

# Letters

## RESEARCH LETTER

### Association Between Family Characteristics and the Effect of Timing of Regular Egg Introduction in Infant Egg Allergy

A recent systematic review of 5 randomized clinical trials, most with fewer than 300 participants completing the individual studies, found that early egg introduction was associated with reduced egg allergy.<sup>1</sup> Infant feeding guidelines are changing to recommend that traditionally allergenic foods, such as eggs, be included in infant diets from 4 to 6 months of age, without exact knowledge of generalizability to different population subgroups.

At about the same time the systematic review<sup>1</sup> was published, we reported the multicenter Starting Time of Egg Protein (STEP) double-blinded randomized clinical trial (n = 820

infants)<sup>2</sup> that found a 25% risk reduction in egg allergy with early regular egg intake from 4 to 6.5 months compared with egg avoidance to 10 months of age, although this did not achieve statistical significance. We had broad eligibility criteria in STEP and investigated in exploratory analyses whether the effect of treatment was modified by maternal, family, or infant characteristics.

**Methods** | In STEP, infants were randomized to receive daily egg powder (egg group, n = 407) or a color- and texture-matched rice powder (control group, n = 413) to 10 months of age.<sup>2</sup> Our exploratory analyses examined whether baseline characteristics<sup>2</sup> subgrouped as dichotomous variables (with continuous characteristics classified around their average value) modified the effect of timing of regular egg introduction on the primary outcome of IgE-mediated egg allergy at 12 months of

**Table. Relative Risk of Egg Allergy by Treatment Group Modified by Maternal, Family, or Infant Characteristics**

|                                                  | No./Total No. (%) <sup>a</sup> |               | Relative Risk<br>(95% CI) <sup>b</sup> | Raw Interaction<br>P Value | Interaction<br>P Value <sup>c</sup> |
|--------------------------------------------------|--------------------------------|---------------|----------------------------------------|----------------------------|-------------------------------------|
| Baseline Characteristics                         | Treatment                      | Control       |                                        |                            |                                     |
| Maternal age, y                                  |                                |               |                                        |                            |                                     |
| <32                                              | 10/177 (5.7)                   | 18/185 (9.7)  | 0.61 (0.29-1.27)                       | .73                        | .98                                 |
| ≥32                                              | 16/194 (8.3)                   | 21/192 (10.9) | 0.72 (0.39-1.32)                       |                            |                                     |
| Maternal occupation <sup>d</sup>                 |                                |               |                                        |                            |                                     |
| Professional/managerial                          | 12/141 (8.5)                   | 22/133 (16.5) | 0.51 (0.27-0.98)                       | .23                        | .80                                 |
| Semiskilled/trade/unskilled/other                | 14/230 (6.1)                   | 17/244 (7.0)  | 0.90 (0.46-1.78)                       |                            |                                     |
| Socioeconomic status <sup>e</sup>                |                                |               |                                        |                            |                                     |
| Lower                                            | 11/146 (7.5)                   | 6/151 (4.0)   | 1.89 (0.73-4.93)                       | .02                        | .11                                 |
| Upper                                            | 15/225 (6.7)                   | 33/226 (14.6) | 0.47 (0.27-0.84)                       |                            |                                     |
| Other children in the home                       |                                |               |                                        |                            |                                     |
| None                                             | 14/178 (7.9)                   | 18/176 (10.2) | 0.73 (0.38-1.41)                       | .75                        | .98                                 |
| ≥1                                               | 12/193 (6.2)                   | 21/201 (10.5) | 0.63 (0.32-1.22)                       |                            |                                     |
| Household total egg intake, eggs/wk <sup>f</sup> |                                |               |                                        |                            |                                     |
| <12                                              | 7/178 (3.9)                    | 19/176 (10.8) | 0.36 (0.16-0.82)                       | .04                        | .26                                 |
| ≥12                                              | 19/192 (9.9)                   | 20/201 (10.0) | 1.03 (0.57-1.85)                       |                            |                                     |
| Maternal egg intake, eggs/wk <sup>f</sup>        |                                |               |                                        |                            |                                     |
| <4                                               | 7/135 (5.2)                    | 11/138 (8.0)  | 0.62 (0.25-1.54)                       | .80                        | .98                                 |
| ≥4                                               | 19/234 (8.1)                   | 28/239 (11.7) | 0.71 (0.41-1.23)                       |                            |                                     |
| Cesarean delivery                                |                                |               |                                        |                            |                                     |
| No                                               | 20/238 (8.4)                   | 27/238 (11.3) | 0.76 (0.45-1.30)                       | .46                        | .95                                 |
| Yes                                              | 6/133 (4.5)                    | 12/139 (8.6)  | 0.51 (0.20-1.29)                       |                            |                                     |
| Dog as a pet                                     |                                |               |                                        |                            |                                     |
| No                                               | 14/207 (6.8)                   | 18/211 (8.5)  | 0.81 (0.42-1.56)                       | .48                        | .95                                 |
| Yes                                              | 12/164 (7.3)                   | 21/166 (12.7) | 0.57 (0.30-1.11)                       |                            |                                     |

<sup>a</sup> No. (%) of infants with IgE-mediated egg allergy in each subgroup.

<sup>b</sup> Adjusted for the stratification variables feeding mode, infant sex, and city.

<sup>c</sup> Interaction P value adjusted for multiple comparisons using the stepdown Sidak procedure.

<sup>d</sup> Using Australian and New Zealand Standard Classification of Occupations.<sup>3</sup>

<sup>e</sup> Postcodes of residential addresses were used to link to Socio-Economic Indexes for Areas deciles.<sup>3</sup> The Index of Socioeconomic Advantage and

Disadvantage is calculated using measures of both advantage and disadvantage, where higher scores indicate a greater degree of advantage. This Socio-Economic Indexes for Areas variable was dichotomized using deciles 1 to 5 for lower and deciles 6 to 10 for upper, where "upper" refers to higher socioeconomic status.

<sup>f</sup> Intake of eggs and egg-containing foods per week.

age. Log binomial regression models, including an interaction term for treatment group and subgroup status, were used to evaluate effect modification. Because STEP was designed to detect main effects, only large interaction effects could be identified in these exploratory analyses. For this reason, we focus primarily on raw interaction *P* values for evidence of effect modification, although for completeness we also present multiple comparison adjusted interaction *P* values. All analyses were performed using SAS version 9.3 (SAS Institute).

Approval for this study was granted by the local institutional review boards/human research ethics committees of Women's and Children's Health Network, Adelaide; Flinders Medical Centre, Adelaide; and Princess Margaret Hospital, Perth. Written informed consent was obtained from parents prior to trial participation.

**Results** | Of 820 infants randomized, 748 (91%) completed an egg allergy assessment at 12 months. Socioeconomic status (SES)<sup>3</sup> modified the effect of early regular egg introduction, with treatment reducing egg allergy rates in higher SES families (egg group: 6.7% vs control group: 14.6%; adjusted relative risk, 0.47; 95% CI, 0.27-0.84; interaction *P* = .02; Table) but not in lower SES families. This result did not appear to be driven by differential compliance; 77.4% of low SES families were classified as per-protocol vs 79.9% of high SES families (*P* = .38), and effect modification by SES was still apparent in per-protocol participants (adjusted interaction *P* = .01).

Total household egg intake also modified the effect of early regular egg inclusion, with treatment decreasing the risk for egg allergy in families who ate fewer than 12 eggs per week at randomization (egg group: 3.9% vs control group: 10.8%; adjusted relative risk, 0.36; 95% CI, 0.16-0.82; interaction *P* = .04; Table) but not in families who ate 12 or more eggs per week. No interaction effects were found for any other baseline characteristics examined (Table).

**Discussion** | Our results suggest that infants from families of higher SES and those who consume few eggs per week could benefit from early regular egg intake. The possible benefit to infants living in households who consume fewer eggs is in keeping with the theory that small infrequent environmental doses may have a sensitizing effect, whereas regular exposure, especially via oral intake, leads to tolerance.<sup>4</sup> As no difference was found in protocol compliance with SES, we have no direct explanation of the differential response in higher SES families. Interestingly, the incidence of egg allergy was highest in these families, which is consistent with earlier observations.<sup>5</sup>

Future research should continue to define subgroups who benefit from regular inclusion of allergenic foods in infant diets. This will enable targeted infant feeding practice guidelines and community education strategies.

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## Secondhand Exposure to Electronic Cigarette Aerosol Among US Youths

Electronic cigarette (e-cigarette) use has increased considerably since these products were introduced into the US marketplace in 2007,<sup>1</sup> and e-cigarettes are the most commonly used tobacco product among US youths.<sup>2</sup> In contrast to combustible tobacco products, e-cigarettes do not produce side-stream emissions from the device itself. However, aerosol is produced during activation of the device, some of which is exhaled into the environment where nonusers can be exposed through inhalation, ingestion, or dermal contact.<sup>3</sup>

Secondhand aerosol (SHA) from e-cigarettes can contain harmful and potentially harmful substances including nicotine, heavy metals, ultrafine particulate, volatile organic compounds such as formaldehyde and acetaldehyde, and other toxicants.<sup>3,4</sup> However, to our knowledge, the extent to which US youths are exposed to SHA is unknown. This study assessed self-reported SHA exposure among US students.

**Methods** | Data came from the 2015 National Youth Tobacco Survey, a cross-sectional survey of US middle school and high school students (n = 17 711). National Youth Tobacco Survey uses a 3-stage sampling design (counties, schools, and classes) to yield nationally representative estimates.<sup>2</sup> Written approval to participate in the survey was obtained from parents