eMethods Supplement

Continuous independent covariates:

Logistic regression is similar to linear regression in assuming linearity of the independent predictor variables, which may not be true of continuous type variables. Smooth plots provide a graphical description of the relation between the continuous independent predictor and the dependent outcome. If there is no change in the relationship, the continuous independent predictor is included in the analysis without any modification. If the relationship between the independent predictor and the outcome changes over the range of values of the independent predictor (examples include bell-shaped or any curvilinear lines), then the independent predictor is divided into separate, continuous variables. The division will occur where the slope of the line changes direction, at the peaks and nadirs. These new variables will then have a linear relation with the dependent predictor over their subset range, while maintaining the power of being a continuous independent predictor. By including all of the variables allows for the entire range of values of the independent predictor to be analyzed and will improve the overall fit of the model. This type of preparatory analysis was performed for the continuous independent covariates which included: endotoxin, β-glucan, *Fel d1*, *Can f1*, *Der p1*, and *Bla g1*). The exception to this was DEP, which was dichotomized at the 66th percentile, in order to be consistent with other analyses from the CCAAPS group. For further information on logistic regression analysis, the readers are referred to other resources.[1,2]

Categorical independent covariates:

Categorical independent predictor variables do not require a similar graphical analysis. These covariates were analyzed using logistic regression. If an association between the independent

covariate and AR was found, at a *p*-value level of <0.2, the independent predictor was included in further multi-variate analysis. If an association between the independent covariate and AR was found at a *p*-value of < 0.2 then the independent covariate was included in the multi-variate analysis.

SPT allergen wheal area:

As noted in the Methods section, logistic regression was used to analyze all 15 aeroallergens and the two food allergens. If an association between the independent allergen wheal area and AR was found, at a p-value level of <0.2 after adjustment for multiple comparisons using the Holms-Sidak test, the independent allergen wheal area was included in further multi-variate analysis.

Multi-variate analysis:

Multi-variate logistic regression was performed for covariates and each age of SPT wheal area, such as age one, two or three, for testing of associations with AR at age four. The "all-subsets" method was used to reduce the number of variables to those that were informative and allowed for best fit.[3] The criteria for removing a variable was if the log likelihood ratio of the reduced model did not decrease significantly and/or the remaining variable coefficients did not change by >20%.

References:

1. LaValley MP. Logistic regression. *Circulation.* May 6 2008;117(18):2395-2399.
2. Harrell J, Frank E. *Regression modeling strategies: with applincation to linear models, logistic regression, and survival analysis.* New York Springer-Verlag New York Inc.; 2001.
3. Goodenough AE, Hart AG, Stafford R. Regression with empirical variable selection: description of a new method and application to ecological datasets. *PLoS One.* 2012;7(3):e34338.

		Age One Wheal Area (n=596) *p*-value	Age Two Wheal Area (n=591) *p*-value	Age Three Wheal Area (n=609) *p*-value
Pollens	Cedar	0.84	0.65	0.48
	Elm	1.0	0.88	**0.01†**
	Maple	1.0	**0.18***	**0.02†**
	Oak	1.0	0.62	0.4
	Fescue	1.0	0.97	**0.01†**
	Timothy	1.0	**0.09***	**0.08†**
	Ragweed	0.94	0.76	0.86
Arthropods	Dust mite	1.0	0.92	0.7
	Cockroach	1.0	1.0	0.98
Mammals	Cat	0.61	**0.16***	0.43
	Dog	1.0	0.99	**0.17†**
Molds	*Alternaria*	1.0	**0.01†**	0.50
	Aspergillus	1.0	0.73	0.79
	Cladosporium	0.96	1.0	1.0
	Penicillium	1.0	0.90	**0.01†**
Foods	Milk	1.0	1.0	1.0
	Egg	1.0	0.85	0.99

Table E1: Holm-Sidak adjusted SPT wheal area at age one, two and three associated with allergic rhinitis (compared to all other phenotypes) at age four. In each year there was at

least one subject whose parent refused testing to Milk and Egg. Therefore, the denominator for age one is 595; for age two 589 (for milk) and 588 (for egg); for age three 609 (for milk) and 602 (for egg).

*P<0.2 †P <0.05 ‡P<0.003

		Age One Wheal Area (n=67) *p*-value	Age Two Wheal Area (n=117) *p*-value	Age Three Wheal Area (n=141) *p*-value
Pollens	**Cedar**	0.99	0.40	1.0
	Elm	1.0	0.94	**0.10**
	Maple	1.0	1.0	1.0
	Oak	1.0	1.0	1.0
	Fescue	1.0	1.0	1.0
	Timothy	1.0	0.98	1.0
	Ragweed	--	1.0	1.0
Arthropods	**Dust mite**	1.0	1.0	1.0
	Cockroach	--	1.0	1.0
Mammals	**Cat**	0.97	1.0	1.0
	Dog	--	1.0	1.0
Molds	***Alternaria***	1.0	1.0	1.0
	Aspergillus	--	1.0	0.99
	Cladosporium	1.0	--	1.0
	Penicillium	1.0	1.0	1.0
Foods	**Milk**	1.0	--	--
	Egg	1.0	1.0	1.0

Table E2: Unadjusted association of allergen wheal areas at ages 1, 2, and 3 (stratified to those were aeroallergen sensitized but asymptomatic) with AR at age 4.

24 *P<0.2 †P <0.05 ‡P<0.003

		Age One Wheal Area (n=41) *p*-value	Age Two Wheal Area (n=100) *p*-value	Age Three Wheal Area (n=109) *p*-value
Pollens	**Cedar**	1.0	0.79	1.0
	Elm	--	1.0	1.0
	Maple	1.0	0.71	0.23
	Oak	1.0	1.0	1.0
	Fescue	1.0	1.0	0.79
	Timothy	0.95	1.0	0.98
	Ragweed	1.0	1.0	1.0
Arthropods	**Dust mite**	--	1.0	1.0
	Cockroach	1.0	1.0	1.0
Mammals	**Cat**	1.0	0.97	1.0
	Dog	1.0	0.95	0.93
Molds	***Alternaria***	1.0	**0.002‡**	1.0
	Aspergillus	0.65	0.97	1.0
	Cladosporium	0.87	1.0	1.0
	Penicillium	1.0	1.0	1.0
Foods	**Milk**	1.0	1.0	1.0
	Egg	1.0	0.78	1.0

Table E3: Unadjusted association of allergen wheal areas at ages 1, 2, and 3 (stratified to those were early AR) with AR at age 4.

*P<0.2 †P <0.05 ‡P<0.003

		Age Two Allergen Wheal Area aOR; 95% CI; *P*-value	Age Three Allergen Wheal Area aOR; 95% CI; *P*-value [1]
Sensitized, but not symptomatic strata	**Elm**	--	1.08; (1.03, 1.21); 0.01
Sensitized and symptomatic (AR) strata	***Alternaria***	1.19; (1.05, 1.48); 0.03	--

Table E4: Stratified adjusted odds ratio of allergen wheal area at age two and three.

Stratified analyses were performed for aeroallergen sensitivity associated with AR at age four. First analysis was to among children who were sensitized but not symptomatic. At age two, no aeroallergen wheal area was significant in multivariable model. At age three, elm wheal area size was significantly associated with AR at age four, with covariates including β-glucan, duration of breastfeeding, and season of birth. The second analysis was among children who were sensitized and symptomatic (i.e. had early onset of AR). At age two, *alternaria* wheal area was significantly associated with AR at age four, with covariates including ethnicity, duration of breastfeeding, and number of children in home at age one. At age three, no aeroallergen was significant in the multivariable model.

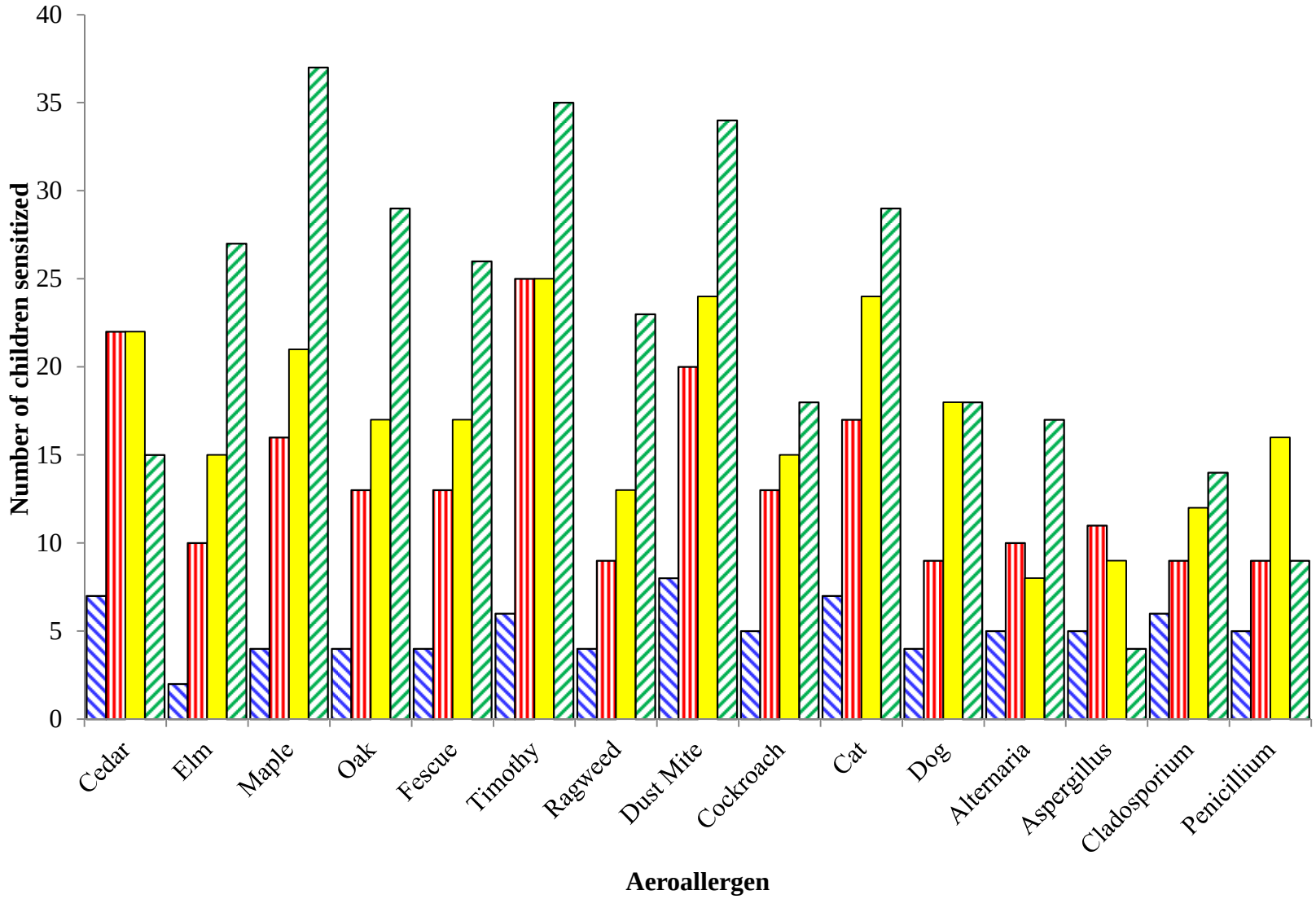

Figure E1- Absolute number of aeroallergen sensitivities among allergic rhinitis children at ages one to four.