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PII: S2213-2198(20)31336-2

DOI: <https://doi.org/10.1016/j.jaip.2020.11.061>

Reference: JAIP 3310

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 20 August 2020

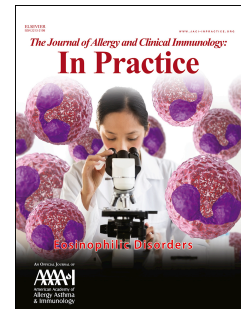
Revised Date: 26 November 2020

Accepted Date: 30 November 2020

Please cite this article as: Loewen K, Moraes TJ, Turvey SE, Mandhane PJ, Sears MR, Subbarao P, Becker AB, Azad MB, Simons E, Prenatal egg consumption and infant sensitization and allergy to egg, peanut and cow's milk, *The Journal of Allergy and Clinical Immunology: In Practice* (2021), doi: <https://doi.org/10.1016/j.jaip.2020.11.061>.

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Prenatal egg consumption and infant sensitization and allergy to egg, peanut and cow's milk

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MB Azad contributed to the study conception and design, reviewed the manuscript and is a current Manitoba site lead.

E Simons contributed to the study conception and design, mentored and conducted the analysis, wrote and revised the manuscript, collected clinical data at the Winnipeg site during this 3-year study period and is a current Manitoba site lead.

All authors contributed substantially to this study.

The authors declare no relevant conflicts of interest.

Funding: The Allergy, Genes and Environment (AllerGen) Network of Centres of Excellence (NCE) and the Canadian Institutes of Health Research (CIHR) provided core funding for CHILD. This study was also funded by the Manitoba Medical Service Foundation and Children's Hospital Research Foundation in Manitoba. ALK-Abello, Mississauga, ON, Canada supplied all allergens for the study and Lincoln Diagnostics Inc., Decatur, IL USA supplied the Duotip-Test II devices and skin testing kits.

Acknowledgement: We are grateful to all the families who took part in this study, and the whole CHILD team, which includes interviewers, nurses, physicians, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, and receptionists.

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Key words: Food sensitization, food allergy, egg, peanut, cow's milk, infant, diet, prenatal, CHILD Cohort Study

Clinical Implications Statement

Children of mothers who ate egg at least daily during pregnancy were more likely to be sensitized to egg and allergic to peanut, after accounting for moderate-to-severe atopic dermatitis, race, timing of infant food introduction and breastfeeding.

Manuscript word count: 1058

Early egg and peanut introduction in infancy have been associated with decreased risk of sensitization and allergy in children. (1-4) Effects of maternal allergen consumption or avoidance during pregnancy on infant sensitization and allergy have been variable. (5) We examined associations between maternal egg consumption during pregnancy and infant sensitization and allergy.

The CHILD Cohort Study has followed 3455 children prospectively from before birth at four Canadian sites (Vancouver, Edmonton, Manitoba, and Toronto). We included 3412 mother-child dyads with maternal allergen consumption prospectively reported at recruitment in the second or third trimester (6) and infant skin prick testing (SPT) data to allergens including egg and peanut at 1 and 3 years. Children with allergy to egg or peanut were sensitized to egg or peanut, not eating the food to which they were sensitized, and had caregiver-reported signs consistent with an IgE-mediated allergic reaction to the food to which they were sensitized. (4) Caregivers prospectively reported their child's earliest consumption of food allergens, current consumption, and signs of allergic reaction every 6 months. In this observational, general-population cohort recruited from 2008-12, families were not provided with recommendations regarding prenatal diet or infant dietary allergen introduction.

Parents reported their personal history of food allergy, other atopic conditions, race, education and socioeconomic status and their child's duration of exclusive breastfeeding (7), number of older siblings, and siblings' food allergies. Atopic dermatitis was defined by clinical history of an itchy rash in the typical distribution during the first year of life and physical examination by a study clinician at age 1 year; moderate-severe atopic dermatitis was distinguished as previously reported. (4)

We examined infant sensitization at ages 1 and 3 years and egg and peanut allergies at 3 years versus prenatal egg consumption, categorically and dichotomized as daily versus less than daily. We used multivariable logistic regression to evaluate the potential confounders described above, based on published associations. Models were built using backward elimination and variables associated with child sensitization or allergy ($p < 0.1$) were considered for inclusion in the final model. To evaluate if the effects of prenatal egg consumption were allergen specific, we examined associations with sensitization to other allergens and prenatal consumption of other food allergens. Because of known associations between timing of infant food allergen introduction and development of food sensitization and allergy in the CHIL cohort (3, 4), ages of infant dietary allergen introduction were also evaluated as potential confounders and effect modifiers.

Among 3412 children with SPT, sensitization was 7.4% to egg, 4.9% to peanut and 1.9% to milk at 1 year and 2.2% to egg, 3.8% to peanut and 1.1% to milk at 3 years. Most mothers (>94%) reported prenatal egg consumption and 113 mothers (3.8%) ate a serving of egg at least daily during pregnancy. Compared to mothers who consumed egg less than once per day, mothers who consumed egg at least daily were less likely to be white ($p < 0.01$) and more likely to introduce their infant to egg before 9 months ($p = 0.005$), but no different with respect to maternal childhood egg allergy ($p = 0.31$), exclusive breastfeeding duration ($p = 0.28$) or daily peanut consumption ($p = 0.58$).

Frequencies of infant egg sensitization (Figure 1) were 18% among infants born to mothers who consumed egg at least daily and 6-8% for infants in all other categories of prenatal egg consumption at 1 year, and showed a similar pattern at 3 years. Peanut sensitization was greater among infants born to mothers who consumed egg (Figure 1) but not peanut (Figure E1) daily.

After adjusting for moderate-to-severe atopic dermatitis in the first year of life, maternal race, paternal race and infant age of egg introduction, daily prenatal egg consumption was associated with child egg sensitization (adjusted odds ratio (OR) 2.64; 95% confidence interval (CI): 1.44-4.83) at 1 year. The association persisted with egg sensitization but not with egg allergy at age 3 years. (Table 1) Prenatal egg consumption was associated with child peanut allergy at age 3 years (adjusted OR 3.01; 95% CI 1.03-8.78) and cow's milk sensitization but not with sensitization to peanut or dust mites. (Table 1) Prenatal peanut and milk consumption were not associated with infant sensitization. (Table 1) Associations with prenatal egg consumption were similar for child egg sensitization when stratified by age of dietary egg introduction and for child peanut and milk sensitization when stratified by ages of dietary peanut and milk introduction, respectively. (Table E1)

These results show robust associations between maternal daily egg consumption during pregnancy and infant egg sensitization at ages 1 and 3 years. The associations between prenatal egg consumption and child peanut allergy and cow's milk sensitization suggest that the effects of maternal egg consumption may not be allergen specific. The associations persist after adjustment or stratification by infant ages of dietary food allergen introduction, despite known relationships of age of food allergen introduction with sensitization and allergy. (1-4) Therefore, the associations with maternal egg allergen consumption during pregnancy appear to be independent of infant allergen consumption and relevant despite the changes in infant introduction of highly allergenic foods that have been recommended since these cohort participants' infancy.

Limitations of this study included lack of power to evaluate stratified associations with egg and peanut allergy at 3 years and absence of double-blind placebo-controlled challenge confirmation of food allergy. We did not examine the amount or form (e.g. degree of cooking and presence of other ingredients) of egg consumed or other dietary habits, and we did not capture postnatal maternal egg consumption. Further research is needed to evaluate possible reasons for the observed threshold effect of daily maternal egg consumption rather than the expected linear dose-response. Variability in the benefits of early egg introduction have been suggested depending on family characteristics, including race/ethnicity (8), and may also depend upon other dietary components. Egg consumption during lactation can result in the transmission of egg components in breastmilk, but does not occur consistently for all women and has an unclear association with infant oral tolerance (9), suggesting that interactions with breastfeeding also warrant further investigation.

In summary, CHILd cohort infants of mothers who ate egg daily during pregnancy were more likely to be sensitized to egg and allergic to peanut in early childhood. Further research should explore possible mechanisms of these associations and examine the potential roles of race/ethnicity, timing of breastfeeding and infant food introduction before making recommendations regarding maternal egg consumption in pregnancy.

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Table 1. Associations between daily prenatal egg, peanut and cow's milk consumption and child sensitization and allergy to egg, peanut and other allergens in the CHILD Cohort

	n*	Unadjusted OR (95% CI)	n*	Adjusted OR† (95% CI)
Daily prenatal egg consumption				
Sensitization to egg at age 1 year	2695	3.10 (1.79-5.37)	2584	2.64 (1.44-4.83)‡
Sensitization to egg at 3 years	2303	5.62 (2.55-12.4)	2227	4.12 (1.76-9.63)
Egg allergy at 3 years	2377	11.0 (1.13-107)	2299	10.6 (0.87-130)
Sensitization to peanut at 1 year	2695	2.47 (1.25-4.88)	2496	1.70 (0.77-3.79)§
Sensitization to peanut at 3 years	2299	2.68 (1.19-6.01)	2132	0.94 (0.31-2.87)§
Peanut allergy at 3 years	2405	4.81 (1.97-11.7)	2241	3.01 (1.03 -8.78)§
Sensitization to cow's milk at 1 year	2992	2.12 (1.32-3.40)	2706	2.34 (1.00-5.46)
Sensitization to cow's milk at 3 years	2475	5.46 (1.84-16.20)	2394	3.60 (1.14-11.35)
Sensitization to dust mites at 1 year	2704		2668	
Sensitization to dust mites at 3 years	2992	2.08 (0.74-5.85)	2706	1.68 (0.58-4.89)
Daily prenatal peanut consumption				
Sensitization to egg at 1 year	2695	1.51 (0.85-2.68)	2660	1.76 (0.97-3.19)
Sensitization to egg at 3 years	2303	1.08 (0.33-3.53)	2227	1.22 (0.36-4.12)
Egg allergy at 3 years	2373		2299	
Sensitization to peanut at 1 year	2695	1.22 (0.58-2.54)	2496	1.60 (0.74-3.45)§
Sensitization to peanut at 3 years	2299	1.34 (0.58-3.16)	2132	2.13 (0.84-5.41)§
Peanut allergy at 3 years	2405	0.88 (0.21-3.69)	2241	1.22 (0.27-5.57)§
Sensitization to cow's milk at 1 year	2992	1.08 (0.65-1.79)	2706	1.28 (0.50-3.26)
Sensitization to cow's milk at 3 years	2475	0.73 (0.098-5.40)	2394	0.77 (0.10-5.84)
Sensitization to dust mites at 1 year	2704	0.71 (0.096-5.29)	2668	0.81 (0.11-6.05)
Sensitization to dust mites at 3 years	2992	0.72 (0.17-2.96)	2706	0.82 (0.20-3.42)
Daily prenatal milk consumption				
Sensitization to egg at 1 year	2912	0.66 (0.50-0.87)	2851	0.75 (0.55-1.00)
Sensitization to egg at 3 years	2482	1.19 (0.67-2.11)	2382	1.62 (0.88-2.99)
Egg allergy at 3 years	2559	0.48 (0.068-3.44)	2409	0.28 (0.025 3.10)
Sensitization to peanut at 1 year	2911	0.96 (0.68-1.37)	2654	1.20 (0.80-1.82)§
Sensitization to peanut at 3 years	2477	1.12 (0.72-1.75)	2266	1.35 (0.79-2.29)§
Peanut allergy at 3 years	2591	1.40 (0.72-2.71)	2384	1.70 (0.79-3.68)§
Sensitization to cow's milk at 1 year	3412	0.49 (0.40-0.59)	2900	0.91 (0.58-1.42)
Sensitization to cow's milk at 3 years	2669	0.74 (0.35-1.54)	2536	1.10 (0.498-2.45)
Sensitization to dust mites at 1 year	2921	0.50 (0.24-1.03)	2859	0.64 (0.30-1.37)

Sensitization to dust mites at 3 years	3412	0.68 (0.41-1.13)	2900	0.64 (0.38-1.07)
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*n represents the number of participants included in each model. †All logistic regression models were adjusted for moderate-to-severe atopic dermatitis in the first year of life, maternal race, and paternal race. Where significant, models evaluating egg sensitization or allergy were also adjusted for age of infant dietary egg introduction‡ and models evaluating peanut sensitization or allergy were also adjusted for age of infant dietary peanut introduction§. Age of infant dietary cow's milk introduction was considered in models evaluating cow's milk sensitization. Other covariables considered as possible confounders in all adjusted models were biological sex, maternal education, socioeconomic status, number of older siblings, siblings with food allergy, maternal food allergy and other atopic conditions, paternal food allergy and other atopic conditions, exclusive breastfeeding at 6 months of life, and study centre. They did not significantly change the models. ¶These model did not run because too few children were present in at least one category.

197 Figure Legend

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199 Figure 1. Proportion of children sensitized to egg at 1 year (N=2695), peanut at 1 year (N=2694), egg at 3
200 years (N=2303), and peanut at 3 years (N=2303), stratified by prenatal egg consumption.

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Table E1. Associations between daily prenatal egg consumption and child sensitization to egg, peanut and cow's milk in the CHILD Cohort: Full population and stratified analyses

	n*	Unadjusted OR (95% CI)	n*	Adjusted [†] OR (95% CI)
Sensitization to egg at age 1 year				
Full population	2695	3.10 (1.79-5.37)	2660	2.61 (1.45-4.69)
Not introduced to egg by 6 months	2483	2.93 (1.61-5.34)	2451	2.38 (1.25-4.50)
Introduced egg by 6 months	134	7.50 (1.19-47.3)	133	5.62 (0.78-40.5)
Not introduced to egg by 9 months	1497	2.80 (1.20-6.50)	1473	2.48 (1.01-6.08)
Introduced egg by 9 months	1120	3.71 (1.73-7.99)	1111	2.68 (1.20-6.01)
Not introduced to egg by 12 months	518	2.86 (0.76-10.7)	502	2.51 (0.60-10.6)
Introduced egg by 12 months	2099	3.28 (1.76-6.12)	2082	2.63 (1.35-5.11)
Sensitization to egg at 3 years				
Full population	2303	5.62 (2.55-12.4)	2227	4.12 (1.76-9.63)
Not introduced to egg by 6 months	2143	5.65 (2.44-13.1)	2079	3.99 (1.61-9.89)
Introduced egg by 6 months	112	‡	109	‡
Not introduced to egg by 9 months	1311	7.15 (2.33-21.9)	1261	5.17 (1.51-17.73)
Introduced egg by 9 months	944	3.62 (1.02-12.8)	927	2.53 (0.68-9.49)
Not introduced to egg by 12 months	464	4.02 (0.47-34.2)	434	3.33 (0.30-37.38)
Introduced egg by 12 months	1791	5.22 (2.11-12.9)	1754	3.54 (1.36-9.23)
Sensitization to peanut at 1 year				
Full cohort	2695	2.47 (1.25-4.88)	2661	1.87 (0.92-3.85)
Not introduced to peanut by 9 months	2115	2.78 (1.29-5.98)	2090	2.03 (0.90-4.59)
Introduced peanut by 9 months	411	‡	406	‡
Not introduced to peanut by 12 months	1355	3.36 (1.52-7.43)	1333	2.32 (0.995-5.42)
Introduced peanut by 12 months	1171	‡	1163	‡
Sensitization to peanut at 3 years				
Full cohort	2299	2.68 (1.19-6.01)	2223	1.39 (0.55-3.51)
Not introduced to peanut by 9 months	1847	2.54 (0.98-6.58)	1795	1.14 (0.37-3.48)
Introduced peanut by 9 months	344	‡	337	‡
Not introduced to peanut by 12 months	1188	2.31 (0.79-6.72)	1146	1.24 (0.40-3.86)
Introduced peanut by 12 months	1003	1.94 (0.25-15.1)	986	‡
Sensitization to cow's milk at 1 year				
Full cohort	2992	2.12 (1.32-3.40)	2706	2.34 (1.00-5.46)
Not introduced to cow's milk by 6 months	1765	2.07 (1.18-3.63)	1551	2.25 (0.74-6.83)
Introduced to cow's milk by 6 months	1225	2.13 (0.87-5.19)	1153	2.51 (0.68-9.28)
Not introduced to cow's milk by 9 months	1063	1.66 (0.86-3.22)	866	0.70 (0.83-5.98)
Introduced to cow's milk by 9 months	1927	2.66 (1.33-5.35)	1838	3.63 (1.44-9.18)
Not introduced to cow's milk by 12 months	375	1.25 (0.52-3.01)	200	‡
Introduced to cow's milk by 12 months	2615	2.48 (1.32-4.65)	2504	2.86 (1.22-6.70)
Sensitization to cow's milk at 3 years				
Full cohort	2475	5.46 (1.84-16.20)	2394	3.60 (1.14-11.35)
Not introduced to cow's milk by 6 months	1418	3.95 (0.87-17.83)	1370	3.03 (0.62-14.73)
Introduced to cow's milk by 6 months	1056	8.47 (1.72-41.58)	1032	5.06 (0.95-27.03)
Not introduced to cow's milk by 9 months	799	2.71 (0.34-21.94)	763	3.02 (0.32-28.08)
Introduced to cow's milk by 9 months	1675	7.89 (2.16-28.81)	1630	5.28 (1.37-20.3)
Not introduced to cow's milk by 12 months	172	‡	150	‡

Introduced to cow's milk by 12 months	2302	7.22 (2.37-22.00)	2243	4.70 (1.46-15.09)
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*n represents the number of participants included in each model. †Logistic regression models were adjusted for moderate-to-severe atopic dermatitis in the first year of life, maternal race, and paternal race. Other covariables considered as possible confounders in the stratified models were biological sex, maternal education, socioeconomic status, number of older siblings, siblings with food allergy, maternal food allergy and other atopic conditions, paternal food allergy and other atopic conditions, exclusive breastfeeding at 6 months of life, and study centre. They did not significantly change the models. ‡These model did not run because too few children were present in at least one category.

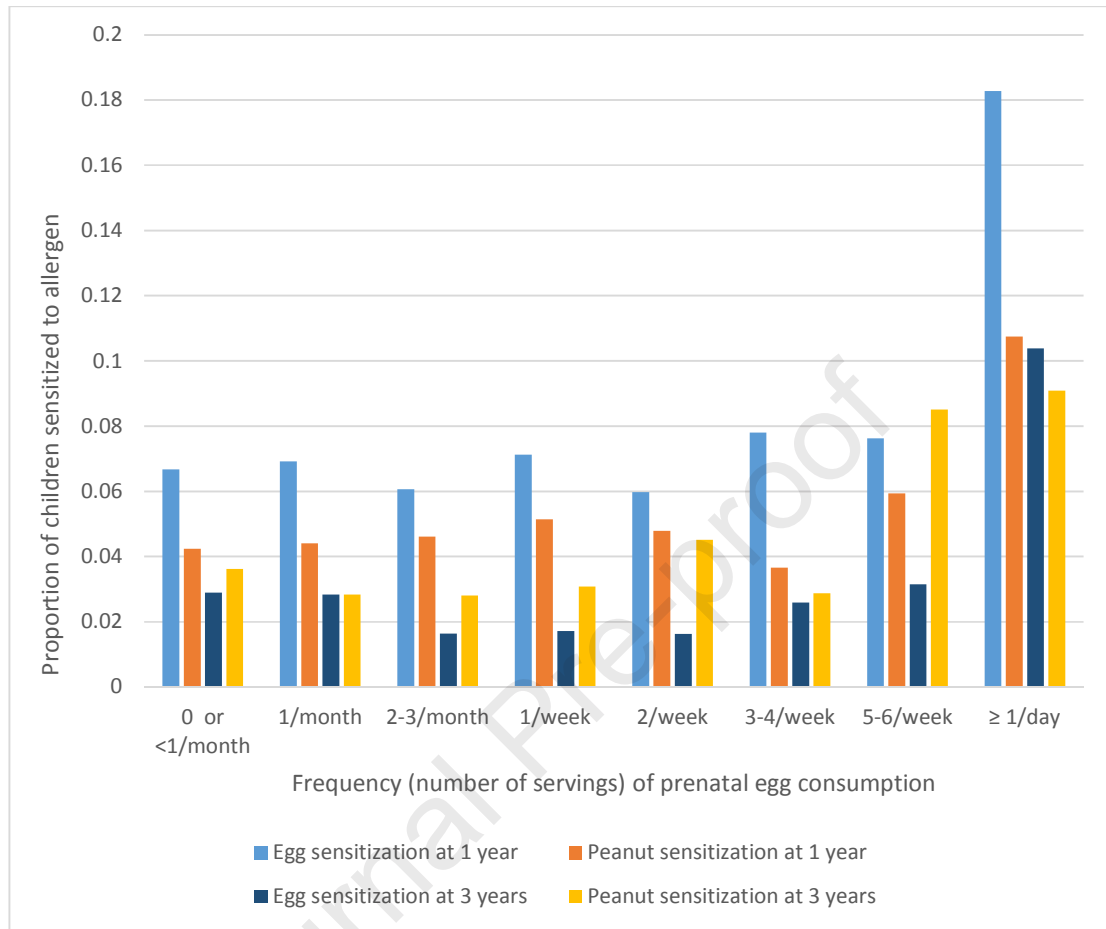


Figure 1. Proportion of children sensitized to egg at 1 year (N=2695), peanut at 1 year (N=2694), egg at 3 years (N=2303), and peanut at 3 years (N=2303), stratified by prenatal egg consumption.

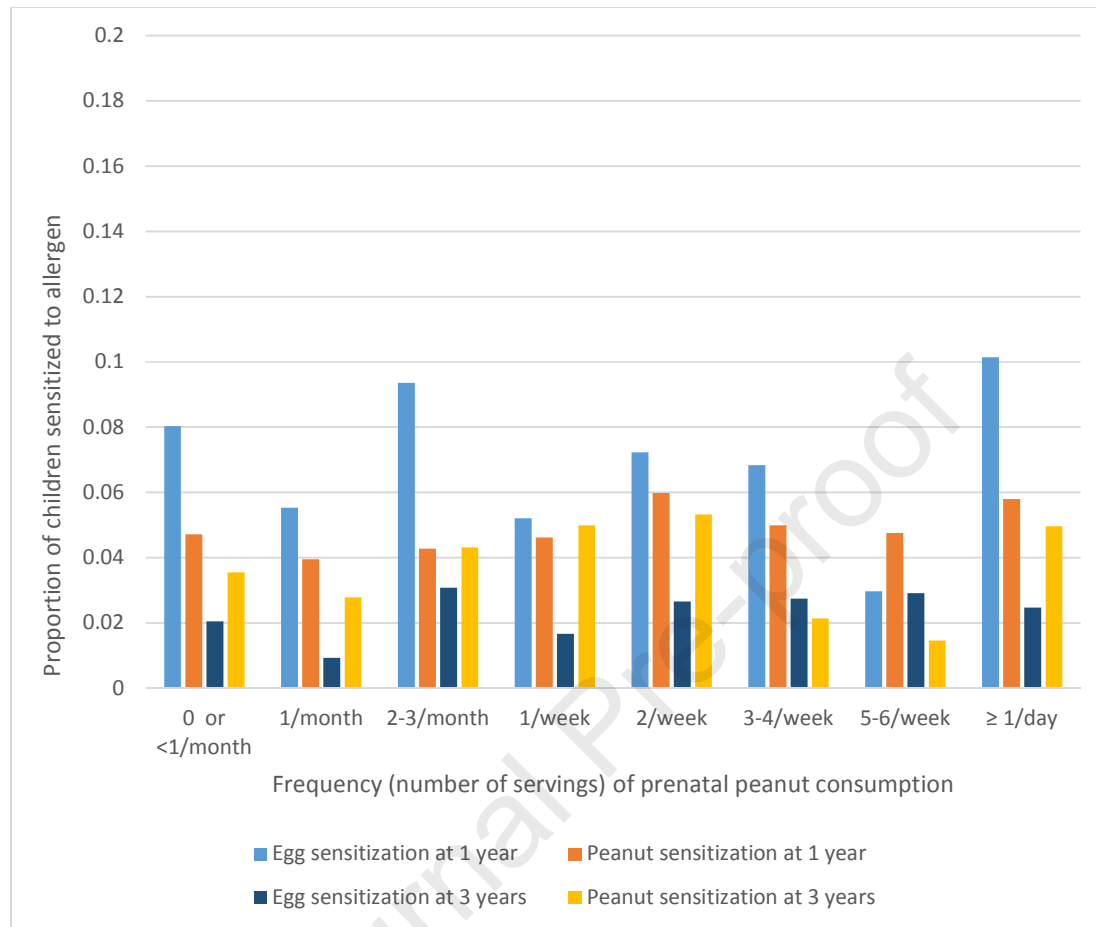


Figure E1. Proportion of children sensitized to egg at 1 year (N=2695), peanut at 1 year (N=2694), egg at 3 years (N=2303), and peanut at 3 years (N=2303), stratified by prenatal peanut consumption.

Figure E1. Proportion of children sensitized to egg at 1 year (N=2695), peanut at 1 year (N=2694), egg at 3 years (N=2303), and peanut at 3 years (N=2303), stratified by prenatal peanut consumption.