

ORIGINAL ARTICLE

Rhinitis, Sinusitis, and Upper Airway Disease

Atopic diseases and type I sensitization from adolescence to adulthood in an unselected population (TOACS) with focus on predictors for allergic rhinitis

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Funding information

This work was supported by Aage Bang's Foundation, Kirsten and Volmer Rask-Nielsens Foundation and Odense University Hospital Research Council.

Abstract

Background: While much is known on childhood atopic diseases, knowledge about persistence of atopic diseases from childhood to adulthood is limited. We therefore aimed to study the clinical course of atopic diseases and type I sensitization prospectively in an unselected cohort of adolescents followed into adulthood.

Methods: A cohort of unselected 8th-grade school children (mean age 14 years) established in 1995 and followed up in 2010 were evaluated with questionnaire, clinical examination, skin prick tests and measurements of specific IgE.

Results: The lifetime prevalence of atopic diseases was high and increased significantly from adolescence (31%) to adulthood (57%); particularly allergic rhinitis increased with an incidence rate of 17.5/1000 person-years. Childhood predictors for adult allergic rhinitis were atopic dermatitis, asthma and asymptomatic sensitization to pollen and house dust mite. Among those with asymptomatic sensitization in adolescence, 53%–78% developed allergic rhinitis in adulthood. Furthermore, type I sensitization increased significantly from adolescence to adulthood mostly due to increased sensitization to pollen. Type I sensitization was found mainly in those with allergic rhinitis. A high number of adults had oral allergy symptoms due to the high number of birch pollen allergic individuals.

Conclusion: Persistence of atopic diseases in adulthood is common, and a high proportion of the adult population is sensitized giving a high prevalence of allergic rhinitis. Many with asymptomatic sensitization in adolescence will develop allergic rhinitis in adult life. The focus should be on prevention of atopic diseases and sensitization already in childhood.

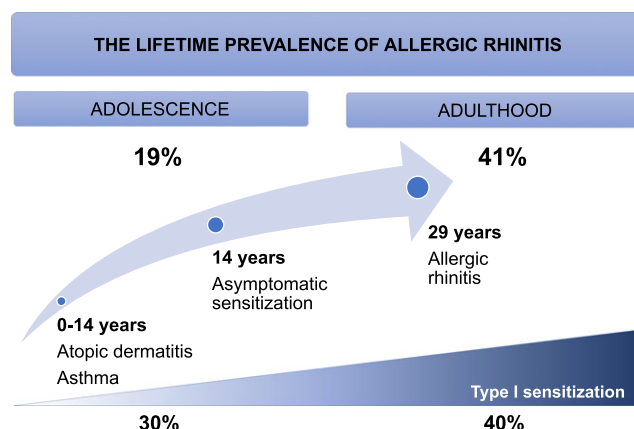
KEYWORDS

allergic rhinitis, asthma, atopic dermatitis, cohort study, sensitization

1 | INTRODUCTION

Atopic diseases are among the most common chronic diseases in children and adolescents, and an increasing prevalence has been observed over several decades.^{1,2} Due to the cohort effect, this

increase should now appear in adulthood. An increase in allergic rhinitis and asthma among young adults has been shown in different cross-sectional studies over time.^{3–5} A few studies have also reported an increased prevalence of sensitization over time when comparing different cohorts.^{3,6–8} A recent cross-sectional study in



GRAPHICAL ABSTRACT

The lifetime prevalence of allergic rhinitis increased significantly from adolescence to adulthood. Childhood predictors for adult allergic rhinitis were atopic dermatitis and asthma. Furthermore, more than half with asymptomatic sensitization to pollen and house dust mite in adolescence developed allergic rhinitis in adult life. Type I sensitization increased significantly from adolescence to adulthood mostly due to increased sensitization to pollen.

the adult population demonstrated a high prevalence of atopic dermatitis, asthma and allergic rhinitis.⁹ However, in adults, only a few studies including all atopic diseases exist.

Prospective cohort studies provide information on the natural course of disease but also enable hypotheses generation on possible cause-effect associations. Comparing results from different studies can be challenging due to different definitions, diagnostic criteria and study designs and measurements of sensitization are not always included. Several prospective, population-based cohort studies have evaluated time trends of allergic sensitization and atopic diseases during childhood¹⁰⁻¹⁵ and a few have been performed during adulthood.^{16,17} However, studies prospectively evaluating the course of allergic sensitization and atopic diseases from childhood or adolescence to adulthood are rare. In a Danish birth cohort study including 193 adults, a clear increase in the prevalence of allergic rhinitis from childhood to adulthood was demonstrated.¹⁸ Also in the German MAS cohort, a high prevalence of atopic diseases was found at age 20, and coexisting atopic diseases were increasingly common throughout adolescence up to adulthood.¹⁹

Recently, we described the course of atopic dermatitis from adolescence to adulthood in the prospective TOACS cohort study.²⁰ The aims of the present study were to evaluate the course of type I sensitization and atopic diseases with a focus on allergic rhinitis from adolescence to adulthood in the TOACS cohort established in 1995 and re-examined 15 years later. The same investigator team performed the study using predefined diagnostic criteria and including questionnaire and clinical examination as well as measurement of specific IgE (sIgE) and skin prick test (SPT).

2 | METHODS

2.1 | Population and study design

Phase one of The Odense Adolescence Cohort Study (TOACS) was conducted in 1995-1996 as a cross-sectional study among 1501 8th-

grade schoolchildren (mean age 14 years) in the Municipality of Odense encompassing questionnaires, interviews, clinical examinations and sIgE measurements.²¹ Phase two was conducted in 1996-1997 as a case-control study.²² Phase three is a follow-up study performed 15 years later in the same population, the participants were now 28-30 years of age (mean 29 years). From the original cohort, 1271 had given consent to be contacted again. An invitation to the follow-up study was sent in 2010 together with a code to an online questionnaire.²⁰ The participants were offered a clinical examination including SPT, sIgE measurement and spirometry. Details about the follow-up study are reported elsewhere.^{20,23}

2.2 | Questionnaire

The responders completed the questionnaire with the same questions on atopic dermatitis, asthma and allergic rhinitis as in phase one.

The lifetime prevalences of asthma and allergic rhinitis were evaluated from the Tuohilampi questionnaire/NOSQ-2002 questionnaire by answering the 2 questions: "have you ever had asthma?" and "have you ever had 'hay fever' or other symptoms of nasal allergy (bouts of sneezing, itchy or running nose) from eg. pollen or animals?"^{24,25}

The lifetime prevalence of atopic dermatitis was defined by published questionnaire criteria.²⁶

The questionnaire in phase 3 also included questions on self-reported food allergy "have you ever been allergic to certain foods or drinks" and "which foods or drinks gives suspicion of allergy?" and OAS (oral allergy syndrome), with the question "have you ever had itching in the mouth, palate, and/or throat after ingestion of fresh fruits, vegetables and/or nuts?" Furthermore, questions on urticaria and angioedema were included.

From the questionnaire, disease estimates were given as lifetime prevalence (birth-present age).

	Participants in the clinical part of the follow-up 2010		Non-participants in the clinical part of the follow-up 2010		
Baseline characteristics 1995	Prevalence (%)		Prevalence (%)		P-value
Sex					<0.001
Female	61.0	286	44.1	427	
Male	39.0	183	55.9	542	
Present or past asthma	11.7	(55/469)	11.8	(114/969)	0.983
Present or past allergic rhinitis	20.5	(96/469)	17.8	(172/969)	0.215
Present or past atopic dermatitis	25.2	(118/469)	19.4	(188/969)	0.012
Positive specific IgE	28.4	(97/341)	30.0	(160/528)	0.558

In 1995, 1438 responded to the questionnaire, 1340 participated in a clinical examination and 869 participated in a blood sample for IgE measurement

TABLE 1 Comparison of baseline characteristics (1995) between participants and non-participants in the clinical part of the follow-up study (2010) including skin prick test and blood sample (specific IgE).

2.3 | Interview and clinical examination

From the clinical examination, disease estimates were given as 1-year period prevalence.

Asthma was defined as 3 or more episodes of wheezing/whistling in the chest and/or dyspnoea and/or cough. Allergic asthma was defined as 3 or more episodes of symptoms either at exposure to known allergens (pollen, animal dander, house dust mite, mould, food) or in certain periods (seasonal variation, diurnal variation, inside/outside).²¹ Those controlled on inhalation steroid were also included.

Rhinitis was defined as one or more of the following symptoms: itching in the nose, watery rhinorrhoea, sneezing, nasal congestion. Allergic rhinitis was defined as one or more of the above-listed symptoms either at exposure to known allergens or in certain periods or which continued for at least 2 weeks without infectious rhinitis or other infections. Allergic rhinitis was separated in seasonal and perennial rhinitis.

The 1-year period prevalence of atopic dermatitis was evaluated according to the Hanifin & Rajka criteria.²⁷

2.4 | Skin prick tests

The skin prick test (SPT) was performed with fresh foods (prick-prick test) and with extracts from Soluprick® (ALK Abello, Hørsholm, Denmark) including a positive control (histamine 10 mg/mL) and a negative control (isotonic NaCl). The allergens are given in Table 4. The SPT was performed according to EAACI guidelines²⁸ with a positive response defined as a wheal diameter ≥ 3 mm.

Immediately after the SPT, the relevance of a positive reaction was carefully evaluated by interview.

2.5 | Blood samples

Serum IgE was analysed by ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden). SIgE analyses included inhalant and food allergens (Figure 2). In those participating in 2010, available serum samples from 1995 were analysed for plane acerifolia, ambrosia artemisiifolia, Parietaria judaica ($n = 322$). Furthermore, analysis of components for peanut and hazelnut together with bet v1 were performed in 2010.

Analyses were performed in accordance with the manufacturer's instructions. A specific IgE level >0.35 kU/L was considered elevated.

2.6 | Ethics

The Regional Ethical Committee for Southern Denmark approved the study (S-VF-19950022).

2.7 | Data handling and statistics

The results are given as prevalence proportions and 95% confidence intervals (95% CI). Comparisons are made by chi-square-based table analysis.

Incidence rates were calculated based on new cases of allergic rhinitis in the period 1995-2010 among those without previously (birth-1995) allergic rhinitis. Logistic regression analysis was performed among the new cases of allergic rhinitis as the dependent variable and asthma, atopic dermatitis, family of atopic diseases, smoking at home in childhood, and sex as the independent variables. Furthermore, a logistic regression model with new cases of allergic rhinitis as the dependent variable and sensitization at 14 years of age as the independent variables was included. Statistical analysis was performed with Stata/SE 12.0 (Stata Corporation, College Station, TX, USA). Statistical significance was defined as $P < 0.05$.

3 | RESULTS

A total of 1206 of the 1271 participants (95%) who gave consent to be contacted again were retrieved in Denmark through the national central person register; four had died, one was missing and 60 had emigrated. The response rate for answering the questionnaire was 74.6% (899/1206) and 469/1206 (38.9%) participated in the clinical examination. The 899 responders in 2010 were a representative part of the 1995 population with the exceptions that significant more women than men responded to the follow-up questionnaire as did those with childhood atopic dermatitis.²⁹ The same was found for participation in the clinical part in 2010 compared to baseline

TABLE 2 Lifetime prevalence of atopic diseases, self-reported food allergy and oral allergy syndrome (OAS), urticaria and angioedema among 29 years old adults in the TOACS cohort evaluated by questionnaire, together with 1 year period prevalence of atopic diseases evaluated by clinical examination $\pm$ SPT

Questionnaire data	Lifetime prevalence % (proportion)
Allergic rhinoconjunctivitis*	40.8 (366/897)
Asthma*	20.2 (181/897)
Atopic dermatitis*	34.1 (306/897)
Food allergy (self-reported)	29.4 (261/889)**
Hazelnut	9.3 (83/889)
Peanut	4.9 (44/889)
Oral allergy syndrome (OAS)	23.0 (204/889)
Urticaria	22.6 (201/889)
Angioedema	4.8 (43/889)
Clinical examination and interview (29 year)	One-year period prevalence % (proportion)
Allergic rhinitis	39.0 (183/469)
Seasonal symptoms	35.4 (166/469)
Perennial symptoms	19.8 (93/469)
Asthma	9.4 (44/469)
Allergic asthma	7.9 (37/469)
Atopic dermatitis	10.0 (47/469)
Clinical examination and interview combined with skin prick test (29 year)	One-year period prevalence % (proportion)
Allergic rhinitis	25.9 (119/460)
Seasonal symptoms	24.8 (114/460)
Perennial symptoms	12.6 (58/460)
Allergic asthma	5.9 (27/460)

*Combining responses from 1995 and 2010.

**8 adults did not answer all questions in the questionnaire.

questionnaire characteristics from 1995 (Table 1). Positive slgE in 1995 was unrelated to response rate in 2010 (Table 1).

3.1 | Lifetime prevalence of asthma, allergic rhinitis, atopic dermatitis and self-reported food allergy in 2010 (questionnaire)

The lifetime prevalence of asthma in the cohort was 20.2% (95% CI 17.6–23.0), and the lifetime prevalence of allergic rhinitis was 40.8% (95% CI 37.6–44.1) without significant gender difference (Table 2, Figure 1). The lifetime prevalence of atopic dermatitis was 34.1% (95% CI 31.0–37.2); women 38.0% vs men 29.1%, $P < 0.005$. In total, 56.9% (510/897) of the population have or have had asthma, allergic rhinitis or atopic dermatitis, with 9.9% (89/897) of the population having or have had all 3 diseases. These figures are based on cumulative results from 1995 to 2010. In 2010, 325 reported ever allergic rhinitis, while additional 41 reported allergic rhinitis in 1995. Of the 325 reporting allergic rhinitis ever in 2010, 253 reported symptoms in April–May (birch pollen season), 288 in June–July (grass pollen season) and 208 in August (mugwort season). Symptoms all year were recorded by 43/253.

Food allergy was reported by 29.4% (95% CI 26.4–32.5) of the population (Table 2). OAS was reported by 22.9% (95% CI 20.2–25.9). Most participants reporting food allergy reported OAS; 90% of those reporting allergy to nuts and 89% of those reporting allergy to peanuts.

Acute or chronic urticaria was reported by 22.6% (95% CI 19.9–25.5) and angioedema by 4.8% (95% CI 3.5–6.5) with 30/889 reporting concomitant urticaria and angioedema (Table 2). Of the 214 with urticaria/angioedema, 86 had a specific suspicion of trigger(s); most common reaction to foods ($n = 42$), pollen ($n = 29$), insects ($n = 20$), animals ($n = 18$) and drugs ($n = 17$), while 16 reported heat, 5 cold and 3 pressure as a trigger.

3.2 | Development of atopic diseases from 1995 to 2010

A significant increase in the lifetime prevalence of allergic rhinitis, asthma and atopic dermatitis was found from 1995 to 2010 (Figure 1A). The lifetime prevalence of allergic rhinitis among the 14-year-old school children was 18.6% increasing to 40.8% 15 years later.

In total, 366/897 had allergic rhinitis: 177 of these were diagnosed in phase 1 (debut 0–14 years of age). In phase 3, further 189 had developed allergic rhinitis. Thus, from 1995 to 2010, 26.3% (189/720) developed allergic rhinitis. The calculated incidence rate of allergic rhinitis from 14 to 29 years was 17.5/1000 person-years without sex difference.

3.3 | One-year period prevalence of asthma, allergic rhinitis and atopic dermatitis in 2010 (clinical examination)

The 1-year period prevalence of asthma was 9.4% (95% CI 6.9–12.4) with allergic asthma in 7.9% (95% CI 5.6–10.7) (Table 2). Allergic rhinitis was found in 39.0% (95% CI 34.6–43.6) with 35.4% of the population having seasonal symptoms and 19.8% perennial symptoms. Among the 183 with allergic rhinitis, 42% (76/183) reported perennial symptoms with exacerbation in the pollen season. The 1-year period prevalence of atopic dermatitis was 10.0% (95% CI 7.5–13.1). No sex differences were found.

Including skin prick test results in the diagnosis of allergic asthma and allergic rhinitis, allergic asthma was found in 5.9% and allergic rhinitis in 25.9% with seasonal symptoms in 24.8% and perennial symptoms in 12.6% (Table 2). In 65.7% (119/181) of those reporting allergic rhinitis, the diagnosis was supported by a positive relevant skin prick test (in 2 of the 183 reporting allergic rhinitis, SPT was not performed). For allergic asthma, 73.0% (27/37) of those reporting symptoms when exposed to a certain allergen had a positive skin prick test to the suspected allergen.

3.4 | Results of skin prick test (SPT) and specific (slgE) in 2010

Sensitization to one or more allergen identified by SPT was found in 40.2% (184/458; 95% CI 35.7–44.8) of the population (Table 4).

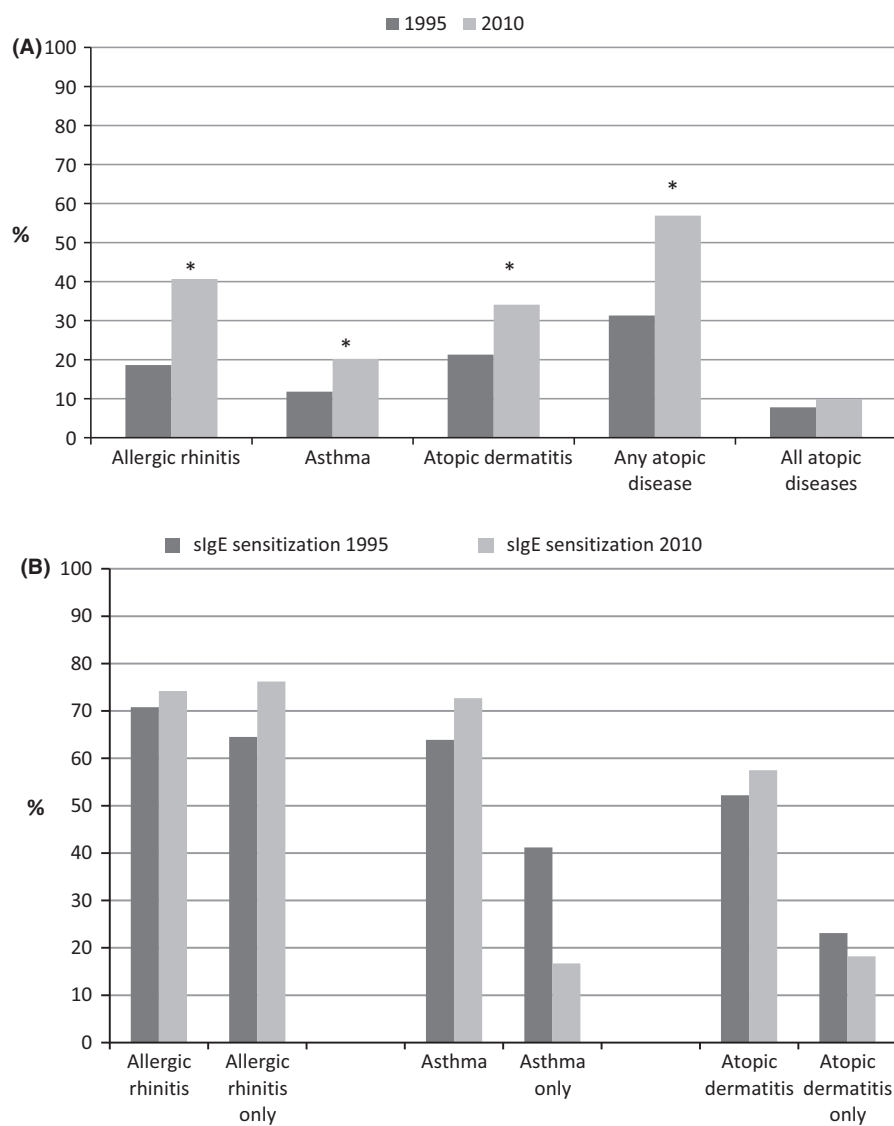


FIGURE 1 (A) Lifetime prevalence of allergic rhinitis, asthma, atopic dermatitis, any atopic disease (allergic rhinitis, asthma and/or atopic dermatitis) and all atopic diseases in the TOACS cohort in 1995 and 2010. * $P < 0.001$ for difference between 1995 and 2010. (B) Sensitisation (sIgE) in relation to allergic rhinitis, asthma and atopic dermatitis in 1995 and 2010 (1 y period prevalence). Note: Only indicates that the 2 other diseases are excluded eg, allergic rhinitis only excluding asthma and atopic dermatitis.

Eleven were excluded from SPT (nine were pregnant and two had a negative reaction to histamine).

Among the aeroallergens, the most common sensitizations were to grass pollen, birch pollen and house dust mites. The majority of participants sensitized to these allergens reported clinical symptoms when exposed to the allergen (Table 4).

Among the food allergens, sensitization was most common to hazelnut (13.1%) and the reaction was clinically relevant in 57% with OAS being the most common symptom (Table 4). All 34 with a clinically relevant reaction to hazelnut were sensitized to birch pollen. Only 4 (0.9%) had a positive SPT to peanut: 2 of these reported mild symptoms. Sensitization to celery was seen in 5.7%, to sesame in 3.9%, soya milk in 3.5% (soya flour in 2.2%), poppy seed in 2.8% and to wheat in 1.5%. The vast majority of these sensitizations were clinically irrelevant.

By sIgE measurement in 466/469, sensitization to one or more allergen was found in 38.6% (180/466; 95% CI 34.2–43.2). Among the aeroallergens, sensitization was most common to grass pollen (23.0%), derm. pteronyssinus (22.1%), derm. farina (22.1%) and birch pollen (15.7%). Among the food allergens, sensitization was most common to

hazelnut (12.7%) followed by celery (6.9%), shrimp (4.1%) and peanut (3.9%), see figure 2, 2010. Among those sensitized to hazelnut ($n = 59$), most were sensitized to bet v1 ($n = 57$) and 58 was sensitized to cor a1, with one co-sensitized to cor a9 and cor a14 (reporting OAS only). One had no reaction to any of the components. Among those sensitized to peanut ($n = 18$), 16 reacted to bet v1, 15 reacted to ara h8, one co-sensitized to ara h1 (reported OAS only), while 3 were negative to all peanut components (2 also negative to bet v1).

Among those without atopic diseases in 2010, 16% were sensitized by SPT and 15% by sIgE measurements, while 19.4% without atopic disease were sensitized by sIgE in 1995.

3.5 | Change in sensitization patterns from 1995 to 2010

In both 1995 and 2010, all participants were offered a blood sample for measurement of sIgE.

From 1995 to 2010, a significant increase in the number of sensitized individuals was found with a prevalence of sensitization to

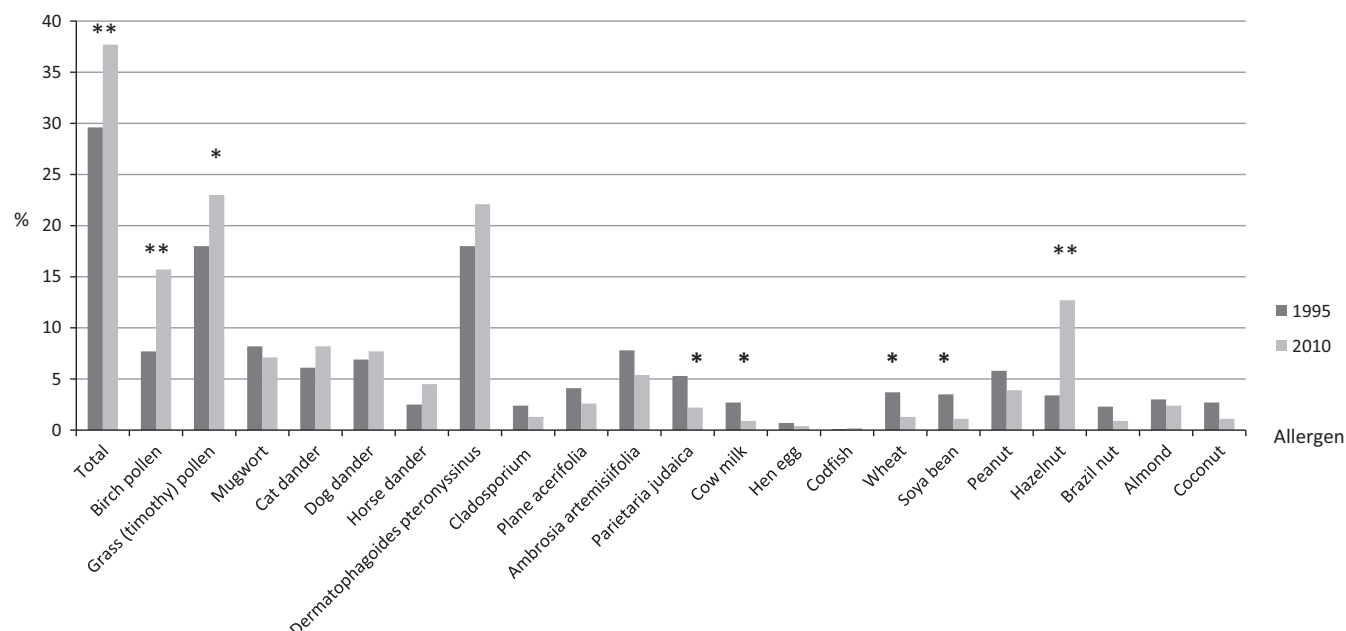


FIGURE 2 Changes in sensitisation patterns from 1995 to 2010. * $P < 0.05$, ** $P < 0.001$ for differences between 1995 ($n = 866$) and 2010 ($n = 466$). Note: In those participating in both 1995 and 2010, available serum sample from 1995 were analysed for London plane, common ragweed, wall pellitory that not were included in the 1995 analyses ($n = 322$). In 1995: A significant sex-difference was found for grass (boys 23.2% vs girls 13.6%), house dust mite (boys 25.3% vs girls 11.9%) and mugwort (boys 10.3% vs girls 6.4%). In 2010: A significant sex difference was found for grass (male 29.1% vs female 19.0%), London plane (male 4.4% vs female 1.4%), and wall pellitory (male 3.9% vs female 1.1%). Furthermore, more male than female were sensitized to wheat, pecan, pistachio, walnut, cashew, and poppy seed.

any aeroallergen or food allergen in 1995 on 29.6% (257/869) increasing to 39.7% (185/466) in 2010 (Figure 2). The significant increase was due to more positive reactions to grass pollen, birch pollen and hazelnut.

Looking at those participating in both 1995 and 2010 ($n = 340$), persistent sensitization was most common for derm. pteronyssinus (87%), birch pollen (86%) and grass (82%). For food allergens, the only sensitized for codfish in 1995 was still sensitized in 2010 and 82% had persistent sensitization for hazelnut, while only 35% had persistent sensitization for peanut.

Among those with atopic diseases during the last year in 1995 (one year period prevalence) respectively 2010, most sIgE sensitization was found in the group with allergic rhinitis (Figure 1B), while those with only asthma or atopic dermatitis were sensitized in line with those without atopic disease (17%, 18% vs 15%).

3.6 | Predictors in adolescence for allergic rhinitis in adulthood

Predictors for new cases of allergic rhinitis in adulthood were childhood atopic dermatitis and asthma, while sex, family history and smoking were nonsignificant (Table 3A).

Pollen and house dust mite sensitization in adolescence were predictors for allergic rhinitis in adulthood, Table 3B. The association between asymptomatic sensitization in adolescence and development of seasonal and perennial allergic rhinitis in adulthood is illustrated in Table 5. Among those with asymptomatic sensitization in adolescence, more than 50% had clinical symptoms 15 years later.

4 | DISCUSSION

Based on questionnaire data, a high prevalence of atopic diseases was found in unselected young adults with 57% of the population having allergic rhinitis, asthma and/or atopic dermatitis and with a significant increase from adolescence to adulthood (Figure 1). The most pronounced increase was for allergic rhinitis due to an increasing sensitization mostly to pollen in the period (Figure 2). Most pollen sensitization was to grass and birch, while plane, common ragweed and wall pellitory are rare sensitizers in Denmark (Figure 2, Table 4). Notably, pollen was the only allergen group for which sensitization increased significantly in the period, which might be related to the change in climate and the increasing pollen counts in the season in many countries.

A questionnaire-based study always carries the risk of misclassification of the diseases compared to the clinical diagnosis, which must be considered "the true diagnosis." However, in this study, the lifetime prevalence of allergic rhinitis by questionnaire was estimated to 41% and the 1-year period prevalence in adulthood to 39% by clinical diagnosis. Including skin prick test results in the clinical criteria, the prevalence was 26% (Table 2). Recent data from other countries also show a very high prevalence of allergic rhinitis; among unselected 16- to 75-year-old persons in Western Sweden, current rhinitis was found in 42.8%,⁹ and in Finland, the prevalence also exceeded 40% in an adult population.³⁰ In Belgium, the prevalence was 31% in a population between 3 and 86 years.³¹ However, the older part of the population was overrepresented, and the study showed that the prevalence of sensitization peaks in the third and fourth decades and then decreases.³¹

TABLE 3 Results on logistic regression based on childhood predictors (0–14 years) and sensitization at 14 years of age

(A) Results of logistic regression on childhood predictors for development of allergic rhinitis in adulthood based on questionnaire data (n = 720)					
		OR (95% CI)		P-value	Proportion in the group developing allergic rhinitis
Atopic dermatitis (0–14 years)	No				
	Yes	1.7 (1.1–2.5)	0.021	49/130 (37.7%)	
Asthma (0–14 years)	No				
	Yes	2.4 (1.2–4.6)	0.009	21/43 (48.8%)	
Family history of atopic disease (0–14 years)	No				
	Yes	1.2 (0.8–1.7)	0.367	102/348 (29.3%)	
Smoking at home (0–14 years)	No				
	Yes	0.9 (0.7–1.3)	0.690	123/474 (26.0%)	
Sex	Male				
	Female	1.0 (0.7–1.4)	0.962		
(B) Results of logistic regression for development of allergic rhinitis in adulthood based on sensitization at 14 years (specific IgE analysis, n = 478)					
		OR (95% CI)	P-value	Asymptomatic sensitization in 1995/New allergic rhinitis 2010 (%)	New allergic rhinitis 2010/Asymptomatic sensitization in 1995 (%)
Any pollen (birch, grass, mugwort)	No	4.0 (1.9–8.5)	<0.001	31/129 (24.0%)	31/49 (63.3%)
	Yes				
House dust mite (Derm. pteronyssinus)	No	2.0 (1.0–3.8)	0.041	28/128* (21.9%)	28/59 (47.5%)
	Yes				
Any pet (cat, dog, hourse)	No	1.3 (0.3–4.7)	0.710	9/129 (7.0%)	9/14 (64.3%)
	Yes				
Mould (Cladosporium)	No	1.9 (0.2–24.5)	0.606	2/128* (1.6%)	2/3 (66.6%)
	Yes				
Any food allergen	No	1.6 (0.5–4.6)	0.424	11/129 (8.5%)	11/19 (61.3%)
	Yes				
Sex	Male	0.8 (0.5–1.2)	0.211		
	Female				

95% CI, 95% confidence interval; OR, Odds ratio Statistical significant results are highlighted in bold.

The regression model is based on the 189 developing allergic rhinitis from 1995 to 2010, the 177 with allergic rhinitis already in childhood are excluded from the analysis (897–177 = 720).

Not all 720 had a blood sample in 1995 therefore 478 were included in the analysis *one developing allergic rhinitis in 2010 had no sIgE for house dust mite and mould in 1995

Our prevalence estimates of asthma and atopic dermatitis were also high but in line with data from other Nordic countries. In our study, the prevalence of asthma may have been overestimated as the definition was broad. The reliability of the diagnosis could have been strengthened by a number of specific lung function tests but this was beyond the scope of the study. However, a prevalence of current asthma on 11.8% among unselected adults in Sweden⁹ is close to our prevalence for current asthma of 9.4% based on the interview. A 1-year period prevalence of atopic dermatitis of 10% based on clinical criteria is lower than in a recent Danish study with a 1-year period prevalence of atopic dermatitis of 19.2% (age 30–40 year) in the general population based on questionnaire data.³² However, by questionnaire, our 1-year period prevalence of atopic dermatitis was also higher (17%) than based on clinical criteria.²⁰ Due to different definitions, questionnaire versus clinical examinations, inclusion of SPT or sIgE in the diagnosis of asthma and allergic rhinitis as well as inclusion of different age groups, caution should

be exercised when comparing studies or drawing conclusions regarding geographical variation in the prevalence of atopic diseases.

An association between asymptomatic sensitization to pollen and house dust mite in adolescence and subsequent development of allergic rhinitis in adulthood was found (Table 3). Among those sensitized in adolescence, 31%–68% had symptoms on allergic rhinitis, while more than 50% of those asymptotically sensitized in adolescence developed clinical symptoms later on (Table 5). Childhood atopic dermatitis and asthma were also associated with the development of rhinitis in adulthood, whereas sex, family history and smoking were not associated. Another Danish study has shown that asymptomatic sensitization is a low risk for onset of symptoms; however, the follow-up period was only 2 years.³³ A study among college students have shown that students skin tested positive have more than twice the risk of developing new allergic rhinitis than do negatively skin tested students over a 23-year period.³⁴ A similar study in German adults aged 25–74 years also showed that allergic sensitization to outdoor

TABLE 4 Result on skin prick test (SPT) in the TOACS cohort 2010 together with symptoms on allergen exposure

	Positive skin prick test % (n)			Relevance % (n)	Symptoms on exposure (n)
	Female (n = 275)	Male (n = 183)	Total (n = 458)		
Pollen, animal dander, house dust mites, mould					
Birch pollen	17.1 (47)	19.1 (35)	17.9 (82)	76.8 (63)	Rh (59), Rh/A (4)
Grass (timothy) pollen	23.6 (65)	31.2 (57)	26.6 (122)	80.3 (98)	Rh (87), Rh/A (10), A (1)
Mugwort	10.9 (30)	9.2 (17)	10.3 (47)	46.8 (22)	Rh (20), Rh/A (1), A (1)
Cat dander	13.1 (36)	14.2 (26)	13.5 (62)	72.6 (45)	Rh (30), Rh/A (11), A (2), UA (2)
Dog dander	10.2 (28)	9.3 (17)	9.8 (45)	46.7 (21)	Rh (12), Rh/A (7), A (1), UA (1)
Horse dander	4.0 (11)	2.2 (4)	3.3 (15)	46.7 (7)	Rh (3), Rh/A (4)
Derm. pteronyssinus	14.9 (41)	21.3 (39)	17.5 (80)	60.0 (48)	Rh (36), Rh/A (8), A (4)
Derm. farinae	10.9 (30)	14.8 (27)	12.5 (57)	63.2 (36)	Rh (26), Rh/A (7), A (3)
Cladosporium herbarum	1.5 (4)	2.7 (5)	2.0 (9)	55.6 (5)	Rh (4), A (1)
Alternaria alternata	2.6 (7)	3.8 (7)	3.1 (14)	28.6 (4)	Rh (2), Rh/A (1), A (1)
Plane (Plane acerifolia)	1.5 (4)	4.4 (8)	2.6 (12)	58.3 (7)	Rh (6), Rh/A (1)
Common ragweed (ambrosia artemisiifolia)	4.7 (13)	6.0 (11)	5.2 (24)	33.3 (8)	Rh (8)
Wall pellitory (Parietaria judaicajudaica)	0.4 (1)	1.6 (3)	0.9 (4)	25 (1)	Rh (1)
Food allergens (fresh)					
Cow milk	1.1 (3)	0.6 (1)	0.9 (4)	0 (0)	—
Hen egg	0 (0)	0.6 (1)	0.2 (1)	0 (0)	—
Codfish	1.1 (3)	0.6 (1)	0.9 (4)	25.0 (1)	OAS, GI (1)
Shrimp	0.4 (1)	0.6 (1)	0.4 (2)	0 (0)	—
Wheat	1.1 (3)	2.2 (4)	1.5 (7)	14.3 (1)	Rh (1)
Soy flour	2.2 (6)	2.2 (4)	2.2 (10)	0 (0)	—
Soy milk	3.6 (10)	3.3 (6)	3.5 (16)	1 (6.3)	OAS (1)
Peanut	1.5 (4)	0	0.9 (4)	50.0 (2)	OAS (1), OAS/UA (1)
Hazelnut	12.0 (33)	14.8 (27)	13.1 (60)	56.7 (34)	OAS (31), OAS/UA (2), OAS/Rh (1)
Brazil nut	0.4 (1)	0.6 (1)	0.4 (2)	50.0 (1)	OAS (1)
Sesame	3.3 (9)	4.9 (9)	3.9 (18)	0 (0)	—
Poppy seed	2.9 (8)	2.7 (5)	2.8 (13)	7.7 (1)	OAS (1)
Celery	5.8 (16)	5.5 (10)	5.7 (26)	11.5 (3)	OAS (3)
Other					
Latex	0 (0)	0 (0)	0 (0)	—	—
One or more positive SPT	36.4 (100)	45.9 (84)*	40.2 (184)		

*P < 0.05 for sex difference.

OAS (oral allergy syndrome), GI (gastro-intestinal symptoms), UA (urticaria, angioedema) Rh (rhinitis), A (asthma).

TABLE 5 The association between asymptomatic sensitization in adolescence and development of symptoms on seasonal allergic rhinitis (pollen) or perennial allergic rhinitis (house dust mite) in adulthood

slgE	Number with elevated slgE in 1995 and participation in 2010	Proportion of sensitized (1995) with seasonal or perennial * allergic rhinitis in 1995	Proportion of asymptomatic sensitized (1995) with seasonal or perennial* allergic rhinitis in 2010	Proportion of asymptomatic sensitized (1995) without symptoms in 2010	Seasonal or perennial * allergic rhinitis in 2010 among those with asymptomatic sensitization in 1995	Number with reproduced elevated slgE 1995–2010
Birch	28	19/28 (68%)	7/28 (25%)	2/28 (7%)	7/9 (78%)	24/28 (86%)
Grass	62	31/62 (50%)	19/62 (31%)	12/62 (19%)	19/31 (61%)	51/62 (82%)
Mugwort	28	17/28 (61%)	6/28 (21%)	5/28 (18%)	6/11 (55%)	13/28 (46%)
House dust mite (Derm. Pt)	52	16/52 (31%)	19/52 (37%)	17/52 (33%)	19/36 (53%)	45/52 (87%)

*Seasonal resp. perennial allergic rhinitis: seasonal is for birch, grass and mugwort, perennial is for house dust mite.

allergens was a predictor for the development of allergic rhinitis during a 10-year period.¹⁷ Furthermore, in a German study, a cohort of 21–47 years olds was followed up after 20 years, and here, new nasal allergy was predicted by eczema, any positive SPT or specific IgE.¹⁶ A positive reaction to birch pollen was the strongest predictor for new-onset nasal allergy. The results are in line with our study. Our study, with the first examination at 14 years, seems to suggest that asymptomatic sensitization already develops during the first 14 years of life. Immunotherapy is used for the treatment for allergic rhinitis. How immunotherapy could affect the prevalence of allergic rhinitis over time and maybe even prevent the development of the disease, if performed early, could be interesting to study in the future.

Like in other recent studies,^{18,31} nearly 40% of the population was sensitized to one or more allergen. In the United States, an even higher prevalence was found with 54.3% of the population being sensitized to one of 10 common allergens.⁷ Most sensitizations were seen in those with allergic rhinitis. Many with asthma and atopic dermatitis were also sensitized; however, excluding concomitant allergic rhinitis, the number sensitized was equal to the sensitizations rate in those without atopic disease (Figure 1). This was already shown in our cohort at the first examination²² and in another recent Danish birth cohort study.¹⁴

Most sensitizations among young adults were found to pollen and house dust mite and most of the reactions were clinically relevant. Most sensitization to food was caused by hazelnut in both SPT and sIgE (13%). By sIgE, many were also sensitized to peanut (4%); however, using SPT, only 1% was sensitized to peanut. As in other studies from birch-endemic regions,³⁵ most sensitization to food in the young adults was due to sensitization to PR-10 protein including cor a1 and ara h8, and most of those reporting food allergy had oral allergy syndrome. None with a positive SPT to foods reported severe allergic reactions. One was diagnosed with fish allergy in adolescence³⁶ and was still allergic in adulthood, and one had baker's rhinitis. Otherwise, only OAS was reported together with mild skin symptoms and rhinitis in pollen allergic patients. As oral food challenge was not included in the study, the prevalence of food allergy could not be evaluated.

Follow-up rates typically decrease during long-term follow-up. This study was originally performed among 1501 schoolchildren with a very high participation rate of 96% in the questionnaire part and 89% in the clinical part.²¹ After 15 years, 75% of the invited participated in the questionnaire part and 39% in the clinical part, significantly more women than men. Comparing the participants in the clinical part of the follow-up with the non-attenders, no differences were found with respect to asthma, allergic rhinitis and sensitization in childhood. The slight overrepresentation of atopic dermatitis patients may cause some selection bias; however, as those with childhood asthma and allergic rhinitis as well as sensitization were evenly distributed, our estimates seem to be representative. This study was initiated in adolescents, and therefore, information on early childhood sensitization is lacking. Furthermore, disease estimates from early childhood could be biased due to recall bias when evaluating the children at 14 years of age. We have previously described recall bias from childhood to adulthood in this cohort³⁷

and recall bias was high for atopic dermatitis (in early childhood), however low for asthma and allergic rhinitis. The data are based on a rather large unselected population with predefined diagnostic criteria, and both questionnaire-based criteria and clinical criteria are used together with several measurements of sensitization.

In conclusion, this study describes a significant increase in atopic diseases and sensitization in an unselected population from childhood to adulthood. Particularly allergic rhinitis increases mainly caused by an increasing sensitization rate to pollen. Childhood predictors for adult allergic rhinitis were atopic dermatitis and asthma, together with asymptomatic sensitization to pollen and house dust mite in adolescence. Among those with asymptomatic sensitization in adolescence, up to 78% developed allergic rhinitis after 15 years.

ACKNOWLEDGMENT

We thank the adults from the TOACS cohort for their cooperation, nurses Lis Lykkegaard and Marianne Hald and laboratory technician Anni Larsen for skilful technical help. Furthermore, Thermo Fisher Scientific, Denmark, is acknowledged for supporting parts of the IgE analyses.

CONFLICT OF INTERESTS

The authors report no potential conflict of interest.

AUTHORS CONTRIBUTIONS

All authors have contributed substantially to conception and design of, or acquisition of data or analysis and interpretation of data. Charlotte G Mortz performed the first part of the study and the follow-up study after 15 years. Carsten Bindslev-Jensen and Klaus E Andersen have supervised all phases of the study. Lars K. Poulsen has helped with the specific IgE analysis. Charlotte G Mortz performed the analysis and interpretation of the data supported by Carsten Bindslev-Jensen, Henrik Fomsgaard Kjaer, Sigurd Broesby-Olsen, Lars Kjærsgaard Poulsen and Klaus Ejner Andersen. Charlotte G Mortz drafted the manuscript and all authors revised it critically. All approved the final version to be published.

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How to cite this article: Mortz CG, Andersen KE, Poulsen LK, Kjaer HF, Broesby-Olsen S, Bindslev-Jensen C. Atopic diseases and type I sensitization from adolescence to adulthood in an unselected population (TOACS) with focus on predictors for allergic rhinitis. *Allergy*. 2019;74:308-317. <https://doi.org/10.1111/all.13630>