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Urbanization is associated with increased asthma morbidity and mortality in Brazil

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This study was conducted at the University of São Paulo.

Abstract

Introduction: Previous cross-sectional studies could establish an association between prevalence of self-reported wheeze and urban–rural environment, but the impact of urbanization on meaningful outcomes of asthma for public health is not established yet.

Objectives: Evaluate the effect of urbanization on asthma burden.

Methods: A time series study of 5,505 Brazilian municipalities. The unit of analysis was the municipality. Two time frames were evaluated: from 1999 to 2001 and from 2009 to 2011. Trends from the first to the second time frame were evaluated. Governmental databases were the source of information. Multivariate binary logistic regression models were used.

Results: In the age range from 5 to 24 years old, municipalities with increase in the proportion of individuals living in urban area had lower odds to reduce hospital admission rate from asthma (OR: .93) and lower odds to reduce death rate from asthma (OR: .88). In the age range from 25 to 39 years old, municipalities with increase in the proportion of individuals living in urban area had lower odds to reduce hospital admission rate from asthma (OR: .93) and lower odds to reduce death rate from asthma (OR: .82). Municipalities that increased access to physicians and that supplied inhaled corticosteroids free of charge for asthma since year 2003 had increased odds to reduce hospital admission and death rates from asthma.

Conclusions: Increase in urban population was associated with lower odds to reduce hospital admission and death rates from asthma in children and young adults living in a transition society.

KEYWORDS
asthma, epidemiology, hospitalization, mortality, treatment, urbanization

1 | INTRODUCTION

The ISAAC study observed worldwide differences in the prevalence of asthma symptoms.[1,2] Higher prevalence was observed in developed countries. Recently, differences in asthma symptoms prevalence reduced due to prevalence increase in countries where it was previously low.[3] It was hypothesized that changes in environment modified the immune system and asthma prevalence. Transition from a rural to an urban society is among environmental changes that mankind faced in recent decades.[4–6] Evidences suggest that IgE-mediated responses may be reduced among individuals living in rural areas, where exposures to childhood infections—including parasites—are intense.[7] This explains the predominance of nonatopic wheeze in rural settings.[8] Lower prevalence of self-reported wheeze in children was observed in rural communities of Africa[9,10] and America.[11–13] Exercise-induced bronchospasm is less frequent in rural populations in Kenya.[14] Rural areas that acquired urban lifestyle had raised frequency of self-reported wheeze.[15]

Self-reported wheeze prevalence differs among rural communities.[16] Some rural settings are not associated with wheeze protection.[17,18] It is speculated that recently urbanized communities have similar prevalence of wheeze in comparison with rural communities.[19]

Previous cross-sectional studies could establish an association between prevalence of self-reported wheeze and urban–rural environment. However, self-reported wheeze is only an estimate of asthma prevalence. It has limited value to measure the effect of urbanization on outcomes of asthma that are meaningful for public health. Previous cross-sectional surveys could not measure the longitudinal effect of in-progress urbanization on asthma burden either. The effect of urbanization on adult subjects with asthma is also unknown. The aim of this study was to evaluate longitudinally the effect of urbanization on hospital admission and death rates from asthma in children and adults living in a transition society.

2 | MATERIALS AND METHODS

This is an ecological study. The unit of analysis was the municipality. Two sets of data were collected. The first set of data was used in cross-sectional analyses to identify risk factors for hospital admission and death rates from asthma in Brazilian municipalities. The second set of data was collected 10 years later. Changes from the first to the second set of data allowed longitudinal perspective, to evaluate if variation of risk factors was associated with variation of hospital admission and death rates from asthma.

2.1 | Data collection

Municipality is the smallest administrative unit composed by a city and a rural area. Urban population was defined as individuals living within the city. Rural population was defined as individuals living outside the city, in the rural area.

Health and socioeconomic information from all 5,505 Brazilian municipalities were analyzed. Data on hospitalizations and deaths were obtained from a national database of the Ministry of Health. Information regarding hospitalizations is forwarded to the Ministry of Health from the hospital in which it occurs. Forms are filled out by a physician; it is compulsory and allows financial reimbursement for the hospital. Mortality data are obtained from death certificates. Certificates are filled out by a physician and forwarded to the Ministry of Health. Hospitalizations and deaths are accounted for the municipality where patients reside.

Outcomes to estimate asthma burden were hospital admission and death rates from asthma. The physician that requested hospital admission or fulfilled death certificate made diagnosis of asthma. It was notified using ICD 10 codes J45.0, J45.1, J45.8, J45.9, and J46. We only considered hospitalizations and deaths that had asthma as the primary cause. Each municipality had its hospital admission and death rate calculated. Two aggregated periods were analyzed: 1999–2001 and 2009–2011. Periods of 3 years minimize possible bias on information of a specific year and random fluctuations of rates in small municipalities. Two age ranges were set: 5–24 and 25–39 years old. Populations over 40 years old were not studied to minimize misdiagnosis with COPD.

Risk factors for asthma morbidity and mortality were evaluated whenever there is a rationale for association and available data for every municipality. Risk factors were *per capita* income, number of physicians per 10,000 inhabitants, proportion of the population living in urban area, number of hospital beds per 10,000 inhabitants, rate of hospital admission from influenza infection per 100,000 inhabitants, and access to inhaled corticosteroid for asthma free of charge supplied by the municipality. These variables were obtained for each municipality.

Number of hospital beds per inhabitant indicates access to health services. Number of physicians per inhabitant and *per capita* income indicate access to prescription and acquisition of medications. Data were adjusted for the access to inhaled corticosteroid for asthma free of charge supplied by the municipality because this medication prevents hospitalizations and deaths from asthma.[20] Data were adjusted for hospital admission rates from influenza infection because this disease induces asthma exacerbation.[21] The physician that requested hospital admission made the diagnosis of influenza infection. It was notified using ICD 10 codes J11, J11.0, J11.1, and J11.8.

The University of São Paulo Institutional Review Board approved the study. Waive of informed consent was obtained.

2.2 | Statistics

Binary logistic regression models were used for cross-sectional analyses of the first set of data, obtained from the aggregated period 1999–2001. Dependent variables were dichotomized: municipality with high or low hospital admission rate from asthma, according to the 50th percentile, and municipality with presence or absence of death from asthma. The rationale of dichotomization is to evaluate outcomes of asthma in a meaningful scale for public health. Independent variables were included in the regression models as ordinal values, stratified according to the quintiles. Data on inhaled corticosteroid for asthma free of charge were not used for the cross-sectional analyses because municipalities started to supply inhaled corticosteroids after year 2003.

Longitudinal evaluation analyzed dependent and independent variables considering their variation from the first to the second study periods. Binary logistic regression models were used. Variation of hospital admission and death rates from asthma were dichotomized: municipalities that did reduce and did not reduce rates. The rationale of dichotomization is to evaluate outcomes of asthma in a meaningful scale for public health. Independent variables were included in the regression models as ordinal values, stratified according the quintiles, except for inhaled corticosteroid, which was dichotomized: municipality with or without access to inhaled corticosteroid for asthma free of charge since 2003. Software was SPSS 13.0. The method of data entry in the adjusted binary logistic regression models was the Backward Likelihood Ratio. We used the Hosmer–Lemeshow test to measure goodness-of-fit and the tolerance test and variance inflation factor to measure collinearity. All requirements for the regressions were met.

3 | RESULTS

Table 1 describes the characteristics of 5,505 municipalities. In the first study period, the median death rate from asthma, among the municipalities that reported at least one death, was .39 per 100,000 inhabitants in the younger age group and .50 per 100,000 inhabitants in the older age group. Median hospital admission rate from asthma, among all the 5,505 municipalities, was 67.74 per 100,000 inhabitants in the younger age range and 90.45 per 100,000 inhabitants in the older age range. Death rates from asthma did not change from the first to the second study period. In the younger age group, considering 407 municipalities with at least one death from asthma in the first or second study period, median of death rates varied from .39 in the first study period to .20 in the second study period. One hundred and eighty-five municipalities reduced death rates, 170 increased death rates, and 52 maintained stable death rates. In the older age group, considering 503 municipalities with at least one death from asthma in the first or second study period, median of death rates varied from .50 in the first study period to .62 in the second study period. Two hundred and fifty-four municipalities reduced death rates and 249 increased death rates. Rates of hospital admission from asthma reduced from the first to the second study period in both age groups. In the younger age group, only 714 (13%) municipalities increased hospital admission rates, and in the older age group, only 886 (16%) municipalities increased hospital admission rates from asthma.

Table 2 presents the binary regression models to identify risk factors for high hospital admission rate from asthma in the first study period. In the younger age range, municipalities with higher proportion of individuals living in urban area had increased odds of high hospital admission rate from asthma (OR: 1.15). Municipalities with higher number of physicians (OR: .84) and higher *per capita* income (OR: .87) had lower odds of high hospital admission rate from asthma. Municipalities with higher rate of hospital admission from influenza infection (OR: 1.16) and higher number of hospital beds (OR: 1.89) had increased odds of high hospital admission rate from asthma. In the older age range, municipalities with higher rate of hospital admissions from influenza infection (OR: 1.05) and with higher number of hospital beds (OR: 1.68) had increased odds of high hospital admission rate from asthma. Municipalities with higher *per capita* income (OR: .85) and higher number of physicians (OR: .83) had lower odds of high hospital admission rate from asthma.

Table 3 presents the binary regression models to identify risk factors for death from asthma in the first study period. Municipalities with higher proportion of individuals living in urban area had increased odds of at least one death from asthma.

Table 4 presents the binary regression models to identify risk factors for reduction of hospital admission rate from asthma from the first to the second study period. In the younger age range, municipalities with higher increase in the proportion of individuals living in urban area (OR: .93) and in the number of hospital beds per inhabitants (OR: .86) had lower odds to reduce hospital admission rate from asthma. Municipalities with higher increase in the number of physicians (OR: 1.13), in *per capita* income (OR: 1.02) and with inhaled corticosteroids for asthma free of charge since 2003 (OR: 1.33) had increased odds to reduce hospital admission rate from asthma. In the older age range, municipalities with higher increase in the proportion of individuals living in urban area (OR: .93) and in the number of hospital beds (OR: .87) had lower odds to reduce hospital admission rate from asthma. Municipalities with higher increase in the number of physicians (OR: 1.07), in *per capita* income (OR: 1.06) and with inhaled corticosteroids for asthma free of charge since 2003 (OR: 1.45) had increased odds to reduce hospital admission rate from asthma.

Table 5 presents the binary regression models to identify risk factors for reduction of death rate from asthma. In the younger age range, municipalities with higher increase in the proportion of individuals living in urban area had lower odds to reduce death rate from asthma (OR: .88). Municipalities with inhaled corticosteroids for asthma free of charge since 2003 had increased odds to reduce death rate from asthma (OR: 1.91). In the older age range, municipalities with higher increase in the proportion of individuals living in urban area had lower odds to reduce death rate from asthma (OR: .82). Municipalities with higher increase in the number of

TABLE 1 Characteristics of Brazilian municipalities in the first and second study periods ($N = 5,505$)

	1999–2001	2009–2011	*P*
Death rate from asthma per 100,000 inhabitants, age 5–24 years old[a]	.39 (.00–2.25)	.20 (.00–1.71)	.37
Death rate from asthma per 100,000 inhabitants, age 25–39 years old[a]	.50 (.00–2.50)	.62 (.00–3.52)	.35
Hospital admission rate from asthma per 100,000 inhabitants, age 5–24 years old	67.74 (.00–265.37)	.00 (.00–68.71)	<.01
Hospital admission rate from asthma per 100,000 inhabitants, age 25–39 years old	90.45 (27.41–248.38)	15.71 (.00–71.68)	<.01
Hospital admission rate from influenza per 100,000 inhabitants, age 5–24 years old	.00 (.00–.00)[b]	.00 (.00–1.83)	<.01
Hospital admission rate from influenza per 100,000 inhabitants, age 25–39 years old	.00 (.00–.00)[b]	.00 (.00–5.99)	<.01
Inhaled corticosteroids for asthma free of charge supplied by the municipality (%)	0 (0)	1,870 (34)	–
Per Capita income[c]	305.00 (169.00–460.00)	454.00 (274.00–636.00)	<.01
Proportion of individuals living in urban area per municipality	59.32 (40.43–77.99)	64.50 (47.01–81.70)	<.01
Number of physicians per 10,000 inhabitants	5.67 (3.18–9.58)	5.70 (3.40–9.65)	<.01
Number of hospital beds per 10,000 inhabitants	21.00 (.00–40.00)	19.00 (.00–38.00)	<.01

[a]Only municipalities with at least one death from asthma in the first or second study period.
[b]Less than 25% of the municipalities had at least one event.
[c]Depicted as present-day currency of Brazil.
Variables are continuous, except “Inhaled corticosteroids for asthma free of charge supplied by the municipality,” which was dichotomized in municipalities that supply or do not supply inhaled corticosteroids for asthma.
Every variable contains 5,505 values, one value per municipality.
Statistics with Wilcoxon Test.
Data depicted as median and 25–75th percentiles.

physicians (OR: 1.15), in the number of hospital beds (OR: 1.20), and with inhaled corticosteroids for asthma free of charge since 2003 (OR: 3.07) had increased odds to reduce death rate from asthma.

4 | DISCUSSION

Our study demonstrated that municipalities with increase in urban population had lower odds to reduce hospital admission and death rates from asthma. To our knowledge, this is the first study to demonstrate that in progress urbanization impacts in outcomes of asthma that are meaningful for public health. Previous surveys evaluated surrogates of asthma, such as self-reported wheeze, and did not establish the longitudinal dynamic of urbanization in their settings. We could also demonstrate for the first time that adult populations with asthma are affected by urbanization. Our observations measure the effect of urbanization on asthma burden from the public health perspective. They emphasize the need of preventive measures at these settings. However, our ecological design does not allow us to conclude about the effect of urbanization at the individual level. This would be an ecological fallacy.

TABLE 2 Binary regression models to identify risk factors for high rate of hospital admission from asthma in the first study period (1999–2001)

	Age 5–24 years old		Age 25–39 years old	
	Crude	Adjusted	Crude	Adjusted
HR rate from influenza infection[a]	1.30 (1.18–1.44)	1.16 (1.05–1.29)	1.05 (1.01–1.11)	1.05 (1.00–1.10)
Per Capita income	1.03 (1.00–1.07)	.87 (.82–.91)	.87 (.84–.91)	.85 (.81–.89)
Population of the municipality	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Supply of inhaled corticosteroids free of charge[b]	–	–	–	–
Proportion of individuals living in urban area	1.18 (1.13–1.22)	1.15 (1.09–1.21)	.91 (.88–.95)	1.00 (.94–1.04)
Number of physicians per inhabitants	1.01 (.99–1.02)	.84 (.80–.88)	.86 (.83–.90)	.83 (.79–.87)
Number of hospital beds per inhabitants	1.80 (1.72–1.87)	1.89 (1.81–1.98)	1.43 (1.38–1.49)	1.68 (1.60–1.75)

[a]Hospital admission rate from influenza infection per 100,000 inhabitants.
[b]Municipalities did not supply inhaled corticosteroids for asthma free of charge before year 2003.
Dependent variable is dichotomized according to the 50th percentile: municipality with high or low hospital admission rate from asthma.
Independent variables analyzed as ordinal values, according to the quintiles.
Independent variables contain 5,505 values, one value per municipality.
Data depicted as odds ratio and 95% confidence intervals.

Urbanization is usually associated with more availability of health resources, which are supposed to reduce asthma burden. However, urban–rural populations have different exposure to infections and air pollution[22,23] that modulate the immune system and may increase asthma severity at urban settings. For instance, helminth infections at rural settings induce anti-inflammatory cytokines, which can reduce airway inflammation[24] and asthma severity.[25] Air pollution at urban settings induces immune-mediated airway inflammation, which may worse asthma severity.[26] Our data demonstrate the necessity of further studies to investigate the biological mechanisms that explain how urbanization influences respiratory health, as urbanization is a fact and is potentially harmful for respiratory health.

Inhaled corticosteroids reduce hospitalizations and deaths from asthma.[20] Some Brazilian municipalities supply inhaled

TABLE 3 Binary regression models to identify risk factors for death from asthma in the first study period (1999–2001)

	Age 5–24 years old		Age 25–39 years old	
	Crude	Adjusted	Crude	Adjusted
HR rate from influenza infection[a]	1.43 (1.24–1.64)	1.25 (1.05–1.49)	1.16 (1.05–1.27)	1.04 (.92–1.18)
Per Capita income	1.50 (1.35–1.66)	.94 (.82–1.08)	1.75 (1.57–1.94)	1.00 (.85–1.14)
Population of the municipality	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Supply of inhaled corticosteroids free of charge[b]	–	–	–	–
Proportion of individuals living in urban area	1.85 (1.65–2.07)	1.25 (1.11–1.43)	2.40 (2.11–2.72)	1.54 (1.32–1.79)
Number of physicians per inhabitants	1.53 (1.38–1.70)	1.00 (.89–1.18)	1.77 (1.60–1.98)	1.05 (.95–1.25)
Number of hospital beds per inhabitants	1.36 (1.25–1.49)	1.11 (.99–1.24)	1.32 (1.21–1.43)	.99 (.89–1.10)

[a]Hospital admission rate from influenza infection per 100,000 inhabitants.
[b]Municipalities did not supply inhaled corticosteroids for asthma free of charge before year 2003.
Dependent variable is dichotomized according to the presence or absence of death from asthma.
Independent variables analyzed as ordinal values, according to the quintiles.
Independent variables contain 5,505 values, one value per municipality.
Data depicted as odds ratio and 95% confidence intervals.

TABLE 4 Binary regression models to identify risk factors for reduction of hospital admission rate from asthma

	Age 5–24 years old		Age 25–39 years old	
	Crude	Adjusted	Crude	Adjusted
Increase in hospital admission rate from influenza infection	1.21 (1.15–1.27)	1.10 (.99–1.20)	1.03 (.98–1.09)	1.03 (.98–1.08)
Increase in *per capita* income	1,04 (1.00–1.08)	1.02 (1.00–1.06)	1.07 (1.02–1.11)	1.06 (1.02–1.11)
Population of the municipality	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Supply of inhaled corticosteroid free of charge since 2003	1.61 (1.44–1.80)	1.33 (1.18–1.50)	1.84 (1.61–2.09)	1.45 (1.26–1.67)
Increase in proportion of individuals living in urban area	.87 (.84–.91)	.93 (.89–.97)	.87 (.83–.91)	.93 (.89–.98)
Increase in number of physicians per inhabitants	1,16 (1.11–1.20)	1.13 (1.08–1.17)	1.09 (1.05–1.14)	1.07 (1.02–1.11)
Increase in number of hospital beds per inhabitants	.91 (.88–.95)	.86 (.82–.90)	.92 (.88–.96)	.87 (.83–.92)

Dependent variable was dichotomized: municipalities that reduced and did not reduce hospital admission rate from asthma.
Independent variables analyzed as ordinal values, according to the quintiles, except "supply of inhaled corticosteroid free of charge since 2003" which was dichotomized in municipalities that supplied or did not supply inhaled corticosteroids for asthma free of charge since 2003.
Every variable contains 5,505 values, one value per municipality.
Data depicted as odds ratio and 95% confidence intervals.

corticosteroids for asthma free of charge since 2003. This public health policy was associated, in previous studies, with reduction of hospitalizations from asthma in one municipality that was benefited from an initiative to enhance distribution of the medication.[27,28] In this study, municipalities that supplied inhaled corticosteroids free of charge had higher odds to reduce hospital admission and death rates from asthma. Policy makers should consider this public health intervention to prevent the increase of asthma burden in transition societies.

TABLE 5 Binary regression models to identify risk factors for reduction of mortality rate from asthma

	Age 5–24 years old		Age 25–39 years old	
	Crude	Adjusted	Crude	Adjusted
Increase in hospital admission rate from influenza infection	1.10 (1.00–1.30)	.97 (.84–1.13)	1.01 (.91–1.13)	.94 (.83–1.07)
Increase in *per capita* income	1.07 (.97–1.17)	.94 (.84–1.06)	1.21 (1.10–1.32)	1.02 (.91–1.14)
Population of the municipality	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Supply of inhaled corticosteroid free of charge since 2003	3.20 (2.38–4.31)	1.91 (1.36–2.68)	5.32 (3.96–7.13)	3.07 (2.22–4.24)
Increase in proportion of individuals living in urban area	.70 (.63–.78)	.88 (.78–.99)	.68 (.61–.75)	.82 (.73–.92)
Increase in number of physicians per inhabitants	1.21 (1.10–1.34)	1.05 (.93–1.18)	1.34 (1.22–1.47)	1.15 (1.04–1.29)
Increase in number of hospital beds per inhabitants	1.21 (1.09–1.35)	.94 (.84–1.06)	1.51 (1.36–1.67)	1.20 (1.08–1.33)

Dependent variable was dichotomized: municipalities that reduced and did not reduce death rate from asthma.
Independent variables analyzed as ordinal values, according the quintiles, except "supply of inhaled corticosteroid free of charge since 2003" which was dichotomized in municipalities that supplied or did not supply inhaled corticosteroids for asthma free of charge since 2003.
Every variable contains 5,505 values, one value per municipality.
Data depicted as odds ratio and 95% confidence intervals.

Hospitalizations from asthma reduced across the country from the first to the second study period. Municipalities with increase in physician per inhabitant had higher odds to reduce hospital admission rates from asthma. Physician influences the care of asthma mainly through the prescription of inhaled corticosteroids. More physicians mean more prescriptions. In municipalities with inhaled corticosteroids free of charge, patients may use the prescription to get the medication from the government. In municipalities without inhaled corticosteroids free of charge, patients may use the prescription to buy inhaled corticosteroids with out-of-pocket money.

In our study, some municipalities reduced and other increased death rate from asthma. Further efforts are necessary to reduce deaths from asthma in Brazil. Municipalities with inhaled corticosteroid free of charge had higher odds to reduce death rates from asthma. Unfortunately, most municipalities do not supply inhaled corticosteroid free of charge in Brazil. Improve access to inhaled corticosteroids and build capacity of health professionals for proper use of asthma medications should contribute to reduce death rates from asthma in most settings.

Positive association between hospital beds per inhabitants and hospitalizations from asthma occurs most likely because hospitalizations depend on available hospital beds. Availability of hospital beds in the municipality did not bias our conclusion because data analyses were adjusted for the availability of hospital beds and hospitalizations and deaths were accounted for the municipality where patients reside, even if it happened in other municipality.

Mortality from asthma accounted only deaths that had asthma as the primary cause. This is important because patients with asthma have high all-cause mortality.[29,30] The physician that requested hospital admission or fulfilled death certificate made the diagnosis of asthma. It was notified using ICD 10 codes. There is no previous study to validate DATASUS ICD-10 codes, but some inaccuracy of data was likely balanced by the countrywide extension of the study and the large sample size. Besides, trends of asthma outcomes derived from the same diagnostic criteria in both study periods.

We conclude that increase in urban population is associated with lower odds to reduce hospital admission and death rates from asthma in children and young adults living in transition societies. Some public health policies such as free inhaled corticosteroids supply for asthma subjects and enhanced access to physicians were associated with higher odds to reduce hospital admission and death rates from asthma. These observations emphasize the need of preventive measures and demonstrate the necessity of further studies to investigate the biological mechanisms that explain how urbanization affects respiratory health.

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CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

All authors contributed equally in data collection, statistical analysis, and manuscript preparation.

ETHICS

The University of Sao Paulo Institutional Review Board approved the study. Waive of informed consent was obtained.

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