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UNDERDIAGNOSIS OF CHILDHOOD ASTHMA: A COMPARISON OF SURVEY ESTIMATES TO CLINICAL EVALUATION

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Abstract
Objectives: Diagnostic patterns play a role in asthma prevalence estimates and could have implications for disease management. We sought to determine the extent to which questionnaire-derived estimates of childhood asthma reflect the disease's true occurrence. **Materials and Methods:** Children aged 6–12 years from Katowice, Poland, were recruited from a cross-sectional survey (N = 1822) via primary schools. Students were categorized into three mutually exclusive groups based on survey responses: "Asthma" (previously diagnosed asthma); "Respiratory symptoms" (no previous diagnosis of asthma and one or more respiratory symptoms during last year), "No respiratory symptoms" (no previous diagnosis of asthma or respiratory symptoms). A sample of children from each group (total N = 456) completed clinical testing to determine asthma presence according to GINA recommendations. **Results:** Based on the survey, 5.4% of children were classified with asthma, 27.9% with respiratory symptoms, and 66.7% with no respiratory symptoms or asthma. All previously known 41 cases of asthma were confirmed. New diagnoses of asthma were made in 21 (10.9%) and 8 (3.6%) of subjects from the "Respiratory symptoms" (N = 192) and "No respiratory symptoms" (N = 223) groups, respectively. The overall prevalence of childhood asthma, incorporating the results of clinical examination, was 10.8% (95% CI: 9.4–12.2), compared to the questionnaire-derived figure of 5.4% (95% CI: 4.4–6.5%) and affected females more than males. **Conclusions:** Asthma prevalence was underestimated in this population possibly resulting from under-presentation or under-diagnosis. This could have potential implications for proper management and well-being of children. Questionnaire estimates of prevalence should be considered carefully in the context of regional diagnostic patterns.

Key words:
Children, Asthma, Clinical epidemiology, Underdiagnosis

INTRODUCTION

Asthma is a global problem affecting approximately 10% of children worldwide, [1,2] with huge individual and societal burden. It is a disease suspected to develop due to both genetic and environmental contributions. While both of these things may affect the development of asthma, diagnostic labeling and patient reporting practices also act as a determinant of asthma prevalence. There is geographic

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variation in asthma prevalence with asthma prevalence typically being higher in westernized nations [1,2]. Temporal variation in asthma prevalence has also been reported [2–4]. The reasons for the apparent geographic and temporal trends in asthma prevalence are unknown but could be at least partially attributed to differences in diagnostic measures and growing public awareness of asthma [5,6] or to differences in environmental exposures. Epidemiological investigations into the occurrence and risk factors of pediatric asthma belong to current research priorities in environmental health and can directly affect patient management and well-being through appropriate management and removal of environmental triggers.

Analysis of associations between pediatric asthma and outdoor and/or indoor environmental exposures is critical in the understanding of asthma etiology. Numerous national and international projects investigating the relationship between pediatric asthma and the environment use a standard respiratory health questionnaire as the principal study tool. Usually the occurrence of pediatric asthma is estimated according to the report of a physician-made diagnosis that was given prior to the survey. Correct and precise diagnosis (case definition) is critical to the reliability of environmental epidemiology inference. Due to a number of reasons, some cases of pediatric asthma remain undiagnosed or wrongly diagnosed and a resulting misclassification affects both internal and external validity of the environmental epidemiology studies completed.

While westernized nations may have a potential problem with overdiagnosis, Eastern European countries may experience underdiagnosis of asthma. In a multicenter study of Central and Eastern Europe, between country comparisons of asthma prevalence showed that differences may depend on the doctor's choice of asthma definition [7]. Potential underdiagnosis was suggested by recent results of the Belarus, Ukraine and Poland Asthma Study (BUPAS) completed in Belarus [8] and Ukraine [9]. There is also some information about underdiagnosis from Poland [10] but like the Belarus and Ukraine studies, there was no clinical validation of asthma from population-based studies. These findings could be important when interpreting changes in asthma prevalence such as those reported from Poland where physician-diagnosed childhood asthma more than doubled between 1993 and 2007 [11,12] but validation of reported asthma must first be investigated.

Given the results of these studies from Central and Eastern Europe, reporting and diagnostic validity are not localized problems and it is important to examine the validity of asthma diagnosis and reporting. An accurate diagnosis of asthma is important in order to plan for adequate management at the individual level but also for estimating the burden of disease in a population to plan future public health programs.

While this is potentially a far-reaching problem, it is also important to study specific regions to have a better understanding of local practices and how it may affect asthma diagnosis and management. Despite this, diagnostic validity of questionnaire reports for the region of Eastern Europe is unknown. In order to ascertain the extent of potential bias that may be present when using questionnaire-derived estimates of childhood asthma, we completed a project that combined a cross-sectional questionnaire study with clinical investigation into unrecognized asthma in children. The objective of our study was to determine the accuracy of self-reported asthma diagnosis as well as the magnitude and factors related to any disagreement in primary-school children.

MATERIAL AND METHODS

Study design and study population

The study was composed of a cross-sectional survey of children aged 6–12 years with a subsequent clinical assessment (Figure 1). The study protocol was approved by the Medical University of Silesia's University Ethics Committee. Primary schools were selected randomly using a cluster sampling design. Within each selected school, all grade I–IV students were invited to participate. The children's parents or legal guardians received questionnaires, explanation letters, and consent forms. Based on the questionnaire responses, children were categorized into 1 of 3 mutually exclusive groups:

- "asthma" – diagnosis of asthma established before the survey;
- "respiratory symptoms" – one or more symptoms of persistent cough outside infections, chest wheezing, attacks of dyspnea during the last 12 months with no previous diagnosis of asthma;
- "no respiratory symptoms" – no previous diagnosis of asthma and no respiratory symptoms during the last 12 months.

All children from the "asthma" group and 60% samples from the other two groups were invited to take part in the clinical evaluation (Figure 1). The number of children approached was chosen based on sample size requirements and to maximize efficiency in sampling. For statistical purposes, we required approximately 30% of the respiratory symptom and control groups. However, to account for the possibility of a lower participation rate, we

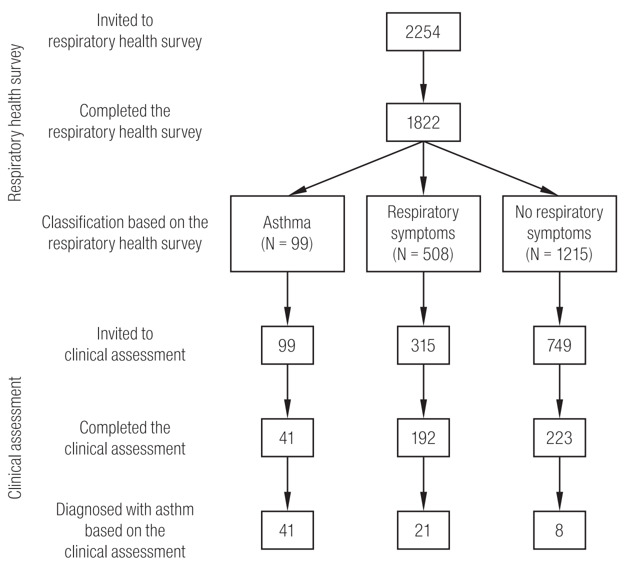

Fig. 1. Flow chart of study design

approached 60% of children in these groups. The samples from the "Respiratory symptoms" and "No respiratory symptoms groups" were chosen randomly. Groups selected by randomization did not differ in age and gender ($p > 0.05$) from the source groups defined by symptoms according to the questionnaire. No more than three weeks passed between the questionnaire collection and clinical testing. In addition to this, information critical to diagnosis that was collected on the questionnaire was asked again as part of the clinical testing.

Questionnaire

The questionnaire was a validated, Polish language version of the children's questionnaire of respiratory symptoms used in The Central European Study of Air Pollution and Respiratory Health (CESAR) and in previous surveys [7,13,14]. This questionnaire collected information on demographics, and respiratory and general health history. Asthma and other diagnoses of allergic diseases/disorders were defined according to the answer to the question "Has the child ever had [a given disease] diagnosed by a physician?" The presence of respiratory symptoms was ascertained by the questions:

- "Has the child ever had wheezing or whistling in the chest at any time in the past?" – ever wheeze.
- "Has the child's chest sounded wheezy or whistling in the last 12 months?" – current wheeze.
- "Has the child ever had attacks of dyspnea?" – ever dyspnea.
- "Has the child had attacks of dyspnea during the last 12 months?" – current dyspnea.
- "Has the child had a dry cough at night in the last 12 months, apart from coughing with a cold or chest infection?" – dry cough at night.
- "Does the child usually cough in the morning in autumn/winter?" – morning cough.
- "Did the child cough on most days for at least 3 months consecutively last autumn/winter?" – chronic cough.

Clinical assessment

The clinical examination was performed by an independent certified pulmonologist who was blinded with respect to the children's respiratory status as determined by the survey. The clinician's task was to divide all children into two categories: "asthma present" or "asthma absent" following GINA guidelines [15] and to determine the severity of asthma according to GINA guidelines (intermittent, mild persistent, moderate persistent, and severe persistent) when asthma was present. The clinical examination included a medical history taken from the parent and child, spirometry, an exercise step test to evaluate nonspecific bronchial hyperresponsiveness, skin prick allergy testing (SPT), and chest x-ray examinations. All of the children underwent spirometry and a clinical evaluation by the physician. Further testing was only completed when there was uncertainty about the final diagnosis of asthma.

Spirometry was performed using an EasyOne spirometer and followed ATS/ERS guidelines [16]. Interpretation was based on reference values established by Dockery and Hsu [17,18]. The submaximal exercise challenge step test was completed according to the protocol described by Gerald et al. [19,20]. Briefly, the child stepped up and down on a single step maintaining a heart rate between 150–200 beats per minute for five minutes. Spirometry was performed 3 and 10 min after completion of the challenge. SPTs were completed following European Academy of Allergy and Clinical Immunology and Polish Allergologic Association guidelines [21]. Allergens tested included: Dust Mite Mix, Dermatophagoides pteronyssinus, Dermatophagoides farinae, grass mixture, mugwort (Artemisia), rye (Secale), hazel (Corylus), Birch (Betulla), Alder (Alnus), Plantin (Plantago), moulds of Alternaria and Cladosporium, cat and dog dander.

Ethics

The procedures followed in the study were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 1983. The project was accepted by local Ethical Commission (NN-013-190/02).

Statistics

Data analysis was performed using Statistica 7.1. Statistical tests of differences in the means of continuous variables were completed using the independent samples t-test if the assumptions were met or the Mann-Whitney U test, if the assumptions were not met. Differences between categorical variables were examined by the chi-square test. Statistical significance was based on $p < 0.05$. We also completed multiple logistic regression with new asthma cases as the outcome (reference: previously diagnosed asthma cases) to identify predictors of newly diagnosed asthma cases from the respiratory symptoms and no respiratory symptoms groups after controlling for potential confounders.

The prevalence of childhood asthma (95% confidence interval) was expressed by two methods. The first as a raw measure based on the questionnaire-derived prevalence. The second as a corrected estimate based on the following steps. The expected prevalence of asthma in the "respiratory symptoms" and "no respiratory symptoms" groups was calculated by multiplying the prevalence of asthma based on the clinical assessments in these groups by the total cross-sectional population in that group. Previously known (questionnaire derived) cases of asthma and expected cases of asthma were then summed and divided by the total population who participated in the respiratory health survey. Finally CIs were calculate using adjusted Wald procedures available in OpenEpi ver 3.01.

RESULTS

The cross-sectional study included 1822 children (response rate: 80.8%) from 7 out of 51 schools in Katowice. This represented 17% of the town's population in the defined age group. Of the study group, 50.2% were girls and the mean age was 8.7 years (SD = 1.2 years). Table 1 shows the questionnaire-derived prevalence of the respiratory outcomes. Boys experienced a significantly higher prevalence of respiratory outcomes than girls with the exception of chronic cough, although wheeze was of borderline statistical significance ($p = 0.06$). Among those who completed the survey, 5.4% were classified as having asthma, 27.9% were classified into the respiratory symptoms group, and 66.7% were classified as no respiratory symptoms.

Clinical assessments were completed for 456 children with 41%, 61% and 31% participation rates for the asthma, respiratory symptoms and no respiratory symptoms groups, respectively. However, 37 children or parents withdrew after initial consent and did not have the diagnostic process completed. Those in the asthma group and the no respiratory symptoms groups were older on average compared to those who did not take part by 0.6 years ($p = 0.02$) and 0.5 years ($p < 0.001$), respectively.

All previously known cases of asthma were confirmed. There were 21 subjects from the "respiratory symptoms" group (10.9%) and 8 subjects from the "no respiratory symptoms" group (3.6%) with newly diagnosed asthma. All newly diagnosed cases were classified as Stage 1 (69%) or Stage 2 (31%) asthma. Previously known (questionnaire-derived) cases included more severe clinical presentations: intermittent – 34.4%, mild persistent – 43.4%, moderate persistent – 18.2% and severe persistent – 4.1%.

Compared with known (questionnaire-derived) asthma cases, children with newly diagnosed asthma were more likely to be girls and less likely to have respiratory or allergic symptoms (Table 2). Results of multivariate analysis which controlled for gender, body mass index, age and parental asthma showed that underreporting of asthma is related to gender (odds ratio = 7.2; 95% CI: 2.2–23).

The newly estimated number of asthma cases was 55 in the "respiratory symptoms" group (10.9% of 508

Table 1. Prevalence of the diagnosis of asthma and current respiratory symptoms based on information from the respiratory health survey

Symptoms	Total (N = 1822) % (95% CI)	Boys (N = 909) % (95% CI)	Girls (N = 913) % (95% CI)	Ch^2 test p*
Asthma diagnosed ever by physician	5.4 (4.4–6.5)	7.1 (5.4–8.7)	3.8 (2.6–5.0)	0.002
Asthmatic, spastic or obstructive bronchitis diagnosed ever by physician	15.7 (14.1–17.4)	19.5 (16.9–22.0)	12.0 (9.9–14.1)	< 0.001
Wheezing or whistling in the chest	8.4 (7.1–9.7)	9.6 (7.7–11.5)	7.2 (5.5–8.9)	0.06
Attacks of dyspnea	4.7 (3.7–5.6)	6.1 (4.5–7.6)	3.3 (2.1–4.4)	0.004
Dry cough during the day or night	15.4 (13.7–17.0)	16.8 (14.4–19.2)	13.9 (11.7–16.1)	0.08
Symptoms after exercise (dyspnea or wheezing or cough)	17.7 (16.0–19.5)	20.0 (17.4–22.6)	15.4 (13.1–17.8)	0.01
Chronic cough	9.9 (8.5–11.2)	10.5 (8.5–12.5)	9.2 (7.3–11.1)	0.3

* Boys vs. girls.

Table 2. Individual characteristics as determined by the questionnaire survey in children with previously known diagnosis of asthma and children with newly diagnosed asthma

Variable	Asthma diagnosed previously (N = 99) n (%)	Newly diagnosed asthma (N = 29) n (%)	Ch² test p*
Gender			
boys	64 (64.6)	10 (34.5)	0.003
girls	35 (35.4)	19 (65.5)	
Age (years)			
7–8	42 (42.4)	16 (55.2)	0.2
9–10	57 (57.6)	13 (44.8)	
Body Mass Index			
20	31 (75.6)	21 (87.5)	0.2
> 20	10 (24.4)	3 (12.5)	
Asthma in mother			
yes	15 (15,6)	5 (17.2)	0.8
no	81 (84.4)	24 (82.8)	
Allergy in mother			
yes	31 (32.3)	9 (32.1)	0.9
no	65 (67.7)	19 (67.9)	
Asthma in father			
yes	7 (7.4)	2 (7.1)	0.9
no	88 (92.6)	26 (92.9)	
Allergy in father			
yes	15 (16.3)	4 (14.2)	0.7
no	77 (83.7)	24 (85.7)	
Chest wheeze ever			
yes	87 (87.9)	13 (44.8)	< 0.0001
no	12 (12.1)	16 (55.2)	
Attacks of dyspnea ever			
yes	66 (68.7)	7 (24.2)	< 0.0001
no	30 (31.3)	22 (75.8)	
Shortness of breath on exertion ever			
yes	53 (54.1)	6 (10.6)	0.001
no	45 (45.9)	23 (79.4)	
Day/night cough during fall and winter			
yes	54 (55.6)	9 (31.0)	0.01
no	43 (44.4)	20 (69.0)	

Table 2. Individual characteristics as determined by the questionnaire survey in children with previously known diagnosis of asthma and children with newly diagnosed asthma – cont.

Variable	Asthma diagnosed previously (N = 99) n (%)	Newly diagnosed asthma (N = 29) n (%)	Ch^2 test p*
Dry cough at night			
yes	29 (30.2)	5 (17.2)	0.1
no	67 (69.8)	24 (82.7)	
Diagnosis of spastic bronchitis (in the past)			
yes	74 (77.1)	11 (40.7)	< 0.001
no	22 (22.9)	16 (59.3)	
Diagnosis of allergic disorders (in the past)			
yes	77 (77.8)	14 (48.3)	0.002
no	22 (22.2)	15 (51.7)	

children) and 44 in the "no respiratory symptoms" group (3.5% of 1215 children). The estimated number of new, previously unknown cases of asthma and previously known 99 cases of asthma were used to calculate the corrected prevalence of asthma in the examined group: (55+44+99)/1822 = 10.8%. Asthma prevalence was higher based on the corrected estimate than the questionnaire-based estimate for both boys and girls, although to a greater extent among girls (boys: 11.1% vs. 7.1%, respectively; girls: 10.4% vs. 3.8%, respectively; Figure 2).

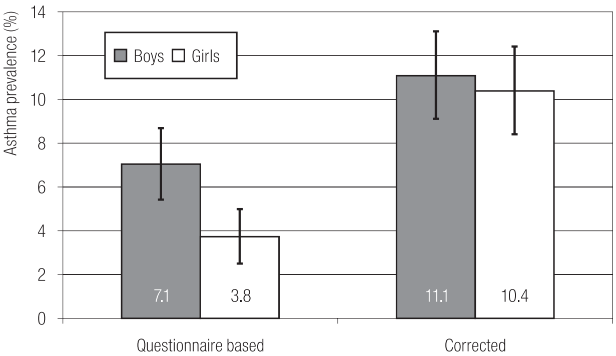

Fig. 2. Prevalence (95% confidence intervals) of childhood asthma provided by respiratory health survey (questionnaire based) and by combination of questionnaire-derived figures and newly diagnosed cases of asthma (corrected prevalence)

DISCUSSION

We completed a study to focus on reporting and diagnosis issues around childhood asthma. This was in light of the fact that there is evidence of misdiagnosis issues in regions of Europe. Our findings suggest that in a large urban population in Poland, a substantial proportion of children, even up to 50%, remain incorrectly undiagnosed. This is similar to estimates provided by previous studies [7,10,22–24]. This has implications globally as it highlights the importance of the establishment and implementation of guidelines to diagnose asthma and to recognize respiratory symptoms, even when mild, as these may be indicators of asthma. Local presenting and diagnosing patterns are important to consider in the assessment of childhood asthma in order to properly recognize, diagnose and manage asthma. Given the results from other Central and Eastern European nations including Belarus [8] this is likely not just a problem in Poland and the results from this current study will be applicable to other countries in the region and should highlight an area of investigation internationally in order to optimize diagnosis and management of childhood asthma.

The majority of new diagnoses of asthma were found among children with current respiratory symptoms, in girls, and were classified as mild intermittent asthma. There are a number of reasons why eligible symptomatic children do not have an established diagnosis, including poor socio-economic standing of families, insufficient awareness or knowledge of respiratory diseases, deficient parental concerns and attitudes to health issues, limited provision and availability of health care services, all of which could lead to underreporting. The reasons may also be related to the specifics of medical practice, including a spectrum from diagnostic standards (and tools) to nosologic preferences [24–28]. The latter explanation was brought about in discussion concerning a relatively low reported prevalence of childhood asthma in the countries of Eastern Europe [7] and suggests that spastic bronchitis was often used in place of asthma as a diagnosis.

It is also intriguing that new cases of asthma were found in some children with no questionnaire-reported current respiratory symptoms. However, such an observation is not isolated. In addition to the absence of respiratory symptoms as determined by questionnaire, some patients do not report their symptoms even during medical examination [20,23,25]. The finding could reflect a low parental concern over these symptoms in a child, low readiness to report mild, intermittent symptoms or insufficient ability to recognize the symptoms especially if their severity is low.

We found that the majority of new cases of asthma were female. Girls could be less likely to present with symptoms or less likely to be diagnosed than boys in this population. While it is generally accepted that boys have a higher asthma prevalence than girls in childhood with a gender switch around puberty, it could be that this difference is smaller than previously thought and girls may in actuality experience milder symptoms early on leading to underreporting or underdiagnosis.

Underreporting of childhood asthma may have contributed to the apparent temporal trend in prevalence of childhood asthma in the region. There is no reason to believe that the margin of underreporting was narrower in the past. On the contrary, improving the availability of diagnostic procedures, shifting diagnostic labeling from "spastic bronchitis" to asthma as well as increasing public awareness of asthma and "learning effect" (repeated respiratory health surveys) imply a larger underdiagnosis of asthma in the past.

By addressing issues in diagnosis, misclassification can be lessened. More accurate diagnosis of asthma is important to patients as it will better determine the clinical management of the individual. Misdiagnosis, and subsequent mismanagement, can result in negative health outcomes including long term airways remodeling [2,29], lower quality of life and further respiratory impairment [15,30]. Thus, it is important to implement measures to accurately diagnose children with asthma.

Our study is not without potential limitations. Most notably, there could be some potential bias as the proportion of children who took part in the clinical assessment varied between groups. The highest participation rate was found among those with respiratory symptoms but without a diagnosis of asthma. This is likely due to concerns by the parents with regard to lung health. Also, those in the asthma and no respiratory symptoms group who took part in the clinical assessments were slightly older on average. However, the actual differences in age were relatively small (approximately 6 months).

In conclusion, the lack of proper diagnosis seems to affect 50% of asthmatic children in Katowice, Poland. Since Katowice is a large urban area with good provision of health care services including a large medical school, it may be that the problem of underreporting of childhood asthma is similar or even bigger in other regions of Poland and Eastern Europe. Moreover, on a global scale, we highlight the need to examine regional reporting and diagnosing patterns in order to most accurately identify asthma in the patient and overall population. It remains unknown to what extent the childhood asthma trend seen in this country over recent decades reflects changes in incidence and to what extent the changes in diagnostic capacity. These findings should also be applied in a more global sense as we try to understand temporal and geographic variation in asthma prevalence.

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