Objectives: The objective of this cohort study was to determine if complications of pregnancy and labor, characteristics at birth, and exposure to infections influence the incidence of asthma in the first 6 years of life.

Design: We identified all children born between 1980 and 1990 in the Province of Manitoba, Canada. We used records of physician contacts (inpatient and outpatient) and services of the universal provincial health insurance plan to follow up 170,960 children from birth to the age of 6 years to identify the first diagnosis of asthma. Information on mothers and siblings was also obtained to determine family history of disease and exposure to infections.

Results: During the study period, a diagnosis of asthma was made in 14.1% of children by the age of 6 years. The incidence was higher in boys than in girls, in those with family history of allergic diseases. It was higher in urban than in rural areas, and lowest in those born in winter. Asthma was more likely in those with low birth weight and premature birth. Certain congenital abnormalities and complications of pregnancy and labor also increased the risk of asthma. The risk of asthma increased with maternal age. Both upper and lower respiratory infections increased the risk of subsequent asthma, and this effect was more important than exposure to familial respiratory infections, which also tended to increase asthma risk. The risk of asthma decreased with the number of siblings when siblings had a history of allergic disorders.

Conclusions: In addition to genetic influences, intrauterine and labor conditions are determinants of asthma. Exposure to both upper and lower respiratory tract infections increases the risk; these infections do not explain the protective effect associated with the increasing number of siblings.

Key words: asthma risk; intrauterine; labor complications; maternal age; siblings effect; upper and lower respiratory tract infections

Abbreviations: CI = confidence interval; HR = hazard ratio; ICD = International Classification of Diseases; LRI = lower respiratory tract infection; MPHRR = Manitoba Population Health Research Repository; URI = upper respiratory tract infection

The prevalence of asthma varies considerably worldwide, and may be increasing. In Canada, asthma is the leading cause of pediatric hospitalization. The onset of asthma is most common in the first year of life, when it is difficult to distinguish it from other wheezing syndromes. Although in many children wheezing is transient, those who wheeze in the first 3 years of life have an increased risk of asthma at the age of 5 to 7 years. The high incidence of asthma in early life has focused attention on environmental factors such as allergen exposures and infections that occur before and soon after birth as potential causes. It is also possible that factors that interfere with normal pregnancy create an intrauterine cytokine environment favoring the development of allergy in those with a genetic predisposition. The objective of this study was to identify factors that may increase the risk of physician-diagnosed asthma in children between birth and the age of 6 years.

Materials and Methods

Database

The Province of Manitoba has a relatively stable population of approximately 1.2 million people, and a universally accessible
health-care system with fee for service as the method of physician payment. Payments depend on submission of claims that include the diagnosis, type of service, and the patient's identifier, date of birth, gender, and residential postal code. There is no record of ethnicity. Nonnominal records of medical services, including hospitalizations, are stored in the Manitoba Population Health Research Repository (MPHRR), and can be ascribed to individual residents through unique anonymous personal identifiers. Between 1980 and 1996, diagnoses were coded according to the ninth revision of the International Classification of Diseases (ICD).\textsuperscript{11} The reliability and validity of the diagnoses and personal information recorded have been established,\textsuperscript{12,13} although not specifically for asthma between birth and age of 6 years.

**Population**

We used the MPHRR to identify study subjects and to track their use of health-care services during the first 6 years of life. We selected all children born in Manitoba between January 1, 1980, and December 31, 1990, who were residents from their birth date and had a hospital delivery record (n = 185,988). Children who were institutionalized or had < 1 year of insurance coverage (n = 8,973), as well as children with missing information (mother's record, birth weight, gestational age, area of residence) were excluded (n = 6,055). After exclusions, there were 170,960 children available for the analysis. The size of annual cohorts was similar, increasing from 14,483 in 1980 to 16,303 in 1990.

**Outcome**

The onset of asthma was defined as follows: (1) the first claim submitted by a physician with a diagnosis of asthma (ICD 493), (2) the second claim (defining asthmatics as those having at least two physician claims), and (3) the first hospital discharge with asthma as the primary diagnosis. Because there were only minor differences in results, we used the first definition in this article.

**Risk Factors**

The MPHRR provided for each child the birth date, gender, and the postal code of the parental residence. Residences were classified as urban (metropolitan Winnipeg, approximately 650,000 or 54% of the total provincial population) or rural (outside Winnipeg, the largest town having 30,000 people). The Winnipeg postal codes were matched with contemporary Canadian census data to obtain the mean household income in that area, an indicator of socioeconomic status. Postal code areas were ranked and divided into quintiles.

For each child, we determined the primary caregiver on the basis of physician office visits made Monday through Friday during the first year of life. The primary caregiver was classified as a general or family medicine practitioner; or pediatrician, if there were more visits to a pediatrician than to a general practitioner; or mixed, if there were more than two visits to both general practitioners and pediatricians. Few children (3.745 or 2.2%) did not visit a physician’s office Monday through Friday in the first year of life.

Children were classified into five groups according to gestational age and four groups according to birth weight, forming approximate quintiles, or quartiles. For each child, we identified selected congenital anomalies (ICD 277, 740–759) and perinatal conditions (ICD 769–770). Using data from the mother and siblings, we determined if the child was exposed to URI or LRI with their ages. For the mother and siblings, we abstracted the dates of all physician visits for asthma, the other respiratory and allergic disorders noted above, as well as URI and LRI and noninfectious gastroenteritis. For mothers, we also identified selected complications of pregnancy (ICD 640–645) and childbirth (ICD 650–652, 660–665, 669). Using data from the mother and siblings, we determined if the child was exposed to URI or LRI in the family during the first and/or the second year of life.

**Analysis**

We used the Cox proportional hazard model\textsuperscript{14} to identify characteristics of the child and of his/her mother and siblings that were significantly associated with the first diagnosis of asthma. Variables associated with pregnancy and birth, as well as characteristics of mothers and siblings, were modeled as time-fixed variables. Variables that changed during the course of the study (onset of respiratory and allergic conditions in infants) were modeled as time-dependent variables. Hazard ratios (HRs) with 95% confidence interval (CI) indicate relative risks of asthma. Statistical significance was defined as p < 0.05 or 95% CI not overlapping the value of 1.0.

**RESULTS**

There were 170,960 newborns followed up to their sixth birthday. Of these, 24,026 newborns (14.1%) were seen for asthma. The incidence was the highest in the first 2 years of life (2.6% and 2.9%, respectively) and declined to 2.0% in years 5 and 6. The

<table>
<thead>
<tr>
<th>Variables</th>
<th>No.</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>83,298</td>
<td>1.00</td>
</tr>
<tr>
<td>Male</td>
<td>87,662</td>
<td>1.43 (1.39–1.47)</td>
</tr>
<tr>
<td>Primary care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family physician (general practitioner)</td>
<td>96,908</td>
<td>1.00</td>
</tr>
<tr>
<td>Pediatrician</td>
<td>53,098</td>
<td>1.33 (1.29–1.37)</td>
</tr>
<tr>
<td>Mixed</td>
<td>17,128</td>
<td>1.37 (1.32–1.43)</td>
</tr>
<tr>
<td>None</td>
<td>3,745</td>
<td>0.91 (0.80–1.04)</td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>81,118</td>
<td>1.00</td>
</tr>
<tr>
<td>Urban Q1</td>
<td>20,109</td>
<td>1.16 (1.11–1.21)</td>
</tr>
<tr>
<td>Urban Q2</td>
<td>14,568</td>
<td>1.19 (1.14–1.25)</td>
</tr>
<tr>
<td>Urban Q3</td>
<td>16,780</td>
<td>1.17 (1.11–1.22)</td>
</tr>
<tr>
<td>Urban Q4</td>
<td>21,080</td>
<td>1.13 (1.09–1.18)</td>
</tr>
<tr>
<td>Urban Q5</td>
<td>17,405</td>
<td>1.12 (1.07–1.18)</td>
</tr>
</tbody>
</table>

*HRs are adjusted for all variables. Q1 to Q5 = areas with the lowest, to areas with the highest mean household income.*
The cumulative incidence increased 2.3 times (95% CI, 2.2 to 2.5) from the cohort born in 1980 to that born in 1990.

Tables 1–4 show variables with significant HRs for the incidence of asthma. These HRs were derived from the model that included all significant time-fixed and time-dependent variables. Table 1 shows that male gender, pediatricians as primary care providers, and urban residence increased the likelihood of asthma. In Winnipeg, the risk did not vary significantly among neighborhoods with different mean income.

Table 2 shows that risk of asthma was elevated in infants with lower birth weight and in those born prematurely. In addition, certain conditions associated with either pregnancy or delivery slightly increased the risk. Multiple gestations were associated with a reduced risk. Cystic fibrosis, respiratory distress syndrome, and congenital anomalies of the respiratory and circulatory system increased the risk of asthma.

Table 3 shows that a maternal history of asthma was a strong predictor of asthma, while a maternal history of allergic rhinitis was less so. The risk of asthma increased with the mother’s age. However,
this was the case only when time-dependent vari-
ables (Table 4) were added to the model; without
them, the risk of asthma in infants was inversely
related to maternal age.

Table 3 also shows that having a sibling was
protective. However, having a sibling with a history
of allergic conditions increased the risk of asthma.
Asthma risk was more strongly associated with
asthma in siblings than with maternal asthma. The
association with maternal or sibling allergic rhinitis
was weaker than that with asthma. A sibling’s history
of noninfectious gastroenteritis and of contact der-
matitis was protective.

Table 4 shows significant time-dependent vari-
ables. A physician’s diagnosis of several atopic con-
ditions and noninfectious gastroenteritis increased
the likelihood of a subsequent diagnosis of asthma.
In addition, both LRI and URI increased the risk of
asthma.

Exposure of an infant during the first or second
year of life to URI or LRI in the mother or siblings
did not affect the risk of asthma when time-depen-
dent variables were in the model (Table 3). Without
time-dependent variables in the model, however, the
significantly increased risk of asthma was associated
with mother’s and sibling’s URI and LRI in both the
first and the second year of life.

Having a sibling was protective (Table 3). We
explored this by substituting the number of siblings
for the categorical sibling variable. When there were
no time-dependent variables in the model, only
children with four or more siblings had a significantly
lower risk of asthma than those without siblings.
When time-dependent variables (Table 4) were in
the model, those with one sibling were protected
(HR, 0.94; 95% CI, 0.91 to 0.97), and protection
increased almost linearly so that the HR for those
with five and more siblings was 0.74 (95% CI, 0.67 to
0.82). We classified children into those with at least
one sibling with asthma, or allergic rhinitis, or atopic
dermatitis, and those without (Fig 1). In the latter,
having a single sibling was protective, and the effect
did not increase with the number of siblings. Those
with siblings with allergic disorders had a higher risk
than those without siblings, but the effect decreased
progressively with the number of siblings.

We also explored the effect of the month of birth
on the risk of asthma (Fig 2). The risk was signifi-
cantly higher for those born between July and De-

cember than for those born between January and
March when the risk was the lowest.

**DISCUSSION**

There are several weaknesses associated with using
administrative databases to study asthma. The
first is the diagnosis of asthma. There is no objective
test for asthma in children,15 and there may be
labeling problems in relation to related diseases. We
relied on the diagnosis submitted by the physician
for payment of services. We defined the onset of
asthma in three different ways and carried out
analyses with each definition as the outcome. Be-
cause the same variables were identified as risk
factors with similar HRs, we report results with onset
of asthma based on the first claim. This gave us
greater power to detect significant associations. We
did not need to worry how to model the first claim
for asthma if the onset was defined as the second
claim, and we did not miss cases because the second
claim occurred after the sixth birthday. Using hospi-
talization as the criterion for asthma diagnosis may
be more specific, and may also reflect the severity of

**FIGURE 1.** HRs (95% CI) for asthma by the number of siblings
for children (top, A) with siblings and (bottom, B) without siblings
with allergy. Reference group is children without siblings.
the disease. However, the subset of children who were hospitalized for asthma was unlikely to be representative of the cohort as a whole.

There are several advantages of using the MPHRR for asthma research. It includes the whole population with universal coverage and access to health care, and has substantial statistical power to detect associations. There is no reporting or recall bias in regard to either asthma or the risk factors examined. We were able to identify objectively the primary caregiver in the first year, and families (mother and siblings), and assess the relationship of their diseases to the onset of asthma in the children studied.

The overall cumulative asthma incidence by age 6 years was 14.1%, similar to 18.2% for the British 1958 birth cohort at age 7 years. Incidence increased 2.3 times between 1980 and 1990, and we controlled for the cohort effect in our analyses. The same risk factors were identified when individual cohorts were examined.

Our finding that asthma was more likely to be diagnosed in boys is consistent with most studies. Primary care pediatricians were more likely to diagnose asthma than family physicians. The increased sensitivity on the part of pediatricians may reflect greater access to guidelines and other educational efforts concerning asthma.

We found that childhood asthma was less common in rural areas than in the urban area, as have others in Canada. This cannot be ascribed to pediatrician supply since we controlled for this effect. There was no association between asthma and urban neighborhood mean household income. This is consistent with our previous studies in contrast to the United States, where asthma in urban children was more common in lower socioeconomic groups than in higher socioeconomic groups.

As others, we found a strong effect of a family history of asthma and allergic disorders on asthma risk. In the present study, childhood asthma was more strongly associated with asthma in siblings than in mothers, presumably because siblings could have inherited an asthmatic predisposition from the father as well as the mother. Our database did not identify the biological father. Independent of familial history, the occurrence of an allergic disorder (for example allergic rhinitis) in a child further increased likelihood of a subsequent diagnosis of asthma (Table 4).

In the New Zealand cohort, low birth weight was not associated with an increased prevalence of asthma. However, our results are consistent with studies showing the association of low birth weight with an increased risk of asthma.

In our study, low gestational age was an additional risk factor for asthma, independent of birth weight. This is in agreement with some other studies, but not all. Since maternal smoking is associated with an increased risk of both low birth weight and premature birth, maternal smoking may underlie the association we found between these factors and asthma.

We found that some congenital anomalies of the respiratory and circulatory system apparently increased the risk of asthma. This was true for both cystic fibrosis and perinatal respiratory distress. This likely represents a labeling problem since these
conditions are associated with bronchial hyperresponsiveness and wheezing.28,29

Certain conditions during pregnancy and labor further increased the risk of asthma in our study. This is consistent with literature30–33 indicating a wide variety of abnormalities of pregnancy and birth can be associated with subsequent asthma in the child. Though maternal asthma increases the risk of complications during pregnancy,34,35 we controlled for this influence.

Others21,36 have found maternal age inversely related to wheezing lower respiratory illness. This may reflect a greater vulnerability of young mothers and higher exposures to risk factors such as smoking. In our study, asthma risk increased with maternal age after we considered time-dependent variables that reflected the child’s own respiratory infections and allergic disorders. Children of younger mothers may be more likely to have URI and LRI, accounting for previous findings.

Our finding that the risk of asthma was lower for infants born in winter months is consistent with findings on the Isle of Wight,17 but not with those in Germany37 or in New Zealand,23 where only skin sensitivity to allergens was associated with season. Businco et al38 found that children with skin reactivity to pollen were significantly more likely to be born during pollen season.

Our study strongly suggests that infections during the first years of life increase the risk of asthma. This might have been expected in the case of LRI, which present major labeling problems. However, we found little difference between the effects of LRI and URI. Our findings are consistent with those of McKeever et al,39 but others40 have reported that URI had a protective effect in terms of subsequent asthma diagnoses.

Respiratory infections in mothers and siblings in the first 2 years significantly increased the likelihood of asthma in study subjects when time-dependent variables were not in the model, but not when time-dependent variables, representing infections in children themselves, were added (Table 3). This suggests that the effects of exposure to respiratory infections were largely mediated by the acquisition of these infections by the children themselves. We found that previous URI predisposed to asthma, in contrast to the hygiene hypothesis,41 which argues that exposure to URI drives the immune system in the T-helper type 1 direction thought to be protective against asthma.40 However, children with siblings having noninfectious gastroenteritis and contact dermatitis were protected. These disorders are poorly defined and very common, and may be proxies for unknown exposures in early life. However, gastroenteritis and contact dermatitis increased asthma risk in the children themselves. The protective effect of siblings has been cited as a proxy for exposure to infections favoring the hygiene hypothesis. The fact that we found that siblings had a protective effect after considering previous URI, gastroenteritis, and contact dermatitis suggests that the effect was not due to exposure to infections.

Finally, the progressive protective effect of sibling number seemed to be restricted to children in atopic families in our study. Celayeon42 et al reported that maternal history of asthma modified the relationship between day care exposure and asthma. However, contrary to their observation that the protective effect of day care exposures was greater in those without maternal asthma, in our study the siblings’ protective effect was greater in those with family history of asthma.

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