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Title: Increasing rates of influenza vaccination were associated with lower asthma prevalence in United States children

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Summary: This study sought to determine whether trends of increasing influenza vaccination contributed to decreasing asthma prevalence in US children. Data were analyzed from the National Health Interview Survey, a cross-sectional US population-based annual survey conducted between 2005 and 2018. There were significant interactions between influenza vaccination and year as predictors of current asthma prevalence at all ages and ages 6-10 and 11-17 years in linear and spline models. That is, there were greater decreases of current asthma prevalence among children who were vaccinated compared to those who were not vaccinated for influenza. Similar results were found among those with high-risk or low-risk of asthma, as judged by personal or family history of atopic disease. The increasing trend of influenza vaccination was associated with reduced odds of current asthma in children. Future research is needed to determine if widespread influenza vaccination may be an important population-based intervention to lower childhood asthma prevalence.

To the editor:

Rapidly changing asthma prevalence trends in the US¹ suggest there are environmental and/or epigenetic factors at play, rather than alterations in population genetics². Respiratory syncytial virus, rhinovirus and influenza are common viral triggers for asthma induction or exacerbation. There is evidence to suggest that influenza vaccination is protective against asthma exacerbation³. We hypothesized that widespread influenza vaccination decreased influenza cases (a potential asthma trigger) and secondarily reduced asthma prevalence in the US population. This study sought to determine whether asthma is associated with increased influenza vaccination and whether influenza vaccination trends contributed to trends of asthma prevalence in US children.

We examined data from the 2005-2018 National Health Interview Survey. The cohort, outcome measures and statistical analyses (SAS v9.4.3 [SAS Institute, Cary, NC]) are described in Supplemental Methods. Multivariable logistic regression models were constructed including current asthma (outcome), influenza vaccination (exposure), survey year (modifier), and an interaction term between influenza vaccination and year, sociodemographic characteristics and comorbidities (confounding variables). Cohorts were stratified by age (0-5/6-10/11-17), personal history of atopic disease (yes [high risk of asthma]/no [low risk of asthma]), and parental history of atopic disease (yes/no). The study was approved by the institutional review board at Northwestern University. Data were analyzed from 124,569 children (weighted frequency 821,695,120) from years 2005-2018 (Supplemental Table 1).

Children with current history of asthma had higher odds of influenza vaccinations overall and when stratified by personal history of atopy or parental history for asthma (Supplemental Results).

Current prevalence of childhood asthma increased from 2005-2006 to a peak around 2011-2012 and decreased to a low in 2017-2018 (Supplemental Results).

There were significant interactions between influenza vaccination and year as predictors for current asthma at ages 6-10 (both: $P < 0.0001$) and 11-17 years (both: $P < 0.0001$) in linear and spline models, but not at ages 0-5 (linear: $P = 0.153$, spline: $P = 0.0901$).

There were greater decreases in the odds of current asthma prevalence among children who were vaccinated (all ages, 6-10, 11-17 years) compared to those who were not vaccinated for influenza (all ages, 6-10, 11-17 years) from 2005-2006 to 2017-2018 (Table 1).

Similar results were observed in those with or without a personal or family history of atopic disease (Table 2 and Supplemental Results). Study strengths and limitations are presented in the supplemental discussion.

Strengths of this study include use of a nationally representative, population-based survey, over 14 years, and controlling of potential confounders. Limitations include lack of data outside US, cross-sectional nature, caregiver reported outcomes, lack of data regarding asthma severity, vaccination route, and other vaccine types, and potential residual confounding (Supplemental Material).

The increasing trend of influenza vaccination may have contributed to the declining prevalence of current asthma among US children in the past decade. The odds of current asthma significantly decreased over time in vaccinated children, while decreasing to a lesser extent in unvaccinated children, overall and in those with or without a personal and/or parental history of atopic disease. Previous retrospective studies found that the influenza vaccination had a protective effect in children asthma and was associated with a reduction of asthma exacerbations and oral steroid use in asthma management^{4,5}. In contrast, one Netherlands-based randomized control trial (n=696) compared the effects of influenza vaccination vs. placebo and found no differences in number or severity of asthma exacerbations, though influenza-related complications and need for ventilation were not assessed⁶. Though we were unable to assess asthma severity, we found that at the population-level, widespread influenza vaccination in children was associated with lower asthma prevalence. Future research is needed to determine if widespread influenza vaccination may be an important population-based intervention to lower childhood asthma prevalence.

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Table 1. Association of current asthma prevalence and year in US children that have and have not received influenza vaccinations.								
Current Asthma	Influenza Vaccine	Adjusted OR (95% CI)						
		2005-2006	2007-2008	2009-2010	2011-2012	2013-2014	2015-2016	2017-2018
Overall	No	1.00 (ref)	0.956 (0.859-1.064)	0.945 (0.854-1.045)	1.008 (0.911-1.115)	0.94 (0.848-1.043)	0.918 (0.823-1.023)	0.824 (0.729-0.932)
	Yes	1.00 (ref)	0.836 (0.721-0.97)	0.685 (0.598-0.784)	0.618 (0.544-0.702)	0.556 (0.489-0.632)	0.575 (0.506-0.655)	0.461 (0.4-0.531)
0-5	No	1.00 (ref)	0.952 (0.756-1.201)	0.785 (0.627-0.983)	0.915 (0.732-1.144)	0.73 (0.576-0.924)	0.562 (0.428-0.739)	0.53 (0.387-0.727)
	Yes	1.00 (ref)	0.776 (0.6-1.005)	0.668 (0.525-0.849)	0.644 (0.515-0.805)	0.471 (0.371-0.597)	0.494 (0.387-0.63)	0.489 (0.374-0.639)
6-10	No	1.00 (ref)	0.857 (0.702-1.047)	1.003 (0.835-1.205)	0.932 (0.77-1.127)	1.029 (0.854-1.239)	1.097 (0.904-1.331)	0.749 (0.594-0.946)
	Yes	1.00 (ref)	0.735 (0.55-0.981)	0.587 (0.451-0.762)	0.544 (0.426-0.694)	0.484 (0.379-0.618)	0.48 (0.375-0.616)	0.312 (0.237-0.411)
11-17	No	1.00 (ref)	1.035 (0.89-1.205)	1.012 (0.877-1.167)	1.141 (0.99-1.315)	0.994 (0.857-1.154)	1.027 (0.882-1.196)	1.025 (0.87-1.209)
	Yes	1.00 (ref)	0.88 (0.689-1.126)	0.642 (0.513-0.802)	0.528 (0.427-0.651)	0.541 (0.44-0.665)	0.566 (0.46-0.696)	0.462 (0.37-0.576)

Adjusted odds ratio were determined by multivariable logistic regression models with current asthma as the dependent variable(outcome) and influenza vaccination (exposure), survey year (modifier), and an interaction term between them (influenza vaccination and year) as the independent variables, controlling for sex (male/female), age (continuous), race (white/non-white), highest household education(less than high school [HS]/≥HS), poverty-to-income ratio (<1.00/≥1.00), insurance coverage (yes/no), number of annual visits to doctor's office and ED (0, 1, 2-3, 4-9, 10-12, 13+), caregiver currently smoking (yes/no), atopic dermatitis (yes/no), hay fever (yes/no), and food allergy (yes/no).

Table 2. Association of current asthma prevalence and year in US children that have and have not received influenza vaccinations by risk and family history of atopy.

Current Asthma	Influenza Vaccine	Adjusted OR (95% CI)						
		2005-2006	2007-2008	2009-2010	2011-2012	2013-2014	2015-2016	2017-2018
Low Risk	No	1.00 (ref)	0.967 (0.844-1.108)	0.974 (0.857-1.108)	0.984 (0.864-1.12)	0.972 (0.851-1.111)	0.832 (0.72-0.961)	0.841 (0.717-0.987)
	Yes	1.00 (ref)	0.824 (0.682-0.995)	0.651 (0.547-0.775)	0.648 (0.551-0.762)	0.547 (0.465-0.645)	0.554 (0.469-0.655)	0.432 (0.359-0.521)
High Risk	No	1.00 (ref)	0.936 (0.788-1.111)	0.896 (0.764-1.052)	1.036 (0.882-1.216)	0.896 (0.76-1.056)	1.032 (0.874-1.218)	0.8 (0.662-0.966)
	Yes	1.00 (ref)	0.877 (0.691-1.114)	0.754 (0.608-0.935)	0.592 (0.483-0.724)	0.58 (0.474-0.711)	0.62 (0.506-0.761)	0.51 (0.41-0.635)
No Family Hx	No	1.00 (ref)	0.971 (0.854-1.104)	0.938 (0.83-1.059)	0.988 (0.874-1.116)	0.976 (0.862-1.105)	0.944 (0.828-1.077)	0.773 (0.665-0.899)
	Yes	1.00 (ref)	0.86 (0.72-1.027)	0.753 (0.641-0.885)	0.631 (0.542-0.735)	0.549 (0.471-0.64)	0.562 (0.48-0.656)	0.457 (0.385-0.542)
Family Hx	No	1.00 (ref)	0.938 (0.771-1.141)	0.956 (0.797-1.146)	1.083 (0.9-1.302)	0.877 (0.724-1.063)	0.83 (0.683-1.008)	0.908 (0.733-1.124)
	Yes	1.00 (ref)	0.724 (0.548-0.956)	0.513 (0.397-0.664)	0.567 (0.446-0.72)	0.542 (0.427-0.688)	0.56 (0.44-0.711)	0.423 (0.327-0.548)

Adjusted odds ratio were determined by multivariable logistic regression models with current asthma as the dependent variable(outcomes) and influenza vaccination (exposure), survey year (modifier), and an interaction term between them (influenza vaccination and year) as the independent variables, controlling for sex (male/female), age (continuous), race (white/non-white), highest household education(less

than high school [HS]/≥HS), poverty-to-income ratio (<1.00/≥1.00), insurance coverage (yes/no), number of annual visits to doctor's office and ED (0, 1, 2-3, 4-9, 10-12, 13+), caregiver currently smoking (yes/no), atopic dermatitis (yes/no), hay fever (yes/no), and food allergy (yes/no).

Supplemental Methods

Study design

The NHIS is a randomly sampled US population-based household survey implemented by trained interviewers in English and Spanish via computer based methods by the National Center for Health Statistics using a multistage sampling procedure and sample weights allowing for nationally representative estimates of the non-institutionalized US population. The sampling methodology of the core NHIS surveys (family, household, child) have remained relatively consistent from 2005 to 2018. Surveys were completed by a caregiver for a random child in each household (if any children are present). A detailed methodology of the NHIS has been previously described¹.

Outcome Measures

Lifetime asthma prevalence was determined by a positive response to “Has a doctor or other health professional ever told you that your child had asthma?” Current asthma prevalence was determined by a positive response to “Does your child still have asthma?” One-year prevalence of influenza vaccination was determined by a positive response to “During the past 12 months, has your child had a flu vaccination?” High risk of asthma was determined by a positive response to a 12-month history of atopic dermatitis, hay fever, or food allergy. Family history of atopy was determined by a positive response to caregiver lifetime history of asthma or hay fever.

Statistical Analysis

Statistical analyses incorporated sample weights that adjusted for age, sex, race, household size and highest education. Weighted frequencies, proportions, and 95% confidence intervals of asthma and influenza vaccination prevalence were estimated per 2-year intervals. Multivariate logistic regression models were constructed with current asthma (yes/no) as the independent variable and influenza vaccination (yes/no) as the dependent variable. Models were adjusted for sex (male/female), age (continuous), race (white/non-white), highest household education (less than high school [HS]/≥HS), poverty-to-income ratio (<1.00/≥1.00), insurance coverage (yes/no), number of annual visits to doctor’s office (0, 1, 2-3, 4-9, 10-12, 13+), number of annual ER visits (0, 1, 2-3, 4-9, 10-12, 13+), caregiver currently smoking (yes/no), atopic dermatitis, hay fever, and food allergy (yes/no) as covariates. Covariates were selected a priori based on previous associations with asthma²⁻⁴; these were all shown to be associated with asthma in bivariable analyses. To determine if associations were different in older children and those with higher risk for asthma, models were repeated with cohorts stratified by age (0-5/6-10/11-17), personal history of atopy (yes [high risk of asthma]/no [low risk of asthma]), and family history of atopy (yes/no).

To determine the relationship between secular trends of influenza vaccination and asthma prevalence, logistic regression models were constructed with current prevalence of asthma, and survey year (2005-2006/2007-2008/2009-2010/2011-2012/2013-2014/2015-2016/2017-2018), influenza vaccination, and a two-way

interaction term between them as the independent variables, and the aforementioned socio-demographics as covariables. A partitioned analysis was included to determine the odds ratio of asthma in those with and without the influenza vaccination within each 2-year bin. Models were tested using linear and spline interactions for survey year. Interactions between covariates were included in the final models if P-value <0.01, cell frequencies >5 for each level of interaction and modification of estimates by >20%. We hypothesized that influenza vaccination may have stronger effects on asthma prevalence in children who are younger and have lower risk for asthma. Thus, models were also stratified by age (0-5/6-10/11-17 years), low and high risk of asthma (yes/no), and family history of atopy (yes/no).

Supplemental Results

Trends of asthma prevalence

Current prevalence [95% CI] of asthma increased from 2005-2006 (9.1% [8.6-9.5%]) to 2009-2010 (9.5% [9.0-10.1%]) and then decreased until 2017-2018 (8.0% [7.4-8.5%]) (Supplemental Figure 1A). Current asthma prevalence decreased in children ages 0-5 years (7.0% [6.2-7.7%] to 4.7% [3.9-5.4%]) and 6-10 years (10.5% [9.5-11.6%] to 8.1% [7.1-9.1%]), but not in ages 11-17 years (9.8% [9.1-10.6%] to 10.6% [9.7-11.5%]).

Trends of influenza vaccination

The proportion of influenza vaccinations continuously increased from 17.2% (16.5-17.8%) to 48.1% (47.0-49.3%) from 2005-2006 to 2017-2018 overall (Supplemental Figure 1B), and in ages 0-5 years (26.3% [25.0-27.5%] to 51.7% [49.9-53.6%]), 6-10 years (15.2% [13.9-16.5%] to 50.1% [48.0-52.2%]), and 11-17 years (11.1% [10.3-12.0%] to 43.8% [42.4-45.3%]).

Association of current asthma and influenza vaccination

Children with current asthma also had higher odds of influenza vaccination overall (1.548 [1.454-1.648]) and in ages 0-5 (1.412 [1.258-1.584]), 6-10 (1.537 [1.375-1.717]), and 11-17 years (1.579 [1.447-1.724]). Similarly, odds of influenza vaccination were higher in children with current asthma when stratified by low (1.525 [1.405-1.656]) and high (1.609 [1.474-1.757]) risk of asthma and without (1.550 [1.456-1.650]) and with (1.539 [1.431-1.655]) family history of atopy. Among those with lifetime asthma, there was a higher rate of influenza vaccination in children with current asthma (48.5%) than without (39.3%) (Chi-Square P-value: <0.0001).

Trends of current asthma and influenza vaccination in different patient subsets

Between 2005-2006 and 2017-2018, current asthma prevalence decreased in children without other atopic disease (6.6% [6.1-7.1%] to 5.3% [4.7-5.9%]), but not in those with ≥ 1 atopic disease (19.3% [17.8-20.9%] to 16.9% [15.3-18.5%]) (Supplemental Figure 2A). Those without parental history of asthma had a decrease in current asthma (7.4% [6.9-7.9%] to 6.2% [5.6-6.8%]), while those with parental history of asthma did not (17.7% [16.0-19.4%] to 16.0% [14.2-17.8%]).

Influenza vaccinations also increased in children with (22.1% [20.5-23.7%] to 51.5% [49.2-53.7%]) and without (16.2% [15.4-17.0%] to 47.6% [46.2-49.0%]) atopic disease, and with (21.1% [19.2-23.0%] to 51.7% [49.3-54.1%]) and without (16.6% [15.8-17.3%] to 47.8% [46.4-49.2%]) family history of atopy (Supplemental Figure 2B).

There were also significant interactions between influenza vaccination and time as predictors of current asthma in children when stratified by personal history of atopic disease and parental history of asthma in both linear and spline models (all $P < 0.0001$). From 2005-2006 to 2017-2018, the odds of current asthma decreased over time in vaccinated children without (0.824 [0.682-995] to 0.432 [0.359-0.521]) and with (0.887 [0.691-1.114] to 0.51 [0.41-0.635]) atopic disease but did not significantly decrease in unvaccinated children (no atopic disease: 0.967 [0.844-1.108] to 0.841 [0.717-0.987]; atopic disease: 0.936 [0.788-1.111] to 0.8 [0.662-0.966]) children. Similarly, the odds of asthma decreased over time in influenza-vaccinated children with (0.724 [0.548-0.956] to 0.423 [0.327-0.548]) and without (0.86 [0.72-1.027] to 0.457 [0.385-0.542]) parental history of asthma, but not in unvaccinated children (without parental asthma: 0.971 [0.854-1.104] to 0.773 [0.665-0.899]; with parental asthma: 0.938 [0.771-1.141] to 0.908 [0.733-1.124]).

Supplemental Discussion

Study Limitations

Strengths of this study include use of a nationally representative, population-based survey, over 14 years, and controlling of potential confounders. However, there are limitations. The survey sampled from the US and may not be generalizable to children of countries. The study was cross-sectional, which precluded the ability to assess individual risk reduction for asthma in vaccinated children or the effect of repeated influenza vaccinations over multiple years. In addition, we are unable to make any statements regarding causality of the associations. Family history of asthma was determined by caregiver report rather than from a clinician's exam. This may lead to potential misclassification, as it was based on a relatively non-specific question "Does your child still have asthma?" Additionally, the symptoms of asthma are often non-specific in infants, which may also be a source of misclassification in analyses of children under 5 years old. Also, parental history of atopic disease was only assessed in one parent. Furthermore, there was a lack of data regarding asthma severity, vaccination route, other vaccine types, and past years of vaccination that may act as potential confounders. Finally, despite controlling for many potential confounders, residual confounding from other factors is possible, e.g. other viruses, diet, and air pollution.

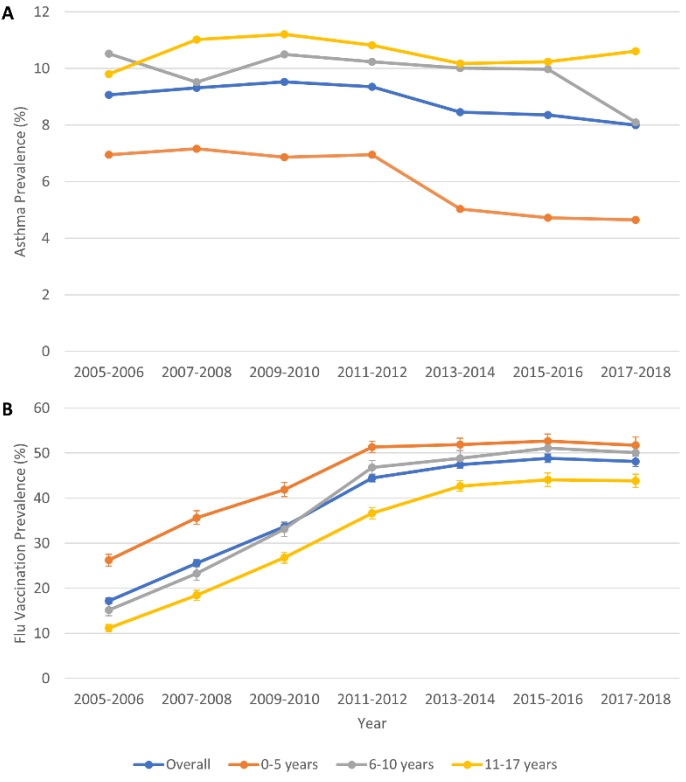
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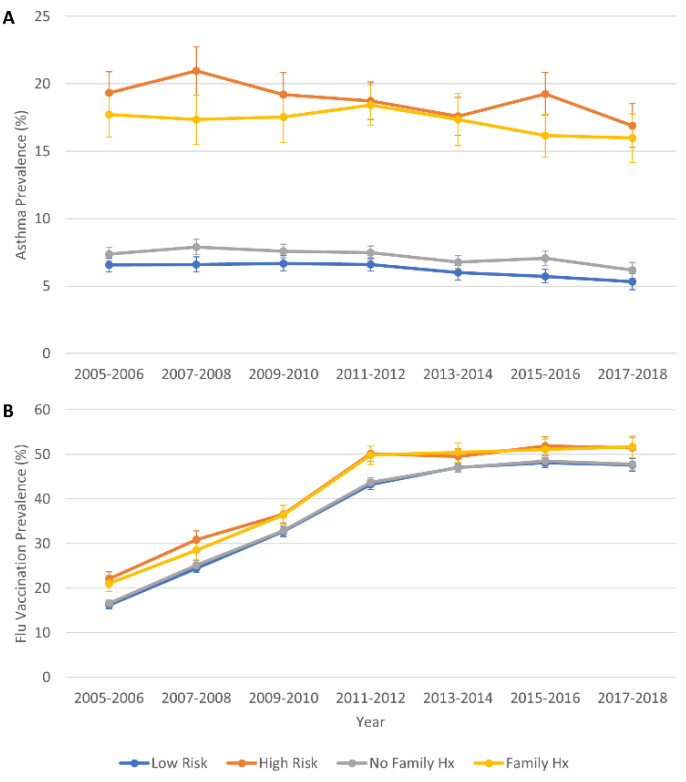
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Supplemental Table 1. Demographics of sample population by current asthma.			
Variable	No Asthma	Current Asthma	P-
Sex			
Male	50.4 (50-50.7)	57.3 (56.1-58.5)	<.0001
Female	49.6 (49.3-50)	42.7 (41.5-43.9)	
Age			
0-5	34.3 (33.9-34.7)	22.7 (21.7-23.8)	<.0001
6-10	27.5 (27.1-27.8)	30.8 (29.7-31.9)	
11-17	38.2 (37.9-38.6)	46.4 (45.2-47.7)	
Race			
White	77.4 (76.8-78)	67.3 (66-68.6)	<.0001
Non-White	22.6 (22-23.2)	32.7 (31.4-34)	
PIR			
<1.00	20.8 (20.3-21.3)	27.7 (26.5-29)	<.0001
≥1.00	79.2 (78.7-79.7)	72.3 (71-73.5)	
Highest Household Education			
<HS	10.1 (9.7-10.5)	10.6 (9.8-11.4)	0.2206
≥HS	89.9 (89.5-90.3)	89.4 (88.6-90.2)	
Insurance			
No	7.1 (6.9-7.4)	4.9 (4.4-5.5)	<.0001
Yes	92.9 (92.6-93.1)	95.1 (94.5-95.6)	
Number of annual office visits			
0	10.1 (9.8-10.3)	4.5 (4-5)	<.0001
1	23.2 (22.9-23.5)	12.7 (12-13.4)	
2-3	37.1 (36.7-37.5)	32.6 (31.5-33.8)	
4-9	24.1 (23.8-24.5)	35.4 (34.3-36.6)	
10-12	2.7 (2.6-2.8)	6.7 (6.1-7.3)	
13+	2.8 (2.6-2.9)	8 (7.3-8.7)	
Number of annual ED visits			
0	81.9 (81.6-82.3)	66 (64.8-67.2)	<.0001
1	12.4 (12.2-12.7)	17.6 (16.7-18.6)	
2-3	4.7 (4.5-4.9)	11.8 (11-12.6)	
4-9	0.8 (0.8-0.9)	4 (3.5-4.4)	
10-12	0.1 (0.1-0.1)	0.4 (0.2-0.5)	
13+	0 (0-0.1)	0.2 (0.1-0.4)	
Caregiver Currently Smoking			
No	85.6 (81.2-82.0)	77.1 (76.1-78.2)	<.0001
Yes	18.4 (18.0-18.8)	22.9 (21.8-23.9)	
Eczema			
No	89.2 (89-89.5)	75.2 (74.1-76.3)	<.0001
Yes	10.8 (10.5-11)	24.8 (23.7-25.9)	
Hay Fever			
No	92.4 (92.1-92.6)	76.6 (75.6-77.6)	<.0001
Yes	7.6 (7.4-7.9)	23.4 (22.4-24.4)	
Food Allergy			
No	95.4 (95.2-95.6)	86.6 (85.7-87.4)	<.0001
Yes	4.6 (4.4-4.8)	13.4 (12.6-14.3)	

Proportions were estimated using sample weights. P-values refer to Chi Square Analysis.



Supplemental Figure 1. Secular trends of (A) current asthma and (B) influenza vaccination prevalence, overall and by age group (0-5/6-10/11-17 years) among US children from 2005-2006 to 2017-2018.



Supplemental Figure 2. Secular trends of (A) current asthma and (B) influenza vaccination prevalence by low and high risk and family history of atopy among US children from 2005-2006 to 2017-2018.