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An international comparison of asthma, wheeze, and breathing medication use among children

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ABSTRACT

Background: There is variation in childhood asthma between countries with typically higher prevalence in "Westernized" nations. We compared asthma, respiratory symptoms, and medication prevalence in Eastern and Central European regions and Canada.

Methods: We conducted a cross-sectional survey study of children (5–15 years) from one urban centre in each of Canada, Belarus, Poland, Republic of Georgia (Adjara), Republic of Macedonia, and Ukraine. Surveys were distributed through randomly selected schools to parents (2013–2015).

Results: The prevalence of asthma differed by country from 20.6% in Canada to 1.5% in Ukraine ($p < 0.001$). This association remained after confounder adjustment. Except for Canada (58.7%) and Poland (42.5%), less than 10% of children with a history of wheeze had a diagnosis of asthma. Regardless of country, more than 50% of children with a diagnosis of asthma used breathing medications in the past year. Finally, except for Georgia (12.1%), all countries had a prevalence of ever wheeze above 20% (23.8% in Poland to 30.9% in Macedonia).

Conclusions: Despite large differences in asthma prevalence, respiratory morbidity was more comparable suggesting asthma prevalence may be underestimated. Further validation of asthma diagnosis is needed. It is important to promote best diagnostic practices among first contact physicians.

1. Introduction

Childhood asthma results in a great deal of burden worldwide as it is prevalent and impacts the individual as well as health care resource use and costs [1–4]. It is well known that there is international variation in childhood asthma prevalence [1,5] with higher asthma prevalence generally observed in Western, industrialized countries including within North America, Australia, and Western Europe while areas such as Eastern and Northern Europe experience lower prevalence [1]. Much of the previous work has been based on the International Study of Asthma and Allergies in Childhood (ISAAC) [1,2,5,6] as well as other studies focused more specifically on differences in asthma prevalence between nations of Western and Eastern influence [7–11]. These previous studies have been critical in our understanding of childhood asthma but continued and more recent investigation of geographic variation is warranted given increases in asthma prevalence primarily in locations of previously low asthma prevalence [5] including in Poland [12], Belarus [13], and the Republic of Georgia [14] along with global Westernization occurring.

The environment and lifestyle have often been the focal point for explanations for the geographic variation in asthma prevalence in children. Recently, it has been suggested that diagnostic differences may account for some of the variation in childhood asthma prevalence [15,16]. Investigation of current geographic differences and patterns could help to identify locations of potential diagnostic labeling issues.

The overall objective of our study was to investigate geographic

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patterns in childhood asthma prevalence and degree of Westernization with a focus on Eastern European countries. Our specific research questions were: 1) Does the prevalence of asthma, wheeze, and breathing medication use differ between locations of varying degrees of Westernization? 2) Are the patterns consistent when comparing characteristics of specific exclusive groups based on the presence of asthma or wheeze?

2. Methods

2.1. Study location, design, and population

This study included data from Regina, Canada; Katowice, Poland; Ternopil, Ukraine; Grodno, Belarus; Skopje, Republic of Macedonia; and Batumi, Republic of Georgia (Adjara). Each of these cities is home to over 125,000 people, located in agricultural regions, and, with the exception of Batumi, is land-locked. The choice of these cities allows a range of "Westernization" from a fully Westernized location in Canada; an Eastern European location with European Union membership (Poland); Eastern European ex-Soviet states (Belarus and Ukraine); a South Eastern European country with past communist influence (Republic of Macedonia); and a country from the Caucuses with a past communist history and ex-Soviet state (Republic of Georgia, Adjara).

This was a cross-sectional study of children aged 5–15 years with questionnaires completed between 2013 and 2016. Following consultation with the school boards, schools were randomly selected in each location. All children from a selected school were eligible for participation. Questionnaires were distributed through the schools to parents for self-completion then returned to the school and collected by research staff.

Prior to data collection, ethical approval was obtained from the local university. School boards approved the study. With the exception of Skopje, Republic of Macedonia, a completed and returned survey implied consent. In Skopje, written consent was required for each completed survey to be included in the study.

2.2. Data collection instruments and operational definitions

Surveys were based on standardized questionnaires including the ISAAC questionnaire [6], American Thoracic Society Children's Respiratory Disease questionnaire [17], and questionnaires used previously in Canadian lung studies [18–20]. Investigators from each location had some discretion on which questions to include in order to maximize practicality and issues of local importance. Items included in the current analyses were identical between locations with the exception of the question regarding asthma used in Belarus. All surveys were translated then back-translated prior to use.

Our primary outcomes were wheeze, asthma, and breathing medication use. Ever wheeze was defined as a positive response to the question: "Has this child ever had wheeze or whistling in the chest in the past?" A positive response to ever wheeze along with a positive response to "Has this child had wheezing or whistling in the chest in the past 12 months?" indicated current wheeze. Breathing medication use was based on "In the past 12 months, has this child taken medicine that your doctor prescribed for a breathing problem?" Ever asthma was defined from the question: "Has this child ever been diagnosed as having asthma by a doctor?" Those with a positive response to ever asthma as well as either current wheeze or breathing medication use in the past 12 months were considered to have current asthma. In Belarus, a history of asthma was based on the question "Has this child ever had asthma?" in addition to the question "Was asthma diagnosed by a doctor?" An overall asthma status variable was also used and defined by the following exclusive groups: no asthma or wheeze, history of ever wheeze but no asthma diagnosis, and a previous diagnosis of asthma.

Location of residence was defined by the city and country of residence. A Westernization gradient variable was created where Canada was the "high" Westernization region; Poland, an Eastern European country in the European Union was categorized as "moderate" Westernization; and the remaining countries (Belarus, Ukraine, Republic of Macedonia, and Republic of Georgia-Adjara) were considered "low" Westernization. This classification scheme was based on the history and governing influence of each country as well as on regional knowledge by study investigators. This definition corresponded with rankings based on the country's 2015 Gross Domestic Product [21]. Data on age, sex, maternal smoking, and paternal smoking were collected in all locations and used in the current analysis as potential confounders. In addition, family history of asthma based on a either the mother or father having a history of asthma and mother's education level as a proxy for socio-economic status (high school education or equivalent vs some or completed university) were included as potential confounders in some analyses. In these latter analyses, data from Ukraine was not included as this information was not available.

2.3. Statistical analysis

Analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 23. Following initial descriptive analyses comparisons between groups were made using the independent chi-squared tests for categorical variables and analysis of variance (ANOVA) for continuous outcomes.

Multiple binary logistic regression was used to investigate the associations between location and each outcome (ever asthma, current asthma, ever wheeze, current wheeze, and breathing medication use) after controlling for potential confounders. The strength of association was assessed by the odds ratio (OR) and 95% confidence interval (CI). A multiple multinomial logistic regression model was fitted where the three category asthma status variable was the outcome.

To characterize specific asthma status groups and compare these groups by location, analyses stratified by asthma and wheeze status were conducted. These considered the prevalence of current status, diagnoses of asthma, and frequency of wheezing or asthma episodes in the past 12 months by country. Statistical comparisons were completed using independent samples chi-squared analysis.

3. Results

Table 1 includes the participation rate and descriptive characteristics of the study population (n = 13,367). The participation rate varied between locations with the lowest in Canada (26.0%) and the highest in Georgia (91%). The mean age in Poland (11 years, standard deviation = 3 years) was higher than other locations. There were also differences in the prevalence of smoking by the mother (lowest in Ukraine: 5.2%; highest in Macedonia: 28.8%) and by the father (lowest in Canada: 18.9%; highest in Georgia: 58.1%). The highest prevalence of a family history of asthma was in Canada, followed by Poland, Republic of Macedonia, and Republic of Georgia. A higher proportion of mothers reported at least some university education in Canada with a lower proportion in Poland.

The prevalence of ever and current asthma in Canada and Poland was significantly ($p < 0.05$) higher than each of the other countries while the differences between the remaining countries (Ukraine, Belarus, Macedonia, and Georgia) were not statistically significant for either ever asthma ($p = 0.28$) or current asthma ($p = 0.52$; Fig. 1). Wheeze prevalence showed less consistent patterns (Fig. 1) between locations and were statistically significant for both ever and current wheeze ($p < 0.001$). The trends across a gradient of Westernization were clear for asthma and wheeze with a decreasing prevalence as degree of Westernization became lower ($p < 0.001$).

There were statistically significant ($p < 0.001$) differences in breathing medication use between locations but the patterns were less clear. Breathing medication use was highest in Ukraine (21.4%) followed by Belarus (19.4%), Poland (18.1%), Macedonia (16.9%),

Table 1
Socio-demographic and participation characteristics of the study population by location.

	Regina, Canada	Katowice, Poland	Skopje, Republic of Macedonia	Ternopil, Ukraine	Grodno, Belarus	Batumi, Republic of Georgia (Adjara)
No. Of study participants	2414	1785	2310	1168	2766	3194
Participation rate, %	26.0	59.7	38.5	58.4	84.3	91.2
Mean age (SD), years *	9.3 (2.6)	11.0 (3.0)	9.9 (2.5)	9.6 (2.2)	10.0 (2.2)	9.5 (2.5)
% Female	50.7	51.6	50.9	53.0	48.9	52.7
% Mother smoking *	13.0	26.1	28.8	5.2	8.1	6.0
% Father smoking *	18.9	34.9	35.6	42.1	52.6	58.1
% With family history of asthma *	19.6	14.5	3.3	NA	1.9	1.6
% Mother with some university education *	78.9	35.9	68.0	NA	74.9	66.7

*$p < 0.05$ when comparing across centers.
NA: Not available.

Canada (15.6%), then Georgia (5.8%). Along a Westernization gradient, the prevalence was 15.6% (High), 18.1% (Moderate), and 14.4% (Low).

After adjusting for potential confounders, the descriptive patterns remained (Table 2). Each location had a reduced risk of current wheeze, ever asthma, and current asthma compared to Canada (most Westernized country) while only Macedonia (increased risk) and Georgia (reduced risk) were statistically different from Canada for ever wheeze. Poland, Ukraine, and Belarus each showed an increased risk of breathing medication use in the past 12 months compared to Canada while Georgia showed a reduced risk of breathing medication use. In general, there were dose-response patterns observed along the Westernization gradient from high Westernization to low Westernization for current wheeze, ever asthma, and current asthma where as Westernization decreased the likelihood of having an outcome were decreased (Table 2). While initially showing a similar pattern with Westernization level, the likelihood of ever wheeze increased as Westernization decreased after adjustment for family history of asthma and mother's education level.

When considering exclusive asthma status categories, in general, in locations of lower asthma prevalence, the prevalence of wheeze without an asthma diagnosis was much higher (Table 3). After adjustment for confounders, locations in Ukraine, Belarus, and Macedonia were all at increased risk of having wheeze without a diagnosis of asthma while children in Georgia were at reduced risk of wheeze without a diagnosis of asthma (Fig. 2). All locations were at a reduced risk of asthma diagnosis compared to Canada (Fig. 2). When considering a gradient of Westernization, there were clear divergent dose-response associations with increasing risk of wheeze without a diagnosis of asthma but a decreasing risk of asthma diagnosis from an area of high to low Westernization (Fig. 2).

Among those who wheezed, there was a much lower prevalence of asthma diagnosis in locations outside of Canada but a higher prevalence of breathing medication use (Table 3). Among those who had wheezed in the past 12 months, children in Poland, Georgia, and Canada tended to wheeze more frequently than children in the other locations (Table 3).

Among those children with a diagnosis of asthma, there were statistically significant differences between locations with regard to the prevalence of current wheeze, breathing medication use, and current asthma although there was not a clear trend by location (Table 3). Among those with a history of asthma, when considered by level of Westernization, there was not a statistically significant difference in the prevalence of current wheeze (High: 45.5%, Moderate: 40.9%, Low: 43.6%, $p = 0.51$) or current asthma (High: 62.1%, Moderate: 67.8%, Low: 65.9%, $p = 0.30$) although the difference was seen when comparing breathing medication use in that subgroup (High: 55.1%, Moderate: 67.1%, Low: 59.2%, $p = 0.01$). Finally, among those with wheeze but no asthma, there was a higher prevalence of breathing medication use as the level of Westernization decreased (High: 22.4%, Moderate: 27.9%, Low: 31.2%, $p = 0.01$).

4. Discussion

We found a lower asthma prevalence in areas of less Westernization despite a high prevalence of wheeze. As Westernization decreased, the risk of asthma decreased while the risk of wheeze without asthma increased. Finally, those outside of the high Westernization area had a higher report of breathing medication use.

We confirmed a higher asthma prevalence in areas of higher Western influence [1,7–9,11,16,22] along a gradient of Westernization, which has been rare to complete. Previous work describing a gradient included a 1996 investigation using the ISAAC survey in 18 centers across Northern, Eastern, and Central Europe [7] and a separate 1996 study of 7–11 year olds residing in Eastern and Central Europe [8] with similar findings. Other studies focused on Westernization have directly compared two locations [9,11,22,23]. It has been some time since the completion of these previous studies. It is important to understand the current patterns in geographic variation to identify disparities between regions and reasons for variation in asthma prevalence.

We previously identified between-country differences in asthma prevalence between Poland, Belarus, and Ukraine and suspected under-diagnosis [16] confirming our other work in the region [24,25]. We confirmed potential under-diagnosis in Poland comparing survey responses to clinical evaluations [15] and expand on the previous evidence by including several additional, heterogeneous locations.

From an earlier study, there was a higher prevalence of asthma among children in West Germany but a higher prevalence of bronchitis among children in East Germany [11]. Similarly, differences in asthma prevalence between countries was much larger than within-country differences in a study from Eastern and Central Europe [8] which also showed that prevalence estimates were similar to Western Europe when asthma prevalence and the prevalence of spastic or obstructive bronchitis were combined [8]. In a separate study, asthma prevalence was higher in Norway compared to Russia yet the prevalence of asthma-like symptoms was higher in Russia [23]. We support these earlier studies and build onto the work by investigating exclusive groups of asthma and wheeze as well as an investigation of breathing medication use and within group analyses.

Under-diagnosis is pertinent to clinical and public health goals. Management may differ based on diagnosis resulting in poor management if an asthma diagnosis is not present, affecting subsequent well-being. Under-diagnosis of asthma could also affect local prevalence estimates, which may impact health care spending. Future work should focus on identifying groups at risk of under-diagnosis and appropriate implementation of asthma management guidelines.

We must consider limitations within our study. Participation rates varied by location which could lead to biased prevalence estimates. However, given the strength of the associations, any suspected bias would likely not change the direction or interpretation of the results. Asthma status based on surveys can lead to misclassification. For practical reasons, surveys are preferred and acceptable in

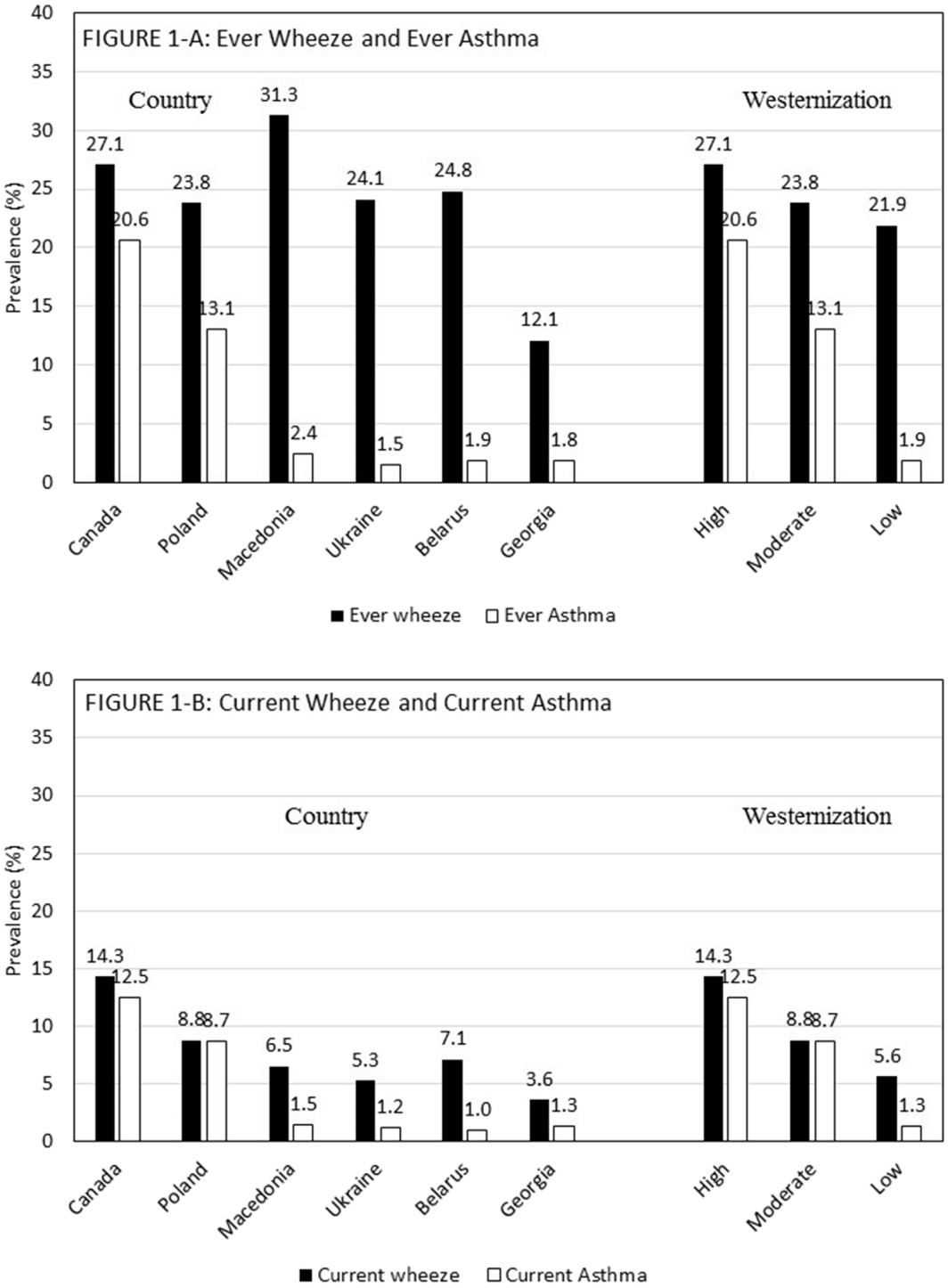

Fig. 1. Prevalence of wheeze and asthma by location [Fig. 1-A shows the prevalence of ever wheeze and ever asthma; Fig. 1-B shows the prevalence of current wheeze and current asthma].

epidemiological studies of asthma prevalence [26] and have acceptable sensitivity and specificity when compared to a blinded physician assessment [27]. While translation may be an issue, the base questions are from the ISAAC survey which has been used worldwide including the languages within the countries where we collected data. We do not have specific information on types and doses of medication use from all locations. As such, we could not evaluate appropriateness of breathing medication use in the current paper. Finally, we only used one location per country. This may not be truly representative of that country.

Our study also had many strengths. We included a large sample size from each location allowing for sufficient statistical power. We also included locations from a range of areas with differing levels of Westernization using a standardized questionnaire with regard to the items of interest. This allowed us to examine differences between locations using consistent methodology and instruments while bringing all of the data to a central analysis in order to allow for control of some of the major potential confounders.

In conclusion, we found a higher asthma prevalence in areas of higher Westernization and with less pronounced or consistent associations with wheeze. Under-diagnosis of asthma may be occurring in

Table 2
Adjusted[a] associations between location and wheeze, asthma, and breathing medication use.

	Ever wheeze OR (95%CI)	Current wheeze OR (95%CI)	Ever asthma OR (95%CI)	Current asthma OR (95%CI)	Breathing medication use OR (95%CI)
Model 1(Country)					
Canada	1.00	1.00	1.00	1.00	1.00
Poland	0.87 (0.74–1.01)	**0.65 (0.52–0.80)**	**0.55 (0.45–0.66)**	**0.68 (0.55–0.85)**	**1.38 (1.16–1.65)**
Macedonia	**1.18 (1.03–1.35)**	**0.43 (0.35–0.53)**	**0.09 (0.07–0.12)**	**0.11 (0.08–0.16)**	1.15 (0.98–1.35)
Ukraine	0.89 (0.75–1.06)	**0.35 (0.27–0.47)**	**0.06 (0.04–0.10)**	**0.09 (0.05–0.16)**	**1.56 (1.29–1.88)**
Belarus	0.89 (0.78–1.01)	**0.47 (0.38–0.57)**	**0.08 (0.06–0.10)**	**0.08 (0.05–0.11)**	**1.41 (1.21–1.65)**
Georgia	**0.36 (0.31–0.42)**	**0.22 (0.17–0.27)**	**0.07 (0.05–0.10)**	**0.09 (0.07–0.13)**	**0.35 (0.29–0.42)**
Model 2 (Westernization)					
High	1.00	1.00	1.00	1.00	1.00
Moderate	**0.85 (0.73–0.99)**	**0.64 (0.52–0.79)**	**0.54 (0.45–0.66)**	**0.68 (0.55–0.85)**	**1.36 (1.14–1.62)**
Low	**0.77 (0.69–0.86)**	**0.36 (0.31–0.42)**	**0.08 (0.06–0.09)**	**0.09 (0.07–0.12)**	0.98 (0.86–1.12)
Model 3 (Westernization)					
High	1.00	1.00	1.00	1.00	1.00
Moderate	0.96 (0.79–1.17)	**0.74 (0.57–0.98)**	**0.59 (0.46–0.75)**	**0.74 (0.55–0.98)**	**1.46 (1.17–1.83)**
Low	0.93 (0.82–1.04)	**0.48 (0.41–0.58)**	**0.10 (0.08–0.13)**	**0.13 (0.10–0.17)**	1.11 (0.96–1.28)
Model 4 (Westernization)					
High	1.00	1.00	1.00	1.00	1.00
Moderate	0.96 (0.82–1.14)	**0.71 (0.56–0.89)**	**0.53 (0.43–0.65)**	**0.68 (0.54–0.87)**	**1.54 (1.28–1.86)**
Low	1.04 (0.93–1.17)	**0.46 (0.39–0.55)**	**0.08 (0.06–0.10)**	**0.09 (0.07–0.12)**	**1.30 (1.13–1.49)**
Model 5 (Westernization)					
High	1.00	1.00	1.00	1.00	1.00
Moderate	1.06 (0.87–1.30)	0.80 (0.60–1.06)	**0.59 (0.46–0.76)**	0.74 (0.55–1.01)	**1.67 (1.32–2.11)**
Low	**1.28 (1.13–1.45)**	**0.62 (0.51–0.74)**	**0.11 (0.08–0.13)**	**0.13 (0.09–0.17)**	**1.58 (1.36–1.84)**

[a] Model 1 and Model 2 are independent models each adjusted for age, sex, maternal smoking, and paternal smoking; Model 3 is adjusted for the same variables as models 1 and 2 but also for family history of asthma; Model 4 is adjusted for the same variables as models 1 and 2 but also for mother's highest level of education; Model 5 is adjusted for the same variables as models 1 and 2 as well as both family history of asthma and mother's education level (NOTE: Models 3, 4, and 5 do not include data from Ukraine); **Bold** indicates a statistically significant ($p < 0.05$) result.

Table 3
Independent asthma and wheeze status and characteristics of those with asthma or wheeze by location.

	Regina, Canada	Katowice, Poland	Skopje, Republic of Macedonia	Ternopil, Ukraine	Grodno, Belarus	Batumi, Republic of Georgia (Adjara)
Among those with ever wheeze						
% with current wheeze	54.2	38.8	21.5	16.9	27.0	25.6†
% who have an asthma diagnosis	58.7	42.5	7.3	6.4	6.6	9.3†
% who used breathing medications (past 12 months)	22.4	27.9	33.6	33.9	34.9	18.3†
Among those with current wheeze						
% who have an asthma diagnosis	65.8	61.4	14.9	19.6	8.1	26.3†
% who used breathing medications (past 12 months)	38.3	53.3	73.6	54.9	61.9	45.2†
% with 1–3 wheeze episodes (past 12 months)	76.0	67.8	90.6	*	92.6	71.3
% with 4–12 wheeze episodes (past 12 months)	19.2	23.5	5.8	*	5.7	21.8
% with > 12 wheeze episodes (past 12 months)	4.8	8.7	3.6	*	1.7	6.9†
Among those with an asthma diagnosis						
% with current wheeze	45.5	40.9	39.6	64.7	30.2	53.6†
% who used breathing medications (past 12 months)	55.1	67.1	62.3	82.4	49.1	58.9†
% with current asthma	62.1	67.8	66.0	82.4	54.7	71.4†
% with 1–3 asthma episodes (past 12 months)	65.0	52.7	78.3	*	*	55.6
% with 4–12 asthma episodes (past 12 months)	25.4	32.9	13.0	*	*	37.0
% with > 12 asthma episodes (past 12 months)	9.6	14.4	8.7	*	*	7.4
Independent asthma and wheeze status						
% No wheeze or asthma	68.6	73.9	69.6	77.6	74.9	87.3
% Ever wheeze but no asthma	11.3	13.2	28.1	21.0	23.2	11.0
% Ever asthma	20.1	12.9	2.3	1.5	1.9	1.8†

*Data was not available.
†$p < 0.05$ between countries.

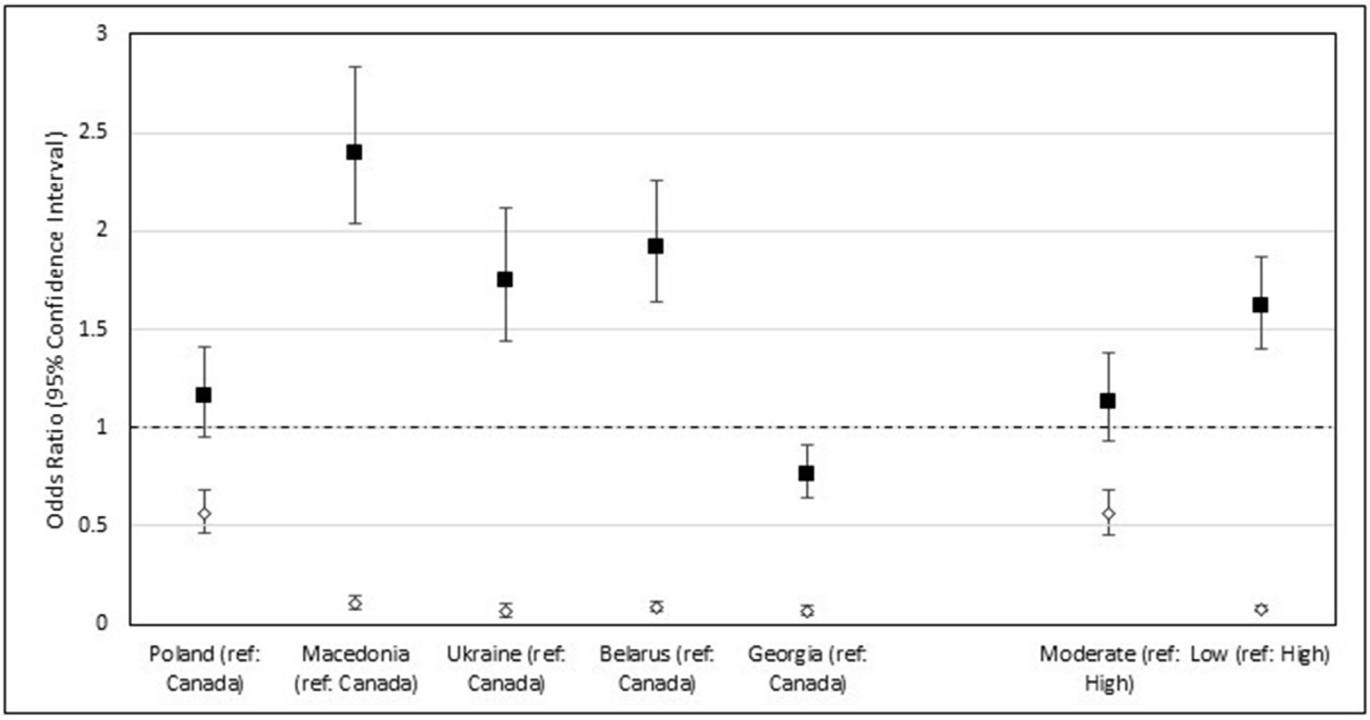

Fig. 2. Adjusted* association between location of residence and asthma status (independent groups of: asthma diagnosed; wheeze with no asthma diagnosis; no asthma, no wheeze). * Adjusted for country, sex, maternal smoking, paternal smoking, and age. Filled squares (■) indicate the associations with wheeze (compared to no asthma, no wheeze); Open circles (○) indicate the associations with asthma (compared to no asthma, no wheeze).

areas of lower Westernization as evidenced by the high wheeze prevalence relative to asthma prevalence and high prevalence of breathing medication use. Further investigation into asthma diagnosing patterns across regions as well as management patterns and asthma severity should be conducted to help explain variations in asthma prevalence. Education and promotion of evidence based and appropriate asthma diagnostic and management practices for front line physicians and health care workers should be completed. While the environment has been a common focus, we suggest that diagnosis and management of asthma also play an important role explaining geographic variation in asthma prevalence.

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Author conflict of interest

None of the authors have any conflicts of interest to declare.

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