

## **Guidelines for Early Food Introduction and Patterns of Food Allergy**

### **Supplemental Methods**

**Interrupted Time Series Analysis.** Our primary outcome models used a generalized least squares (GLS) method using monthly data on the percentage of two-year olds with IgE-mediated food allergy between 1/1/2014 and 1/1/2020 to perform segmented linear regression with fixed effects of time interval, food guidelines status (pre- and post-guidelines), and an interaction term for time elapsed since the start of the guidelines. We accounted for autocorrelation in the GLS model by using an autoregressive moving-average correlation structure (corARMA) with maximum likelihood. This method allowed us to add the corARMA structure by specifying values of the autoregressive order (p) and moving-average order (q). We used Akaike information criterion (AIC) to choose the values of p and q for the model with the lowest AIC value.<sup>1</sup> We determined the coefficients and 95% confidence intervals for the effect of the interaction term, which estimates the slope change between the post-guidelines regression line slope and the counterfactual trend line slope. In addition, we extrapolated the pre-guidelines trend line to the post-guidelines period and calculated the mean difference in outcome between the post-guidelines regression line and pre-guidelines extrapolated line at time points subsequent to the publication of early food introduction guidelines. The confidence interval for this difference value was obtained by bootstrapping using 500 resamples of the data and using the 2.5% and 97.5% values of the difference from the two regression lines. Data were analyzed using R software (version 3.6).

<sup>1</sup>Schaffer AL, Dobbins TA, Pearson SA. Interrupted time series analysis using autoregressive integrated moving average (ARIMA) models: a guide for evaluating large-scale health interventions. *BMC Med Res Methodol*. 2021 Mar 22;21(1):58.

## **Supplemental Figure Legends**

**Supplemental Figure 1. Cox proportional hazards modeling.** Proportion of children with atopic dermatitis (AD) diagnosis during the post-guidelines (or post-addendum guidelines) versus pre-guidelines periods. Results are shown for models adjusted for age at cohort entry, sex, race, and ethnicity. Dashed lines represent 95% confidence intervals. HR, hazard ratio.

**Supplemental Figure 2. Interrupted time analysis, post-initial guidelines.** Monthly percentages of two-year old children with IgE-mediated food allergy (IgE-FA) diagnosis before and after the publication of early introduction guidelines (intervention, vertical black line). The solid teal, dashed red, and solid red lines represent the pre-intervention, counterfactual, and post-intervention trend lines, respectively.

**Supplemental Figure 3. Interrupted time analysis, post-addendum guidelines.** Monthly percentages of two-year old children with IgE-mediated food allergy (IgE-FA) diagnosis before and after the publication of early introduction addendum guidelines (intervention, vertical black line). The solid teal, dashed red, and solid red lines represent the pre-intervention, counterfactual, and post-intervention trend lines, respectively.

### **Supplemental Figure Alt Text**

**Supplemental Figure 1.** Graphs of Cox proportional hazards models, comparing post-guidelines (purple) vs. pre-guidelines (teal) or post-addendum guidelines (red) vs. pre-guidelines (teal) cohorts, with the x-axis depicting age in years and y-axis depicting the proportion of children with atopic dermatitis (AD). For all comparisons, the risk of development of atopic dermatitis by age two, as quantified by the hazard ratio (HR), was significantly higher in the post-guidelines and post-addendum cohorts.

**Supplemental Figure 2.** Interrupted time series line graph depicting monthly intervals (x-axis) and percentages of two-year old children diagnosed with IgE-mediated food allergy (y-axis) before and after the publication of initial early introduction guidelines (intervention, vertical black line) and prior to the publication of post-addendum guidelines. Compared with the slope of the counterfactual trend line (dotted red), which is an extrapolation of the pre-intervention trend line (teal), the slope of the post-intervention trend line (solid red) demonstrates a significant decline in the rate of diagnosis of IgE-mediated food allergies.

**Supplemental Figure 3.** Interrupted time series line graph depicting monthly intervals (x-axis) and percentages of two-year old children diagnosed with IgE-mediated food allergy (y-axis) before the publication of initial early introduction guidelines and after the publication of early introduction addendum guidelines (intervention, vertical black line). Compared with the slope of the counterfactual trend line (dotted red), which is an extrapolation of the pre-intervention trend

line (teal), the slope of the post-intervention trend line (solid red) demonstrates a significant decline in the rate of diagnosis of IgE-mediated food allergies.

## Supplemental Tables

**Table S1: Geographic distribution of subjects<sup>1</sup>**

| State          | Pre-guidelines |        | Post-initial guidelines |        | Post-addendum guidelines |        |
|----------------|----------------|--------|-------------------------|--------|--------------------------|--------|
|                | <i>n</i>       | %      | <i>n</i>                | %      | <i>n</i>                 | %      |
| Alabama        | –              | –      | 11                      | 0.024  | –                        | –      |
| Arizona        | 8              | 0.021  | 10                      | 0.021  | –                        | –      |
| California     | 22             | 0.057  | 27                      | 0.058  | –                        | –      |
| Colorado       | 15             | 0.039  | 6                       | 0.013  | –                        | –      |
| Connecticut    | 11             | 0.029  | 8                       | 0.017  | –                        | –      |
| Delaware       | 182            | 0.472  | 178                     | 0.381  | 148                      | 0.374  |
| Florida        | 47             | 0.122  | 39                      | 0.084  | 13                       | 0.033  |
| Georgia        | 391            | 1.013  | 460                     | 0.985  | 249                      | 0.629  |
| Illinois       | 10             | 0.026  | 13                      | 0.028  | –                        | –      |
| Indiana        | 8              | 0.021  | –                       | –      | –                        | –      |
| Kansas         | 6              | 0.016  | –                       | –      | –                        | –      |
| Kentucky       | 53             | 0.137  | 48                      | 0.103  | 27                       | 0.068  |
| Louisiana      | –              | –      | 6                       | 0.013  | –                        | –      |
| Maryland       | 35             | 0.091  | 444                     | 0.951  | 278                      | 0.702  |
| Massachusetts  | 12             | 0.031  | 6                       | 0.013  | –                        | –      |
| Michigan       | 14             | 0.036  | 8                       | 0.017  | –                        | –      |
| New Jersey     | 4,478          | 11.603 | 4,836                   | 10.360 | 4,065                    | 10.267 |
| New Mexico     | 37             | 0.096  | 20                      | 0.043  | 13                       | 0.033  |
| New York       | 153            | 0.396  | 125                     | 0.268  | 66                       | 0.167  |
| North Carolina | 2,423          | 6.278  | 5,977                   | 12.804 | 3,544                    | 8.951  |
| Ohio           | 15             | 0.039  | 10                      | 0.021  | –                        | –      |
| Oklahoma       | –              | –      | 6                       | 0.013  | –                        | –      |
| Pennsylvania   | 20,633         | 53.462 | 22,915                  | 49.090 | 23,656                   | 59.746 |
| South Carolina | 4,803          | 12.445 | 6,670                   | 14.289 | 3,814                    | 9.633  |
| Tennessee      | 14             | 0.036  | 12                      | 0.026  | –                        | –      |
| Texas          | 1,842          | 4.773  | 1,364                   | 2.922  | 792                      | 2.000  |
| Vermont        | 778            | 2.016  | 908                     | 1.945  | 574                      | 1.450  |
| Virginia       | 43             | 0.111  | 29                      | 0.062  | 10                       | 0.025  |
| Washington     | 10             | 0.026  | 8                       | 0.017  | –                        | –      |
| West Virginia  | 7              | 0.018  | –                       | –      | –                        | –      |
| Unreported     | 2,544          | 6.592  | 2,536                   | 5.433  | 2,345                    | 5.923  |
| <b>Total</b>   | 38,594         | 100.0  | 46,680                  | 100.0  | 39,594                   | 100.0  |

<sup>1</sup>Geographic distribution of children was inferred based on zipcode data. The “Unreported” category includes children for whom geographic data was unavailable and those from states in which there were five or fewer subjects (to protect patient privacy).

**Table S2: Mean and cumulative observation time of cohorts**

|   | <b>Minimum 2-year observation</b>            |                  |  |                  |
|---|--|------------------|--|------------------|
|   | <b>Mean observation time (person-months)</b> |                  | <b>Cumulative observation time (person-months)</b> |                  |
|   | <b>IgE-FA</b>                                | <b>No IgE-FA</b> | <b>IgE-FA</b>                                      | <b>No IgE-FA</b> |
|   |  |                  |  |                  |
| <b>Pre-guidelines<sup>1</sup></b>           | 32.4   | 30.5             | 24,785   | 1,152,010        |
| <b>Post-guidelines<sup>2</sup></b>          | 33.3   | 29.9             | 19,187   | 1,378,582        |
| <b>Minimum 1-year observation</b>           |  |                  |  |                  |
|   | <b>Mean observation time (person-months)</b> |                  | <b>Cumulative observation time (person-months)</b> |                  |
|   | <b>IgE-FA</b>                                | <b>No IgE-FA</b> | <b>IgE-FA</b>                                      | <b>No IgE-FA</b> |
|   |  |                  |  |                  |
|   |  |                  |  |                  |
| <b>Pre-guidelines<sup>3</sup></b>           | 22.9   | 20.8             | 12,864   | 792,146          |
| <b>Post-initial guidelines<sup>4</sup></b>  | 24.1   | 21.5             | 11,492   | 991,183          |
| <b>Post-addendum guidelines<sup>5</sup></b> | 22.3   | 20.6             | 8,220  | 809,228          |

<sup>1</sup>Cohort entry between September 1, 2012 and August 31, 2014 and observation until August 31, 2016 (as illustrated in **Figure 1A**)

<sup>2</sup>Cohort entry between September 1, 2015 and August 31, 2017 and observation until August 31, 2019 (as illustrated in **Figure 1A**)

<sup>3</sup>Cohort entry between September 1, 2012 and August 31, 2014 and observation until August 31, 2015 (as illustrated in **Figure 1B**)

<sup>4</sup>Cohort entry between September 1, 2015 and August 31, 2017 and observation until August 31, 2018 (as illustrated in **Figure 1B**)

<sup>5</sup>Cohort entry between February 1, 2017 and January 31, 2019 and observation until January 31, 2020 (as illustrated in **Figure 1B**)

IgE-FA, IgE-mediated food allergy

**Table S3: Demographic features of study cohorts with and without atopic dermatitis**

|                           | Minimum 2-year observation  |       |          |       |                              |       |          |       |          |
|---------------------------|-----------------------------|-------|----------|-------|------------------------------|-------|----------|-------|----------|
|                           | Pre-guidelines <sup>1</sup> |       |          |       | Post-guidelines <sup>2</sup> |       |          |       |          |
|                           | AD                          |       | No AD    |       | AD                           |       | No AD    |       |          |
|                           | <i>n</i>                    | %     | <i>n</i> | %     | <i>n</i>                     | %     | <i>n</i> | %     | <i>P</i> |
| Age at cohort entry       |                             |       |          |       |                              |       |          |       |          |
| 0-4 months                | 4,795                       | 93.0  | 30,785   | 92.0  | 8,840                        | 96.0  | 35,281   | 94.0  | ****     |
| 5-8 months                | 227                         | 4.0   | 1,421    | 4.0   | 238                          | 3.0   | 1,186    | 3.0   | *        |
| 9-12 months               | 135                         | 3.0   | 1,231    | 4.0   | 141                          | 2.0   | 994      | 3.0   | *        |
| Sex                       |                             |       |          |       |                              |       |          |       |          |
| Male                      | 2,830                       | 55.0  | 16,980   | 51.0  | 5,067                        | 55.0  | 18,916   | 50.0  | ****     |
| Female                    | 2,327                       | 44.0  | 16,456   | 49.0  | 4,152                        | 45.0  | 18,545   | 50.0  | ****     |
| Unknown                   | 0                           | 0.0   | 1        | 0.0   | 0                            | 0.0   | 0        | 0.0   |          |
| Race <sup>6</sup>         |                             |       |          |       |                              |       |          |       |          |
| White                     | 2,198                       | 43.0  | 20,182   | 60.0  | 3,882                        | 42.0  | 22,608   | 60.0  | ****     |
| Black                     | 2,011                       | 39.0  | 7,507    | 22.0  | 3,353                        | 36.0  | 7,629    | 20.0  | ****     |
| Asian or Pacific Islander | 281                         | 5.0   | 1,398    | 4.0   | 550                          | 6.0   | 1,456    | 4.0   | ****     |
| Other                     | 181                         | 4.0   | 1,610    | 5.0   | 495                          | 5.0   | 3,156    | 8.0   | ***      |
| Unknown                   | 486                         | 9.0   | 2,740    | 8.0   | 939                          | 10.0  | 2,612    | 7.0   | ****     |
| Ethnicity                 |                             |       |          |       |                              |       |          |       |          |
| Non-Hispanic              | 4,630                       | 90.0  | 29,150   | 87.0  | 8,275                        | 90.0  | 32,401   | 86.0  | ****     |
| Hispanic                  | 459                         | 9.0   | 3,713    | 11.0  | 783                          | 8.0   | 3,673    | 10.0  | ****     |
| Other                     | 68                          | 1.0   | 574      | 2.0   | 161                          | 2.0   | 1,387    | 4.0   | NS       |
| Total                     | 5,157                       | 100.0 | 33,437   | 100.0 | 9,219                        | 100.0 | 37,461   | 100.0 |          |

|                     | Minimum 1-year observation  |      |          |      |                              |      |          |      |          | Post-addendum guidelines <sup>5</sup> |      |          |      |          |
|---------------------|-----------------------------|------|----------|------|------------------------------|------|----------|------|----------|---------------------------------------|------|----------|------|----------|
|                     | Pre-guidelines <sup>3</sup> |      |          |      | Post-guidelines <sup>4</sup> |      |          |      |          | AD                                    |      | No AD    |      |          |
|                     | AD                          |      | No AD    |      | AD                           |      | No AD    |      |          | AD                                    |      | No AD    |      |          |
|                     | <i>n</i>                    | %    | <i>n</i> | %    | <i>n</i>                     | %    | <i>n</i> | %    | <i>P</i> | <i>n</i>                              | %    | <i>n</i> | %    | <i>P</i> |
| Age at cohort entry |                             |      |          |      |                              |      |          |      |          |                                       |      |          |      |          |
| 0-4 months          | 4,019                       | 93.0 | 31,561   | 92.0 | 8,050                        | 96.0 | 36,071   | 94.0 | ****     | 7,539                                 | 96.0 | 30,356   | 96.0 | ****     |
| 5-8 months          | 181                         | 4.0  | 1,467    | 4.0  | 215                          | 3.0  | 1,209    | 3.0  | ***      | 164                                   | 2.0  | 791      | 2.0  | ****     |
| 9-12 months         | 113                         | 3.0  | 1,253    | 4.0  | 132                          | 2.0  | 1,003    | 3.0  | **       | 113                                   | 1.0  | 631      | 2.0  | ****     |
| Sex                 |                             |      |          |      |                              |      |          |      |          |                                       |      |          |      |          |
| Male                | 2,417                       | 56.0 | 17,393   | 51.0 | 4,680                        | 56.0 | 19,303   | 50.0 | ****     | 4,467                                 | 57.0 | 15,984   | 50.0 | ****     |
| Female              | 1,896                       | 44.0 | 16,887   | 49.0 | 3,717                        | 44.0 | 18,980   | 50.0 | ****     | 3,349                                 | 43.0 | 15,794   | 50.0 | ****     |
| Unknown             | 0                           | 0.0  | 1        | 0.0  | 0                            | 0.0  | 0        | 0.0  |          | 0                                     | 0.0  | 0        | 0.0  |          |

| Race <sup>7</sup>         |       |       |        |       |       |       |        |       |      |       |       |        |       |      |
|---------------------------|-------|-------|--------|-------|-------|-------|--------|-------|------|-------|-------|--------|-------|------|
| White                     | 1,848 | 43.0  | 20,532 | 60.0  | 3,500 | 42.0  | 22,990 | 60.0  | **** | 3,124 | 40.0  | 18,435 | 58.0  | **** |
| Black                     | 1,681 | 39.0  | 7,837  | 23.0  | 3,082 | 37.0  | 7,900  | 21.0  | **** | 2,846 | 36.0  | 6,472  | 20.0  | **** |
| Asian or Pacific Islander | 228   | 5.0   | 1,451  | 4.0   | 506   | 9.0   | 1,500  | 4.0   | **** | 473   | 6.0   | 1,314  | 4.0   | **** |
| Other                     | 154   | 4.0   | 1,637  | 5.0   | 452   | 5.0   | 3,199  | 8.0   | **** | 382   | 5.0   | 2,393  | 8.0   | **** |
| Unknown                   | 402   | 9.0   | 2,824  | 8.0   | 857   | 10.0  | 2,694  | 7.0   | **** | 991   | 13.0  | 3,164  | 10.0  | **** |
| Ethnicity                 |       |       |        |       |       |       |        |       |      |       |       |        |       |      |
| Non-Hispanic              | 3,889 | 90.0  | 29,891 | 87.0  | 7,531 | 90.0  | 33,145 | 87.0  | **** | 7,011 | 90.0  | 27,566 | 87.0  | **** |
| Hispanic                  | 368   | 9.0   | 3,804  | 11.0  | 722   | 9.0   | 3,734  | 10.0  | **** | 675   | 9.0   | 3,074  | 10.0  | **** |
| Other                     | 56    | 1.0   | 586    | 2.0   | 144   | 2.0   | 1,404  | 4.0   | NS   | 130   | 2.0   | 1,138  | 4.0   | NS   |
| Total                     | 4,313 | 100.0 | 34,281 | 100.0 | 8,397 | 100.0 | 38,283 | 100.0 |      | 7,816 | 100.0 | 31,778 | 100.0 |      |

<sup>1</sup>Cohort entry between September 1, 2012 and August 31, 2014 and observation until August 31, 2016 (as illustrated in **Figure 1A**)

<sup>2</sup>Cohort entry between September 1, 2015 and August 31, 2017 and observation until August 31, 2019 (as illustrated in **Figure 1A**)

<sup>3</sup>Cohort entry between September 1, 2012 and August 31, 2014 and observation until August 31, 2015 (as illustrated in **Figure 1B**)

<sup>4</sup>Cohort entry between September 1, 2015 and August 31, 2017 and observation until August 31, 2018 (as illustrated in **Figure 1B**)

<sup>5</sup>Cohort entry between February 1, 2017 and January 31, 2019 and observation until January 31, 2020 (as illustrated in **Figure 1B**)

<sup>6</sup>The category “Unknown” is comprised of subjects with self-identified unknown race, whereas “Other” comprises all other entries including “American Indian or Alaska native,” “Mixed racial group,” and “Race not available.”

AD, atopic dermatitis

Statistical testing was performed to compare the association of each demographic characteristic with AD status in the pre- versus post-guidelines periods.

\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$ ; \*\*\*\*  $p < 0.0001$ ; NS, not significant



**Table S4: Demographic features of children with IgE-mediated peanut allergy**

|                            | Minimum 2-year observation  |       |                              |       |           | Minimum 1-year observation  |       |                              |       |           |                                       |       |           |
|----------------------------|-----------------------------|-------|------------------------------|-------|-----------|-----------------------------|-------|------------------------------|-------|-----------|---------------------------------------|-------|-----------|
|                            | Pre-guidelines <sup>1</sup> |       | Post-guidelines <sup>2</sup> |       | <i>P</i>  | Pre-guidelines <sup>3</sup> |       | Post-guidelines <sup>4</sup> |       | <i>P</i>  | Post-addendum guidelines <sup>5</sup> |       | <i>P</i>  |
|                            | <i>n</i>                    | %     | <i>n</i>                     | %     |           | <i>n</i>                    | %     | <i>n</i>                     | %     |           | <i>n</i>                              | %     |           |
| <b>Age at cohort entry</b> |                             |       |                              |       |           |                             |       |                              |       |           |                                       |       |           |
| 0-4 months                 | 330                         | 93.0  | 291                          | 93.0  | <i>NS</i> | 287                         | 94.0  | 227                          | 92.0  | <i>NS</i> | 167                                   | 95.0  | <i>NS</i> |
| 5-8 months                 | 15                          | 4.0   | 11                           | 4.0   |           | 11                          | 4.0   | 10                           | 4.0   |           | 7                                     | 4.0   |           |
| 9-12 months                | 10                          | 3.0   | 10                           | 3.0   |           | 8                           | 3.0   | 10                           | 4.0   |           | 2                                     | 1.0   |           |
| <b>Sex</b>                 |                             |       |                              |       |           |                             |       |                              |       |           |                                       |       |           |
| Male                       | 228                         | 64.0  | 192                          | 62.0  | <i>NS</i> | 195                         | 64.0  | 152                          | 62.0  | <i>NS</i> | 104                                   | 59.0  | <i>NS</i> |
| Female                     | 127                         | 36.0  | 120                          | 38.0  |           | 111                         | 36.0  | 95                           | 38.0  |           | 72                                    | 41.0  |           |
| <b>Race<sup>6</sup></b>    |                             |       |                              |       |           |                             |       |                              |       |           |                                       |       |           |
| White                      | 206                         | 58.0  | 189                          | 61.0  | <i>NS</i> | 184                         | 60.0  | 146                          | 59.0  | <i>NS</i> | 101                                   | 57.0  | <i>NS</i> |
| Black                      | 72                          | 20.0  | 45                           | 14.0  |           | 56                          | 18.0  | 37                           | 15.0  |           | 21                                    | 12.0  |           |
| Asian or Pacific Islander  | 25                          | 7.0   | 33                           | 11.0  |           | 19                          | 6.0   | 27                           | 11.0  |           | 13                                    | 7.0   |           |
| Other                      | 18                          | 5.0   | 16                           | 5.0   |           | 14                          | 5.0   | 13                           | 5.0   |           | 17                                    | 10.0  |           |
| Unknown                    | 34                          | 10.0  | 29                           | 9.0   |           | 33                          | 11.0  | 24                           | 10.0  |           | 24                                    | 14.0  |           |
| <b>Ethnicity</b>           |                             |       |                              |       |           |                             |       |                              |       |           |                                       |       |           |
| Non-Hispanic               | 334                         | 94.0  | 289                          | 93.0  | <i>NS</i> | 288                         | 94.0  | 231                          | 94.0  | <i>NS</i> | 160                                   | 91.0  | <i>NS</i> |
| Hispanic                   | 16                          | 5.0   | 16                           | 5.0   |           | 15                          | 5.0   | 10                           | 4.0   |           | 9                                     | 5.0   |           |
| Other                      | 5                           | 1.0   | 7                            | 2.0   |           | 3                           | 1.0   | 6                            | 2.0   |           | 7                                     | 4.0   |           |
| <b>Total</b>               | 355                         | 100.0 | 312                          | 100.0 |           | 306                         | 100.0 | 247                          | 100.0 |           | 176                                   | 100.0 |           |

<sup>1</sup>Cohort entry between September 1, 2012 and August 31, 2014 and observation until August 31, 2016 (as illustrated in **Figure 1A**)

<sup>2</sup>Cohort entry between September 1, 2015 and August 31, 2017 and observation until August 31, 2019 (as illustrated in **Figure 1A**)

<sup>3</sup>Cohort entry between September 1, 2012 and August 31, 2014 and observation until August 31, 2015 (as illustrated in **Figure 1B**)

<sup>4</sup>Cohort entry between September 1, 2015 and August 31, 2017 and observation until August 31, 2018 (as illustrated in **Figure 1B**)

<sup>5</sup>Cohort entry between February 1, 2017 and January 31, 2019 and observation until January 31, 2020 (as illustrated in **Figure 1B**)

<sup>6</sup>The category “Unknown” is comprised of subjects with self-identified unknown race, whereas “Other” comprises all other entries including “American Indian or Alaska native,” “Mixed racial group,” and “Race not available.”

Chi-square or Fisher’s Exact Test was used to determine whether there was a difference between pre- vs. post-guidelines status for each demographic characteristic. *NS*, not significant.

**Table S5: Demographic features of children with IgE-mediated egg allergy**

|                            | Minimum 2-year observation  |       |                              |       |           | Minimum 1-year observation  |       |                              |       |           |                                       |       |           |
|----------------------------|-----------------------------|-------|------------------------------|-------|-----------|-----------------------------|-------|------------------------------|-------|-----------|---------------------------------------|-------|-----------|
|                            | Pre-guidelines <sup>1</sup> |       | Post-guidelines <sup>2</sup> |       | <i>P</i>  | Pre-guidelines <sup>3</sup> |       | Post-guidelines <sup>4</sup> |       | <i>P</i>  | Post-addendum guidelines <sup>5</sup> |       | <i>P</i>  |
|                            | <i>n</i>                    | %     | <i>n</i>                     | %     |           | <i>n</i>                    | %     | <i>n</i>                     | %     |           | <i>n</i>                              | %     |           |
| <b>Age at cohort entry</b> |                             |       |                              |       |           |                             |       |                              |       |           |                                       |       |           |
| 0-4 months                 | 234                         | 91.0  | 311                          | 95.0  | <i>NS</i> | 213                         | 91.0  | 258                          | 95.0  | <i>NS</i> | 219                                   | 98.0  | <i>NS</i> |
| 5-8 months                 | 11                          | 4.0   | 10                           | 3.0   |           | 10                          | 4.0   | 9                            | 3.0   |           | 3                                     | 1.0   |           |
| 9-12 months                | 12                          | 5.0   | 5                            | 2.0   |           | 10                          | 4.0   | 4                            | 1.0   |           | 1                                     | 0.0   |           |
| <b>Sex</b>                 |                             |       |                              |       |           |                             |       |                              |       |           |                                       |       |           |
| Male                       | 159                         | 62.0  | 204                          | 63.0  | <i>NS</i> | 143                         | 61.0  | 167                          | 62.0  | <i>NS</i> | 149                                   | 67.0  | <i>NS</i> |
| Female                     | 98                          | 38.0  | 122                          | 37.0  |           | 90                          | 39.0  | 104                          | 38.0  |           | 74                                    | 33.0  |           |
| <b>Race<sup>6</sup></b>    |                             |       |                              |       |           |                             |       |                              |       |           |                                       |       |           |
| White                      | 159                         | 62.0  | 207                          | 63.0  | <i>NS</i> | 147                         | 63.0  | 170                          | 63.0  | <i>NS</i> | 160                                   | 72.0  | <i>NS</i> |
| Black                      | 35                          | 14.0  | 44                           | 13.0  |           | 29                          | 12.0  | 37                           | 14.0  |           | 13                                    | 6.0   |           |
| Asian or Pacific Islander  | 26                          | 10.0  | 27                           | 8.0   |           | 24                          | 10.0  | 25                           | 9.0   |           | 19                                    | 9.0   |           |
| Other                      | 11                          | 4.0   | 12                           | 4.0   |           | 10                          | 4.0   | 8                            | 3.0   |           | 15                                    | 7.0   |           |
| Unknown                    | 26                          | 10.0  | 36                           | 11.0  |           | 23                          | 10.0  | 31                           | 11.0  |           | 16                                    | 7.0   |           |
| <b>Ethnicity</b>           |                             |       |                              |       |           |                             |       |                              |       |           |                                       |       |           |
| Non-Hispanic               | 238                         | 93.0  | 293                          | 90.0  | <i>NS</i> | 216                         | 93.0  | 246                          | 91.0  | <i>NS</i> | 208                                   | 93.0  | <i>NS</i> |
| Hispanic                   | 18                          | 7.0   | 28                           | 9.0   |           | 16                          | 7.0   | 22                           | 8.0   |           | 9                                     | 4.0   |           |
| Other                      | 1                           | 0.0   | 5                            | 2.0   |           | 1                           | 0.0   | 3                            | 1.0   |           | 6                                     | 3.0   |           |
| <b>Total</b>               | 257                         | 100.0 | 326                          | 100.0 |           | 233                         | 100.0 | 271                          | 100.0 |           | 223                                   | 100.0 |           |

<sup>1</sup>Cohort entry between September 1, 2012 and August 31, 2014 and observation until August 31, 2016 (as illustrated in **Figure 1A**)

<sup>2</sup>Cohort entry between September 1, 2015 and August 31, 2017 and observation until August 31, 2019 (as illustrated in **Figure 1A**)

<sup>3</sup>Cohort entry between September 1, 2012 and August 31, 2014 and observation until August 31, 2015 (as illustrated in **Figure 1B**)

<sup>4</sup>Cohort entry between September 1, 2015 and August 31, 2017 and observation until August 31, 2018 (as illustrated in **Figure 1B**)

<sup>5</sup>Cohort entry between February 1, 2017 and January 31, 2019 and observation until January 31, 2020 (as illustrated in **Figure 1B**)

<sup>6</sup>The category “Unknown” is comprised of subjects with self-identified unknown race, whereas “Other” comprises all other entries including “American Indian or Alaska native,” “Mixed racial group,” and “Race not available.”

Chi-square or Fisher’s Exact Test was used to determine whether there was a difference between pre- vs. post-guidelines status for each demographic characteristic. *NS*, not significant.

**Table S6: Demographic features of children with IgE-mediated milk allergy**

|                            | Minimum 2-year observation  |       |                              |       |           | Minimum 1-year observation  |       |                              |       |           |                                       |       |           |
|----------------------------|-----------------------------|-------|------------------------------|-------|-----------|-----------------------------|-------|------------------------------|-------|-----------|---------------------------------------|-------|-----------|
|                            | Pre-guidelines <sup>1</sup> |       | Post-guidelines <sup>2</sup> |       | <i>P</i>  | Pre-guidelines <sup>3</sup> |       | Post-guidelines <sup>4</sup> |       | <i>P</i>  | Post-addendum guidelines <sup>5</sup> |       | <i>P</i>  |
|                            | <i>n</i>                    | %     | <i>n</i>                     | %     |           | <i>n</i>                    | %     | <i>n</i>                     | %     |           | <i>n</i>                              | %     |           |
| <b>Age at cohort entry</b> |                             |       |                              |       |           |                             |       |                              |       |           |                                       |       |           |
| 0-4 months                 | 154                         | 91.0  | 132                          | 96.0  | <i>NS</i> | 132                         | 90.0  | 110                          | 95.0  | <i>NS</i> | 75                                    | 91.0  | <i>NS</i> |
| 5-8 months                 | 10                          | 6.0   | 3                            | 2.0   |           | 8                           | 5.0   | 3                            | 3.0   |           | 3                                     | 4.0   |           |
| 9-12 months                | 6                           | 4.0   | 3                            | 2.0   |           | 6                           | 4.0   | 3                            | 3.0   |           | 4                                     | 5.0   |           |
| <b>Sex</b>                 |                             |       |                              |       |           |                             |       |                              |       |           |                                       |       |           |
| Male                       | 99                          | 58.0  | 90                           | 65.0  | <i>NS</i> | 85                          | 58.0  | 76                           | 66.0  | <i>NS</i> | 51                                    | 62.0  | <i>NS</i> |
| Female                     | 71                          | 42.0  | 48                           | 35.0  |           | 61                          | 42.0  | 40                           | 34.0  |           | 31                                    | 38.0  |           |
| <b>Race<sup>6</sup></b>    |                             |       |                              |       |           |                             |       |                              |       |           |                                       |       |           |
| White                      | 101                         | 59.0  | 76                           | 55.0  | <i>NS</i> | 88                          | 60.0  | 63                           | 54.0  | <i>NS</i> | 56                                    | 68.0  | <i>NS</i> |
| Black                      | 36                          | 21.0  | 26                           | 19.0  |           | 27                          | 18.0  | 24                           | 21.0  |           | 7                                     | 9.0   |           |
| Asian or Pacific Islander  | 16                          | 9.0   | 19                           | 14.0  |           | 14                          | 10.0  | 15                           | 13.0  |           | 6                                     | 7.0   |           |
| Other                      | 5                           | 3.0   | 3                            | 2.0   |           | 5                           | 3.0   | 2                            | 2.0   |           | 3                                     | 4.0   |           |
| Unknown                    | 12                          | 7.0   | 14                           | 10.0  |           | 12                          | 8.0   | 12                           | 10.0  |           | 10                                    | 12.0  |           |
| <b>Ethnicity</b>           |                             |       |                              |       |           |                             |       |                              |       |           |                                       |       |           |
| Non-Hispanic               | 162                         | 95.0  | 127                          | 92.0  | <i>NS</i> | 138                         | 95.0  | 108                          | 93.0  | <i>NS</i> | 78                                    | 95.0  | <i>NS</i> |
| Hispanic                   | 8                           | 5.0   | 10                           | 7.0   |           | 8                           | 5.0   | 8                            | 7.0   |           | 4                                     | 5.0   |           |
| Other                      | 0                           | 0.0   | 1                            | 1.0   |           | 0                           | 0.0   | 0                            | 0.0   |           | 0                                     | 0.0   |           |
| <b>Total</b>               | 170                         | 100.0 | 138                          | 100.0 |           | 146                         | 100.0 | 116                          | 100.0 |           | 176                                   | 100.0 |           |

<sup>1</sup>Cohort entry between September 1, 2012 and August 31, 2014 and observation until August 31, 2016 (as illustrated in **Figure 1A**)

<sup>2</sup>Cohort entry between September 1, 2015 and August 31, 2017 and observation until August 31, 2019 (as illustrated in **Figure 1A**)

<sup>3</sup>Cohort entry between September 1, 2012 and August 31, 2014 and observation until August 31, 2015 (as illustrated in **Figure 1B**)

<sup>4</sup>Cohort entry between September 1, 2015 and August 31, 2017 and observation until August 31, 2018 (as illustrated in **Figure 1B**)

<sup>5</sup>Cohort entry between February 1, 2017 and January 31, 2019 and observation until January 31, 2020 (as illustrated in **Figure 1B**)

<sup>6</sup>The category “Unknown” is comprised of subjects with self-identified unknown race, whereas “Other” comprises all other entries including “American Indian or Alaska native,” “Mixed racial group,” and “Race not available.”

Chi-square or Fisher’s Exact Test was used to determine whether there was a difference between pre- vs. post-guidelines status for each demographic characteristic. *NS*, not significant.

**Table S7: Hazard ratios for unadjusted and adjusted Cox proportional hazards models<sup>1</sup>**

|  |                         | Peanut IgE-FA     |          | ≥1 IgE-FA         |          | AD                |          |
|--|-------------------------|-------------------|----------|-------------------|----------|-------------------|----------|
|  |                         | HR (95% CI)       | <i>P</i> | HR (95% CI)       | <i>P</i> | HR (95% CI)       | <i>P</i> |
| <b>Post-initial guidelines vs. pre-guidelines</b>  |                         |                   |          |                   |          |                   |          |
|  | <b>Unadjusted model</b> | 0.66 (0.55, 0.78) | ≤0.0001  | 0.69 (0.61, 0.78) | ≤0.0001  | 1.66 (1.60, 1.72) | ≤0.0001  |
|  | <b>Adjusted model</b>   | 0.65 (0.55, 0.77) | ≤0.0001  | 0.69 (0.61, 0.78) | ≤0.0001  | 1.69 (1.63, 1.75) | ≤0.0001  |
| <b>Post-addendum guidelines vs. pre-guidelines</b> |                         |                   |          |                   |          |                   |          |
|  | <b>Unadjusted model</b> | 0.57 (0.48, 0.69) | ≤0.0001  | 0.65 (0.57, 0.74) | ≤0.0001  | 1.89 (1.82, 1.96) | ≤0.0001  |
|  | <b>Adjusted model</b>   | 0.55 (0.46, 0.66) | ≤0.0001  | 0.63 (0.55, 0.72) | ≤0.0001  | 1.88 (1.81, 1.96) | ≤0.0001  |

<sup>1</sup>Hazard ratios were determined to compare the rate of development of peanut IgE-mediated food allergy, one or more IgE-mediated food allergies, or atopic dermatitis between post-guidelines vs. pre-guidelines cohorts, with a minimum observation period of one year (as illustrated in **Figure 1B**). Cox proportional hazards models were either unadjusted or adjusted for the following covariates: age at cohort entry, sex, race, and ethnicity. AD, atopic dermatitis; HR, hazard ratio; IgE-FA, IgE-mediated food allergy; 95% CI, 95% confidence interval.

**Table S8: Interrupted time analysis<sup>1</sup>**

| <b>IgE-FA</b>  |                                  |          |  |          |  |          |
|--|----------------------------------|----------|--|----------|--|----------|
|  | <b>Interaction term (95% CI)</b> | <b>P</b> | <b>Mean difference, post-guidelines start (95% CI)</b> | <b>P</b> | <b>Mean difference, post-guidelines end (95% CI)</b> | <b>P</b> |
| <b>Post-guidelines (initial and addendum) vs. pre-guidelines</b> | -0.027 (-0.051, -0.0029)         | 0.03     | 0.35 (-0.091, 0.72)                                    | 0.08     | -0.91 (-2.96, 0.78)                                  | 0.32     |
| <b>Post-guidelines (initial) vs. pre-guidelines</b>              | -0.021 (-0.044, 0.0017)          | 0.08     | 0.30 (-0.052, 0.74)                                    | 0.13     | -0.38 (-1.76, 0.87)                                  | 0.56     |
| <b>Post-guidelines (addendum) vs. pre-guidelines</b>             | -0.025 (-0.052, 0.0010)          | 0.07     | 0.029 (-0.38, 0.36)                                    | 0.97     | -0.86 (-2.08, 0.49)                                  | 0.19     |
| <b>Peanut IgE-FA</b>   |                                  |          |  |          |  |          |
|  | <b>Interaction term (95% CI)</b> | <b>P</b> | <b>Mean difference, post-guidelines start (95% CI)</b> | <b>P</b> | <b>Mean difference, post-guidelines end (95% CI)</b> | <b>P</b> |
| <b>Post-guidelines (initial and addendum) vs. pre-guidelines</b> | -0.012 (-0.031, 0.0074)          | 0.23     | 0.19 (-0.14, 0.48)                                     | 0.24     | -0.53 (-1.96, 0.69)                                  | 0.43     |
| <b>Post-guidelines (initial) vs. pre-guidelines</b>              | -0.012 (-0.036, 0.012)           | 0.32     | 0.18 (-0.15, 0.48)                                     | 0.26     | -0.27 (-1.20, 0.79)                                  | 0.58     |
| <b>Post-guidelines (addendum) vs. pre-guidelines</b>             | -0.014 (-0.031, 0.0039)          | 0.13     | -0.033 (-0.31, 0.23)                                   | 0.81     | -0.51 (-1.45, 0.60)                                  | 0.30     |

<sup>1</sup>Interrupted time analysis was performed using monthly data for two-year old children diagnosed with at least one IgE-mediated food allergy or peanut IgE-mediated food allergy. Pre-guidelines (1/1/2014 to 8/31/2015) diagnosis rates were compared with rates during post-guidelines periods ("initial and addendum" = 9/1/2015 to 1/31/2020; "initial" = 9/1/2015 to 8/31/2018; "addendum" = 2/1/2017 to 1/31/2020). The interaction term was quantified to estimate the slope change between the slope of the post-guidelines regression line and the pre-guidelines counterfactual trend line. Mean differences in outcome between the post-guidelines regression line and pre-guidelines counterfactual line were determined at the beginning and end of the post-guidelines periods.

IgE-FA, IgE-mediated food allergy; 95% CI, 95% confidence interval.