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Article type : Original Article

Title: Rural to urban migration contributes to the high burden of asthma in the urban area.

Running head: Rural to urban migration and asthma

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/crj.13058

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Authorship statement: Eduardo Vieira Ponte, Adelmir Souza-Machado, Maurício Barreto and Álvaro Cruz participated in the data analyzes and manuscript preparation. Aline Lima, Paula Almeida and Juliana Jesus participated in the data collection, data analyzes and manuscript preparation.

Disclosure statement: This study was funded by CNPq-Brazil, FAPESB-Brazil (PRONEX 020/2009, grant# 6353 PNX 0018/2009) and GlaxoSmithKline (Program Trust in Science). Álvaro A Cruz reports grants from National Research Council of Brazil and GSK, and personal fees from AstraZeneca, Novartis, Boehringer Ingelheim, Merck, Sharp & Dohme, GSK, Sanofi and CHIESI. Eduardo Vieira Ponte, Aline Lima, Paula Almeida, Juliana Jesus, Adelmir Souza-Machado and Maurício Barreto report no conflict of interest

Abstract

Introduction: It is unknown whether rural-urban migration contributes to worse the burden of asthma in the cities. **Objectives:** The aim of this study was to evaluate whether subjects with asthma that migrated from rural areas to a large urban center in Brazil have more severe disease than asthmatic subjects that was born and always lived in the urban area. **Methods:** This is a case-control study. We enrolled two groups of subjects with asthma currently living in a large urban center in Brazil: 486 subjects with moderate-severe asthma and 432 subjects with mild asthma. **Results:** Rural-urban migrants had higher odds of moderate-severe asthma [adjusted OR 1.57, 95 CI (1.18-2.01)] and uncontrolled symptoms of asthma [adjusted OR 1.80, 95 CI (1.16-2.76)] than urban-born subjects. **Conclusions:** Rural-urban migrants in Brazil have more severe asthma than urban-born subjects.

Our results suggest that rural-urban migration is associated with the high burden of asthma in the urban area.

Keywords: Inhaled corticosteroids, treatment, case-control study, uncontrolled symptoms, environment

INTRODUCTION

Urbanization has been an overwhelming global process in recent decades. There are evidences that living in urban areas is associated with higher asthma prevalence and worse asthma outcomes. For instance, large epidemiological cross-sectional studies demonstrated that children from urban areas have more wheezing [1; 2] and a countrywide study in Brazil demonstrated that urbanization is associated with higher rates of hospital admission and death due to asthma [3].

It is a matter of major interest to investigate the causes behind the association between urbanization and asthma symptoms, as it may unveil strategies for prevention. The current concept is that intrinsic aspects of the urban environment increase the burden of asthma within urban centers. For example, air pollution in urban areas favors allergic inflammation of the airways and increases the morbidity of respiratory diseases [4, 5]. Besides, urbanization is associated with less exposure to infections that modulate the immune system, which might contribute to increase the severity of asthma symptoms in urban areas [6].

Rural-urban migration is an important component of the urbanization process. Subjects from rural areas migrate to urban centers due to multiple reasons, which include looking for medical assistance as health resources are limited in many rural settings. In a cross sectional study, the prevalence of wheezing in urban areas was higher among children who migrated from rural areas in comparison with urban-born children [7]. Thus, we hypothesize that rural-urban migration contributes to increase the burden of asthma in urban centers. The fundament of this hypothesis lays in the concept that rural-urban migrants have more severe asthma than urban-born subjects. The aim of this study was to investigate whether rural migrants with asthma living in a large urban center in Brazil have higher odds of moderate-severe asthma, uncontrolled symptoms of asthma or airway obstruction in comparison with subjects who were born and always lived in the urban area.

MATERIAL AND METHODS

This is a case-control study. We enrolled a case group of subjects with moderate-severe asthma and a control group of subjects with mild asthma. We recruited subjects with moderate-severe asthma from the ProAR Clinic, which is the healthcare facility for subjects with moderate-severe asthma in Salvador City, Brazil. The ProAR Clinic admits subjects with moderate-severe uncontrolled asthma [8, 9]. Once admitted, subjects have periodic clinical follow-up with a multidisciplinary team specialized in asthma care, have access to inhaled corticosteroids (ICS), Long Acting Beta₂ agonist (LABA) and Short Acting Beta₂ agonist (SABA) without cost. The recruitment of subjects with mild asthma occurred in primary healthcare facilities of Salvador City. In Brazil, the primary healthcare facility is the place for following up

mild asthma subjects. Once admitted in the primary healthcare facility, mild asthma subjects have periodic clinical follow-up with family physician, have access to ICS and SABA without cost. The primary healthcare facility forward moderate-severe asthma subjects to the ProAR clinic. The enrollment period was from January 2013 to July 2015. All eligible subjects were recruited sequentially. The Institutional Review Board of the Federal University of Bahia approved the study. All subjects signed informed consent.

Subjects enrolled in the study were assessed by the research team, performed spirometry, skin prick test (SPT) to aeroallergens, answered the Asthma Control Questionnaire (ACQ₆) and provided a blood sample.

The inclusion criteria for the study group with moderate-severe asthma were asthma diagnosis, age above 18 years, at least one year of follow-up in the ProAR Clinic, impossibility of withdrawing the ICS during the follow-up and current residence in the urban area of Salvador City. The inclusion criteria for the control group with mild asthma were asthma diagnosis, age above 18 years, controlled asthma at the time of enrollment, not having used ICS during the last three months and current residence in the urban area of Salvador City. The definition of controlled asthma was the ACQ₆ score ≤ 1.5 and lung function without airway obstruction. Exclusion criteria for the two study groups were pregnancy, smoking history above nine pack-years and any concomitant disease that might interfere with the assessment of asthma.

The tools for the diagnosis of asthma were the physician evaluation, spirometry and chest radiography. Two physicians skilled in the assessment of subjects with asthma validated the diagnosis of asthma independently. A third physician decided in case of disagreement. The physicians interviewed and examined the subjects enrolled in the study. Medical records were reviewed. The physicians valued symptoms such as recurrent wheezing, cough or dyspnea and evidences of symptom improvement after ICS or bronchodilators. Lung function had to be normal or show airway obstruction. All subjects performed a chest radiography. The attending physician requested a computerized tomography (CT) of the chest according to clinical judgment. We excluded subjects with relevant abnormalities in the chest radiography or CT.

Definition of the study variables

The aim of the study was to investigate whether rural-urban migrants have more severe asthma than urban-born subjects. The benchmarks of asthma severity were diagnosis of moderate-severe asthma, uncontrolled symptoms of asthma and airway obstruction (dependent variables).

The definition of rural area was a place outside the limits of the city, where subjects cultivate vegetables or breed animals for consumption or commercialization. The definition of rural-urban migrant was a subject that was born and raised in the rural area beyond the age of 5 years, but is currently living in the urban area of Salvador City for at least one year. The definition of urban-born subject was a subject that was born and always lived in the urban area of Salvador City.

Definition of benchmarks for asthma severity: the dependent variables

The criterion of uncontrolled symptoms of asthma was the ACQ₆ score above 1.5.

The ACQ₆ is a self-administered questionnaire that measures the severity of asthma symptoms in the previous seven days. Higher ACQ₆ scores are indicative of more symptoms. We validated the ACQ₆ questionnaire for the Portuguese language of Brazil previously [10].

The criteria of airway obstruction were the post-bronchodilator FEV₁/FVC ratio below the lower limit of normal (LLN) and the FEV₁ below 80% of predicted [11]. We updated the spirometer software with the Brazilian values of normality. We used the Koko® spirometer.

Skin prick test

We used the SPT to identify atopic subjects. The criterion of atopy was a positive SPT to any relevant aeroallergen. We tested the antigens of *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Blomia tropicalis*, *Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus niger*, *Alternaria alternata*, *Blatella germanica*, *Cladosporium herbarum*, *Periplaneta americana*, *Paspalum notatum*, *Cynodon dactylon*, dog and cat dander. We measured the wheal diameters 15 minutes after puncture. The test was positive when the antigen induced a reaction 3 mm greater than the negative control with saline solution.

Analysis of blood samples

Subjects provided a peripheral blood sample to count cells and to measure total IgE. We used the automated method to count blood cells and the peripheral blood eosinophil count to identify subjects with the eosinophilic phenotype of asthma. The cutoff we adopted was 0.22×10^9 cells/L⁻¹. This cutoff was validated for this purpose [12]. We did not use induced sputum to identify the eosinophilic phenotype of asthma because induced sputum in our center is not feasible on a large sample and eosinophil count in the induced sputum is quite modified by the high dose of ICS as used in the case group of subjects with moderate-severe asthma [13].

We measured total IgE of all subjects by the chemoluminescence method. We classified subjects according to the total IgE value: normal or above the upper limit of normality. The cutoff to discriminate the groups was 160 UI/ml.

Statistical analysis

We performed crude and adjusted binary logistic regression analyzes to evaluate whether rural-urban migrants have higher odds of moderate-severe asthma as compared with urban-born subjects and, among the case group of moderate-severe asthma, we evaluate whether rural-urban migrants have higher odds of uncontrolled symptoms of asthma or airway obstruction. The method of data entry in the regressions was the Backward Likelihood Ratio. We used the Hosmer-Lemeshow test to measure goodness-of-fit and the Tolerance test and the Variance Inflation

Factor to measure collinearity. The model and the data fit together and there was no collinearity (SPSS 13.0).

In this study, response to bronchodilator in the spirometry was not an exclusion criterion because subjects enrolled in the study had been using moderate-high dose of ICS or were mild controlled asthmatics. This profile of asthmatic subjects frequently do not show response to bronchodilator in the spirometry [13]. We believe it is not adequate to exclude subjects with typical symptoms of asthma, according to the judgment of two skilled physicians, because of the lack of response to bronchodilator in the spirometry. It would bias the results or limit the external validity of the conclusions. However, we run a validation analysis with the subsample of subjects with positive response to bronchodilator in the spirometry. The definition of response to bronchodilator was more than 12 percent increase in the FEV1 after 400 mcg of salbutamol.

RESULTS

We enrolled 486 subjects in the group of moderate-severe asthma and 432 subjects in the group of mild asthma. The study groups were different in most clinical characteristics. Subjects with moderate-severe asthma compared to mild asthma were older [years of age, 50 (42-61) vs 35 (25-45), $p<0.01$] and were more frequently rural-urban migrants (51% vs 31%, $p<0.01$) (Table 1). It is noteworthy that rural-urban migrants came from more than 80 different rural areas (not shown in the table).

Table 2 presents the regression analyzes that evaluated the relationship between migratory status and study groups. We adjusted the regressions for the age of the subjects and gender. We depicted the results as odds ratio (OR) and 95 confidence intervals. Rural-urban migrants had higher odds of moderate-severe asthma [adjusted OR 1.57, 95 CI (1.18-2.01)] than urban-born subjects. The same association was observed in the subgroup analysis comprising subjects with response to bronchodilator in the spirometry [adjusted OR 1.62, 95 CI (1.20-2.19)] (not shown in the table).

Table 3 describes the characteristics of subjects with moderate-severe asthma grouped according to the migratory status: rural-urban migrants vs urban-born subjects. Rural-urban migrants were older, more exposed to household air pollution, vaginal birth delivery and had more siblings ($p<0.05$). In the group of rural-urban migrants, the median age of first asthma symptoms was 13 years and the median age at the time of migration was 15 years. Rural-urban migrants were less atopic and had more uncontrolled symptoms of asthma ($p<0.05$). The dose of ICS, lung function and the frequency of eosinophilic phenotype were similar between groups.

Table 4 presents regression analyzes comprising only the group of subjects with moderate-severe asthma. We evaluated the relationship between the migratory status and uncontrolled asthma symptoms, airway obstruction, atopy or eosinophilic asthma. We adjusted the regressions for age, dose of inhaled corticosteroids, number of siblings, gender, atopy as measured by the skin prick test and previous exposure to household air pollution . We depicted results as odds ratio (OR) and 95 confidence intervals. Rural-urban migrants had higher odds of uncontrolled

symptoms of asthma [adjusted OR 1.80, 95 CI (1.16-2.76)] than urban-born subjects, but did not have more airway obstruction [adjusted OR 0.97, 95 CI (0.60-1.57)]. Rural-urban migrants had lower odds of positive skin prick test [adjusted OR 0.51, 95 CI (0.32-0.71)] and lower odds of high total IgE [adjusted OR 0.66, 95 CI (0.43-0.99)] than urban-born subjects. There was no association between the migratory status and eosinophilic asthma [adjusted OR 0.95, 95 CI (0.61-1.47)]. We observed the same results in the sub-sample with response to bronchodilator in the spirometry (Table 5).

DISCUSSION

Our study demonstrated that migrants from rural areas to a large urban center in Brazil were more likely to have moderate-severe asthma than urban-born subjects and, among those with moderate to severe asthma, rural-urban migrants were more likely to have uncontrolled symptoms of asthma. Although this study is not a final evidence, our results are consistent with the hypothesis that rural-urban migration is associated with the high burden of asthma in the urban area. Our study adds new information to the current concept that the high burden of asthma in urban centers is the consequence of intrinsic aspects of the urban environment, such as more air pollution and less infections [3, 14]. We propose two hypothesis to explain the greater severity of asthma among rural-urban migrants. It is possible that limited health resources in rural areas led subjects with moderate-severe asthma to migrate to urban centers. This possibility is in line with a recent evidence of lower prevalence but more severe asthma symptoms among subjects living in rural areas [15]. The other possible explanation is that rural-urban migrants with asthma are more

susceptible than urban-born subjects to get worse airway inflammation and asthma symptoms when exposed to environmental hazards in urban centers. However, the latter hypothesis is not coherent with the current concept that the rural environment exposes subjects to immunomodulatory stimuli that downregulate the immune response, prevents airway inflammation and exacerbation of asthma [3, 16, 17]. It would be unexpected someone with immune hyporesponsiveness developing more exaggerated immune response to environmental antigens.

Our study demonstrated that atopy, according to the result of the skin prick test or total IgE, was less frequent among rural-urban migrants in comparison to urban-born subjects. Age and ICS did not bias this association, as we adjusted the analyzes for these confounding variables [18]. As before mentioned, the explanation for this association is that the rural environment exposes subjects to immunomodulatory stimuli that downregulate the immune system, preventing inappropriate immune response to non-harmful environmental antigens [16]. Our study adds to the current knowledge, as we demonstrated that the exposure to the rural environment assured a long-term immunological footprint, even after the cessation of the exposure.

A remarkable aspect of our study is that rural-urban migrants came from as many as 80 different rural areas. It improves the external validity of the results. If most subjects had come from the same rural area, the specificities of one or a few rural areas might have biased the results. A limitation of our study is that we did not obtain *in loco* information about the characteristics of the rural areas. However, we obtained some information, such as exposure to household air pollution, vaginal birth delivery, breast-feeding and the number of siblings, which characterize rural-urban differences

in Brazil. The comparison of these variables between rural-urban migrants and urban-born subjects indicates that the groups represent different populations. Another limitation of this study is that we did not obtain a random sample from the general population, as it would demand screening a very large number of subjects to identify 486 moderate-severe asthmatics. We recruited mild asthmatics from the primary healthcare setting and moderate-severe asthmatics from the secondary healthcare setting because, in the Brazilian healthcare system, subjects with mild asthma are followed up in the primary healthcare setting while subjects with moderate/severe asthma are referred for follow up in the secondary healthcare setting. The rural-urban migrant do not have priority or disregard in the flow of referral, therefore, the recruitment strategy did not bias the conclusions. Besides, the recruitment settings provide a representative sample of asthmatic subjects living in Salvador City, as demonstrated elsewhere [19].

In conclusion, subjects that migrated from rural areas to a large urban center in Brazil had more severe asthma than subjects that was born and always lived in the urban center. Besides, rural-urban migrants were less likely atopic than urban-born subjects. These results support the hypothesis that rural-urban migration contributes to the high burden of asthma in the urban area. This is a new perspective that contributes to understand the concept that urbanization is associated with worse asthma outcomes.

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Table 1. Characteristics of the subjects enrolled in the study groups

	Moderate-severe asthma (n=486)	Mild asthma (n=432)	P
Female gender – n (%)	405 (83)	337 (78)	0.04
Age - median (IQ)	50 (42-61)	35 (25-45)	<0.01
Rhinitis diagnosis - n (%)	463 (95)	389 (90)	<0.01
Migrants from rural to urban area - n (%)	247 (51)	135 (31)	<0.01
Previous exposure to household air pollution - n (%)	298 (61)	152 (34)	<0.01
Vaginal birth delivery - n (%)	443 (91)	347 (80)	<0.01
History of breastfeeding - n (%)	332 (68)	330 (76)	<0.01
Number of siblings - median (IQ)	6 (4-9)	4 (2-7)	<0.01
Age of onset of asthma symptoms - median (IQ)	8 (1-24)	7 (1-18)	0.03
Use of ≥ 800 mcg of inhaled budesonide for asthma – n (%)	460 (95)	0 (0)	<0.01
Daily use of long acting beta 2 agonist - n (%)	466 (96)	0 (0)	<0.01
Uncontrolled asthma symptoms - n (%) ^a	172 (35)	0 (0)	<0.01
FVC percent of predicted after bronchodilator - median (IQ)	84 (75-93)	86 (78-94)	0.04
FEV ₁ percent of predicted after bronchodilator - median (IQ)	70 (59-81)	86 (77-94)	<0.01
Airway obstruction - n (%)	236 (48)	0 (0)	<0.01
Positive skin prick test to common aeroallergens – n (%)	283 (59)	277 (65)	0.15
Total IgE > 160 UI/ml - n (%)	345 (71)	257 (60)	<0.01
Eosinophilic phenotype - n (%) ^b	277 (57)	227 (53)	0.25

We used the Mann-Whitney Test for continuous variables and the Chi-Square Test for dichotomous variables

IQ = Interquartile range

^aAsthma Control Questionnaire score > 1.5

^bBlood eosinophil count > 220/mm³

Table 2. Binary logistic regression analyzes to evaluate whether the migratory status is associated with moderate-severe asthma.

	Crude OR (95 CI)	Adjusted OR (95 CI) ^a
Moderate-severe asthma		
Urban born subjects	-	-
Migrants from rural to urban area	2.25 (1.71-2.94)	1.57 (1.18-2.01)

^aAdjusted for age and gender

Table 3. Characteristics of the subjects with moderate-severe asthma grouped according to the migratory status.

	Rural-urban migrants (n=245)	Urban-born subjects (n=241)	P-value
Female gender - n (%)	213 (87)	194 (81)	0.06
Age - median (IQ)	55 (46-64)	46 (36-57)	<0.01
Rhinitis diagnosis - n (%)	231 (94)	232 (96)	0.30
Age of migration from rural to urban area - median (IQ)	15 (11-19)	-	-
Previous exposure to household air pollution - n (%)	206 (84)	66 (27)	<0.01
Vaginal birth delivery - n (%)	242 (99)	228 (95)	0.04
History of breastfeeding - n (%)	218 (89)	204 (85)	0.21
Number of siblings - median (IQ)	7 (4-10)	5 (3-8)	<0.01
Age of onset of asthma symptoms - median (IQ)	13 (5-27)	5 (1-18)	<0.01
Use of ≥ 800 mcg of inhaled budesonide for asthma – n (%)	231 (94)	229 (95)	0.72
Use of long acting beta 2 agonist for asthma - n (%)	236 (96)	228 (95)	0.62
Uncontrolled asthma symptoms - n (%) ^a	98 (40)	74 (31)	0.03
FVC percent of predicted after bronchodilator - median (IQ)	86 (75-96)	84 (75-91)	0.24
FEV ₁ percent of predicted after bronchodilator - median (IQ)	70 (58-81)	71 (59-82)	0.64
Airway obstruction - n (%)	123 (50)	113 (48)	0.52
Positive skin prick test to common aeroallergens - n (%)	134 (55)	173 (72)	<0.01
Total IgE > 160 UI/ml - n (%)	145 (59)	176 (73)	<0.01
Eosinophilic phenotype - n (%) ^b	134 (55)	142 (59)	0.35

We used the Mann-Whitney Test for continuous variables and the Chi-Square Test for dichotomous variables.

IQ = Interquartile range.

^aAsthma Control Questionnaire score > 1.5

^bBlood eosinophil count > 220/mm³

Table 4. Binary logistic regression analyzes to evaluate whether the migratory status is associated with benchmarks of asthma severity and atopy, in the group of subjects with moderate-severe asthma (n=486).

	Crude OR (95 CI)	Adjusted OR (95 CI)
Uncontrolled asthma symptoms ^{a b}		
Urban born subjects	-	-
Migrants from rural to urban area	1.51 (1.04-2.19)	1.80 (1.16-2.76)
Airway obstruction ^a		
Urban born subjects	-	-
Migrants from rural to urban area	1,13 (0.79-1.61)	0.97 (0.60-1.57)
Positive skin prick test to aeroallergens ^c		
Urban born subjects	-	-
Migrants from rural to urban area	0.48 (0.33-0.72)	0.51 (0.32-0.71)
Total IgE > 160 UI/ml ^c		
Urban born subjects	-	-
Migrants from rural to urban area	0.54 (0.37-0.79)	0.66 (0.43-0.99)
Eosinophilic asthma ^{c d}		
Urban born subjects	-	-
Migrants from rural to urban area	0.84 (0.59-1.21)	0.95 (0.61-1.47)

^aAdjusted for age, dose of inhaled corticosteroids, number of siblings, gender, atopy as measured by the skin prick test and previous exposure to household air pollution

^bAsthma Control Questionnaire score > 1.5

^cAdjusted for age, dose of inhaled corticosteroids, number of siblings, gender and previous exposure to household air pollution

^dBlood eosinophil count > 220/mm³

Table 5. Binary logistic regression analyzes to evaluate whether the migratory status is associated with benchmarks of asthma severity and atopy, in the group of subjects with moderate-severe asthma and positive response to bronchodilator (n=420).

	Crude OR (95 CI)	Adjusted OR (95 CI)
Uncontrolled asthma symptoms ^{a b}		
Urban born subjects	-	-
Migrants from rural to urban area	1.45 (0.98-2.16)	1.46 (1.01-2.21)
Airway obstruction ^a		
Urban born subjects	-	-
Migrants from rural to urban area	1.19 (0.81-1.78)	1.03 (0.62-1.70)
Positive skin prick test to aeroallergens ^c		
Urban born subjects	-	-
Migrants from rural to urban area	0.49 (0.32-0.74)	0.49 (0.32-0.74)
Total IgE > 160 UI/ml ^c		
Urban born subjects	-	-
Migrants from rural to urban area	0.43 (0.28-0.66)	0.53 (0.34-0.84)
Eosinophilic asthma ^{c d}		
Urban born subjects	-	-
Migrants from rural to urban area	0.73 (0.49-1.07)	0.87 (0.58-1.31)

^aAdjusted for age, dose of inhaled corticosteroids, number of siblings, gender, atopy as measured by the skin prick test and previous exposure to household air pollution

^bAsthma Control Questionnaire score > 1.5

^cAdjusted for age, dose of inhaled corticosteroids, number of siblings, gender and previous exposure to household air pollution

^dBlood eosinophil count > 220/mm³