

Alpha-gal sensitization among young adults is associated with male sex and polysensitization



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Clinical Implications

Approximately 6% of young adults from the general population are sensitized to α -Gal, but mammalian meat allergy is rare. Independent risk factors for sensitization are tick bites, male sex, and polysensitization to food/airborne allergens.

Galactose- α -1,3-galactose (α -Gal) syndrome (AGS) is characterized by delayed severe allergic reactions after consumption of mammalian meat or mammalian-derived products and is caused by immunoglobulin E (IgE) antibodies against the carbohydrate α -Gal.^{1,2} AGS is most common at middle age, and the route of sensitization appears to be through tick bites.^{2,3} The prevalence of IgE reactivity to α -Gal differs, 1%-25% depending on region, being more frequent in areas where ticks are common.² Atopy has been suggested as a risk factor for α -Gal sensitization.³ Here, we explored the prevalence of IgE to α -Gal and mammalian meat allergy among young adults in the general population and elucidated the impact of sensitization to other food or airborne allergens, tick bites, and sex on IgE reactivity to α -Gal.

We investigated the population-based birth cohort BAMSE (N = 4089), comprising individuals followed up to young adulthood,⁴ from urban and semiurban areas of Stockholm, where the tick *Ixodes ricinus* is prevalent.⁵ At 24 years of age, blood samples were analyzed for IgE to α -Gal (o215, bovine thyroglobulin) in addition to 14 common food and airborne allergens, and at 4, 8, and 16 years of age, the same common food and airborne allergens were analyzed (ImmunoCAP).⁴ Sensitization was divided into mono- (1 allergen), oligo- (2 to 3 allergens), or poly- (≥ 4 allergens) sensitization. At 24 years of age, the participants answered questionnaire including symptoms and tick bites. *Symptoms to mammalian meat* was defined as questionnaire reported reduced consciousness, asthma, swollen face, lips or throat, hoarseness, urticaria, vomiting, abdominal pain or rhinoconjunctivitis after ingestion of meat, or avoiding meat due to previous symptoms or allergy test. *Symptoms to milk* was defined as above but not including abdominal symptoms or avoidance. *Mammalian meat allergy* was defined as sensitization to alpha-Gal (≥ 0.10 kU_A/L) in combination with symptoms to mammalian meat. The main study population comprised subjects with complete data on specific IgE and complete answers on the questions on tick bites and reactions to food items at 24 years of age. The subpopulation was defined as above and additional

complete data on specific IgE from the 4-, 8-, and 16-year follow-ups. The χ^2 test was used to compare proportions between 2 groups. Odds ratios were calculated with logistic regression. Correlations between levels of specific IgE were analyzed with Spearman's rho and comparison of median levels of specific IgE with quantile regression (STATA; Stata Corp, College Station, Texas). *P* values $< .05$ were considered statistically significant. The study was approved by Swedish Ethical Review, Stockholm, Sweden, and all participants provided written informed consent.

In this study population of 2201 individuals, the prevalence of IgE reactivity to α -Gal at 24 years of age was 5.9% (median IgE level to α -Gal: 0.26 kU_A/L; range: 0.10-37.0 kU_A/L), a prevalence similar to that seen for soy (5.5%) and wheat (6.0%). Subjects sensitized to α -Gal were significantly more often sensitized to other food (peanut, soy, wheat, milk, egg, fish) and airborne (cat, dog, horse, pollen, mites, mold) allergens. Twenty-four percent were sensitized to any other food item. Half (50.4%) of the α -Gal positive subjects were sensitized to the α -Gal-containing allergen sources cat, dog, and/or milk. However, no correlations between IgE levels to α -Gal and cat ($r = 0.036$), dog ($r = -0.064$), or milk ($r = 0.149$) were noted. Thus, the rate of sensitization cannot be explained by IgE reactivity to these α -Gal-containing allergen sources.

The majority of the study population (81.4%) reported that they had been tick bitten. Among the 129 α -Gal-sensitized subjects, this proportion reached 93.0%. A significantly higher number of subjects reported tick bites within the last 2 years among α -Gal-sensitized subjects compared with nonsensitized subjects (44.2% vs 24.2%, $P < .001$). The proportion of sensitized subjects increased with increasing number of tick bites (Figure E1, A, available in this article's Online Repository at www.jaci-inpractice.org), and in a multiple regression model, the odds ratio (OR) for α -Gal sensitization if > 10 tick bites was 5.5 (95% confidence interval [CI]: 2.7-11.2) compared with subjects without tick bites (Table I). The strong association between tick bites and α -Gal sensitization is in line with previous reports^{2,3} and is here for the first time shown to be present already in young adults.

IgE reactivity to α -Gal was significantly more common among males than females (8.9% vs 3.4%, $P < .001$) (Figure E1, B, available in this article's Online Repository at www.jaci-inpractice.org). The OR for males to be sensitized to α -Gal at 24 years compared with females was 2.8 (95% CI: 1.9-4.0) (Table I). However, there was no difference in the α -Gal IgE levels between males and females (median IgE: 0.31 vs 0.20 kU_A/L, $P = .165$). An overrepresentation of males among α -Gal positive subjects has been previously described and interpreted as differences in tick exposure (such as outdoor activities) between men and women.^{6,7} In our study, males reported more tick bites than females, but the association remained significant after adjustment, although residual confounding cannot be ruled out.

The OR to be sensitized to α -Gal also increased for sensitization to multiple allergen sources, but not to 1 specific allergen source, and remained significant after adjustment for tick bites and male sex (OR: 2.9, 95% CI: 1.9-4.2) (Table I). Polysensitization, but not mono- or oligosensitization, was associated

TABLE 1. Odds ratios for sensitization to α -Gal at 24 years of age in relation to number of tick bites, sex, sensitization to food allergens, sensitization to cat/dog/horse, sensitization to pollen, and sensitization to mites/mold, respectively (n = 2201)

Variable	Sensitization to α -Gal at 24 y (n = 129, 5.9%)						
	n	n	%	OR _c	95% CI	OR _a	95% CI
No. of tick bites							
0	409	9	2.2	ref	ref	ref	ref
1-10	1240	58	4.7	2.2	1.1-4.4	2.1	1.0-4.4
>10	552	62	11.2	5.6	2.8-11.5	5.5	2.7-11.2
Sex							
Female	1225	42	3.4	ref	ref	ref	ref
Male	976	87	8.9	2.8	1.9-4.0	2.3	1.6-3.4
Sensitization							
Negative	1229	47	3.8	ref	Ref	ref	ref
Food allergens*	30	2	6.7	1.8	0.4-7.8	2.0	0.5-8.8
Cat/dog/horse	39	0	0.0	n.a.	n.a.	n.a.	n.a.
Pollen allergens†	166	5	3.0	0.8	0.3-2.0	0.8	0.3-1.9
Mites/mold	54	3	5.6	1.5	0.4-4.9	1.4	0.4-4.7
≥2 allergen sources	683	72	10.5	3.0	2.0-4.3	2.9	1.9-4.2

Cutoff 0.1 kU_A/L. Multivariate logistic regression model including, sex, number of tick bites, and sensitization.

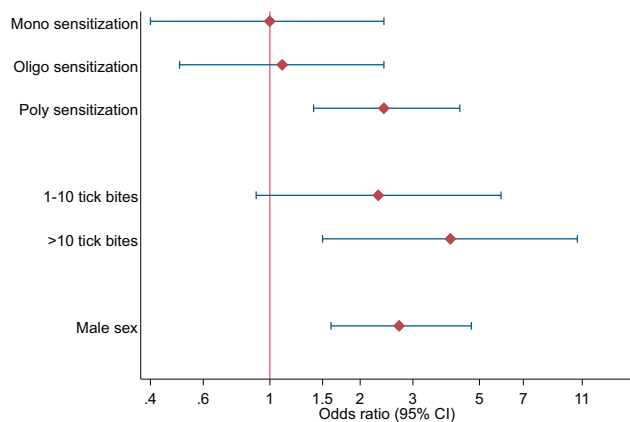
CI, Confidence interval; n.a., not applicable; OR_a, adjusted odds ratio; OR_c, crude odds ratio.

Italic style is used for the 95% CI.

Bold style is used for the significant values (CI lower limit >1.0).

*Any of peanut, soy, wheat, milk, egg, or fish.

†Any of birch, grass, or mugwort.

**FIGURE 1.** Adjusted odds ratios for sensitization to α -Gal at 24 years of age in relation to mono-, oligo-, or polysensitization at any time point up to 16 years of age. Multivariate model including sensitization, sex, and number of tick bites. CI, Confidence interval.

with α -Gal sensitization (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Stratifying the number of sensitizations into food allergens and airborne allergens, respectively, the association remained significant for polysensitization to food allergens as well as to airborne allergens (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). In a subpopulation of 1216 BAMSE subjects, who provided blood samples at 4, 8, 16, and 24 years, a longitudinal analysis, including number of sensitizations, number of tick bites, and sex, revealed that polysensitization at any time point up to 16 years of age was significantly associated with

α -Gal sensitization at 24 years (OR: 2.4, 95% CI: 1.4-4.3) (Figure 1). This suggests that no allergen source per se is important for the development of α -Gal sensitization, and the previously reported risk factor of sensitization to airborne allergens^{3,7} may be extended to food allergens. Particularly, polysensitization seems to be a risk factor for α -Gal sensitization.

Only 2.3% of the α -Gal-sensitized subjects (n = 3) reported symptoms after ingestion of mammalian meat, corresponding to a population-based prevalence of 0.1% of mammalian meat allergy among young adults. None reported specific symptoms to milk. Two were males and 1 was female; all reported tick bites. Two had α -Gal specific IgE levels of ≥ 2.0 kU_A/L, a level which has been suggested as relevant for the diagnosis of AGS.⁸ It could be suspected that patients may not identify their symptoms as related to mammalian meat intake due to the delay of symptom onset.⁸ Asking for typical symptoms of mammalian meat allergy, not specifically related to intake of red meat, still no overrepresentation of symptoms among the α -Gal-sensitized subjects compared with the nonsensitized subjects was noted (data not shown). The low prevalence of mammalian meat allergy found at young adulthood is in line with previous research showing that symptoms, although existing at all ages, are dominating at middle age.^{3,8} It may be that at this young age, levels of IgE to alpha-Gal are still low and repeated tick bites are required for symptoms to develop.

The strengths of the study include the population-based design, the sample size, and long follow-up time. A comparison between the study populations and the original cohort was made without any major differences.⁹ Limitations are the lack of α -Gal IgE measurements before the age of 24 years and that reported symptoms were questionnaire based only.

Taken together, in this large general young adult population, sensitization to α -Gal was approximately 6%, but symptoms suggestive of mammalian meat allergy were rare. Risk factors

for α -Gal sensitization were tick bites, male sex, and polysensitization.

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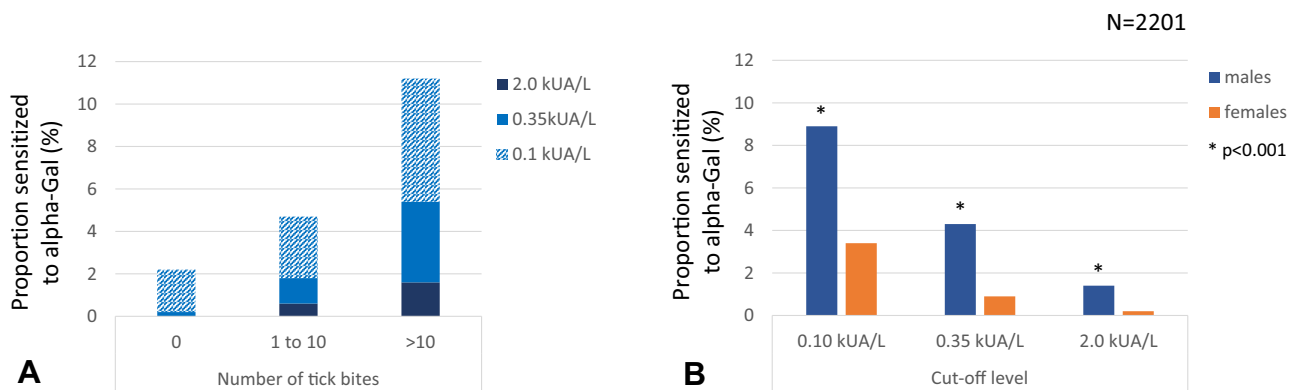


FIGURE E1. Proportion sensitized to α -Gal at 24 years of age in relation to (A) number of tick bites and (B) males and females.

TABLE E1. Odds ratios for sensitization to α -Gal at 24 years in relation to mono-, oligo-, or polysensitization at 24 years

No. of sensitizations	Sensitization to α -Gal at 24 y (n = 129, 5.9%)								
	n	n	%	OR _c	95% CI	OR ¹ _a	95% CI	OR ² _a	95% CI
All allergens*									
No sensitization (0)	1230	47	3.8	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>
Monosensitization (1)	92	2	2.2	0.6	<i>0.1-2.3</i>	0.6	<i>0.1-2.4</i>		
Oligosensitization (2-3)	318	16	5.0	1.3	<i>0.7-2.4</i>	1.3	<i>0.7-2.3</i>		
Polysensitization (≥ 4)	561	64	11.4	3.2	2.2-4.8	3.1	2.1-4.7		
Food allergens†		n	%	OR _c	95% CI	OR ¹ _a	95% CI	OR ² _a	95% CI
No sensitization (0)	1230	47	3.8	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>
Monosensitization (1)	26	0	0.0	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Oligosensitization (2-3)	97	11	11.3	3.2	1.6-6.4	3.4	1.7-6.9	2.4	<i>0.5-11.0</i>
Polysensitization (≥ 4)	68	20	29.4	10.5	5.8-19.1	10.8	5.8-20.3	7.6	1.7-34.6
Airborne allergens‡		n	%	OR _c	95% CI	OR ¹ _a	95% CI	OR ³ _a	95% CI
No sensitization (0)	1230	47	3.8	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>
Monosensitization (1)	82	2	2.4	0.6	<i>0.2-2.6</i>	0.6	<i>0.1-2.6</i>	0.6	<i>0.1-2.4</i>
Oligosensitization (2-3)	269	15	5.6	1.5	<i>0.8-2.7</i>	1.5	<i>0.8-2.8</i>	1.4	<i>0.7-2.5</i>
Polysensitization (≥ 4)	590	63	10.7	3.0	2.0-4.5	2.9	1.9-4.3	2.1	1.3-3.3

Cutoff 0.1 kU_A/L.

CI, Confidence interval; n.a., not applicable; OR_c, crude odds ratio; OR¹_a, adjusted odds ratio: number of sensitizations adjusted for sex and number of tick bites; OR²_a, adjusted odds ratio: number of sensitizations adjusted for sex, number of tick bites, and sensitization to any inhalant allergen; OR³_a, adjusted odds ratio: number of sensitizations adjusted for sex, number of tick bites, and sensitization to any food allergen.

Italic style is used for the 95% CI.

Bold style is used for the significant values (CI lower limit >1.0).

*N = 2201.

†N = 1421, subjects with airborne allergens only are excluded from the analysis.

‡N = 2171, subjects with food allergens only are excluded from the analysis.