

Asthma is associated with preterm birth but not small for gestational age status among a population-based cohort of Medicaid-enrolled persons <10 years of age

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Abstract

Background. Few population-based studies have evaluated the association between birth weight or gestation and subsequent clinically significant asthma.

Methods. We linked birth records to a Medicaid billing file for 37,349 Alaska residents less than 10 years of age who were enrolled in Medicaid for at least 365 days during 1999-2002. The occurrence of asthma and lower respiratory infections during the study period was based on standard International Classification of Diseases 9th Revision codes. The association between gestational age or small for gestational age status and asthma outcomes was adjusted for recent history of lower respiratory infection, years of Medicaid enrollment, age at enrollment, and a variety of birth-related factors.

Results. Among children less than 5 years of age, the adjusted odds ratio for developing asthma decreased by 5.5% (95%CI: -0.2, 10.9) and 7.9% (95%CI:5.2, 10.4) per additional week of gestational age for children without and with any lower respiratory tract infection, respectively. For children 5 years of age and older, the adjusted odds ratio for developing asthma decreased by 3.4% (95%CI: -2.8, 9.8) and 3.7% (95%CI: -2.0, 9.2) per additional week of gestation for those without and with lower respiratory tract infection, respectively. Among all children with asthma, the adjusted odds ratio for asthma hospitalization decreased by 6.9% (95%CI: 2.1, 11.5) for each additional week of gestational age. Small for gestational age status was not significantly associated with asthma outcomes.

Conclusions. Preterm birth but not small for gestational age status predicted subsequent asthma outcomes. Adverse effects of preterm birth on asthma outcomes persist past age 5 years.

INTRODUCTION

Previous studies have found an increased risk of asthma among low birth weight [1][2][3][4] or preterm [4][5][6][7][8] infants. Most of these studies have evaluated differences in lung function, such as forced vital capacity (FVC) or the forced expiratory volume in one second (FEV1) rather than differences in seeking clinical care. It may be that preterm or low birth weight birth leads to physiological changes but not impairment severe enough to lead to care seeking.

Additionally, previously identified associations may result in part from confounding by respiratory tract infection.[9][10][11][12] Studies that have adjusted for respiratory tract infection during analysis [13][14][15] generally have found reduced effects of birth characteristics.[14][15] Few of these studies have had large or population-based study groups. Thus, questions still remain regarding the contribution of birth characteristics to subsequent asthma independent of the risk of respiratory tract infections, whether measurable effects are of clinical significance, and if so whether clinically significant effects remain beyond early childhood. The current study evaluated Medicaid-enrolled Alaskans <10 years of age to determine if low birth weight or preterm birth was associated with future diagnosis of asthma when controlling for temporally associated lower respiratory tract infection.

METHODS

Healthcare in Alaska

During the study period, health care services in Alaska were delivered through a variety of private, public, non-profit, Native Corporation, and Indian Health Service entities. Alaska Natives constituted the state's largest racial minority and predominant rural residents and usually received services through Native Corporation and Indian Health Service facilities. Care in most small villages was provided at clinics staffed by Village Health Aides with support provided by physicians based at regional centers. For Medicaid enrolled persons, all in-state facilities billed Medicaid regardless of where a specific individual obtained care.

Based on 2001 census data, the proportion of all Alaska Natives <10 years of age enrolled in Medicaid ranged from 62-80% over the study period compared to 15-21% for non-Natives. Little differences in Medicaid enrollment percentages existed by Anchorage and non-Anchorage residence.

Data sources

The methods for the construction of the Medicaid data file have been previously described.[16][17] In brief, a file was constructed containing information on all persons less than 10 years of age enrolled in Medicaid at some time during January 1, 1999 through December 31, 2002. An outcomes file was created that contained all provider, inpatient facility, and outpatient clinic approved billing claims for all outcomes of interest (see Case Definitions below). A separate file contained data on asthma medications.

To link the Medicaid and birth certificate files, the Alaska Bureau of Vital Statistics performed six steps. The great majority of children were linked through an exact match of social security number and at least one of six additional criteria (42%) or an exact match of first and last names and date of birth (56%); four additional steps were used to link the remaining 2%.

Available data from the birth certificate included birth weight and gestational age, birth residence, method of delivery, presence of multiple gestation birth, maternal and paternal age and education, and prenatal maternal tobacco, oral tobacco, and alcohol use. Other than asthma and respiratory infection variables, analyzed data from the Medicaid file included age, gender and race.

Definitions

Asthma: An approved claim for any asthma-related medication and care based on International Classification of Diseases, 9th Revision (ICD-9) codes 493.0x-493.9x, the standard codes for asthma. Asthma-related hospitalization included any approved claim for which asthma was recorded as a discharge diagnosis.

Lower respiratory illness: An approved claim for ICD-9 code 466.0 (bronchitis), 466.1 (bronchiolitis), 480-487 (pneumonia and influenza), 490 (bronchitis not specified as acute or chronic), or 510-511 (empyema and pleurisy).

Preterm birth: A birth certificate report of gestation less than 37 weeks calculated as the period beginning with the first day of the last menstrual period to the day of birth.

Small for gestational age (SGA): Based on published data,[18] SGA was defined as a weight less than the 10th percentile for gestational age at birth.

Analysis

There were 72,642 in-state residents under 10 years of age enrolled in Medicaid at some point during the four-year study period and 54,412 (75%) could be matched to the birth certificate file. Because of concern that some children enrolled for only brief periods would not have an opportunity to be identified as having one of the study outcomes, we limited analysis to the 41,341 persons enrolled for more than 365 days over the course of the study. Of these, 37,349 had data available for all analyzed variables.

The primary risk factors of interest were gestational age and birth weight. To avoid issues of multi-collinearity between these two variables, we used SGA status rather than birth weight. Children with a history of preterm or SGA birth may present more frequently with asthma because they have an increased risk of concurrent respiratory infection. The study databases, however, did not allow us to evaluate the possibility that early respiratory tract infection constitutes part of the causal pathway of any identified association between preterm birth and asthma. Specifically, in this study the diagnosis of asthma could precede or follow the development of lower respiratory tract infections.

Univariate models were constructed to evaluate the association between asthma outcomes and gender,[19] Alaska Native status and Anchorage residence,[16][17] Caesarian [20] and multiple gestation birth,[21] and maternal age, education, and prenatal tobacco use[22], and any lower respiratory tract infection (inpatient and outpatient). Separate univariate models were constructed for children younger than 5 years and those age 5 through 9 years. Alaska Native status was based on the race reported during the first year of Medicaid enrollment while Anchorage residence was determined at birth.

Multivariate models were constructed for two outcomes: any asthma diagnosis among all children and in-patient asthma admission among asthmatics. All models were adjusted for the following potential confounders:maternal prenatal tobacco use, Alaska Native race, Anchorage residence, Caesarian and multiple gestation birth, mother's age, mother's education, years of Medicaid enrolment (minimum of one), and age at Medicaid enrollment. In addition to these variables, stratification by LRI and age group varied by outcome (see below).

We constructed four sets of multivariate models. For all models we determined if interaction was present between SGA and gestational age; because interaction was not identified during any analysis, these results are not presented. The four model sets included:

- 1) In model set 1, gestational age was defined as a categorical variable with groups <32 weeks, 32 through 36 weeks and 37 weeks and greater. Asthma was the outcome variable and models were stratified simultaneously by age (<5 and 5+ years) and history of LRI for four total strata.
- 2) In model set 2, analysis was restricted to persons with asthma and the outcome was inpatient asthma. Gestational age groups were identical to those in the previous model set. Stratification by age group and LRI status was not possible when evaluating asthma hospitalization among persons with asthma because small numbers prevented meaningful analysis.
- 3) In model set 3, gestational age was left as a continuous variable to determine the overall percent decrease in the odds ratio – per additional week of gestational age – for presentation for asthma or inpatient asthma among persons with asthma. For models evaluating asthma as an outcome, we stratified simultaneously by age group and history of LRI. Stratification was not possible when evaluating asthma hospitalization among persons with asthma because small numbers prevented meaningful analysis.
- 4) In model set 4, to allow graphical representation of odds ratio by gestational age, gestational age was defined as <28 weeks, 37 weeks or more, and one or two week periods between these two extremes. Outcomes included asthma and inpatient asthma among persons with asthma. None of the models were stratified by history of LRI or age group because the number of children within gestational age category became too small for meaningful analysis.

All analyses were conducted with SAS version 8.2 proc logistic procedure (Cary, N.C.) software.

RESULTS

Population characteristics

Of the 37,349 study subjects, there were 1,565 (4.2%) with asthma, of whom 236 (15.1%) had at least one asthma-associated hospitalization. There were 18,129 (48.5%) Alaska Natives, 12,498 (33.5%) Anchorage residents, and 24,633 (66.0%) children <5 years of age. Among all study subjects, 12,038 (32.2%) had a lower respiratory tract infection of whom 1,542 (12.8%) were hospitalized. Among 24,633 children age <5 years, 9,617 (37.2%) had a lower respiratory tract infection of whom 1,164 (12.1%) were hospitalized; 4,298 total cases and 808 hospitalizations were associated with bronchiolitis. Among all study subjects, 41 (0.1%) were born at <32 weeks and SGA, 435 (1.2%) at <32 weeks and not SGA, 401 (1.1%) at 32 through 36 weeks and SGA, 2,480 (6.6%) at 32 through 36 weeks and not SGA, 2,228 (6.0%) at 37+ weeks and SGA, and 31,764 (85.0%) at 37+ weeks and not SGA.

Univariate Analysis

Among children less than 5 years of age, of the outcomes evaluated a history of lower respiratory illness was most strongly associated with asthma and asthma hospitalization among persons with asthma (Table 1A). Other variables associated with one or both outcomes included Anchorage residence, Alaska Native race, and multiple gestation and Caesarian birth, and gestational age. Findings were similar for children 5 through 9 years of age (Table 1B).

Table 1A. Univariate association between risk factors and asthma or asthma hospitalizations among children less than 5 years old enrolled in Medicaid; Alaska, January 1999 through December 2002.

Variable	Any asthma		Inpatient asthma among persons with asthma	
	%	Prevalence ratio	%	Prevalence ratio
Anchorage residence				
yes (n=8,570)	5.8	1.7 (1.5, 1.9)	14.3	0.6 (0.5, 0.8)
no (n=16,063)	3.5	Referent	23.2	Referent
Alaska Native race				
yes (n=11,442)	4.8	1.3 (1.1, 1.4)	24.3	1.8 (1.4, 2.4)
no (n=13,191)	3.8	Referent	13.3	Referent
Female				
yes (n=11,963)	3.1	0.6 (0.5, 0.7)	15.4	0.7 (0.6, 1.0)
no (n=12,670)	5.3	Referent	21.0	Referent
Multiple gestation				
yes (n=702)	7.3	1.7 (1.3, 2.3)	21.6	1.1 (0.7, 2.0)
no (n=23,931)	4.1	Referent	18.9	Referent
Caesarian birth				
yes (n=3,525)	5.3	1.3 (1.1, 1.5)	18.6	1.0 (0.7, 1.4)
no (n=21,108)	4.1	Referent	19.1	Referent

Maternal prenatal tobacco use				
yes (n=7,367)	4.5	1.1 (1.0, 1.2)	20.5	1.1 (0.9, 1.5)
no (n=17,266)	4.2	Referent	18.3	Referent
Gestational age				
<32 weeks (n=346)	12.1	3.1 (2.3, 4.1)	42.9	2.4 (1.87, 3.6)
32-36 weeks (n=1,999)	6.8	1.7 (1.5, 12.1)	21.3	1.2 (0.9, 1.7)
37+ weeks (n=22,634)	3.9	Referent	17.5	Referent
Small for gestational age				
yes (n=1,770)	5.4	1.3 (1.0, 1.6)	24.2	1.4 (0.9, 1.9)
no (n=22,863)	4.2	Referent	18.5	Referent
Mother <20 years old				
yes (n=4,562)	4.3	1.0 (0.9, 1.2)	21.9	1.2 (0.9, 1.6)
no (n=20,071)	4.3	Referent	18.3	Referent
Mother <12 years of school				
yes (n=6,341)	4.7	1.1 (1.0, 1.3)	23.0	1.3 (1.0, 1.7)
no (n=18,292)	4.1	Referent	17.4	Referent
Lower respiratory infection				
any (n=9,617)	8.8	6.3 (5.4, 7.3)	22.0	3.3 (2.0, 5.5)
none (n=15,016)	1.4	Referent	6.7	Referent

Table 1B. Univariate association between risk factors and asthma or asthma hospitalizations among children age 5 through 9 years enrolled in Medicaid; Alaska, January 1999 through December 2002.

Variable	Any asthma		Inpatient asthma among persons with asthma	
	%	Prevalence ratio	%	Prevalence ratio
Anchorage residence				
yes (n=3,928)	5.9	1.8 (1.5, 2.2)	6.0	0.8 (0.4, 1.5)
no (n=8,788)	3.2	Referent	7.8	Referent
Alaska Native race				
yes (n=6,687)	3.1	0.6 (0.5, 0.7)	7.6	1.2 (0.6, 2.2)
no (n=6,029)	5.0	Referent	6.6	Referent
Female				
yes (n=6,510)	3.6	0.8 (0.7, 1.0)	5.9	0.7 (0.4, 1.4)
no (n=6,206)	4.4	Referent	8.0	Referent
Multiple gestation birth				
yes (n=316)	3.2	0.8 (0.4, 1.4)	40.0	6.3 (2.7, 14.4)
no (n=12,400)	4.1	Referent	6.4	Referent

Caesarian birth				
yes (n=1,593)	6.5	1.8 (1.4, 2.2)	9.6	1.5 (0.8, 3.0)
no (n=11,123)	3.7	Referent	6.4	Referent
Maternal prenatal tobacco use				
yes (n=4,593)	3.7	0.9 (0.7, 1.0)	8.8	1.4 (0.8, 2.7)
no (n=8,123)	4.2	Referent	6.1	Referent
Gestational age				
<32 weeks (n=130)	10.0	2.6 (1.5, 4.4)	15.4	2.5 (0.7, 9.4)
32-36 weeks (n=882)	5.3	1.4 (1.0, 1.8)	12.8	2.0 (0.9, 4.7)
37+ weeks (n=11,704)	3.9	Referent	6.2	Referent
Small for gestational age				
yes (n=1,900)	4.0	1.0 (0.7, 1.4)	13.9	2.1 (0.9, 5.2)
no (n=11,816)	4.0	Referent	6.5	Referent
Mother <20 years old				
yes (n=2,246)	3.5	0.8 (0.7, 1.1)	14.0	1.2 (0.9, 1.6)
no (n=10,470)	4.3	Referent	5.8	Referent
Mother <12 years of school				
yes (n=3,640)	5.0	0.8 (0.7, 1.0)	4.8	0.6 (0.3, 1.4)
no (n=10,601)	3.8	Referent	7.8	Referent
Lower respiratory infection				
any (n=2,421)	11.4	5.0 (4.2, 5.9)	9.4	2.2 (1.1, 4.5)
none (n=10,295)	2.3	Referent	4.2	Referent

Multivariable Analysis

Model set number 1. In models with gestational age grouped into three categories, the odds ratio for the development of asthma was between 2.0 and 2.3 for gestational age <32 weeks regardless of stratification by age group at enrollment or history of LRI (Tables 2A and 2B). However, associations were not significant for all strata. Gestational age of 32 through 36 weeks was significantly associated with the development of asthma only for children less than 5 years of age with a history of LRI (OR 1.6, 95%CI: 1.2, 2.0) and children age five years and older with no history of LRI (OR 1.6, 95%CI: 1.0, 2.5). Small for gestational age was not significantly associated with asthma across all strata.

Table 2A. Association between asthma and gestational age or small for gestational age (SGA) status among Medicaid-enrolled children less than 5 years of age, stratified by lower respiratory infection (LRI); Alaska, January 1999 through December 2002.

Variable	No LRI (n=15,016)		Any LRI (n=9,617)	
	aOR*	95% CI	aOR*	95% CI
Gestation < 32 weeks	2.3	1.0, 5.4	2.2	1.5, 3.3

Gestation 32-36 weeks	1.0	0.6, 1.7	1.6	1.2, 2.0
Gestation 37+ weeks	Referent	Referent	Referent	Referent
SGA	1.2	0.8, 2.0	1.1	0.9, 1.4
Not SGA	Referent	Referent	Referent	Referent

*aOR = adjusted odds ratio. Adjusted for years of Medicaid enrollment, age at enrollment, sex, Alaska Native race, birth residence, Caesarean and multiple gestation birth, maternal age, maternal education, and maternal prenatal tobacco use

Table 2B. Association between asthma and gestational age or small for gestational age (SGA) status among Medicaid-enrolled children 5 through 9 years of age, stratified by lower respiratory infection (LRI); Alaska, January 1999 through December 2002.

Variable	No LRI (n=15,016)		Any LRI (n=9,617)	
	aOR*	95% CI	aOR*	95% CI
Gestation < 32 weeks	2.0	0.8, 5.2	2.3	1.0, 5.2
Gestation 32-36 weeks	1.6	1.0, 2.5	1.3	0.8, 2.0
Gestation 37+ weeks	Referent	Referent	Referent	Referent
SGA	0.7	0.4, 1.2	0.9	0.5, 1.4
Not SGA	Referent	Referent	Referent	Referent

*aOR = adjusted odds ratio. Adjusted for years of Medicaid enrollment, age at enrollment, sex, Alaska Native race, birth residence, Caesarean and multiple gestation birth, maternal age, maternal education, and maternal prenatal tobacco use

Model set number 2. In the model evaluating the association between gestational age and hospitalization for asthma among children with asthma, stratification by LRI and age group status was not performed. In this unstratified model, gestational age <32 weeks, but not 32 through 36 weeks, was associated with hospitalization for asthma when compared to normal gestation children (Table 3). Small for gestational age status was associated with asthma, but the association did not achieve statistical significance.

Table 3 Association between inpatient asthma and gestational age or small for gestational age (SGA) status among 1,565 Medicaid-enrolled children with asthma <10 years of age; Alaska, January 1999 through December 2002.

Variable	aOR*	95% CI
Gestation < 32 weeks	3.4	1.8, 6.4
Gestation 32-36 weeks	1.2	0.8, 1.9
Gestation 37+ weeks	Referent	Referent
SGA	1.7	1.0, 2.7
Not SGA	Referent	Referent

*aOR = adjusted odds ratio. Adjusted for years of Medicaid enrollment, age at enrollment, sex, Alaska Native race, birth residence, Caesarean and multiple gestation birth, maternal age, maternal education, and maternal prenatal tobacco use

Model set number 3. When gestational age was left as a continuous variable, the adjusted odds ratio for developing asthma decreased by 7.6% (95% CI: 5.7, 9.5) per additional

week of gestational age among all children. Among children with asthma, the decrease in the adjusted odds ratio for asthma hospitalization decreased by 6.9% (95%CI: 2.1, 11.5) for each additional week of gestational age.

Among children less than 5 years of age, the adjusted odds ratio for developing asthma decreased by 5.5% (95%CI: -0.2, 10.9) and 7.9% (95%CI:5.2, 10.4) per additional week of gestational for children without and with any lower respiratory tract infection, respectively. For children 5 through 9 years of age, the adjusted odds ratio for developing asthma decreased by 3.4% (95%CI: -2.8, 9.8) and 3.7% (95%CI: -2.0, 9.2) per additional week of gestation for those without and with lower respiratory tract infection, respectively.

Model set number 4. When gestational age was grouped into seven categories, all categories of gestational age <37 weeks were significantly associated with the development of asthma. A dose-response effect was observed, with the adjusted odds ratio decreasing as gestational age increased (Figure 1). For the model evaluating inpatient asthma among children with asthma, the adjusted odds ratio was similarly high for the three categories of gestational age <32 weeks while the adjusted odds ratio was near one for all categories of gestational age of 32 weeks and greater (Figure 2).

DISCUSSION

This large, population-based study identified an association between preterm birth, but not SGA status, and subsequent risk of clinical asthma among persons <10 years of age. This effect was observed among children less than 5 and 5 through 9 years of age. Among children with asthma, preterm birth also increased the risk of asthma hospitalization.. These data support previous studies that have identified an association between prematurity and alterations in pulmonary function, including those that have found effects extending into adolescence [1] [5] [7] [23][24][25][26] and adult life.[27] Furthermore, our stratified analyses suggest that previously reported associations probably are not due solely to preterm birth increasing the risk of respiratory tract infection .

Recent studies have found a relationship between intrauterine growth retardation and bronchopulmonary dysplasia.[28][29][30] Pulmonary damage from bronchopulmonary dysplasia, in turn, has been associated with asthma [6][7][23][24][25], providing a potential mechanism by which low birth weight might increase asthma risk. All of these studies, though, evaluated the effect of asthma on lung function rather than clinical illness. Several studies evaluating clinical illness as an outcome have found an association between low birth weight and future asthma risk [31][32][33] while others have not [5][34]. These studies, however, did not evaluate the independent effect of prematurity and birth weight on asthma or the association between SGA status and asthma. One study that evaluated gestational age and birth weight found that birth weight adjusted for gestational age was strongly associated with lung function but that gestational age alone more accurately reflected respiratory illness.[4] A second study found that following adjustment for confounding factors, birth weight was not associated with either adult lung function or asthma symptoms.[35] Our results support existing

evidence that low birth weight independent of gestational age does not increase the risk of clinically significant asthma.

Most [4][5][6][7][8] but not all [34][35] published studies have found that preterm birth leads to increased risk of clinical asthma or decreased lung function. Few studies, though, have attempted to quantify the impact of prematurity on asthma outcomes. Consistent with our results, a single study found that each additional week of gestation reduced the risk of severe wheeze by 10%. [5] In our study, the largest impact occurred at less than 32 weeks gestation. Nevertheless, some effect is observed between 32 through 36 weeks gestation. Since the occurrence of births is much greater at 32 through 36 than less than 32 weeks gestation, it is likely that the greatest impact on asthma will occur by extending these later gestation births.

Our study had several limitations. Because children were not necessarily continuously enrolled over the 4-year study period, we may have missed children with milder asthma who presented infrequently for care and thus our results may not be generalizable to this population; we controlled for this to some extent by limiting analysis to children enrolled for at least 365 days. Children born prematurely may have more opportunities to have asthma diagnosed and reported because they present more frequently with other medical conditions; this ascertainment bias may have overestimated the association between preterm birth and asthma. We only studied the Medicaid population and thus results may not be generalizable to other groups. We did not evaluate lung function. Finally, we could not evaluate the possibility of a causal link between respiratory infection and asthma.

We believe that this is the largest population-based study yet conducted that has evaluated the association between birth outcomes and clinically significant asthma. Among children born at <32 weeks, the 4-year asthma prevalence was 10% or greater regardless of whether children were younger or older than 5 years, while among those with asthma 15-43% required hospitalization, depending on age. Consequently, preterm children should be evaluated for the development of asthma and treated aggressively when asthma is identified. Each additional week of gestation decreased overall asthma risk by 7.6% and the risk of asthma hospitalization among children with asthma by 6.9%. Thus, measures that prolong gestation could possibly have a modest effect on asthma burden among children born preterm.

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ETHICAL ISSUES

This study involved linkage of existing legally authorized administrative databases housed at the Alaska Department of Health and Social Services. No novel data were obtained. Under these circumstances of routine public health evaluation, institutional review board approval and informed consent were neither sought nor obtained.

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FIGURE LEGENDS

Figure 1: Association between asthma and gestational age among children less than 10 years old enrolled in Medicaid, adjusted for years of Medicaid enrollment, age at enrollment, sex, Alaska Native race, birth residence, cesarean and multiple birth, maternal prenatal tobacco use, maternal age, and maternal education; Alaska, January 1999 through December 2002.

Figure 2: Association between inpatient asthma and gestational age among asthmatic children less than 10 years old enrolled in Medicaid, adjusted for years of Medicaid enrollment, age at enrollment, sex, Alaska Native race, birth residence, cesarean and multiple birth, maternal prenatal tobacco use, maternal age, and maternal education; Alaska, January 1999 through December 2002.



