Online Data Supplement

Evidence of a causal role of winter virus infection during infancy on early childhood asthma

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METHODS

We conducted a population-based cohort study of 95,310 children who were born in the state of Tennessee from 1995 through 2000 and continuously enrolled in the Tennessee Medicaid Program (TennCare) until age five and a half years, representing 25% of the births in Tennessee. In 1994, TennCare replaced the federal Medicaid program, as a state-based managed health care program that covered Medicaid-eligible individuals and the uninsured (1). We defined continuous enrollment as no more than 21 days of non-enrollment from the date of birth through the first birthday and no more than 60 days of non-enrollment from age three and a half years through five and a half years. We only included children who were born in seasons for which we have complete data for July to June periods in order to assess winter virus seasonality, and who were born prior to June 2000, so that we could follow all children until they were five and a half years of age by 2005, the most recent year for which we have data. The protocol was approved by the Institutional Review Boards of Vanderbilt University and the Tennessee Department of Health.

Data were obtained from linked TennCare administrative data files and Tennessee State vital records files using previously described methods (2, 3). There are significant quality assurance efforts that go into the development of the datasets used for this research, as well as the established linking algorithms (4-8). Analysis files contained no personal identifiers and study results are reported in aggregate and cannot be linked to individuals. Demographic characteristics identified from TennCare enrollment files

included: self-reported race (black, white, other), region of residence (urban, suburban, rural) and infant gender. Demographic variables determined from infant birth certificate data included: birth weight, self-reported maternal smoking during pregnancy, maternal age at delivery, maternal education level, marital status, living siblings, and estimated gestational age in weeks.

As bronchiolitis hospitalizations are known to correlate strongly with circulation of RSV (9), we determined the seasonal variation of winter viruses for each July – June period using the weekly frequency of infant hospitalizations for bronchiolitis. We identified hospitalizations with International Classification of Diseases (ICD-9) codes for bronchiolitis (466.1) and/or RSV pneumonia (480.1). To capture the seasonality of winter viruses, we counted infant bronchiolitis hospitalizations in a much larger population which included all infants who were born during July 1994 to June 2001 and were ever enrolled in TennCare, during any period in infancy during the study period (N = 426,385). The winter virus peak for each season was defined as the first day of the week with the highest number of bronchiolitis hospitalization events. The primary predictor of interest was the infant age in days at the first winter virus peak following birth.

Early childhood asthma, was defined between ages three and a half to five and a half years utilizing health encounter and pharmacy claims data, as has been previously described (10, 11). We identified asthma at age three and a half to five and a half years to exclude the transient wheezing phenotype. Our data are available to 2005, therefore,

we were able to follow all study children until age five and a half years. Children with an ICD-9-CM diagnosis code of 493 (asthma) in any of the nine diagnostic fields for inpatient, other hospital care or outpatient physician visit claims (two outpatient physician visits separated by at least 30 days were required) were considered to have asthma. In addition, children with two prescriptions for any short-acting beta-agonist or two prescriptions for montelukast in a 365 day period prior to Food and Drug Administration approval of montelukast for allergic rhinitis, or a single prescription for any other asthma medication were considered to have asthma (8, 10-12). The algorithm used to diagnose childhood asthma is similar to that used by other US Medicaid systems, a modified algorithm of the Council of State and Territorial Epidemiologists (CSTE), which has been shown to have 90% sensitivity, 95% specificity, 94% PPV, and 92% NPV in identifying childhood asthma (13). The revised CSTE algorithm requires at least one inpatient, outpatient physician visit, and emergency department visit care listing asthma as primary discharge diagnosis during a 12-month period, or at least one asthma medication dispensing event. We allowed two follow up years instead of one to capture children with mild asthma, but required two outpatient visits instead of one to be specific. Our requirements of two prescriptions for short-acting beta-agonist or montelukast in one year period also keep our algorithm specific in capturing children with asthma. In addition, children with congestive heart failure, chronic aspiration, hypogammaglobulinemia or another immunodeficiency disorder, pulmonary fibrosis, $alpha_1$-anti-trypsin deficiency, cystic fibrosis, and cancer involving the lung were excluded (10, 11). Children with early childhood asthma who had a history of one or more hospitalizations or visits to an emergency department for asthma or who were given

a prescription for a course of corticosteroids as rescue therapy between ages four to five and a half years were classified as having high-risk asthma. In addition, 2006 data for the first half of the year were available and thus asthma status between ages six to eight years and eight to ten years was ascertained for a subset of ten year old children who were continuously enrolled in TennCare.

Maternal asthma was defined for the subset of women continuously enrolled in TennCare for at least 180 days prior to pregnancy (last menstrual period minus 180 days, N = 54,235 [56.9%]) through the date of delivery with no more than 45 days of non-enrollment. Maternal asthma was ascertained using a similar algorithm as for childhood asthma (10, 11).

Statistical Analysis

Descriptive statistics were expressed as proportions for categorical variables and as means and standard deviation, or median and interquartile ranges for continuous variables depending on the distribution of the variables. Univariate and multivariable logistic regression models were constructed to analyze the relationship of infant age in days at the winter virus peak with the risk of both early childhood asthma, and among the sub-group with high-risk childhood asthma. The multivariable models were adjusted for potential confounding variables measured at the time of the infant's birth, including gender, race, birth weight, gestational age, number of living siblings, region of residence, maternal smoking, marital status, maternal education, and season. Restricted cubic splines with four knots were applied to best fit the non-linear association of infant age at the winter

virus peak with childhood asthma and infant bronchiolitis (14). Subgroup analyses with children who encountered either an early winter viral peak (before December 31) or late winter viral peak (after January 1) were done, and the relationship of childhood high-risk asthma and infant age at winter virus peak was assessed. We assessed for interactions between infant age at the winter virus peak and other covariates (gender, race, birth weight, gestational age, other living siblings, region of residence, maternal smoking, maternal asthma, maternal education, and marital status) by including cross products in the model. The 95% confidence interval (CI) for the infant age at the winter virus peak associated with the highest risk to develop early childhood and high-risk asthma were estimated using bootstrap method (14). A nested subgroup in whom maternal history was available served as the cohort to assess interaction between infant age at the winter virus peak and the familial risk factor, maternal asthma. Infants who were born before 1997 and were ten years old during 2006 were followed and their asthma status ascertained between both ages six to eight years and eight to ten years. Rates of bronchiolitis visits (including hospitalizations, emergency department visits and outpatient visits) per 1,000 children were calculated for children born in each study season, and the cumulative incidence of current high-risk childhood asthma, offset by 5-years, is graphically represented. R-software version 2.6.1 (www.r-project.org) and SAS version 9.1 (SAS Institutes; Cary, NC) were used for data analyses. We used a two-sided 5% significance level for all statistical inferences.

RESULTS

Nearly 15% of study children had early childhood asthma between ages three and a half to five and a half years. Among them, 8% required hospitalization for their asthma attacks, 27% required emergency department visits for asthma, and 31% had at least one outpatient visit for asthma during this period (Table E1). In addition, the population studied who met our enrollment criteria of remaining in the TennCare medical insurance system throughout early childhood was similar in most respects to the general TennCare population (Table E2). Notable differences include our study population having a higher proportion of Blacks, a higher proportion of children with no older siblings, higher urban residency, lower maternal education, and a higher proportion of single mothers.

In addition to what is reported in our manuscript, we did a univariate analysis of infant age at the winter virus peak on childhood high-risk asthma, and the results were similar to the multivariable analysis which adjusted for available potential confounders. In our restricted cubic spline model the knot values were chosen as recommended by Harrell (14). Sensitivity analyses indicated that the results of this model were quite robust with regard to the precise knot placements. A four-knot model tracked changes in morbidity well without being excessively sensitive to perturbations in the data. The results of four- through seven-knot models were similar to those of the four-knot model that we employed in this investigation. We additionally estimated the effect of infant age at the winter virus peak on high-risk childhood asthma by excluding infants who were born within 28 days following the peak, as the first winter virus peak they would

encounter would be in the following season, yet they would likely have significant exposure risk during early infancy. The results from this subgroup analysis were unchanged from the primary analysis. Further subgroup analysis of children born in each of the study season, which includes seasons with an early winter virus peak or late winter virus peak revealed the same pattern of increased risk of high-risk asthma related to timing of birth in relationship to the winter virus peak. Similarly, both term infants, as well as premature infants (< 37 weeks of gestational age) had the same pattern of increased high-risk asthma risk related to timing of birth in relationship to the winter virus peak.

We further studied the relationship of infant age at the winter virus peak on early childhood asthma between ages three and a half to five and a half years. Children who were 119 days (95% CI 101-132 days) old at the winter virus peak had the highest risk of developing early childhood asthma compared with children who were either younger or older at the winter virus peak (Figure E2). The infant age at the winter virus peak for early childhood asthma is nearly identical to the infant age at the winter virus peak which conferred the highest risk of bronchiolitis (122 days with 95% CI 118 – 126 days) and high-risk childhood asthma (121 days with 95% CI 108 – 131 days). There was a 17% increase in odds of developing early childhood asthma for children who were 119 days of age at the winter virus peak compared with infants who were 365 days old at the peak [Adjusted Odds Ratio (AOR): 1.17, 95% CI 1.10-1.24]. The relationship between infant age at the winter virus peak and early childhood asthma was unchanged in subgroup of

children with maternal history available and maternal asthma status was additionally adjusted for in the model.

DISCUSSION

The estimated maximum absolute risk difference in childhood asthma that is associated with infant age at the winter virus peak is 1.7%. For those infants who are three to four months of age during the winter virus peak and thus at increased risk of developing asthma, it is possible that either delay of viral exposure until they are older, or prevention would decrease their absolute risk of developing asthma by up to 1.7%. If we assume infant birth is equally distributed across the 12 months each year, among the 4,138,349 infants born annually in the US (15), there will be 689,725 infants each year who are three to four months of age during the winter virus peak. Therefore, prevention or delay of viral infection during this high risk period, could prevent 11,725 cases of early childhood asthma each year. Thus 11,725 cases of asthma are attributable to when an infant is born. These results underestimate the impact of winter viruses on early asthma development since not all infants who are approximately four-months of age at the winter virus peak are infected, and this number would be even greater if prevention or delay were applied to infants at intermediate age risk during the winter virus peak, and included other respiratory viral pathogens that likely contribute to asthma inception.

References

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Figure legends

Figure E1. Seasonality of winter viruses between July 1, 1995 to June 30, 2001. There was a total of 46,613 bronchiolitis hospitalizations captured among 426,385 infants who were ever enrolled in TennCare and experienced bronchiolitis hospitalizations during infancy over the six seasons. For each season, the first day of the week with the highest bronchiolitis hospitalization frequency was considered the winter virus peak for that season; the exact dates of the winter virus peak for each season are labeled.

***Figure E2*.** Differential risk of developing early childhood asthma in relationship to infant age at winter virus peak. Results were obtained from a multivariable logistic regression model, adjusted for gender, infant race, birth weight, gestational age, number of living siblings, region of residence, maternal smoking, marital status, maternal education, and season. (A) Predicted probability and 95% CI of developing current early childhood asthma by infant age in months at the winter virus peak (χ^2_3=31.66, p<0·001). The area under the curve is equal to the asthma prevalence of the population. (B) Adjusted Odds Ratio and 95% CI of developing current early childhood asthma relative to children who were 12 months old at the winter virus peak. Infants who were one year old at winter virus peak served as the reference group.

***Figure E3*.** Predicted probability and 95% CI of developing current high-risk childhood asthma by infant age in months at the winter virus peak in subgroups of children A: who experienced a clinically significant bronchiolitis and B: who did not experience a clinically significant bronchiolitis during infancy. Results were obtained from a

multivariable logistic regression model, adjusted for gender, infant race, birth weight, gestational age, number of living siblings, region of residence, maternal smoking, marital status, maternal education, and season. The area under the curve is equal to the high-risk asthma prevalence of the population for each subgoup.

TABLE E1. Type of asthma attacks being defined in children with early childhood asthma between ages three and a half to five and a half years (n=14,074).

Type	**Childhood asthma** N (%)
Hospitalization	1,192 (8.5%)
Emergency department visit	3,795 (27.0%)
Physician visit	4,382 (31.1%)
Asthma specific medication	4,705 (33.4%)

TABLE E2. Infant and maternal characteristics of children who were born between July 1, 1995 to June 30, 2000 and ever enrolled in TennCare (n=303,493), representing 80% of total TennCare enrollees per annual births during our study period in Tennessee.

Characteristics	**Children included in the cohort*** N=95,310 (31.4%)		**Children not included in the cohort†** N=208,183 (68.6%)		**Total TennCare enrollees** N=303,493‡	
	n	**% (95% CI)**	**n**	**% (95% CI)**	**n**	**% (95% CI)**
Infant race						
White	50,951	53.4 (53.1, 53.8)	133,677	64.2 (64.0, 64.4)	184,628	60.8 (60.7, 61.0)
Black	37,739	39.6 (39.3, 40.0)	50,995	24.5 (24.3, 24.7)	88,734	29.2 (29.1, 29.4)
Other	6,620	6.9 (6.8, 7.1)	23,511	11.3 (11.2, 11.4)	30,131	9.9 (9.8, 10.0)
Infant gender						
Male	48,895	51.3 (51.0, 51.6)	106,783	51.3 (51.1, 51.5)	155,678	51.3 (51.1, 51.5)
Female	46,615	48.7 (48.4, 49.0)	101,400	48.7 (48.5, 48.9)	147,815	48.7 (48.5, 48.9)
Siblings (n=194,590)						
None	39,574	41.6 (41.2, 41.9)	45,395	45.7 (45.4, 46.0)	84,969	43.7 (43.4, 43.9)

One or more	55,644	58.4 (58.1, 58.8)	53,977	54.3 (54.0, 54.6)	109,621	56.3 (56.1, 56.6)
Region of residence (n=193,083)						
Urban	45,555	48.2 (47.9, 48.6)	40,732	41.3 (41.0, 41.6)	86,287	44.7 (44.5, 44.9)
Suburban	21,514	22.8 (22.5, 23.1)	26,528	26.9 (26.6, 27.2)	48,042	24.9 (24.7, 25.1)
Rural	27,359	29.0 (28.7, 29.3)	31,395	31.8 (31.5, 32.1)	58,754	30.4 (30.2, 30.6)
Maternal marital status (n=194,782)						
Single	61,702	64.7 (64.4, 65.0)	51,379	51.7 (51.3, 52.0)	113,081	58.1 (57.8, 58.3)
Married	33,606	35.3 (35.0, 35.6)	48,095	48.3 (48.0, 48.7)	81,701	41.9 (41.7, 42.2)
Maternal smoking during pregnancy (n=194,198)						
No	69,602	73.2 (73.0, 73.5)	75,056	75.7 (75.4, 75.9)	144,658	74.5 (74.3, 74.7)
Yes	25,420	26.8 (26.4, 27.0)	24,120	24.3 (24.1, 24.6)	49,540	25.5 (25.3, 25.7)
Maternal education level (n=194,402)						

<12	42,249	44.4 (44.1, 44.7)	30,767	31.0 (30.7, 31.3)	73,016	37.6 (37.3, 37.8)
12	41,563	43.7 (43.4, 44.0)	45,461	45.8 (45.5, 46.1)	87,024	44.8 (44.5, 45.0)
>12	11321	11.9 (11.7, 12.1)	23041	23.2 (22.9, 23.5)	34362	17.7 (17.5, 17.8)
		Median (IQR[§])		**Median (IQR)**		**Median (IQR)**
Birth weight, grams (n=194,764)	95,304	3203 (2863, 3544)	99,460	3232 (2863, 3600)	194,764	3232 (2863, 3572)
Gestational age, weeks (n=194,049)	95,148	39.1 (38.1, 40.1)	98,901	39.1 (38.1, 40.1)	194,049	39.1 (38.1, 40.1)
Maternal Age, years (n=194,376)	95,125	22 (19, 26)	99,251	22 (19, 27)	194,376	22 (19, 26)

*Children who were continuous enrolled in TennCare with no more than 21 days of non-enrollment from the date of birth through the first birthday and no more than 60 days of non-enrollment from age three and a half years through five and a half years, and hence were included in our study cohort. .

†Children who were ever enrolled in TennCare but not meet our continuous enrollment criteria for the study and hence were not included in our study cohort.

[‡]Children who were born during our study period and ever enrolled in TennCare.

[§]IQR: interquartile range

Figure E1.

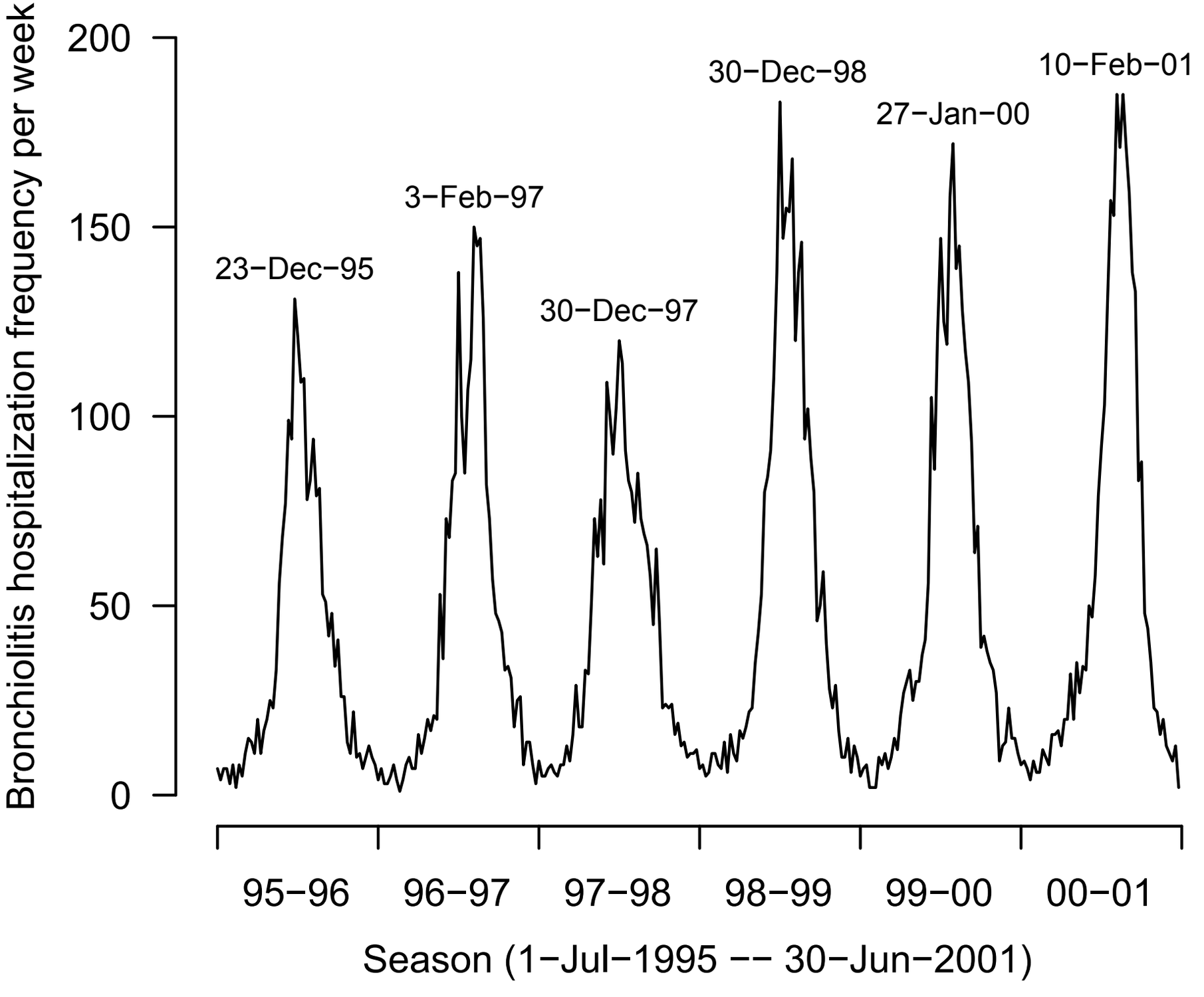

Bronchiolitis hospitalization frequency per week
200
150
100
50
0
23−Dec−95
3−Feb−97
30−Dec−97
30−Dec−98
27−Jan−00
10−Feb−01
95−96
96−97
97−98
98−99
99−00
00−01
Season (1−Jul−1995 −− 30−Jun−2001)

Figure E2.

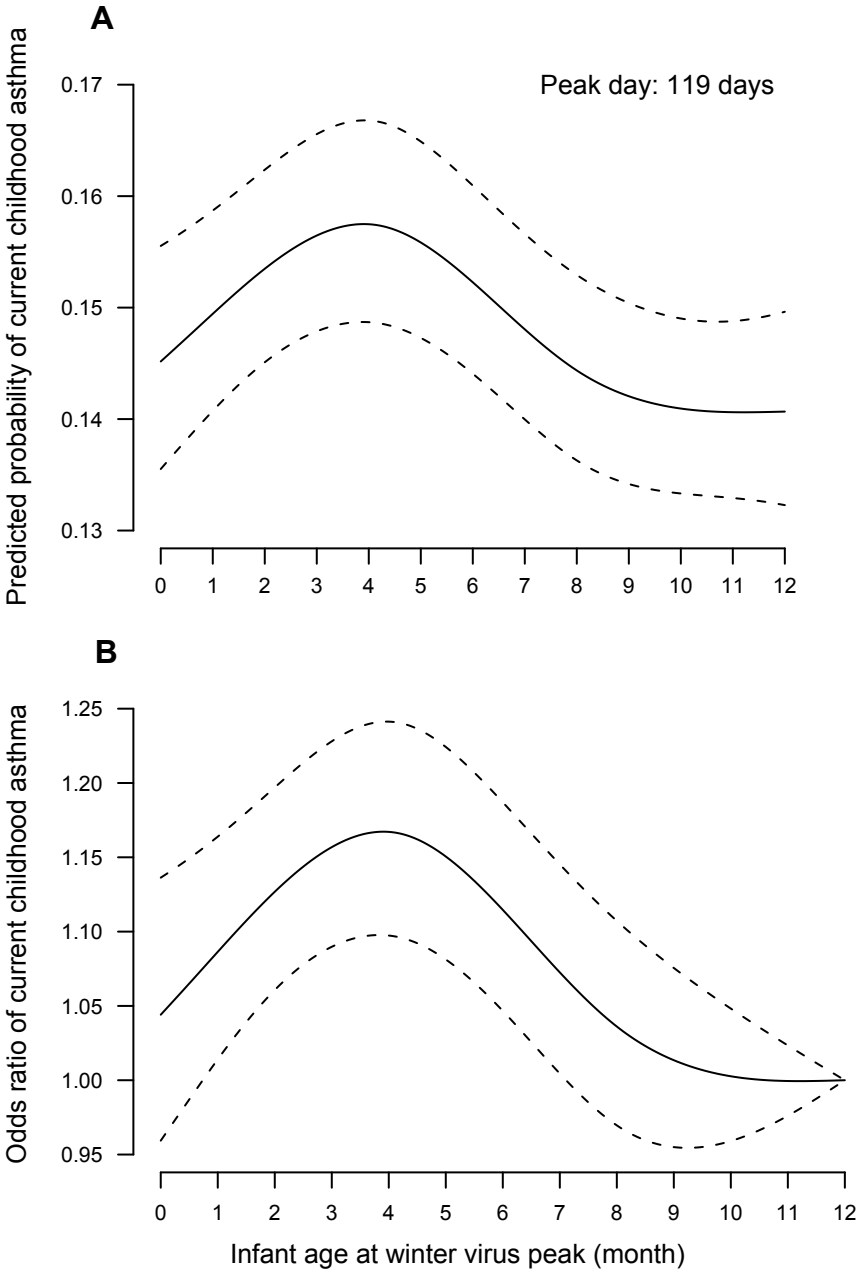
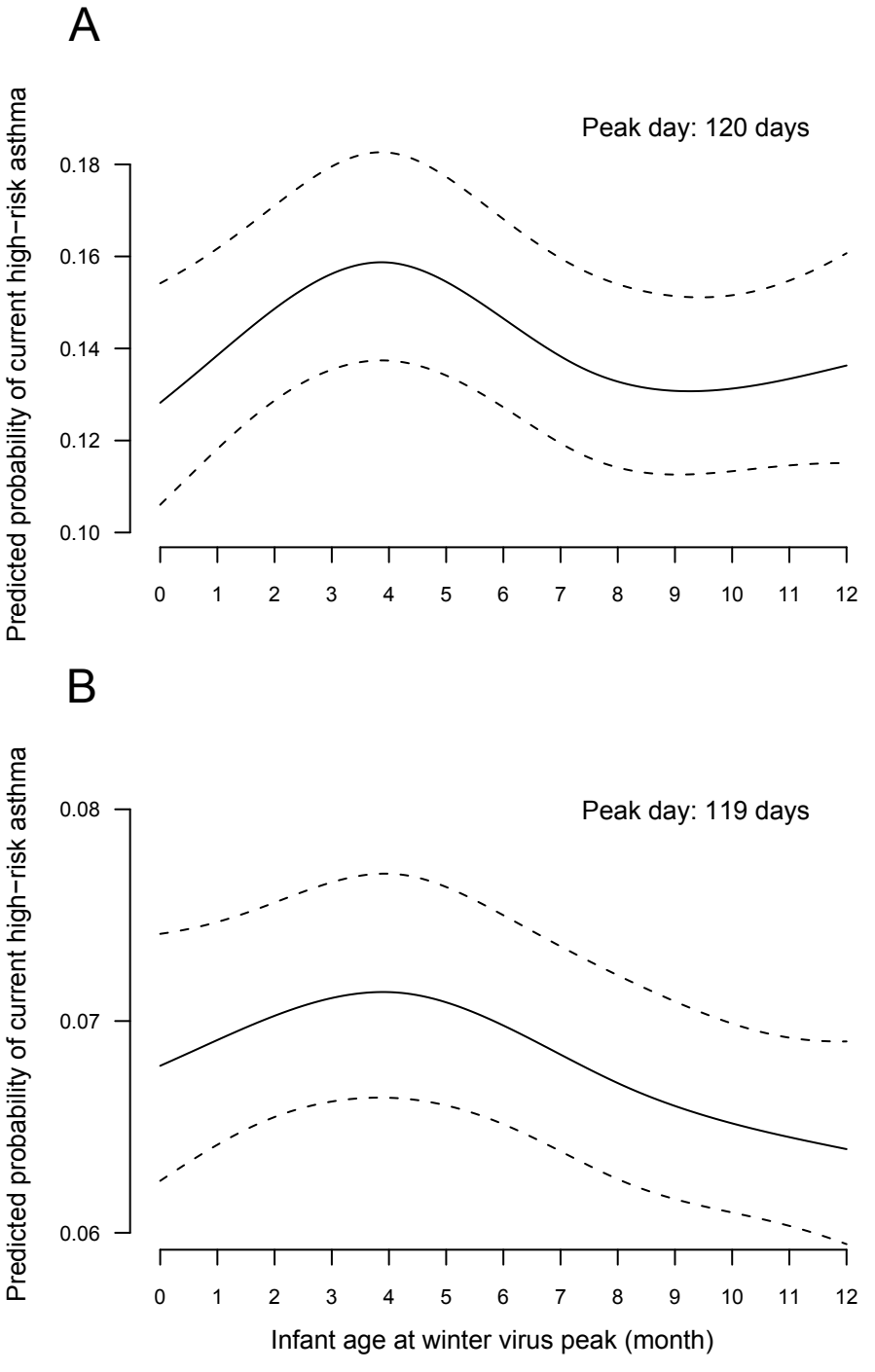

A
Peak day: 119 days
Predicted probability of current childhood asthma
0.17
0.16
0.15
0.14
0.13
0 1 2 3 4 5 6 7 8 9 10 11 12
B
Odds ratio of current childhood asthma
1.25
1.20
1.15
1.10
1.05
1.00
0.95
0 1 2 3 4 5 6 7 8 9 10 11 12
Infant age at winter virus peak (month)

Figure E3.


A
Peak day: 120 days
Predicted probability of current high−risk asthma
0.18
0.16
0.14
0.12
0.10
0 1 2 3 4 5 6 7 8 9 10 11 12
B
Peak day: 119 days
Predicted probability of current high−risk asthma
0.08
0.07
0.06
0 1 2 3 4 5 6 7 8 9 10 11 12
Infant age at winter virus peak (month)