Study of Kazakhstan inpatient childhood asthma: assessment of prevalence and factors influencing treatment adherence

Badanie dotyczące astmy dziecięcej wymagającej leczenia szpitalnego w Kazachstanie: ocena rozpowszechnienia i czynników wpływających na przestrzeganie zaleceń terapeutycznych

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Summary

Background: Up to date, the assessment of adherence to the treatment of children with asthma in Kazakhstan has not been carried out yet.

Objective: The study aimed to evaluate the level of therapeutic adherence of paediatric patients with asthma in urban and rural areas of Kazakhstan. In addition, the validity and reliability of a structured scale for assessing adherence in patients with asthma was also scrutinized.

Methods: A prospective study of verified cases of bronchial asthma of 518 children in the dispensary control in the Children's City Clinical Hospital N2 (Almaty, Kazakhstan) was conducted in the period from 2018 to 2020. Children with asthma were sub-divided into 2 groups: urban and rural residents. The demographic and clinical characteristics, external and social factors of the patients were analysed. Patient adherence to treatment was assessed using the Lebanese Medication Adherence Scale-14(LMAS-14). The reliability was tested using the measure of internal consistency (Cronbach's alpha). Data were collected after the discharge from the hospital (T1) and after 6 months (T2).

Results: Urban and rural patients made up 81.3% vs. 18.7% respectively. Children aged 5-12 years accounted for 70.6%. Male gender was predominant in all groups (p=0.73). Better financial situation, education were noted by 90.5% and 95.5% of urban parents (p=0.001). The influence of external factors (dampness, coal heating and possession of pets) was higher in rural areas (p=0.001).The results of study based on the LMAS-14 questionnaire (T1 period) showed no significant differences. However, in the T2 period, the adherence of urban children was higher than rural ones (p=0.001). The Cronbach's α was 0.606 for the total score. According to the results of a survey after 18 months, a significant relationship was found between the levels of adherence and the frequency of asthma attacks (p=0.001).

Conclusion: In 2018-2020, a low therapeutic adherence of children with asthma, especially in a rural area, was detected in the territory of the Republic of Kazakhstan. Our findings indicate the necessity to develop effective measures to regulate and increase adherence to treatment of patients, especially those living in rural areas.

Keywords: *Asthma, Children; Risk factors, Epidemiology, Adherence*

Streszczenie

Wprowadzenie: Do tej pory nie przeprowadzono jeszcze oceny przestrzegania zaleceń terapeutycznych dzieci z astmą w Kazachstanie.

Cel pracy: adanie miało na celu ocenę poziomu przestrzegania zaleceń terapeutycznych przez pacjentów pediatrycznych z astmą na obszarach miejskich i wiejskich Kazachstanu. Ponadto przeanalizowano również trafność i rzetelność ustrukturyzowanej skali do oceny przestrzegania zaleceń przez pacjentów z astmą.

Materiał i metody: Przeprowadzono prospektywne badanie zweryfikowanych przypadków astmy oskrzelowej u 518 dzieci w przychodni kontrolnej Dziecięcego Miejskiego Szpitala Klinicznego N2 (Ałmaty, Kazachstan) w okresie od 2018 do 2020 roku. Dzieci z astmą podzielono na 2 grupy : mieszkańcy miast i wsi. Analizie poddano charakterystykę demograficzną, kliniczną, czynniki zewnętrzne i społeczne pacjentów. Przestrzeganie przez pacjentów leczenia zostało ocenione za pomocą libańskiej skali przylegania leków 14 (LMAS-14). Rzetelność testowano za pomocą miary spójności wewnętrznej (alfa Cronbacha). Dane zebrano po wypisaniu ze szpitala (T1) i po 6 miesiącach (T2).

Wyniki: Pacjenci z miast i wsi stanowili odpowiednio 81,3% vs 18,7%. Dzieci w wieku 5-12 lat stanowiły 70,6%. We wszystkich grupach dominowała płeć męska (p=0,73). Lepszą sytuację materialną, wykształcenie odnotowało 90,5% i 95,5% miejskich rodziców (p=0,001). Wpływ czynników zewnętrznych (wilgotność, ogrzewanie węglowe i posiadanie zwierząt domowych) był większy na terenach wiejskich (p=0,001). Wyniki badań kwestionariusza LMAS-14 (okres T1) nie wykazały istotnych różnic. Jednak w okresie T2 adhezja dzieci miejskich była wyższa niż wiejskich (p=0,001). α Cronbacha dla wyniku całkowitego wyniosło 0,606. Zgodnie z wynikami ankiety przeprowadzonej po 18 miesiącach stwierdzono istotną zależność między poziomem przestrzegania zaleceń a częstością ataków astmy (p=0,001).

Wnioski: W latach 2018-2020 na terenie Republiki Kazachstanu wykryto niski poziom przylegania terapeutycznego dzieci z astmą, zwłaszcza na terenach wiejskich. Nasze wyniki wskazują na konieczność opracowania skutecznych środków regulacji i zwiększenia przestrzegania leczenia pacjentów, zwłaszcza mieszkających na terenach wiejskich.

Słowa kluczowe: *Astma, Dzieci; Czynniki ryzyka, epidemiologia, przestrzeganie zaleceń*

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Introduction:

Asthma is one of the most frequently detected pathologies of childhood that can lead to the problems with the respiratory system [1-5], including the development of chronic obstructive pulmonary disease [6]. The recent increase in cases of bronchial asthma has been associated with the growth of industrialization and environmental pollution [7-9].

There are various external factors that can potentially trigger the development of asthma [3, 10, 11]. It encompasses demographic, environmental, social, racial, behavioural and lifestyle issues [12]. All factors can be categorized into two groups: allergic and non-allergic ones [13]. However, all risk factors cannot be considered separately due to the presence of additional circumstances such as the availability and quality of medical care, adherence to treatment, economical situation, and territorial differences in places of residence [14].

According to the results of some studies, the prevalence of asthma is higher among children living in an urban area in contrast to rural residents [15]. Despite the lower registration of cases of asthma among children in rural areas, the irregularity of check-ups, the severity of the disease and the incidence of life-threatening complications in the countryside are much higher compared to the urban population [16].

Therefore, there is a need in improving and optimization of adherence to treatment, including inhalation techniques and self-control training [17]. In medical practice, poor adherence of paediatric patients diagnosed with asthma remains a serious problem. According to some reports, the level of adherence to treatment is about 50 % only [18]. This fact may be explained by the complex treatment regimens and a number of various medications, which often need to be used at different times during the day [19].

Hence, monitoring the treatment process in children of different ages, depending on the place of residence is highly critical. Moreover, the monitoring can help to determine the level of adherence to the treatment of these groups of patients.

According to the official statistical data (2019), 58.2 % of people were urban residents and 41.8 % live in rural areas of Kazakhstan [20]. The results of an earlier study conducted in Kazakhstan showed a high prevalence of bronchial asthma in the adult population [21]. However, in Kazakhstan, asthma among children in rural and urban environments has not been studied yet. The purpose of this study was to evaluate the level of therapeutic adherence in paediatric patients with asthma in urban and rural areas of Kazakhstan.

Methods:

Ethical Issues:

The study was approved by the Ethics Committee of S.D. Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan (protocol of the Local Ethics Committee No.45/89 dated by January 5, 2017).

Data collection:

We carried out a prospective study of verified cases of bronchial asthma of 518 children in the dispensary control in the Children's City Clinical Hospital N2 (Almaty, Kazakhstan) was conducted in the period from 2018 to 2020. Participation of children in the study was possible only upon obtaining informed written consent from parents or guardians.

Children's City Clinical Hospital N2 is a medical institution that provides specialized-planned, emergency-planned and hospital-replacing emergency care for the children's population of Almaty and other regions of Kazakhstan. In this regard, the results of analysis of cases of morbidity in children with asthma who have undergone treatment in this medical institution can be generally extrapolated for all Kazakhstan' regions.

Inclusion criteria were as follows: the presence of a signed informed consent for participation in the study of a child from a parent / guardian; the presence of a verified diagnosis of asthma; and age up to 18 years.

For the purpose of comparative analysis of morbidity in children with asthma, the patients were divided into 2 study groups: city residents and rural residents, depending on the place of residence. The clinical and demographic characteristics of the participants were studied in both groups.

In addition, demographic indicators such as age and gender were also evaluated. According to the WHO classification by age, children were divided into 4 age groups: neonates and infants (<1 y), young children (1 – 4 y), older children (5 – 12 y) and adolescents (13 – 18 y) [22].

In fact, about 130 different nationalities live in the territory of Kazakhstan, where Kazakhs and Russians are prevailing parts of the population [23]. In our study, the patients were divided by ethnicity into 4 groups: Kazakhs, Russians, Uighurs and others. This division was due to the fact that among children with bronchial asthma (in addition to Kazakhs and Russians) a sufficient number of Uighurs was identified, and other ethnic groups constituted a small proportion.

The presence of concomitant diseases such as cardiovascular disease, arterial hypertension, diabetes mellitus, obesity, anaemia, congenital defects, chronic liver, kidney and nervous system diseases were determined. Asthma was classified among children in three types (in terms of severity): mild, moderate and severe [24]. According to GINA classification, the severity of asthma was determined by the volume of therapy [25]. Mild asthma consisted of next indicators: symptoms more than once a week but less than once a day, exacerbations may affect activity and sleep, nocturnal symptoms more than twice a month, forced

expiratory volume in one second ($FEV_{1)}$ or peak expiratory flow (PEF) ≥80% predicted; and PEF or FEV_1 variability <20–30%; Moderate asthma was determined with followed characteristics: symptoms daily, exacerbations may affect activity and sleep, nocturnal symptoms more than once a week, daily use of inhaled short-acting β2-agonist, FEV_1 or PEF 60–80% predicted, and PEF or FEV_1 variability >30%; Severe asthma was described as: symptoms daily, frequent exacerbations, frequent nocturnal asthma symptoms, limitation of physical activities, FEV_1 or PEF ≤60% predicted, PEF or FEV_1 variability >30%;

The information from patients' medical history was used to determine the premature birth or full-term birth, and the predisposition for the development of asthma. Hereditary factors included the history of asthma cases among first-line relatives as well as the presence of other allergic diseases (atopic dermatitis or allergic rhinitis) among relatives. Non-hereditary factors encompassed the presence of any allergic disorders, passive smoking, air contamination at the place of living or outside, presence of pets in the house [26]. A history of allergic disorders and allergic sensitization symptoms such as allergic disease, food allergy, pruritus / lacrimation, sneezing / runny nose, recurrent itchy rash, and fever was also studied.

The socio-ecological characteristics of children's families were studied (based on the place of residence). The survey method determined the level of the family's financial situation and the education of the parents. In addition, the indicators of living conditions such as dampness in the house, heating capacity (coal / gas / central or stove heating), and the presence of pets in the house (dogs / cats) were also studied.

The assessment of therapeutic adherence in children with asthma was carried out using an indirect method: the Lebanese Medication Adherence Scale-14 (LMAS-14) [27]. The purpose of this validated questionnaire is to determine the frequency of non-adherence to prescribed drugs adherence to treatment in chronic diseases. LMAS contained 14 Likert scale questions with four options to answer each (coded from zero (less adherence) to three (higher adherence)) [27]. Patient's score may range from 0 (lowest adherence) to 42 (highest adherence) [28]. Patients who scored 38-42 points were considered highly adherent, while the patients scored 35-37 points as moderately adherent, and less than 35 points as poorly adhered. Questions from the LMAS-14 questionnaire are presented in Table 1.

To determine the internal consistency, Cronbach's alpha coefficient was calculated [29]. Cronbach's alpha was rated at T1 and T2. Values above 0.6 were considered as satisfactory. In our study, a Cronbach's alpha value below 0.5 was considered unacceptable [29].

The results of the Reliability test are presented in Table 2. The reliability of individual questions was almost similar in all the subgroups. The Cronbach's α was 0.606 for the total score.

The data were collected using electronic questionnaires ('SurveyMonkey') filled out by participants (a parent / guardian). Information was taken after the discharge from the hospital (within 6-12 days) (T1), and after 6 months

Table 1. Lebanese Medication Adherence Scale-14 (LMAS-14).

№	Question	Points
1	Do you forget to give your child medications when you are busy (intensive work or traveling)?	0-3
2	Do you forget to give your child medication if you are invited to lunch or dinner?	0-3
3	Do you forget to give your child medication?	0-3
4	Do you get late when it comes to buying medicine packs when they become empty?	0-3
5	Do you stop giving your child medications if they forbid the child to eat certain foods because of the possible interaction of food with medications?	0-3
6	Will you stop giving your child medications without consulting a doctor if your neighbour/relative has been taking a drug like yours for a long time and it has caused side effects?	0-3
7	Do you stop giving your child medications without consulting a doctor if laboratory tests show improvement during treatment?	0-3
8	Do you stop giving your child medications without consulting a doctor if the child does not get better during treatment?	0-3
9	Do you stop giving medications without consulting a doctor if the child feels better during treatment?	0-3
10	Do you decide to stop giving certain medications without consulting a doctor if you notice that your child is taking too many medications every day?	0-3
11	Do you stop giving your child medication if you get bored with it?	0-3
12	Do you stop giving medications to your child if he has side effects?	0-3
13	Do you stop giving your child medications if your insurance doesn't cover them?	0-3
14	Will you stop buying packages of medicines if you think they are expensive?	0-3

Table 2. Reliability test.

Items	Cronbach's α
Question 1	0,542
Question 2	0,618
Question 3	0,544
Question 4	0,609
Question 5	0,547
Question 6	0,598
Question 7	0,617
Question 8	0,634
Question 9	0,593
Question 10	0,603
Question 11	0,784
Question 12	0,674
Question 13	0,543
Question 14	0,589

Alpha reliability = 0.606

(T2) after the hospital discharge. In some cases, patients were called by phone or sent a reminder by email.

Flow chart of study participants is presented in Figure 1. Among all children discharged from the inpatient hospital (n = 565), n = 47 (8.3 %) patients were not included in the study due to the several reasons: diagnosis was not verified (n = 19; 40.4 %), patients rejected to participate before beginning of the study (n = 13; 27.7 %), other reasons (n = 15; 31.9 %). In total, the data from 127 (30.2 %) urban patients and 41 (7.7 %) rural patients were not included in the LMAS-14 adherence assessment. The exclusion of patients from the survey was associated with refusal to continue participating in the survey n = 44 (42.3 %), filling out an electronic questionnaire only in one period T1 or T2 n = 77 (45.8 %), moving and changing address / contact information n = 17 (10.1%) and other reasons n = 30 (17.9%). Thus, the study analysed the adherence of n = 294 children living in the urban and n = 56 children in the rural areas.

To study the relationship between the level of adherence according and the frequency of asthma attacks since the start of treatment, n = 294 patients living in the city and n-56 patients living in the city were called to obtain

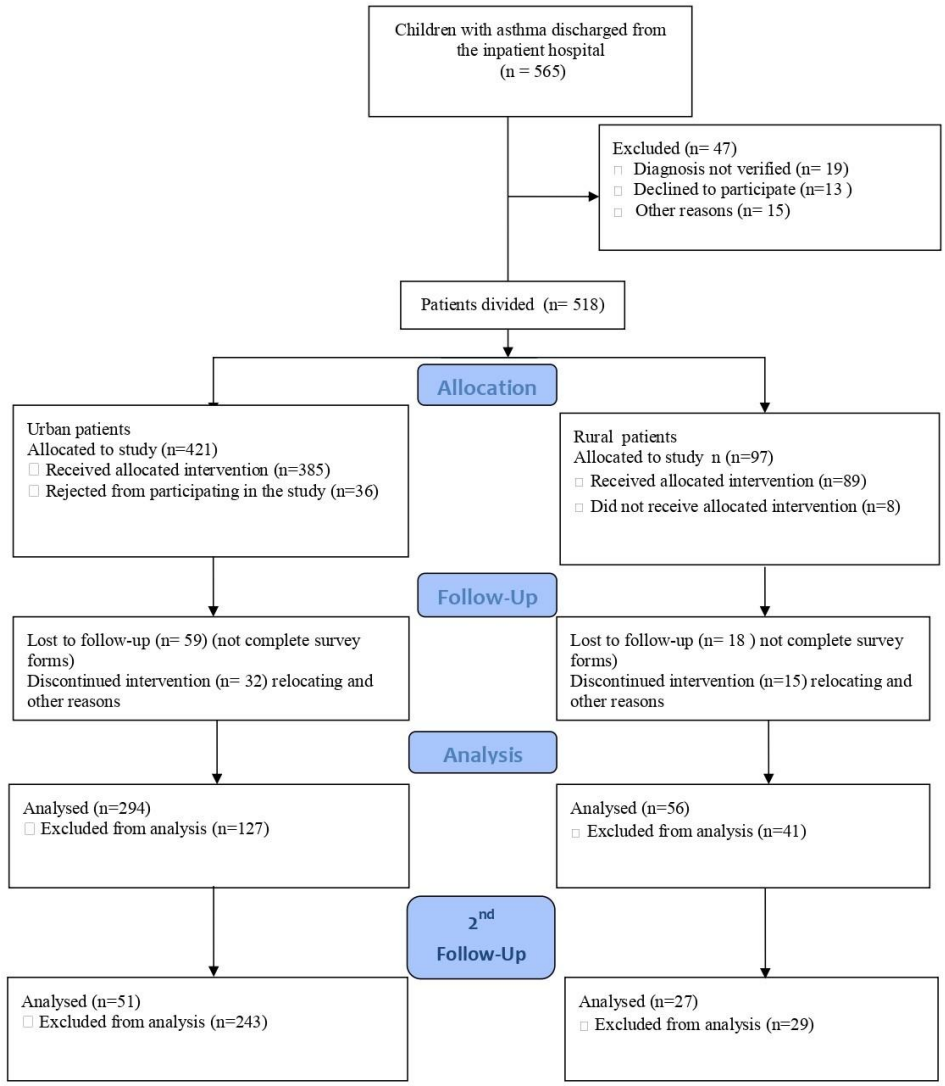

Figure 1. Flow chart of study participants.

information on the frequency of asthma attacks (after 18 months). There were n = 51 urban and n = 27 rural residents who answered the call, and the children's data on the frequency of asthma attacks were included in the analysis.

Statistical analysis:

All statistical calculations were performed using SPSS software (version 25.0, IBM SPSS Inc., Chicago, USA). A *p*-value < 0.05 was considered statistically significant. All data were summarized using descriptive statistics methods. The Chi-square test was employed to compare categorical indicators, and the relationship between risk factors and places of residence was assessed using the odds ratio. Corresponding confidence intervals of 95 % (95 % CI) were also calculated.

Results:

Demographic and clinical characteristics of 518 children included in the study are presented in Table 3. By place of residence, the urban patients were n = 421 (81.3 %) and the residents of the rural place n = 97 (18.7%). The average age of children with a confirmed diagnosis of asthma in urban and rural areas was 8 (5-11) and 7 (5-10) years, respectively ($p = 0.16$).

The largest cohort of residents in the urban and in the rural area was children aged 5-12 years (70.6 %), and the smallest one was the children with asthma aged up to 1 year 2.1 % (n = 11).

In terms of gender, males prevailed in the two groups (62.3 %), while 37.7 % were female (OR 1.08, 95 % CI 0.68-1.70, $p = 0.73$).

By nationality, Kazakhs made up 71.0 % of the total number (n = 368), among whom the inhabitants of the urban and rural areas were n = 313 (74.3 %) and n = 55 (56.2 %), respectively. Uyghurs made up 14.1 % in total, and Russians and other nationalities 9.6 % and 5.3 %, respectively. The groups differences were considered statistically significant ($p = 0.001$).

There was no statistically significant difference between the children of the urban and rural places in the presence of concomitant diseases ($p > 0.05$). However, in comparison with the rural dwellers, all concomitant diseases were prevalent in children living in the city. It encompasses cardiovascular pathology (n = 23 / 5.4 %) (OR 5.54, 95% CI 0.74-41.5, $p = 0.63$), hypertension and chronic liver disease (n = 16 / 3.8%) (OR 3.79, 95% CI 0.49-28.9, $p = 0.21$) and obesity (n = 18 / 4.3 %) (OR 1.40, 95% CI 0.40-4.84, $p = 0.77$).

According to the severity of asthma, a moderate type was determined in urban residents (n = 282 / 67.0 %), and 56.7 % (n = 55) of rural children. A severe type of this disease was recorded in almost ¼ (n = 132) of all cases of asthma with some predominance in rural residents (31.9 %) in comparison with urban residents (24.0 %). However, no statistically significant difference was detected ($p = 0.14$).

According to birth history infromation, in the two groups, 85.1 % (n = 441) children were full-term infants (OR 1.15, 95% CI 0.61-2.22) ($p = 0.75$). As for the hereditary factor, 54.6 % (n = 230) of urban residents and 44.3 % (n = 43) of children living in the rural area had a hereditary burden of asthma in the first line of relatives. Nevertheless, no statistically significant significance was detected (OR 0.66, 95% CI 0.42-1.03) ($p = 0.18$).

The analysis of medical history of children with asthma (Table 3) showed that allergic disease (on average) affected 16.4 % (n = 85) patients, with a slight dominance among children living in the city (OR 1.20, 95% CI 0.64-2.23, $p = 0.56$). In general, food allergy prevailed in all groups n = 79 (15.2 %), but without a statistically significant difference between rural and urban residents (OR 1.08, 95% CI 0.57-2.02, p = 0.80).

No significant differences were found out for allergic symptoms, such as pruritus / watery eyes (OR 1.05, 95% CI 0.55-2.00, $p = 0.87$), sneezing / runny nose (OR 0.90, 95% CI 0.49-1.68, $p = 0.76$), recurrent itchy rash (OR 0.89, 95% CI 0.48-1.64, $p = 0.71$) and fever (OR 0.96, 95% CI 0.51-1.81, $p = 0.91$).

According to the results of social characteristics presented in Table 4, in comparison with children with asthma living in rural areas n = 17 (17.5%), families of children living in the city n=381 (90.5%) had a relatively good financial situation, with a statistically significant difference (OR 0.022, 95% CI 0.012-0.04)($p = 0.001$). Also in terms of education, the parents of urban children in 95.5 % were better educated, while this indicator in the rural dwellers was just 12.4 % (n = 12) (OR 0.007, 95% CI 0.003-0.014, $p = 0.001$).

The dampness in the house was detected in 86.6 % (n = 84) in the rural place, and in the urban area this unfavourable factor was accounted only 4.3 % (n = 18) (OR 0.003, 95% CI 0.003-0.015, $p = 0.001$). The rural residents predominantly used coal heating (n = 91 or 94.0 %), whilst the urban residents did not use at all (OR 0.014, 95% CI 0.006-0.031, $p = 0.001$).

The presence of pets in dwellings was confirmed by 98.9 % (n = 96) of families with children with asthma living in the rural regions, and only 4.0% (n = 17) of urban residents kept pets at home (OR 2281.41, 95% CI 299.92-17353.97, $p = 0.001$).

The smoking of one of the parents was noted by 13.4% of rural residents and 9.0% of urban residents, which was regarded as a statistically insignificant difference (OR 1.56, 95% CI 0.79-3.05) ($p = 0.19$).

Mann-Whitney test was utilized for the assessment of adherence to therapy according to the medication adherence scale (Table 5). At the time of discharge from the city hospital (T1), the adherence indicator was 40.1 ± 1.9 (95 % CI 39.12-41.32). It was higher compared to the results of adherence of children with asthma in the rural place 38.9 ± 1.3 (95 % CI 38.64-40.49). However, there was no statistically significant difference ($p = 0.06$). After a period of 6 months (T2), the level of therapeutic adherence of children in rural areas was reduced to 33.3 ± 1.7 (95 % CI 30.41-38.59), in comparison with adherence of children living in the urban area 38.1 ± 2.6 (95 % CI 36.4-40.32) with a statistically significant difference ($p = 0.001$). As for intragroup comparison result regarding Wilcoxon test in the results of adherence of children with asthma compared to group of children living in the city ($p \leq 0.052$) in the rural place was observed a statistically significant difference ($p \leq 0.041$).

Table 3.Clinical and demographic characteristics of children with asthma living in urban and rural place.

Characteristics	Place of residence		Total	*p*
	Urban n(%)	Rural n(%)	518	
	421(81.3)	97(18.7)		
Age groups				
neonates & infants (<1)	9 (2.2)	2 (2.1)	11(2.1)	
young children (1-4)	78 (18.5)	21 (21.6)	99 (19.1)	0.63
older children (5-12)	297 (70.5)	69 (71.1)	366 (70.6)	
adolescents (13-18)	37 (8.8)	5 (5.2)	42 (8.1)	
Age*	7.7±3.4	7.2±3.3	7.6±3.4	0.16
Gender				
Male	264 (62.7)	59(60.8)	323 (62.3)	0.73
Female	157 (37.3)	38(39.2)	195 (37.7)	
Nationality				
Kazakhs	313 (74.3)	55 (56.7)	368 (71.0)	
Russians	48 (11.4)	2 (2.1)	50 (9.6)	0.001
Uighurs	38 (9.0)	35 (36.1)	73 (14.1)	
Others	22 (5.3)	5 (5.1)	27 (5.3)	
Co-morbidities				
Cardiovascular disease	23 (5.4)	1(1.0)	24 (4.6)	0.63
Hypertension	16 (3.8)	1(1.0)	17 (3.3)	0.21
Diabetes	7 (1.7)	2 (2.1)	9 (1.7)	0.67
Obesity	18 (4.3)	3 (3.1)	21 (4.0)	0.77
Chronic kidney disease	15 (3.6)	4 (4.1)	19 (3.7)	0.76
Chronic liver disease	16 (3.8)	1(1.0)	17 (3.3)	0.21
Chronic neurological disease	10 (2.4)	0 (0)	10 (1.9)	0.22
Anemia	14 (3.3)	4 (4.1)	18 (3.5)	0.75
Congenital malformation	10 (2.4)	1 (1.0)	11 (2.1)	0.69
Level of severity				
Mild	38 (9.0)	11 (11.4)	49 (9.4)	
Moderate	282 (67.0)	55 (56.7)	337 (65.1)	0.14
Severe	101 (24.0)	31 (31.9)	132 (25.5)	
Full-term or premature infants (birth history)				
Full-term	357 (84.8)	84 (86.6)	441 (85.1)	0.75
Premature	64 (15.2)	13 (13.4)	77 (14.9)	
Heredity anamnesis				
Hereditary	230(54.6)	43 (44.3)	273 (52.7)	0.18
Not hereditary	191(45.4)	54 55.7)	245(47.3)	
Allergic disorders previously diagnosed by a doctor				
Allergic disease	71 (16.9)	14 (14.4)	85 (16.4)	0.56
Food reaction	65 (15.4)	14 (14.4)	79 (15.2)	0.80
Itching / watery eyes	59 (14.0)	13 (13.4)	72 (13.9)	0.87
Sneezing / runny nose	60 (14.3)	15 (15.4)	75 (14.5)	0.76
Recurrent itchy rash	59 (14.0)	15 (15.4)	74 (14.3)	0.71

*The data are represented as M±SD

Table 4. Characteristics of social and environmental factors of children with asthma living in urban and rural place.

Socio-ecological characteristics (n %)	Place of residence, n (%)		Total, n (%)	p value *
	Urban 421 (81,3)	Rural 97 (18,7)	518 (100)	
Good financial situation of the family	381 (90.5)	17 (17.5)	398 (76.8)	0.001
Above high school (both parents)	402 (95.5)	12 (12.4)	414 (79.9)	0.001
Dampness in the house	18 (4.3)	84 (86.6)	102 (19.7)	0.001
Coal heating	0 (0)	91 (94.0)	91 (17.6)	0.001
Pets (dog / cat) at home	17 (4.0)	96 (98.9)	113 (21.8)	0.001
Exposure to tobacco smoke at home	38 (9.0)	13 (13.4)	51 (9.8)	0.19

Table 5. Mean and standard deviation of the assessment of adherence to treatment in the urban/ rural groups.

Medication adherence	Group		Results of the intergroup test
	City	Rural	
Period T1			
Mean ± SD	40.1±1.9	38.9±1,3	p=0.06 (a)
CI = %95	39.12, 41.32	38.64, 40.49	
Period T2			
	38.1±2.6	33.3±1.7	
Mean ± SD			p =0.001 (a)
CI = %95	36.4, 40.32	30.41, 38.59	
Intragroup comparison result	p ≤0.052 (b)	p ≤0.041 (b)	
a- Mann–Whitney U test, b-Wilcoxon test.			

Table 6. Indicators of the frequency of asthma attacks in participants with different levels of adherence after 18 months.

Question	Low adherers (N)		Medium adherers (N)		High adherers (N)		P
	Urban (13)	Rural (9)	Urban (23)	Rural (10)	Urban (15)	Rural (8)	
How many times have you experienced asthma attacks since the start of the study?	0,84±1,67	1,2±1,64	0,43±0,78	0,5±0,7	0,21±0,71	0,26±0,59	0,001
P	0.608		0.823		0.622		

The incidence rate of asthma attacks in children with different levels of adherence after 18 months are presented in Table 6. Among 'low adherers' who completed the survey, the incidence of asthma attacks was higher in the group of patients living in the countryside (1.2 ± 1.64) compared to patients from the city. (0.84 ± 1.67). However, there was no statistically significant difference (p = 0.608). In addition, in 'medium adherers', asthma attacks were more often recorded in rural patients (0.5 ± 0.7) in comparison with patients living in the city (0.43 ± 0.78). Nonetheless, no statistically significant difference was detected (p = 0.608). In 'high adherers', the frequency of asthma attacks in patients living in the village was 0.26 ± 0.59, and in patients living in the city this indicator was lower (0.21 ± 0.71). According to the obtained data, 'high adherers' in comparison with 'Low adherers' showed a statistically significant decrease in the incidence of asthma ($p \leq 0.001$). Moreover, the chi-square test showed a significant relationship between the three categories of adherence in patients (urban and rural patients) and the incidence of asthma attacks ($\chi 2=7.279$, p=0.001).

Discussion:

To the best of our knowledge, this is the first study conducted in Kazakhstan to determine adherence to treatment of children diagnosed with asthma. The data obtained after a 6-month observation period showed a lower adherence of paediatric patients living in rural areas.

The number of children with a confirmed diagnosis of asthma who were urban residents amounted to almost ¾ (81.3 %) of all registered patients (during the study period). This finding can be explained by few factors, including the air pollution of urban areas and increased level of allergic disorders [30]. On the other hand, it can be associated with the better accessibility of healthcare for the urban population, in contrast to rural areas [31, 32]. Apart from that, it is also necessary to take into account the lack of medical specialists and diagnostic equipment in rural areas that can affect the frequency of patients' referral and prevention of the development of unwanted complications [33].

In our study, the average age of children with asthma varied on average from 5 to 10 years. Some previously published reports showed the vulnerability of children in the age range of 5-9 years with a high prevalence of asthma (2.65 %). It was assumed that in this age range children due to the weak and not fully formed immune systems are more likely to develop respiratory tract infections and asthma [34].

The number of males prevailed among the urban and rural residents (62.3 %). Our findings confirm the results of previous studies, where this fact may be partially explained by gender differences in genetic susceptibility and hormonal status [35]. In regard to ethnicity, representatives of the Kazakh nationality dominated among other nationalities.

No statistically significant relationship between the development of asthma and concomitant diseases was determined (in our study). Nonetheless, the results of other studies showed that this relationship may exist, for example, with the incidence of type 1 diabetes [36], and obesity [37].

According to our data, in the overwhelming majority of cases, patients were admitted in a moderate or severe condition during the initial visit to a medical institution. Therefore, such a circumstance may explain the late diagnosis or low adherence to treatment.

Many studies indicate that the presence of perinatal events, including premature birth due to incomplete maturation of the foetal lungs at the time of birth [38], may be a trigger for the development of asthma [39, 40]. According to our findings, premature babies were found slightly less than 1/5 of all diagnosed cases of asthma.

It has been previously shown that the heredity is one of the risk factors affecting the development of asthma [41], in particular the burden of the history on the paternal side [42]. In our study, the hereditary factor in the development of asthma showed a fairly high proportion, since the family predisposition to this disease was 54.6 % in children living in the urban and in 44.3% of rural residents, respectively (although there was no statistical significance).

It is known that the presence of allergic diseases in the anamnesis can potentiate the development of cases of asthma morbidity [43, 44]. According to results acquired, among the total number of cases in both urban and rural areas, 14-16 % of children were diagnosed with any type of allergic diseases.

Socio-economic factors also play a significant role in the development of asthma [45]. The results of previously published studies indicate that the proportion of children suffering from asthma and belonging to families with a good financial situation is much lower than among financially disadvantaged segments of the population [46]. Moreover, according to some studies, the unfavourable material economic environment of parents in their childhood can lead to worse outcomes of the course of asthma in their children [47]. These findings require further research to clarify the causal relationship. In our study, in comparison with rural residents, urban residents had a better financial situation and the accessibility of appropriate education. Therefore, there is a need to reduce the modifiable risk factors (such as economics) that can lead to the development of asthma, in particular in children [48].

In addition, our results showed that household factors such as dampness in the house and the use of stove heating prevailed in rural areas. The data from available literature demonstrate that the presence of mould and dampness in living quarters can adversely affect the health of residents, with an increase in the chances of developing asthma, shortness of breath and allergic rhinitis [49, 50]. Besides, the level of allergisation due to keeping animals in the house was high amongst villagers.

It must also be noted that the hypothesis about the influence of tobacco smoke as a risk factor was not confirmed in our study. However, the results of some studies indicate that smoking of at least one parent in the house or second-hand smoke increases the chances of developing asthma in children [51, 52].

Given the current situation with the COVID-19 pandemic, it can also negatively affect the process of providing medical care to patients with chronic diseases, including children with asthma [53]. Therefore, it is necessary to develop measures to increase adherence to treatment of patients, especially those living in rural areas. It is also critical for paediatric practice, where a low adherence of patients remains one of the biggest problems in the treatment process of severe asthma [54].

According to previous studies, non- adherence among paediatric patients increases the threat to health on average from 33% to as much as 71% [55]. In this regard, identifying individual and family reasons for low commitment is crucial [56].

The disappointing results on adherence of paediatric patients in the Republic of Kazakhstan, especially in the rural places could be explained by a relatively low level of quality of life of the rural place dwellers. Children with asthma living in rural areas may face additional barriers to health care, such as the lack of local health care providers [57]. In addition, it encompasses difficult socio-economic and living conditions, which might play the role of risk factors for the development of asthma in children in this area. According to previously conducted research, the majority of asthma deaths occur in children from socially and economically disadvantaged families, which should be prevented by improving family education [58], monitoring compliance with medication rules and improving communication between medical professionals and families. In this regard, it is necessary to take measures at the government level to regulate the social and medical sphere, aimed at increasing adherence to treatment of patients, especially those

living in rural areas. To date, the creation of an effectively implemented asthma control program that includes family training [59], easy access to a medical service provider by phone, prompt attention during exacerbations, frequent monitoring [60], the use of innovative methods [61] can improve adherence.

Study limitations

This study has several limitations. This study did not cover laboratory data, spirography results and patient treatment regimens. Such a limitation was dictated by the main goal of the study to assess adherence to treatment of children with asthma and factors affecting adherence. Another limitation of this study is the rather low level of completion of all stages of observation. From the moment of recruitment in the T1 period, only 70% of cases of bronchial asthma among children in the urban and 58% in the rural place were included in the analysis. Unfortunately, after 6 months, these indicators in the groups of patients from the urban and rural area were reduced to 12.1% and 28%, respectively.

Conclusion:

The results demonstrated a low therapeutic adherence of children with asthma in the Republic of Kazakhstan in 2018-2020, especially in the rural places. These disappointing results on adherence of paediatric patients could be explained by a relatively low level of quality of life of the rural place dwellers. It encompasses difficult socio-economic and living conditions, which might play the role of risk factors for the development of asthma in children in this area. In this regard, it is necessary to take measures at the government level to regulate the social and medical sphere, aimed at increasing adherence to treatment of patients, especially those living in rural areas.

Conflicts of interest:

The authors declare no conflict of interest.

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