) facial pain or pressure or (iv) reduction in the sense of smell, with at least one of the symptoms being nasal blockage or nasal discharge.

-Diabetes and hypertension; defined as currently taking medication for the condition.

Symptoms of disturbed sleep 3–5 times a week include snoring, difficulties inducing sleep, difficulties maintaining sleep, excessive daytime sleepiness, and early morning awakenings.

Nocturnal asthma-like symptoms include nocturnal chest tightness, breathlessness, and nocturnal cough.

## Statistical Analysis

The program STATA IC (version 15), College Texas USA, was used for statistical analyses. The categorical variables were presented in percentages. Chi2-tests and unpaired t-tests were used in the bivariable analyses and binomial logistic regression in the multivariable analyses. The estimates were adjusted for age, sex, smoking status, BMI, and study Centre in the multivariable analyses. Potential differences in the association between men and women, smokers and non-smokers, allergic rhinitis and no allergic rhinitis, as well as age, were studied with analyses of interactions. A p-value < 0.05 was considered statistically significant.

## Results

### Basic Characteristic

Of the 1578 subjects with asthma-related symptoms, 632 subjects (40.1%) had never been diagnosed as having asthma (Figure 1). The proportion of men was significantly higher in the group without an asthma diagnosis than among those with a diagnosis (Table 1). Furthermore, subjects without an asthma diagnosis were significantly older, were more often current smokers, had a lower educational level, and were more often on antihypertensive medication than those with an asthma diagnosis. The group without a diagnosis also had a higher prevalence of sleeping disturbances such as snoring, difficulty initiating sleep, daytime sleepiness, and early morning awakenings. The group with diagnosed asthma had a significantly higher prevalence of allergic rhinitis and nocturnal chest tightness than the group without a diagnosis.

### Risk Factors for Not Having an Asthma Diagnosis

Independent risk factors for not being diagnosed with asthma despite having asthma-related symptoms were analysed with multivariable analysis adjusted for age, gender, smoking history, BMI, and study centre. The following independent risk factors were identified: male sex, higher age, current smoking, low educational level and low level of physical activity (Table 2). We also found that not having an asthma diagnosis was independently associated with hypertension, difficulties inducing sleep, and excessive daytime sleepiness (Table 2). Those with a diagnosis were more likely to have nocturnal chest, nocturnal breathlessness and allergic rhinitis than those not diagnosed with asthma (Table 2).

**Table 1** Characteristics of Patients with Asthma-Related Symptoms with or without Asthma Diagnosis (%)

	Diagnosis (n=946)	No Diagnosis (n=632)	P
Male	38.3	45.9	0.003
Age groups (years)			
15–24	18.2	12.0	<0.001
25–34	26.3	17.1	
35–44	20.7	19.4	
45–54	14.8	20.2	
55–64	12.1	19.2	
65–75	8.0	12.2	
Smoking status			
Never	60.5	43.1	<0.0001
Former	25.8	26.0	
Current	13.7	30.9	
Educational level			
Elementary	11.0	21.1	<0.0001
High school	31.5	34.1	
University	57.5	44.8	
BMI			
<20	7.1	5.4	0.149
20–24.9	47.3	43.5	
25–29.9	30.2	33.2	
>30	15.4	17.9	
Physical activity level			
Low	23.9	34.5	<0.0001
Medium	54.4	47.3	
High	21.8	18.2	
Night symptoms			
Nocturnal chest tightness	48.1	41.1	0.007
Nocturnal breathlessness	23.3	22.0	0.55
Nocturnal coughing	49.2	48.3	0.75
Comorbidity			
Allergic rhinitis	70.2	43.9	<0.001
Chronic rhinosinusitis	3.5	4.1	0.51
Hypertension	10.4	19.8	<0.001
Diabetes	2.6	3.4	0.43
Symptoms disturbing sleeping			
Snoring	22.0	28.3	0.005
Difficulties initiating sleep	22.3	29.9	0.001
Difficulties maintaining sleep	35.5	40.8	0.035
Excessive daytime sleepiness	44.0	50.9	0.007
Early morning awakenings	21.0	28.4	0.001

**Note:** Chi2-tests and unpaired t-tests were used in the bivariable analyses.

**Table 2** The Correlation of Not Having an Asthma Diagnosis in Patients with Asthma-Related Symptoms Was Calculated as Odds Ratio (OR) with 95% Confidence Intervals (95% CI) and Adjusted for Age, Gender, Smoking History, BMI, and Study Centre

	<b>Adjusted OR (95% CI)</b>	<b>P</b>
Male	1.46 (1.17–1.81)	0.001
<b>Age (years)</b>		
15–24	1	–
25–34	0.89 (0.62–1.29)	0.55
35–44	1.24 (0.86–1.79)	0.26
45–54	1.73 (1.18–2.54)	0.005
55–64	2.13 (1.43–3.18)	<0.0001
65–75	2.17 (1.39–3.40)	0.001
<b>Smoking status</b>		
Never	1	–
Former	1.08 (0.82–1.4)	0.59
Current	2.92 (2.22–3.84)	<0.0001
<b>Educational level</b>		
Elementary	1.43 (1.01–2.01)	0.04
High school	1.08 (0.84–1.38)	0.54
University	1	–
<b>BMI</b>		
<20	0.9 (0.57–1.45)	0.68
20–24.9	1	–
25–29.9	0.99 (0.77–1.28)	0.93
>30	1.06 (0.76–1.45)	0.72
<b>Level of physical activity</b>		
Low	1.36 (1.06–1.74)	0.016
Normal	1	–
High	1.04 (0.78–1.38)	0.81
<b>Comorbidity</b>		
Allergic rhinitis	0.37 (0.30–0.47)	<0.0001
Chronic rhinosinusitis	0.96 (0.56–1.67)	0.90
Hypertension	1.50 (1.06–2.12)	0.02
Diabetes	0.89 (0.46–1.71)	0.72
<b>Night symptoms</b>		
Nocturnal chest tightness	0.67 (0.54–0.83)	<0.0001
Nocturnal breathlessness	0.77 (0.59–0.996)	0.047
Nocturnal coughing	0.86 (0.69–1.07)	0.17
<b>Symptoms disturbing sleeping</b>		
Snoring	1.01 (0.78–1.31)	0.91
Difficulties initiating sleep	1.33 (1.04–1.71)	0.03
Difficulties maintaining sleep	1.02 (0.82–1.28)	0.84
Excessive daytime sleepiness	1.36 (1.09–1.69)	0.01
Early morning awakenings	1.20 (0.93–1.55)	0.16

## Interaction Analyses

The association between not having an asthma diagnosis and current smoking was stronger in men than in women (adjusted OR (95% CI), 3.49 (2.13–5.74) vs 2.81 (1.52–3.12),  $p_{\text{interaction}}=0.02$ ), and the association between not being diagnosed and low educational level was only found in men (adjusted OR (95% CI) 1.88 (1.06–3.31) vs 1.15 (0.74–1.80),  $p_{\text{interaction}}=0.04$ ). No significant interactions were observed for age or allergic rhinitis.

## Discussion

Our results show that the presence of asthma-related symptoms without an asthma diagnosis was more common in men, smokers, those of higher age, individuals with low educational level, those with low level of physical activity, having hypertension, and those who report sleep problems or daytime sleepiness, compared to those with symptoms and an asthma diagnosis. On the other hand, nocturnal asthma symptoms and allergic rhinitis were related to a higher likelihood of being diagnosed with asthma.

In the present study, men with asthma-related symptoms were almost 50% more likely not to have an asthma diagnosis than women with similar symptoms. One reason for this could be that asthma is more common among adult females than adult males.<sup>20,21</sup> This may increase the risk of a missed diagnosis in men. We have previously found that women with asthma-related symptoms use antiasthmatic medications more often than men.<sup>22</sup> Women with persistent asthma are more likely to use inhaled corticosteroids daily.<sup>23</sup>

Higher age was associated with not having an asthma diagnosis in our study. It has previously been reported that a higher age of asthma symptom onset increased the risk of a missed asthma diagnosis.<sup>2</sup> In addition, other diseases such as COPD, heart failure, obesity and anaemia, which also cause respiratory symptoms, are more common in older than younger subjects.<sup>24</sup> Furthermore, our results indicate that a higher educational level correlated to appropriate asthma diagnosis if presenting with asthma symptoms. This result is consistent with a previous study from Columbia.<sup>11</sup> On the other hand, a study from Australia showed no link between the absence of asthma diagnosis and educational level, whereas lower-income and birthplace outside country was associated with underdiagnosis.<sup>25</sup>

Current smokers had a three times higher risk of not having an asthma diagnosis than those who never smoked. One reason for this could have been that COPD is a common cause of asthma-related symptoms in smokers. However, participants with diagnosed COPD were excluded from the present study. In accordance with our analysis, previous studies have shown that smokers with asthma-related symptoms use less asthma medication.<sup>22</sup> Also, smokers with persistent asthma are less likely to use inhaled corticosteroids regularly as these individuals attribute their asthma symptoms to smoking rather than to asthma.<sup>23,26</sup>

In a previous study using the GA2LEN questionnaire, asthma was more prevalent in groups with a higher reported level of physical activity.<sup>13</sup> A low level of physical activity was associated with not having an asthma diagnosis. This may explain why the group with low physical activity was diagnosed to a lower extent than those being more physically active. Since physical activity can trigger asthma symptoms, the group with a low level of physical activity would be less likely to experience airway symptoms triggered by exercise.<sup>21</sup>

We found that subjects with asthma-related symptoms and known hypertension were less likely to have an asthma diagnosis than those without hypertension. One reason for this might be that dry cough is the common adverse effect of frequently used hypertension medication such as angiotensin-converting enzyme inhibitors (ACEIs).<sup>27</sup> Use of ACEIs is also linked to an increased level of bradykinin,<sup>27</sup> which may exacerbate pre-existing airway hyperresponsiveness and lead to asthma symptoms.<sup>28</sup>

In our study, sleep disturbances, such as difficulties initiating sleep and excessive daytime sleepiness, were associated with not having an asthma diagnosis. Although sleep disturbance is a frequent symptom in asthma,<sup>29</sup> it might also be attributed to several other somatic and psychiatric conditions.<sup>30,31</sup>

Having allergic rhinitis and nocturnal asthma-related symptoms increased the likelihood of an asthma diagnosis. A high degree of awareness in the society of the close association between nasal allergy and asthma<sup>29,32</sup> and that nocturnal symptoms are common in asthma<sup>33</sup> are possible explanations.

## Strengths and Weaknesses with This Study

A strength of our study is the high number of participants of different ages, from both sexes and different Swedish cities. Our study also has several limitations, including its basis on questionnaire data, leading to over- or under-reporting of conditions and symptoms. Both asthma and asthma symptoms were self-reported. The definition of asthma was based on one question, which makes it weaker than the definition of asthma symptom, based on affirmative answers to three questions. Also, we did not have information on the asthma symptom onset and duration. This would be interesting in order to determine which age group of patients was particularly vulnerable for underdiagnosed asthma. In addition, the response frequency to the survey was 56% which may lead to selection bias.

## Conclusions

Men, older subjects, smokers, and subjects with low educational levels and low physical activity have a lower prevalence of diagnosed asthma despite presenting asthma-related symptoms. The results may partly be explained by a higher prevalence of other disorders that cause respiratory symptoms in these populations and indicate that underdiagnosis of asthma might be more prevalent in these groups.

## Disclosure

The authors report no conflicts of interest in this work.

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