The use of allergen-specific IgE tests in general practice

Mie Hessellund Samson[1], Mette Østergaard[2], Jurgita Janukonyte[2] & Alisa Devedzic Kjaergaard[3]

ABSTRACT

INTRODUCTION: In Denmark, diagnosing and treating allergy is mainly performed by general practitioners (GPs), but precise expectations of the GPs are not described in guidelines. Furthermore, very little is known about GPs' use of allergen-specific immunoglobulin E (sIgE) tests. The aim of this study was to describe the use of these tests in the Central Denmark Region.

METHODS: We performed analyses on data from all sIgE tests ordered by GPs in the Central Denmark Region in 2015. A test was considered positive if the serum level of IgE was ≥ 0.35 kU/l.

RESULTS: Serum levels of sIgE were determined in 26,129 patients, equivalent to 2% of the Danish population. A total of 106,237 tests were performed, the majority as part of screening algorithms for inhalant and food allergens. Screening was ordered 20,697 times for inhalation allergens and 12,999 times for food allergens. Additionally, a considerable number of tests for antibiotics (n = 4,407), insect venom (n = 748) and other allergens were performed (n = 824). Positive rates were determined for various allergens in relation to gender and age. The rates were generally higher than rates known to be present in the background population. A higher percentage of females than males was tested. However, positive rates were generally lower in females than in males.

CONCLUSIONS: This is the first descriptive analysis of the use of testing for sIgE in general practice. Results from this study may be used to optimise how GPs order and interpret sIgE tests in the future.

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In Denmark, almost all patients initially see their general practitioner (GP) in case of allergy symptoms. Indeed, the Danish National Health Authority (DNHA) recommends that the majority of allergy patients be diagnosed and treated by the GPs without any contact to allergy specialists [1]. However, the most recent guideline published by the DNHA on allergy diagnosis and treatment is from 2006 [2] and fails to clearly describe how or who to test for allergy, or when referral to a specialist is needed.

Allergy diagnoses should be based on the combined use of a detailed clinical history and assessment of sensitisation [3]. Sensitisation testing is usually performed as measurements of serum allergen-specific immunoglobulin E (sIgE) and/or skin prick tests. At the individual level, sensitisation assessed by sIgE tests is only loosely related to the probability of having clinical symptoms of allergy. A detailed patient history is needed to decide whether sIgE testing is warranted, and thus raise the positive predictive value of the test. If there is correspondence between the clinical history and sensitisation tests, a diagnosis may be made. If not, other sensitisation tests and/or challenge tests are needed [4]. In the Central Denmark Region, the regional reimbursement to the GPs in relation to patient diagnosis and treatment covers sIgE testing, but not other sensitisation tests, which are therefore not performed by GPs. According to the Danish Society of Allergology, it is relevant for GPs to test for sensitisation only against the following allergens: birch, grass, mugwort, horse, dog, cat, house dust mites and certain moulds. Testing for all other allergens should be done only by specialists [5]. A clinical guideline made by specialists in the region has similar recommendations about inhalant allergens, but also recommends testing for food allergens [6]. The guideline thus recommends the use of sIgE screening tests (a mix of the most relevant allergens) for inhalant allergens and food allergens, **Figure 1**, and other sIgE tests only in case of direct suspicion of a specific allergen. No studies describe to which extent these recommendations are followed by the GPs. The aim of this study was to describe the use of sIgE tests in the Central Denmark Region with a view to enabling a discussion about whether allergy diagnostics by GPs may be optimised.

METHODS

Anonymised data were obtained from the laboratory information system LABKA II of the Central Denmark Region. Information on date of sampling, test results, gender and age of the patient was gathered for all sIgE tests ordered by GPs in the region during 2015. Each individual participated only once for each sIgE performed, as any subsequent result on the same sIgE test was omitted (n = 734). The number of GPs in 2015 was obtained from the Central Denmark Region and

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1) Department of Clinical Biochemistry, Aarhus University Hospital
2) Department of Clinical Biochemistry, Regional Hospital Central Jutland, Silkeborg
3) Department of Clinical Epidemiology, Aarhus University Hospital, Denmark

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population sizes were collected from Statistics Denmark.

Statistical analyses

Stata 13.1 (StataCorp LLC, USA) was used for all calculations. Comparison between genders and age groups was performed by Kruskal-Wallis or χ^2-test.

Specific-IgE tests

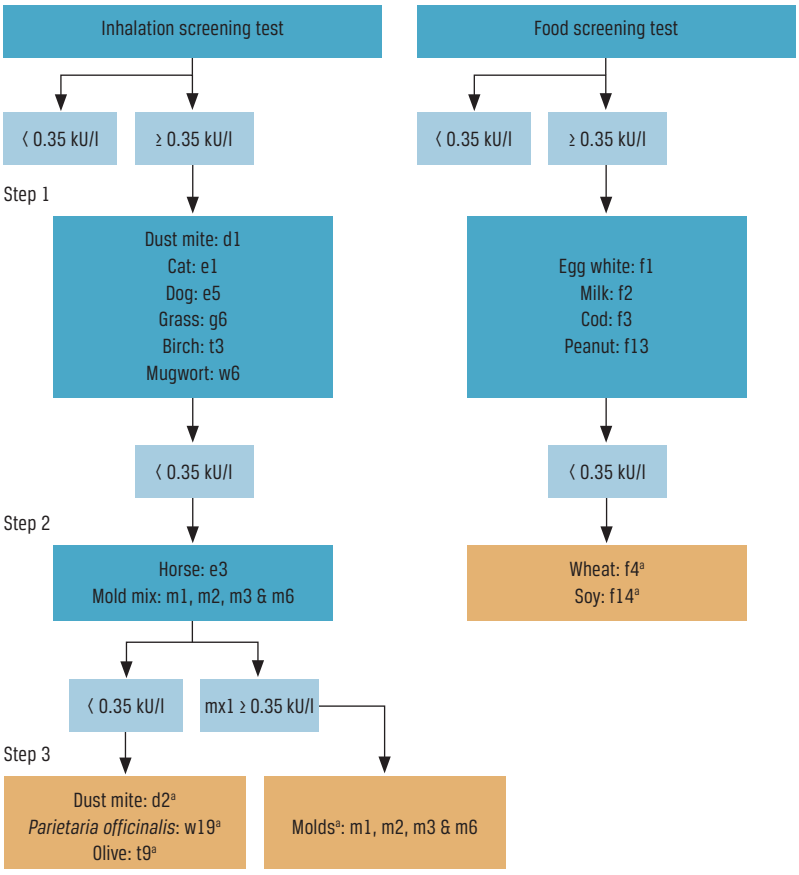
All sIgE tests were performed at Aarhus University Hospital, Horsens Regional Hospital, the Regional Hospital of Central Jutland, or Regional Hospital of West Jutland using the routine method applied by the laboratories (ImmunoCAP method on Phadia 250 or Phadia 1000 instruments, Thermo Fisher Scientific, Sweden).

The GPs order tests in a web-based ordering system, where a test menu is available which as a minimum includes the two sIgE screening tests for inhalation and food allergens. It is, however, always possible to order any sIgE test by adding free text during the ordering process. When a GP orders a screening test, a positive result will elicit further testing to isolate the specific allergen(s) producing the positive result. This occurs automatically in a stepwise process (two steps for the inhalation test and one step for the food test) so that the allergens that are considered more likely to be involved in sensitisation are elicited in the first step(s). One more step exists in both of these algorithms. The tests in this step will only be performed if it is specifically requested by the GP. The algorithms are described in Figure 1. A test was considered positive if the result was ≥ 0.35 kU/l.

Trial registration: not relevant.

FIGURE 1

Algorithms for the screening for inhalation and food allergens in the Central Denmark Region.



a) Only performed if GPs manually order the tests based on the results of the previous steps in the algorithm.

RESULTS

A total of 26,129 patients, corresponding to 2% of the total population of all ages were tested for sensitisation. In all, 106,237 tests were performed, corresponding to an average of four tests per patient. **Table 1** shows the numbers for males and females by age groups. Females were heavily overrepresented in the age groups ≥ 10 years, but males had more tests per patient than females ($p < 0.001$). Of all the tests performed, 31% were positive. However, 38% of the patients tested positive to at least one allergen. Between GPs, this ranged 0-56%. The positive rates were highest among males (40-56%), but also high for females aged 10-30 years (41%).

A list of sIgE tests performed is presented in **Table 2**. The most common tests were the two screening tests. For the allergens contained in step one of the algorithms, most tests were performed as part of this algorithm, but 8% of the tests were ordered directly, without initially ordering the screening tests. Some of the tests contained in subsequent steps were also ordered directly, either together with the screening test (overruling the algorithm) or without the screening test. This is reflected in, e.g., the large number of tests performed for the mold fungus mix. Moreover, 4,407 tests for antibiotics were performed, 748 for insect venom and finally 824 tests representing 121 different allergens were performed including allergen mixes, natural extracts and recombinant components.

Figure 2 shows the tests grouped by age and gender for the different groups of allergens. In all groups, females were overrepresented and this was especially pronounced for antibiotics. For both inhalation and food allergens, most tests were performed in patients aged 10-30 years, except for males who were tested for food allergens among whom the largest number of tests were performed in those < 10 years. For antibiotics and insect venoms, more tests were generally performed in adults.

The positive rate per allergen is shown in Table 2. Screening tests were more often positive for inhalant

TABLE 1

Population characteristics according to gender and age groups.

		< 10 yrs		10-30 yrs		≥ 30 yrs		p-value[c]	
	Total	females	males	females	males	females	males	gender	age
Population of Central Denmark Region[a], N (%)	1,291,643 (100)	71,390 (5.5)	74,599 (5.8)	164,456 (12.7)	173,712 (13.5)	409,782 (31.7)	397,704 (30.8)	-	-
Patients, n (%) [% of total population]	26,129 (100) [2.0]	1,192 (4.6) [1.7]	1,434 (5.5) [1.9]	6,047 (23.1) [3.7]	3,922 (15.0) [2.3]	8,381 (32.1) [2.0]	5,153 (19.7) [1.3]	< 0.0001	< 0.0001
Performed tests, n	106,237	4,617	6,485	25,435	20,218	28,074	21,408	0.04[d]	< 0.0001[d]
Tests per patient, n	4.1	3.9	4.5	4.2	5.2	3.3	4.2	< 0.0001	< 0.0001
Positive rate[b], all allergens, %	38	35	44	41	56	26	40	< 0.0001	< 0.0001
Age of patients, yrs, mean (range)	32 (0.16-98.5)	6.4 (0.16-9.9)		20.1 (10.0-29.9)		49.4 (30.0-98.5)		-	-

a) Source: Statistics Denmark.
b) Defined as a patient with ≥ 1 positive specific immunoglobulin E test.
c) χ^2-test.
d) Kruskal-Wallis test.

allergens than for food allergens (42% versus 9%), but with considerable variance in the subsequent testing for single allergens. The positive rates for tests ordered as single tests were comparable to those of tests performed as part of the screening algorithms. The positive rates for antibiotics were low (between 2% and 6%, depending on age and sex), but higher for wasp and bee venom (60% and 26%, respectively).

Figure 2 also shows positive rates for the different groups of allergens, grouped by age and gender. For inhalation allergens, the highest positive rates were found for patients aged 10-30 years, and this was also the group counting the largest number of tests performed.

For food allergens, the positive rates were higher for younger patients. For antibiotics and insect venoms, the older age groups tended to have the highest positive rates. Females had the lowest positive rates in all groups except for antibiotics, where the rates recorded for the genders were comparable.

DISCUSSION

This is the first time the extent of sIgE allergy testing at GPs in Denmark has been described. We found that 2% of the population was being tested annually. Besides tests for inhalant and food allergens, we also recorded a high number of tests for antibiotics, insect venom and other allergens. Finally, positive rates were determined. The findings are discussed below.

Since sensitisation is only loosely related to symptoms, annual testing of 2% of the population seems very comprehensive. Unfortunately, the GP guideline [2] only lists symptoms of allergy but does not elaborate on how to select patients for testing. Correspondingly, the differences in positive rates between GPs suggest differences in patient selection.

Positive rates were comparable for tests whether ordered as part of the screening or as single tests. We might have expected the rate to be higher when ordering individual tests than when ordering screenings, but this finding may indicate that the screening actually includes relevant allergens. On the other hand, the GPs may not be selective enough when ordering single tests. Further studies are needed to evaluate this.

In this study, we used a cut-off of 0.35 kU/l, based on a Danish consensus decision. All studies referred to in this study use this cut-off.

A Danish study from 2013 [7] tested an unselected cohort of 276 children at 1.5, five, ten, 15 and 26 years of age and found that age is associated with an increasing sensitisation rate to common allergens, corresponding to the two screening panels of this study. The same is true for our data when looking at the younger age groups. The study finds no significant differences between genders at 1.5 or 26 years, while sensitisation is significantly more frequent in boys aged five, ten and 15 years. In contrast, we found higher positive rates among males than among females at all ages. These differences may, in part, be due to the age groups not being directly comparable between the studies. The previous study also studied sensitisation rates for inhalation and food allergens across ages, and found that the prevalence of sensitisation against inhalation allergens increased with age, whereas the opposite was true for food allergens. This is in line with our findings and with those reported in a review from 2014 [8]. A Danish study from 2005 exploring a cohort of 495 families, established by including new-born infants and their

families (parents and siblings), found that the prevalence of food allergy confirmed by oral challenge was slightly lower in children than in adults [9].

Whether this discrepancy may be explained by differences in prevalence of allergy proven by challenge tests and sensitisation rates, respectively, remains unclear.

We found a correlation between the number of tests performed and the positive rate in all age groups except for females aged 10-30 years in regards to food allergens, where the number of tests was very high. This may be due to a generally lower threshold among females to seek medical advice, and may explain why females were more frequently tested than males, whereas

TABLE 2

Number of individuals tested and positive rates according to individual allergens.

	Total		Performed with screening[b]		Performed without screening[b]		
Allergen[a]	individuals tested, n	positive rate, %	individuals tested, n (%)	positive rate, %	individuals tested, n (%)	positive rate, %	p-value[c], positive rates[b]
Inhalation allergens screening t3, g6, w6, e1, e5, d1, e3, m2, d2, t9, W19	20,697	42	-	-	-	-	-
Inhalation allergens: step 1 in Figure 1							
Dust mite, *Dermatophagoides pteronyssinus:* d1	9,429	54	8,700 (92)	54	729 (8)	55	0.49
Cat: e1	9,398	23	8,664 (92)	23	734 (8)	24	0.64
Dog: e5	9,386	23	8,665 (92)	23	721 (8)	25	0.19
Grass: g6	9,357	60	8,642 (92)	60	715 (8)	57	0.05
Birch: t3	9,361	37	8,641 (92)	37	720 (8)	31	0.001
Mugwort: w6	9,365	26	8,651 (92)	26	714 (8)	23	0.003
Inhalation allergens: step 2 in Figure 1							
Horse: e3	498	8	474 (95)	8	24 (5)	9	0.38
Mold mix: m1, m2, m3, m6	4,566	5	4,298 (94)	5	268 (6)	6	0.58
Inhalation allergens: step 3 in Figure 1							
Dust mite, *Dermatophagoides farinae:* d2	45	38	-	-	-	-	-
Mold:							
Penicillium chrysogenum: m1	22	9	-	-	-	-	-
Cladosporium herbarum: m2	29	7	-	-	-	-	-
Aspergillus fumigatus: m3	25	8	-	-	-	-	-
Alternaria alternata/tenuis: m6	31	19	-	-	-	-	-
Olive: t9	14	0	-	-	-	-	-
Parietaria officinalis: w19	8	0	-	-	-	-	-
Food allergens screening f1, f2, f3, f4, f13, f14	12,999	9	-	-	-	-	-
Food allergens: step 1 in Figure 1							
Egg white: f1	1,254	26	1,166 (93)	25	88 (7)	31	0.26
Milk: f2	1,341	40	1,227 (91)	39	114 (9)	43	0.46
Cod: f3	1,254	4	1,169 (93)	3	85 (7)	8	0.01
Peanut: f13	1,260	39	1,169 (93)	39	91 (7)	30	0.06
Food allergens: step 2 in Figure 1							
Wheat: f4	67	4	-	-	-	-	-
Soy: f14	26	4	-	-	-	-	-
Antibiotics							
Penicilloyl G: c1	1,536	-	-	-	-	-	-
Penicilloyl V: c2	1,624	6	-	-	-	-	-
Ampicilllin: c5	794	2	-	-	-	-	-
Amoxicillin: c6	453	2	-	-	-	-	-
Insect venom							
Honey bee: i1	349	26	-	-	-	-	-
Wasp: i3	399	60	-	-	-	-	-
Other							
All other	824	27	-	-	-	-	-

a) Coded corresponding to the International Union of Pure and Applied Chemistry terminology.
b) Calculations were performed only for steps 1 and 2 of inhalation allergens panel and step 1 of food allergens panel according to Figure 1.
c) Pearson's χ^2-test comparing rates for test performed either as part of a screening or as direct orders.

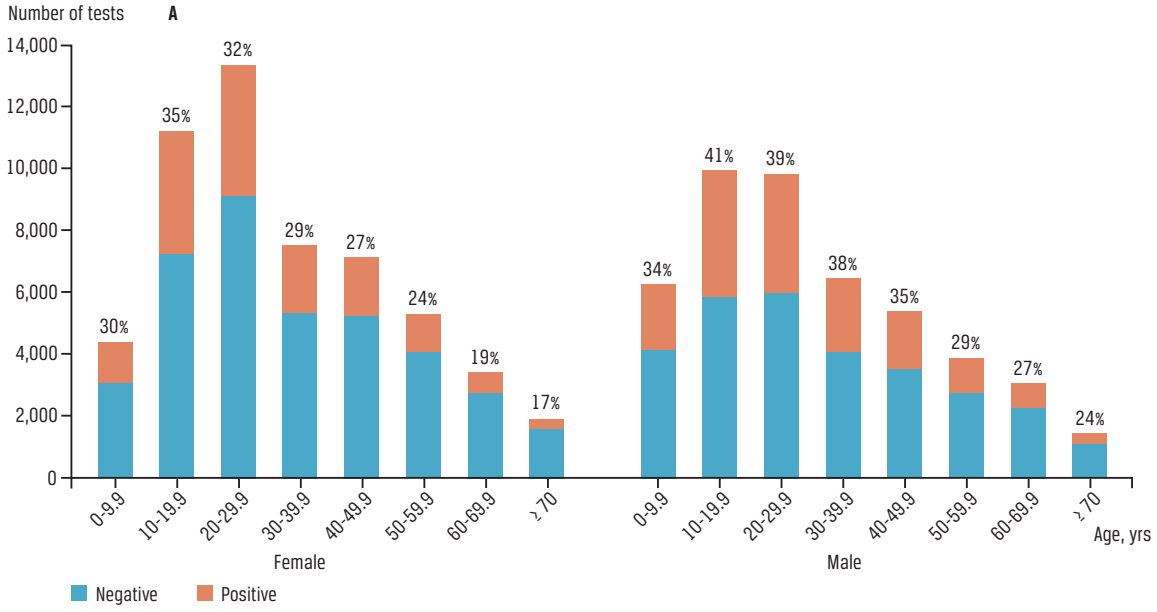
males had more tests performed per patient and were generally sensitised more frequently.

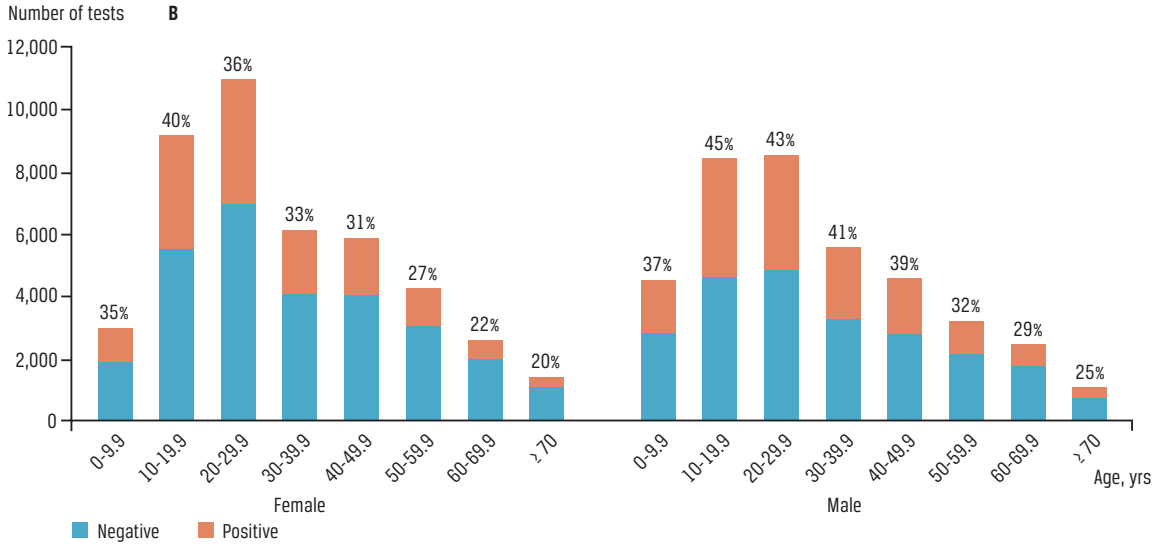
Focusing on inhalation allergens only, the prevalence of allergic rhinitis among Danish adults (18-69 years of age) is reported to be approx. 23% when patients are tested for a panel of inhalation allergens similar to the one used in this study (diagnosed based on skin prick test and symptoms) [10]. We generally found higher sensitisation rates for the screening test for inhalant allergens in this age group (22-45%).

The individual inhalant allergen that people were most commonly sensitized to was grass (60% positive), whereas moulds and horse were less frequent (5-8% positives). Our finding thus supports the algorithm that

FIGURE 2

Number of individuals tested and positive rates for different groups of allergens according to ten-year age groups and gender. p-values are for the Kruskal-Wallis test performed on positive rates across gender and age. **A.** Common allergens (inhalation and food allergens as defined below): p_{age} and p_{sex}: ⟨ 0.0001. **B.** Inhalation allergens: dust mites ((d1) and (d2)), cat (e1), dog (e5), grass (g6), birch (t3), mugwort (w6), horse (e3), mold mix (mx1), individual molds ((m1), (m2), (m3) and (m6)), olive (t9) and *Parietaria officinalis* (w19): p_{age} and p_{sex}: ⟨ 0.0001. **C.** Food allergens: egg white (f1), milk (f2), cod (f3), peanut (f13), wheat (f4) and soy (f14)): p_{age} and p_{sex}: ⟨ 0.0001. **D.** Antibiotics allergens: penicilloyl G (c1), penicilloyl V (c2), ampicilllin (c5) and amoxicillin (c6): p_{age} = 0.85, p_{sex} = 0.52,. **E.** Insect venom allergens: honey bee (i1) and wasp (i3) p_{age} = 0.03, p_{sex} = 0.007. For further description of the allergens, please see Table 2.





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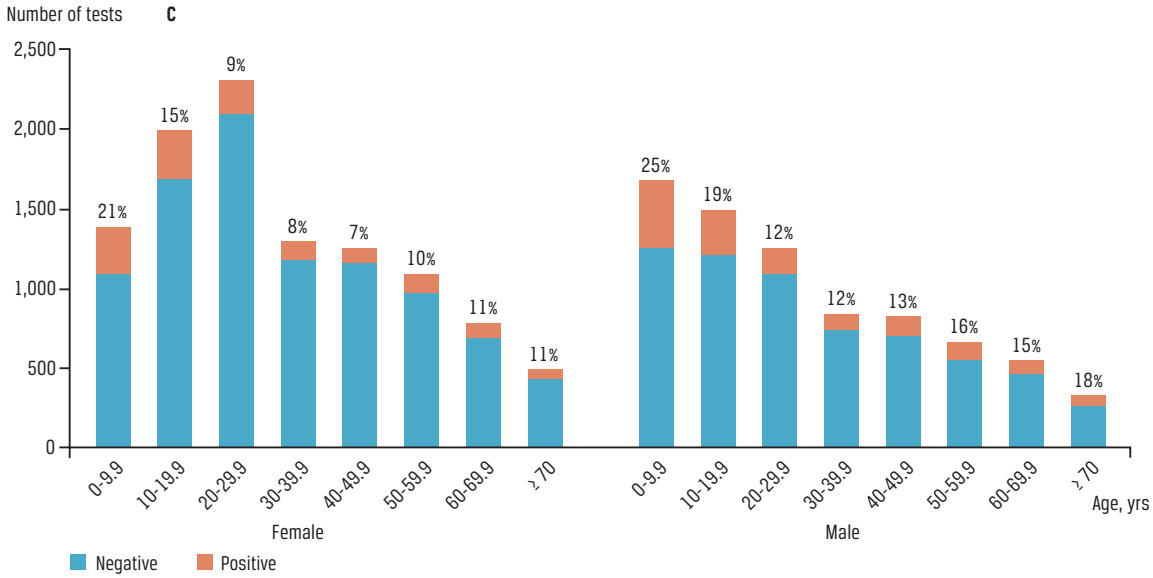

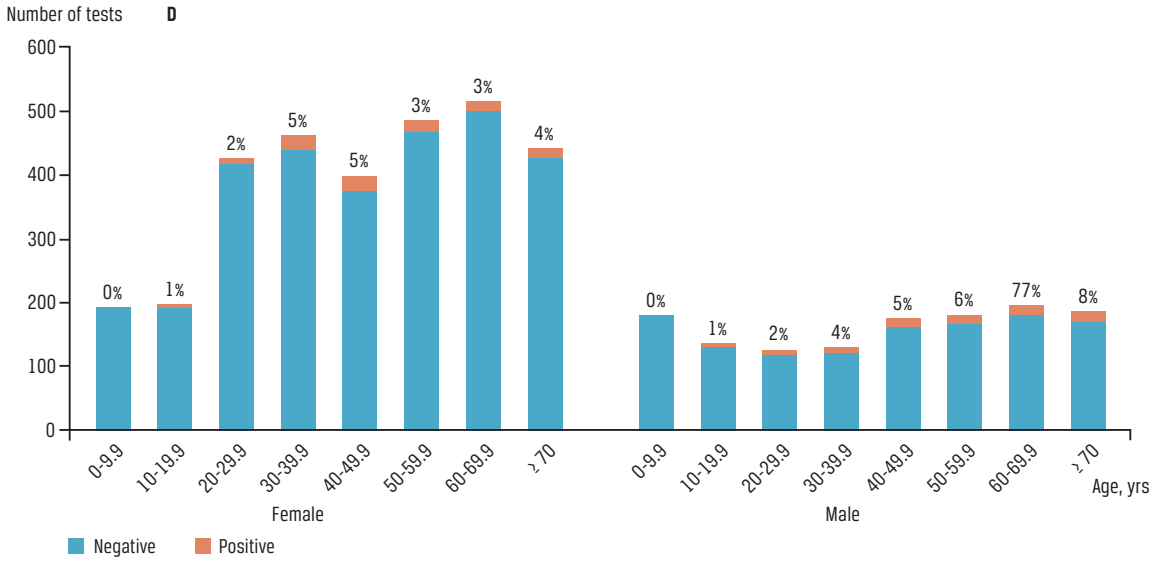

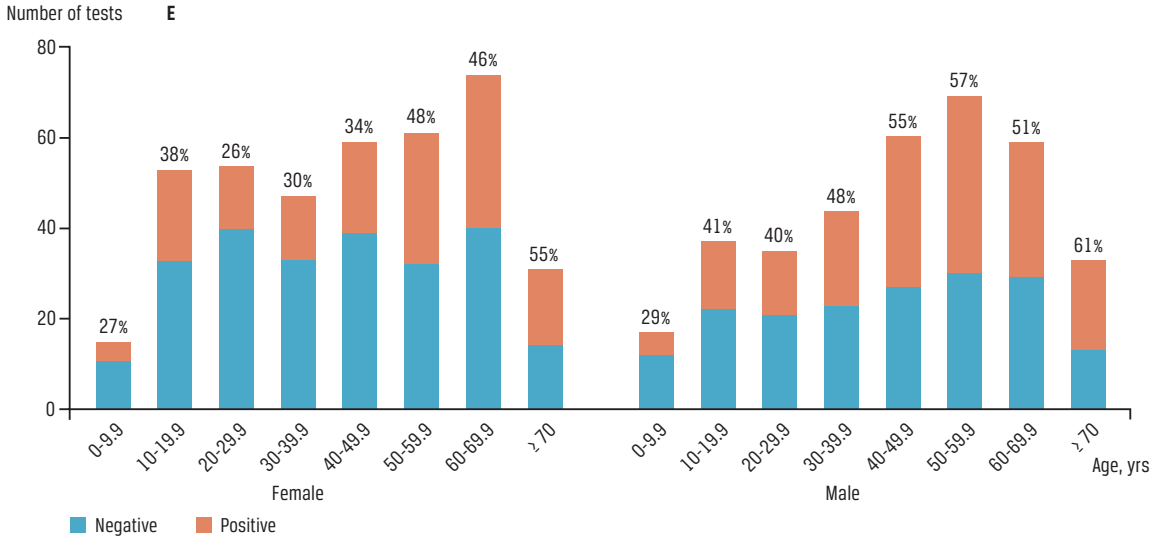

recommends testing for moulds and horse sIgE only in patients who tested negative to the other antigens of the screening test

For the individual food allergens, the positive rates were high for milk, peanut and egg white (40%, 39% and 26%), but low for cod, wheat and soy (all 4%). As for the inhalation allergens, these tests were mostly performed as part of the screening, and data may only be used to evaluate the relevance of the included tests. It may therefore be considered to move cod to step two of the algorithm, where the test is performed only if the results of step one are negative. The Danish study from 2005 [11] found the highest prevalence of allergies to be those against peanut, cow's milk, hen's egg, codfish, shrimp and wheat. All of these allergens except shrimp are included in our screening test. A decision to change the contents of the tests would require more recent data than ours as new food items are introduced rapidly these years, changing the sensitisation patterns [11].

The prevalence of allergy against antibiotics remains unknown. False negative results of sIgE test are common and it is debated whether sIgE tests are of any value in diagnosing these allergies [12-14]. Correct diagnosis relies heavily on in vivo tests (skin prick test and challenge tests) and must be timed appropriately. In our study, 4,407 tests, of which only 2-6% were positive, were performed (Table 2). The low positive rates may be explained by inappropriate selection of patients, incorrect timing of the testing and/or false negative results. It remains unknown which of these patients were referred to specialists for further testing.

Widespread consensus exists that bee and wasp venom allergy diagnoses should be made by specialists and only in case of systemic reactions [15]. sIgE tests for these venoms are neither sufficiently sensitive nor sufficiently specific to stand alone [16]. The prevalence of true bee and wasp allergy in the population is low (0.2-7.5%) [17, 18], but the sensitisation rates are substantially higher and are estimated to range 9.3-28.7% for adults [19] and 3.7% for children [17, 20]. Still, 748 patients were tested for sIgE against bee or wasp venom at GPs. It remains unknown whether these patients were referred to a specialist after their initial sIgE testing. Besides the above discussed allergens, a total of 121 other allergens were tested for, amounting to a total of 824 tests. No guidelines or other literature recommends testing for these, often very rare, allergens at the GPs.

CONCLUSIONS

This study is, to the best of our knowledge, the first to document the extent of sIgE allergy testing performed by GPs in Denmark. This study focuses on a fragment of the diagnostic process that occurs at the GPs, as no information on symptoms, clinical findings or diagnoses was available. Future studies including these parameters are warranted to fully evaluate both the extent and the repertoire of testing used in primary healthcare.

CORRESPONDENCE: *Mie Hessellund Samson*. E-mail: miesamso@rm.dk
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