

Dear Editor,

Thank you for suggestion to improve the manuscript.

We have accepted all changes made to the manuscript. New changes according to your comments are tracked and highlighted in yellow.

Thank you for inserting into the results section the numbers we quote in the discussion, abstract or tables. We have added missing values and now in discussion and abstract we quote only those numbers which are also present in results section.

QoL of children with asthma in this study was determined only by PedsQL which has self- and proxy- reports and consists of two scales (asthma symptoms and treatment). We tried to clarify this in the results section.

We have specified the name of ethical committee (Vilnius regional ethical committee) and clarified that parents signed separate the informed consent forms to participate in the study.

Thank you for considering and revising the updated manuscript.

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I have a fundamental problem with the QoL figures quoted in this study. In the abstract you quote mean values for the total??? self and proxy reports. In the results you quote median values (I have added the mean values quoted in the abstract in). I assume these are also total scores? Then in the Discussion you quote another set of figures that do not appear in either the abstract or the Results, namely the self and proxy symptom and treatment scores. It is important that there is consistency and any figures quoted elsewhere in the paper are quoted in the Results. I feel the Results section is not as detailed as it should be.

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Commented [A3]: This version of your paper includes my editing suggestions. To avoid me spending time reading the whole paper again when the next draft is submitted, please ensure that you accept all the changes I have made that you agree with. The only changes I should be able to see on the next draft are the changes that you have made to this edited draft. As well as tracking the changes, please highlight them in yellow so that I can pick them out quickly.

The self-reported quality of life of Lithuanian children with asthma was comparable to Western populations

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Short title: Quality of life in children with asthma

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ABSTRACT

Aim: Quality of life (QoL) has been widely researched among children with asthma in Western countries, but there is a lack of data from Eastern Europe, where the prevalence is relatively low, but hospital admission rates are higher. We evaluated the overall level and major determinants of QoL in Lithuanian children aged 5-11 years with asthma.

Methods: This study was carried out in six asthma outpatient clinics in the two largest cities of Lithuania from January 2015 to July 2016. The children's QoL was measured using the Pediatric Quality of Life Inventory (PedsQL) asthma module, which was completed by the child and one parent.

Results: We collected questionnaires from 226 children (68% boys) with a mean age of 8 (± 2): 65% had mild asthma, 31% had moderate asthma and 4% had severe asthma. One in ten had

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been hospitalised in the preceding six months. The mean self-reported QoL score was 74 and parent-reported QoL score was 73. QoL was associated with asthma severity and control, shortness of breath and the child's general health, but not socioeconomic factors.

Conclusions: The overall level and major determinants of QoL in children with asthma in Lithuania were comparable with Western populations.

Keywords: Asthma; Children; Epidemiology; Lithuania; Quality of life

Abbreviations:

QoL Quality of life

PedsQL Pediatric Quality of Life Inventory

SD Standard deviation

IQR Interquartile range

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Key notes:

- There is a lack of data on childhood asthma in Eastern Europe, where the prevalence is relatively low, but hospital admission is higher.
- We evaluated the overall level and major determinants of quality of life in 226 Lithuanian children aged 5-11 years attending asthma outpatient clinics in Lithuania's largest cities.
- The overall level and major determinants of quality of life of Lithuanian children with asthma were comparable with Western populations.

INTRODUCTION

Childhood asthma is a common chronic disease (1) that influences the quality of life (QoL) of patients and their family members (2,3). Studies have shown that the QoL of children with asthma is lower compared with their healthy peers and with children with cardiac conditions or diabetes (4). Asthma can affect a child's QoL due to symptoms that restrict everyday activities, the need for preventer and reliever medication and scheduled and unscheduled healthcare attendances (2,5). The QoL of parents whose children have asthma may be affected by anxiety and financial costs related to their child's disease (6). Childhood asthma can be perceived as placing a burden on the patient throughout their lifetime, as well as on the family and wider society (7,8).

The application of QoL tools in clinical practice is increasing as part of a welcome shift to patient-centred healthcare (9). In Western societies, QoL has been shown to be determined by several factors, such as asthma severity and control, coexistent hayfever and exposure to smoking (5,7). The QoL of children in Eastern European countries is not known, but may differ to that in Western Europe, since childhood asthma outcomes are different in Eastern European countries. For example, the Baltic States, which includes Lithuania, has the highest rates of hospital admissions for childhood asthma in Europe (10). Another contrast between East and West is that the prevalence of asthma in Lithuanian children is low, but rising (10), compared with high-income Western European countries, where the prevalence is high but static and possibly falling in some areas (6).

This study investigated the QoL of children aged 5-11 with asthma in Lithuania, as independently determined by the children and their parents. We also tested the hypothesis that QoL would be poorer in Lithuania than in Western countries.

PATIENTS AND METHODS

Study design and recruitment

This was a cross-sectional study where children and their parents were asked to take part during scheduled outpatient visits to a paediatric pulmonologist. Participants had to meet the following inclusion criteria: aged between five and 11 years old, asthma diagnosis from a paediatric

pulmonologist, attending a specialist clinic and no history of chronic respiratory conditions other than asthma. Data were collected between January 2015 and July 2016 in six different specialist outpatient clinics in the two largest cities of Lithuania. Children under five years of age were ineligible since they are not usually able to self-report QoL (11,12). Children over 11 years of age were excluded since their parent or caregiver reported QoL may be inaccurate, because the parents of older children have relatively less contact with their child and are less involved in their child's asthma care (13). As a result they may not accurately report their child's QoL.

Asthma diagnosis and management in Lithuania

Under the Lithuanian national childhood asthma guidelines, asthma can initially be diagnosed by a family doctor, but the diagnosis must then be verified within three months by a paediatric pulmonologist and the severity confirmed using the Global Initiative for Asthma guidelines (14). After the diagnosis has been confirmed, children should then visit the paediatric pulmonologist once a year if they have mild asthma, twice a year for moderate asthma and every three months for severe asthma (15).

Questionnaires used

QoL was assessed using the Lithuanian version of the Pediatric Quality of Life Inventory (PedsQL) Asthma Module Short Form (SF 22) (16). Questionnaires were independently completed by both the children and their caregivers, in order to provide a comprehensive evaluation of the child's QoL. **The QoL score is presented as a total number which is comprised of a symptom scale and a treatment scale:** 11 questions assess sustained difficulties owing to disease symptoms (symptoms scale) and another 11 questions assess limitations experienced owing to disease treatment (treatment scale). Any difficulties experienced were scored from zero for never to four for almost always and later converted to a 100-point scale (11). Higher scores correspond to better QoL. Parents also completed a questionnaire that captured details of their child's asthma, environmental and social details (Supplement S1). Asthma control was evaluated using the Childhood Asthma Control Test, which was completed by the children and their parents.

Sample size

Of the 59,890 children aged 5-11 years living in the two major cities of Lithuania covered by this study, 4.28% had an asthma diagnosis (17), which was equivalent to 2,563 children. Previous studies indicated asthma related QoL scores were over 80 (18). We calculated that a sample size of 226 would represent the population with a confidence level of 95% and 5% precision (19).

Analysis

The statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corporation, New York, USA). Cronbach alpha reliability statistics were calculated for overall QoL and also for the symptoms and treatment scales for the self-reports and proxy-reports. Mann-Whitney and Kruskal-Wallis tests were used to study the association between QoL dichotomous and categorical variables, respectively. Spearman correlation was used to assess associations between QoL and continuous or ordinal variables. Variables significantly associated with QoL in the univariate analysis ($p < 0.05$) were used for the multivariate analysis. There is no clinical cut-off value for QoL scores (11) and since they were not normally distributed they were placed by rank into three groups, which each contained an equal number. In the multivariate analysis, children with QoL values in the highest third tercile, with a QoL score of more than 81.8%, were said to have good QoL and formed the reference group. Binary logistic regression was used to relate QoL to uncontrolled asthma with a Childhood Asthma Control Test score of less than 20 (20), the presence of asthma symptoms, hayfever and, or, eczema, exposure to pets and smoking, recent hospitalisation and overall poor health. Only statistically significant covariates were left in the final models and descriptive statistics of the models' R^2 value were also considered.

The study was approved by **Vilnius regional** ethical committee. **Parents signed the informed consent forms to participate in the study.**

RESULTS

Study participants

We invited 399 children to take part in the study and 301 (75%) participated: 45 children with asthma diagnosed by the family doctor, but not confirmed by paediatric pulmonologist, were excluded and the questionnaires were incomplete for 30 children. Therefore the results from 226

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children and their parents or caregivers were included to the final analysis. The mean age and standard deviation (SD) of the children was 8 (± 2) and 68% were boys.

The majority of the participants (65%) had mild asthma, almost one-third (31%) had moderate asthma and the remaining 4% had severe asthma. More than 10% of the respondents had been hospitalised for asthma in the preceding six months. The median Childhood Asthma Control Test score was 20, interquartile range (IQR) was 18–23. Three-quarters of children lived with both parents. Almost half of the fathers (46%) and 63% of the mothers had tertiary education. One-third of the families had monthly incomes of up to 300 Euros per person and 12% had at least 600 Euros per person. The number of families receiving social allowances as the main source of income was 14%. Further characteristics of the study population are presented in Table S1.

QoL levels and associated factors

The QoL of children with asthma was evaluated PedsQL Asthma Module. The median (IQR) total self-reported PedsQL score was 76 (66–86) and the mean total self-reported QoL score was 74. The median (IQR) total parent-reported QoL score was 73 (60–86) and the mean total score was 73. Both the children and their parents rated the treatment scale higher than the symptoms scale ($p < 0.001$): the mean self-reported scores were 68 and 81 respectively and the mean parent-reported scores were 66 and 80 (Table 1). There was acceptable internal consistency and reliability of the PedsQL scales, with a Cronbach alpha coefficient of >0.7 for all QoL scales.

Univariate associations between QoL and possible risk factors are shown in Table 2. Lower QoL was associated with more severe asthma, worse general health, experience of shortness of breath during the previous year, a lower Childhood Asthma Control Test score, and receiving social allowances as the main source of income. The QoL reported by parents was associated in univariate associations with the five factors associated with child-reported QoL and additionally with: hospitalisation due to asthma within the previous six months, perceived difficulties due to asthma, being exposed to pets at home and having eczema and hayfever ($p < 0.05$). There were no significant associations between self-reported or parent-reported QoL and gender, age, smoking exposure, family income or parents' education.

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In the multivariate analysis, the children's self-reported low QoL scores were associated with moderate and severe asthma, poor asthma control and shortness of breath during the previous year (Table 3) and the parental reports of reduced QoL were independently associated with these three factors, plus poor general health.

DISCUSSION

This study explored the QoL of children with asthma living in Lithuania, one of the Baltic States, where the prevalence of asthma has been reported to be lower and hospital admissions for asthma are higher than in Western countries. The main finding was that the QoL of 5–11-year-old Lithuanian children with asthma, and the factors associated with QoL, were comparable to studies in Western populations.

The results of our study were consistent with previous studies in Western populations where the same instrument was used (21-23). A study in the USA (21) reported mean symptom and treatment scale self-reported QoL scores of 68 and 80, which are comparable to the corresponding values of 68 and 81 in our study. A Greek study (22) reported mean self-reported symptom and treatment QoL scores of 70 and 88 for children with mild asthma and also parent-reported scores of 68 and 90, which were to the parental values of 66 and 80 in our study. Finally in a Portuguese study (23), self-reported symptom and treatment QoL scores were 67.4 and 85.4. Despite some differences in the characteristics of the populations studied and the different healthcare systems, our findings suggest that the QoL of children across Europe are very similar and determined by common factors. The similarity of the factors associated with the QoL scores suggests that the challenges faced by children with asthma across Europe are mostly consistent and a common pan-European approach to the management of childhood asthma would be valid.

We observed good agreement between child and parent reported QoL, which was consistent with a study in Greece (22). Children and parents indicated many common factors that were independently related to QoL, but the parents identified additional factors associated with QoL, suggesting a slightly different perspective. We also observed that children evaluated their QoL scores slightly higher than their parents. This has also been reported in children recruited in

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hospital clinics (24), but it is interesting to note that differences in child and parent reported QoL were less evident when they were recruited from community clinics. These findings suggest that while parents and children have a similar perspective of the children's QoL, perhaps the parent's perspective is more complex. Ultimately, however, the child's perspective takes precedence over the parent's perspective.

A minimal clinically important difference in the PedsQL score for asthma has not been specified, but one study stated that for the general PedsQL scale it was 4.4 for child and 4.5 for parent proxy-

reports (25). In our study the difference in the PedsQL scores for the child's overall health status, asthma control, asthma severity and respiratory symptoms by both the self-reports and by the proxy reports were at least 10 and we interpret this difference as being of clear clinical relevance

(Table 2). Among the factors identified by parents but not children as being associated with their child's QoL (Table 2), the magnitude of QoL reduction was less than 10 and perhaps of less certain clinical relevance and none were significantly related to QoL in the multivariate model (Table 3),

Our multivariate analysis identified relationships between low QoL scores with not-controlled, moderate and severe asthma, poor child's health condition and shortness of breath during the last year. These factors are recognised determinants of QoL in children with asthma in other populations (5,7,26). For example, studies in Brazilian (26) and Greek (5) children have reported an association between asthma control and QoL and this might reflect the fact that respiratory symptoms are common to both QoL and control questionnaires. A study conducted in Scotland (7) found, in the multivariate analyses, that QoL was associated with the severity of asthma, socioeconomic status, second-hand smoking exposure and allergic comorbidities. In the present study these associations were present in the univariate analysis, but only severity remained significant in the multivariate analysis (7). Importantly, the Scottish study did not include asthma control in the multivariate model and this probably explains the apparently different outcomes reported.

One of the strengths of our study was that it aimed to evaluate the QoL of children with asthma in one of the Baltic States, which are known to have a relatively low prevalence of asthma, but relatively high hospital admission rates (10). Our study population was typical for children with

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asthma in Lithuania in terms of gender and asthma severity distribution: twice as many boys than girls were diagnosed with asthma in Lithuania (27) and the prevalence of severe asthma was less than 3% (28). In our population, 14% of families received social allowances and the corresponding proportion for Lithuanian families was 8% according to the official national Government statistics for 2015. Another strength was the use of Lithuanian PedsQL Asthma Module SF 22 for the first time, which provided a possibility to explore QoL by self-reports and proxy-reports. Data were collected in the two largest regional centres in Lithuania where children with asthma from urban and rural areas come to consult a paediatric pulmonologist and, therefore, the results are likely to be generalizable across Lithuania. Finally, we excluded children from the analysis if their asthma status was uncertain and we only included those with a diagnosis confirmed by paediatric pulmonologist. Therefore, the diagnosis of asthma in our population was robust.

There are potential limitations which should be borne in mind when considering our results. First, our results may not necessarily be extrapolated to children outside the 5-11 year age range. Second, our study sample was relatively small and, although we have been able to show how our results are comparable with other reports, there is a need for further evaluation of QoL in children with asthma in Eastern European countries to confirm our results. Thirdly, some patients declined to participate and this might have introduced bias to our study population. Fourth, we cannot comment on any difference in QoL in children with and without asthma since we did not include control subjects. Finally, we did not have objective physiological measurements, such as spirometry, to compare to QoL in this study.

CONCLUSION

The QoL of children with asthma in Lithuania was comparable to QoL in other European countries. The rating from the children and parents were highly correlated, but the children rated their QoL better than their parents. The factors associated with QoL, such as asthma severity and poor control, were mostly similar to those in Western countries. Associations with socioeconomic factors, allergic comorbidities and exposure to smoking were seen in other populations, but not in

ours. Further understanding of QoL and its determinants will lead to patient-centred interventions than improve the QoL of children with asthma.

FUNDING

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

REFERENCES

1. Asher I, Pearce N. Global burden of asthma among children. *Int J Tuberc Lung Dis* 2014; 18: 1269-78.
2. Global Asthma Network. The Global Asthma Report 2014. Auckland, New Zealand: *Global Asthma Network*, 2014. Available from: URL: http://www.globalasthmareport.org/resources/Global_Asthma_Report_2014.pdf
3. Mussaffi H, Omer R, Prais D, Mei-Zahav M, Weiss-Kasirer T, Botzer Z, et al. Computerised paediatric asthma quality of life questionnaires in routine care. *Arch Dis Child* 2007; 92: 678-82.
4. Varni JW, Limbers CA, Burwinkle TM. Impaired health-related quality of life in children and adolescents with chronic conditions: a comparative analysis of 10 disease clusters and 33 disease categories/severities utilizing the PedsQL™ 4.0 Generic Core Scales. *Health Qual Life Outcomes* 2007; 5: 43.
5. Petsios KT, Priftis KN, Hatziaorou E, Tsanakas JN, Antonogeorgos G, Matziou VN. Determinants of quality of life in children with asthma. *Pediatr Pulmonol* 2013; 48: 1171-80.
6. Pawankar R, Canonica GW, Holgate ST, Lockey RL. White Book on Allergy. Milwaukee: *World Allergy Organization*, 2013.
7. Taminskiene V, Mukhopadhyay S, Palmer C, Mehta A, Ayres J, Valiulis, A, et al. Factors associated with quality of life in children with asthma living in Scotland. *Pediatr Pulmonol* 2016; 51: 484-90.
8. Bousquet J, Barbara C, Bateman E, Bel E, Bewick M, Chavannes N, et al. AIRWAYS-ICPs (European Innovation Partnership on Active and Healthy Ageing) from concept to implementation. *Eur Respir J* 2016; 47: 1028-33.
9. Ravens-Sieberer U, Herdman M, Devine, J Otto C, Bullinger M, Rose M, et al. The European KIDSCREEN approach to measure quality of life and well-being in children: development, current application, and future advances. *Qual Life Res* 2014; 23: 791-803.

10. Gibson GJ, Loddenkemper R, Lundback B, Sibille Y. Respiratory Health and Disease in Europe: the new European Lung White Book. *Eur Respir J* 2013; 42: 559-63.
11. Varni JW. Scaling and scoring of the Pediatric Quality of Life Inventory™PedsQL™. Lyon: *Mapi Research Trust*, 2014.
12. Jardine J, Glinianaia SV, McConachie H, Embleton ND, Rankin J. Self-reported quality of life of young children with conditions from early infancy: a systematic review. *Pediatrics* 2014; 134: e1129-48.
13. Orrell-Valente JK, Jarlsberg LG, Hill LG, Cabana MD. At what age do children start taking daily asthma medicines on their own? *Pediatrics* 2008; 122: e1186-92.
14. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2011. Available from: URL: <http://www.ginasthma.org>
15. Vaideliene L, Vaitkaitiene E, Kudzyte J, Valiulis A. Vaikų bronchų astmos diagnostikos ir gydymo protokolas. Vilnius: *Lietuvos Respublikos sveikatos apsaugos ministerija*, 2015/ Protocol of diagnostic and treatment of bronchial asthma in children. Vilnius: Lithuanian Ministry of Health, 2015. Available from: URL: <http://sam.lrv.lt/diagnostikos-gydymo-metodikos-ir-rekomendacijos/diagnostikos-ir-gydymo-protokolai>
16. Chan KS, Mangione-Smith R, Burwinkle TM, Rosen M, Varni, JW. The PedsQL™: Reliability and validity of the short-form generic core scales and asthma module. *Med Care* 2005; 43: 256-65.
17. Health information centre of Hygiene Institute. Social Insurance Fund Board data. Available from: URL: http://sic.hi.lt/php/serg15.php?dat_file=serg15.txt.
18. Feng L, Zhang Y, Chen R, Hao Y. The Chinese version of the Pediatric Quality of Life Inventory™(PedsQL™) 3.0 Asthma Module: reliability and validity. *Health Qual Life Outcomes* 2011; 9: 64.
19. Naing L, Winn T, Rusli BN. Practical issues in calculating the sample size for prevalence studies. *Arch Orolfac Sci* 2006; 1: 9-14.

20. Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA, *et al.* Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol* 2006; 117: 549-56.
21. Thissen D, Varni JW, Stucky BD, Liu Y, Irwin DE, DeWalt DA. Using the PedsQL™ 3.0 asthma module to obtain scores comparable with those of the PROMIS pediatric asthma impact scale (PAIS). *Qual Life Res* 2011; 20: 1497-505.
22. Kalyva E, Eiser C, Papathanasiou A. Health-Related Quality of Life of Children with Asthma: Self and Parental Perceptions. *Int J Behav Med* 2016; 23: 730-7.
23. Lima L, Lemos MS. The usefulness of a condition-specific measure (child-report) for the evaluation of the adaptation of children with asthma. *Child Health Care* 2016; 1-16.
24. Lin CY, Su CT, Wang JD, Ma HI. Self-rated and parent-rated quality of life (QoL) for community-based obese and overweight children. *Acta Paediatrica* 2013, 102: e114-9.
25. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL™* 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr* 2003; 3: 329-41.
26. Pereira ED, Cavalcante AG, Pereira EN, Lucas P, Holanda MA. Asthma control and quality of life in patients with moderate or severe asthma. *J Bras Pneumol* 2011; 37: 705-11.
27. Kudzyte J, Griska E, Bojarskas J. Time trends in the prevalence of asthma and allergy among 6–7-year-old children. Results from ISAAC phase I and III studies in Kaunas, Lithuania. *Medicina (Kaunas)* 2008; 44: 944-52.
28. Lai C, Beasley R, Crane J, Foliaki S, Shah J, Weiland S. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2009; 64: 476-83.