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The association of prenatal risk factors with childhood asthma

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ABSTRACT

Objective: The purpose of the study was to examine the relationship of maternal complications during pregnancy and prenatal exposures with childhood asthma among low-income families in Karachi, Pakistan. **Methods:** Parents/guardians of children with and without asthma visiting a charity hospital were enrolled. Information about prenatal and perinatal exposures was collected. Univariable and multiple stepwise logistic regression analysis were conducted to explore the relationship of socio-demographic, maternal complications during pregnancy, access to prenatal care, and exposure to animals and pests while pregnant with childhood asthma. **Results:** Maternal symptoms of nocturnal cough (adjusted OR [aOR] = 2.87, 95% CI = 1.60–5.14) and wheezing (aOR = 5.57, 95% CI = 2.32–13.37) during pregnancy significantly increased the odds of childhood asthma. The family history of asthma or hay fever, also elevated the odds of childhood asthma (adjusted OR [aOR] = 5.86 (3.03–11.34). The odds of asthma among children whose mothers received prenatal care by Dai, an unskilled health worker, were significantly elevated. Lastly, prenatal exposure to rats/mice and contact with goats while pregnant was significantly associated with childhood asthma. Whereas, prenatal exposure to cows/cattle reduces the odds of childhood asthma. **Conclusions:** This study identified important maternal and prenatal risk factors for childhood asthma, the majority of which are avoidable. Appropriate steps are needed to create awareness about the prenatal risk factors in this population.

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Introduction

Asthma is a chronic inflammatory respiratory disease that affects nearly 235 million people and 14% of children worldwide [1]. Although the prevalence of asthma among children varies worldwide, it is becoming increasingly prevalent in developing countries [2] especially in densely populated areas [3] while the prevalence of asthma in developed countries has plateaued [4]. In Pakistan, the prevalence of childhood asthma has ranged between 10 and 16% [5,6]. The rising prevalence of childhood asthma cannot be explained by genetic susceptibility alone [2] which indicates that mediating environmental factors may also play a role [7]. The exact cause for the variability in the worldwide prevalence of childhood asthma is unknown [7], but it burdens the healthcare system [8] and has significant societal costs [9].

Several prenatal factors have been related to childhood asthma. Maternal complications such as vaginal bleeding during pregnancy have been shown to

increase the risk of childhood asthma [10]. Low birth weight [11–13] and forceps-assisted deliveries both increase the risk of childhood asthma [13] as well as maternal smoking during pregnancy which also has a similar effect [11,13,14]. Studies have found that maternal illnesses such as diabetes, atopy, asthma, and hypertension during pregnancy increase the risk of the child developing asthma [14–18] yet frequent maternal exposure to farm animals during pregnancy is protective for childhood asthma [19].

There is a paucity of data from low-to-middle income countries where the burden of disease including childhood asthma is higher than developed countries. In an earlier report using the same study population, we found substantially elevated risk of mental health and developmental comorbidities among children with asthma [20]. The purpose of this study was to examine the relationship of maternal complications during pregnancy and prenatal exposures with the development of childhood asthma among low-income families in Karachi, Pakistan.

Table 1. Descriptive characteristics and univariable ORs (95% confidence intervals) of the study sample.

	<i>n</i>	%	Univariable OR (95% CI)
<i>Socio-demographic characteristics</i>			
Sex of child (Girl)	209	52.3	0.71 (0.48–1.05)
Family income at the time of delivery of the child, Mean (SD)*	5876 (3357)		1.00 (0.99–1.00)
Family history of asthma or hay fever	122	30.5	6.73 (4.06–11.15)
Firstborn child	138	34.5	1.90 (1.25–2.89)
Maternal smoking in pregnancy	23	5.8	1.10 (0.47–2.56)
<i>Maternal complications during pregnancy</i>			
Maternal asthma	10	2.5	4.17 (0.87–19.88)
Severe Headache	318	79.5	1.09 (0.67–1.78)
Blurred Vision	263	65.8	1.63 (1.07–2.47)
Swelling of Hands	242	60.5	1.25 (0.84–1.87)
Swelling of Face	214	53.5	0.97 (0.66–1.44)
Vaginal bleeding or spotting	47	11.8	1.91 (1.02–3.59)
Nocturnal cough	186	46.5	3.12 (2.07–4.71)
Shortness of breath	211	52.8	3.50 (2.31–5.29)
Wheezing or whistling in chest	82	20.5	10.86 (5.40–21.84)
High Blood Pressure	69	17.3	2.73 (1.56–4.76)
<i>Access to Prenatal Care</i>			
Received prenatal care			
No	199	49.8	1.00
Doctor/Nurse	178	44.5	0.90 (0.60–1.36)
Midwife	17	4.3	1.41 (0.52–3.86)
Dai	5	1.3	3.96 (0.43–36.06)
Normal vaginal delivery (without any use of forceps or cesarean section)			
Yes	374	93.5	1.00
No, delivery was forceps assisted	9	2.3	2.09 (0.51–8.47)
No, delivery was C-section	11	2.8	1.25 (0.38–4.18)
Birthweight of Child			
Average	251	62.8	1.00
Small or very small	113	28.3	6.31 (3.79–10.50)
Missing	36	9.0	4.90 (2.26–10.63)
<i>Own Animals/Livestock While Pregnant</i>			
Cat	90	22.5	2.59 (1.58–4.25)
Dog	64	16.0	2.01 (1.16–3.50)
Cow/Cattle	20	5.0	0.82 (0.33–2.02)
Goat	80	20.0	2.34 (1.40–3.92)
Sheep	9	2.3	1.28 (0.34–4.82)
Poultry, e.g., chicken	37	9.3	1.54 (0.77–3.1)
<i>Evidence of Pests while pregnant</i>			
Cockroaches	250	62.5	2.65 (1.73–4.06)
Rats/Mice	228	57.0	2.19 (1.45–3.29)

*Pak Rupees (1USD = 100 PKR at the time of study).

Methods

A hospital-based case-control study of 400 children was conducted in the outskirts of Karachi, a megacity of more than 20 million population in Pakistan. The detailed description has been provided elsewhere [20,21]. Briefly, the study population comprised of parents' or guardians of children with ($n = 200$) and without ($n = 200$) asthma who visited *Koochi Goth* General Hospital from April to November in 2012 for their regular care. A local primary care physician evaluated each child clinically and enrolled the child based on respiratory signs and symptoms. After obtaining the informed consent, three hospital nurses interviewed child's parent or guardian in the local language. The child was not interviewed.

The outcome variable was a clinical diagnosis of asthma defined based on evaluation by the primary care physician. Primary exposures of interest, relevant to this paper, were pregnancy complications,

own animals and livestock while pregnant, evidence of pests at home while pregnant with the child, pre-natal care, mode of delivery, and the child's birth weight. Most respondents were not able to recall the weight of the child at birth or did not weigh the child. Therefore, respondents were also asked if at the time of birth the child was very large, larger than average, average, smaller than average, or very small [22].

We used information on characteristics that could potentially influence the association between exposures of interest and childhood asthma including child's sex (male/female), family income of the household at the time of delivery of the child (entered as a continuous variable), child is a firstborn (categorized as yes/no), family history of asthma or hay fever (categorized as yes/no), and history of smoking by child's mother while pregnant (categorized as yes/no).

Table 2. Association of prenatal factors with childhood asthma.

	Multivariate OR (95%CI)
<i>Socio-demographic characteristics</i>	
Family history of asthma or hay fever	5.86 (3.03–11.34)
<i>Maternal complications during pregnancy</i>	
Nocturnal cough	2.87 (1.60–5.14)
Wheezing or whistling in chest	5.57 (2.32–13.37)
<i>Access to Prenatal Care</i>	
Received prenatal care	
No	1.0
Doctor/Nurse	1.30 (0.71–2.36)
Midwife	0.90 (0.20–3.99)
Dai	22.95 (1.96–268.81)
<i>Birthweight of Child</i>	
Average	1.0
Small or very small	2.90 (1.42–5.94)
Missing	1.20 (0.42–3.43)
<i>Own Animals/Livestock While Pregnant</i>	
Cow/Cattle	0.12 (0.03–0.53)
Goat	3.49 (1.62–7.51)
<i>Evidence of Pests while pregnant</i>	
Rats/Mice	2.32 (1.60–5.14)

Backward stepwise logistic regression using the criteria $Pr(0.1)$ and $Pe(0.05)$. Categorical variables were retained if at least one of the categories was significant.

Data were analyzed using Stata statistical software package, version 14.0 (College Station, TX). Frequency distribution of variables by cases/control status was compared using chi-square test. Univariable logistic regression analysis was conducted. We used backward stepwise logistic regression to select the final model. Variables significant at p values 0.05 were retained in the final model. The study was approved by the institutional review board of the University of North Carolina at Charlotte.

Results

Table 1 displays descriptive characteristics and univariable association of socio-demographic, maternal complications during pregnancy, access to prenatal care, and exposure to animals and pests while pregnant with childhood asthma. Among socio-demographic variables family history of asthma or hay fever and being firstborn child were significantly associated with childhood asthma in the univariate analysis. The odds of childhood asthma are significantly elevated in the univariate analysis for maternal complications such as blurred vision, vaginal bleeding or spotting, nocturnal coughs, shortness of breath, wheezing and whistling in chest, and high blood pressure. Similarly, children who were born small or very small had more than sixfold elevated odds of childhood asthma. Lastly, *in utero* exposure to cats, dogs, goat cockroaches and rats was significantly associated with childhood asthma in the univariate analysis.

Table 2 displays the multivariate odds ratios for the association between prenatal factors and childhood asthma. The family history of asthma or hay fever was almost sixfold elevated among children with asthma (adjusted OR = 5.86, 95% CI = 3.03–11.34). Nocturnal cough (adjusted OR = 2.87, 95% CI = 1.60–5.14) and wheezing or whistling in chest (adjusted OR = 5.57, 95% CI = 2.32–13.37) during pregnancy was significantly associated with childhood asthma. Receiving prenatal care from a Dai (unskilled provider) significantly elevated the odds of childhood asthma (adjusted OR = 22.95, 95% CI = 1.96–268.81).

Among mothers that owned goats during pregnancy the odds of childhood asthma were more than threefold elevated (adjusted OR = 3.49, 95% CI = 1.62–7.51). Whereas, owning a cow/cattle during pregnancy was protective against childhood asthma. Lastly, the evidence of rats/mice during pregnancy was significantly associated with twofold elevated odds of childhood asthma (adjusted OR = 2.32, 95% CI = 1.60–5.14).

Discussion

The present study found that certain prenatal maternal exposures and complications during pregnancy significantly increased the child's risk of asthma later in life.

This study found nocturnal cough and maternal wheezing during pregnancy increases the risk of childhood asthma. Approximately 21% of respondents complained of wheezing during pregnancy and more than twice reported nocturnal cough and shortness of breath while pregnant. The presence of maternal respiratory symptoms during pregnancy may be indicative of undiagnosed or uncontrolled maternal asthma. Mothers with uncontrolled asthma during pregnancy are more likely to experience adverse birth outcomes such as preterm labor, hypertension, and giving birth to low birth weight babies [16,23,24]. Although maternal asthma was not selected in the final model, the odds of childhood asthma were more than fourfold elevated in the univariable analysis. Respiratory problems are common comorbidities with asthma [25]. Among women of child-bearing age, 7–10% reportedly suffer from asthma which makes it one of the common chronic conditions requiring treatment among pregnant women [16]. Asthma is also associated with preeclampsia, and asthma attacks during pregnancy can severely interfere with fetal development and with oxygen delivery to the fetus [16]. Hypertension during pregnancy can lead to

preeclampsia, a potentially life-threatening medical condition characterized by a sudden increase in blood pressure typically after the 20th week of pregnancy [17,26]. Preeclampsia could lead to decreased fetal airway growth [27]. In the current study more than 17% of respondents suffered from high blood pressure during pregnancy and the odds of childhood asthma were more than twofold elevated in the univariable analysis. The presence of these maternal complications in the increasing number of respondents while pregnant with a child with asthma merits further studies.

Globally, only 85% of pregnant women receive at least one skilled prenatal visit while the World Health Organization recommends at least four visits [28]. In high-income countries, nearly all women have access to skilled prenatal care, whereas, in low-income countries, only 40% have the same access [29]. In the Sindh province in Pakistan, where Karachi is located, an estimated 80% of ever-married women reported receiving skilled prenatal care, but only 40% reported visiting a skilled provider four or more times [30]. Access to skilled prenatal care and its utilization is an important determinant of the health of a developing fetus [31,32] and the risk of having a low birthweight baby doubles if the mother receives inadequate prenatal care [33]. Two large meta-analyses have reported that children with low birth weight have a higher risk of asthma and other diseases later in life [34,35]. In the current study, almost half of the respondents reported receiving no prenatal care and most of the self-reported maternal symptoms and complications were substantially elevated in this group (data not shown). Children who were born small or very small had almost threefold elevated odds of asthma, and the risk increased to almost 15 among children born to mothers who did not receive prenatal care (unadjusted OR = 14.98, 95% CI = 7.09–31.01). Pakistan spends less than 1% of GDP on health, one of the lowest expenditure on health in the world. There is a need to provide affordable skilled prenatal care to pregnant mothers for a healthy pregnancy and healthy development of the fetus, which can only be possible by making policy changes at the national level.

Previous studies have shown that exposure to farm animals reduces the risk of childhood asthma [36]. A study in New Zealand found that prenatal exposure to farm animals lowered the risk of childhood asthma in farmers' children [19]. Authors suggest that the reason for this protection is because the fetus's immune system is being primed by maternal immune responses [19]. The present study, however, found that prenatal exposure to cows and cattle only lowered the asthma

risk. Prenatal exposure to goats increases the risk of childhood asthma by more than threefold. Differences in the study population and the environment may account for discrepant results.

Prenatal exposure to rats/mice increases the risk of childhood asthma in our study. Rats and mouse infestation are not uncommon in low-income families in Pakistan. Mouse allergens are a known risk factor for asthma among children especially in inner cities [35,36]. Rat allergens were found in 33% of inner-city homes [37]. Others have reported the prevalence of mouse allergens of 18–22% [38]. In our study, 57% of respondents reported rats/mice infestation. Prenatal exposure to pest has been shown to sensitize the developing fetus [39].

There are several limitations to this study. Since this was a case-control study presence of selection bias and recall bias were a major concern. The study site, Koochi Goth General Hospital, is a charity hospital that cares for the local community free of charge. Although unlikely but there is a possibility that cases and controls from places outside the hospital's service area may have come to the hospital for care hence resulting in selection bias. The outcome, child's asthma status, was determined clinically by the primary care physician but exposure data were self-reported. Differential recall of exposures by mothers of children with asthma as compared to mothers of children without asthma could result in differential misclassification (recall) bias. Such type of bias is more common in case-control studies of children with severe medical conditions such as birth defects, and hence less likely to have occurred in our study. Also, the study was designed to ask several different types of exposures, and it is unlikely that respondents of children with asthma were more or less likely to remember prenatal exposures. Hence, misclassification of exposures is most likely to be non-differential resulting in a bias towards the null value. To minimize interviewer bias, the three nurses who interviewed study participants were blinded to the asthma status of the child. Nonetheless, interviewer bias in face-to-face studies is difficult to eliminate completely. Prenatal exposure to pests was not measured objectively and may have resulted in misclassification errors. The current study was done at one regional hospital. Future larger national level studies are needed to generalize our results beyond the regional nature of our study.

In conclusion, this study finds that certain prenatal complications that are mostly preventable increase the odds of childhood asthma. There is also evidence

indicating that prenatal exposure to certain animals, livestock, and pests are related to childhood asthma.

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Disclosure Statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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