

Asymptomatic skin sensitization to birch predicts later development of birch pollen allergy in adults: A 3-year follow-up study

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Background: The skin prick test is the allergologic test of choice, but asymptomatic skin sensitization to aeroallergens is common. However, no data in the literature describe the clinical phenotype of asymptomatic sensitized adults.

Objective: The purposes of this investigation were to provide a clinical characterization of skin test-positive subjects without symptoms and to ascertain the predictive values of common allergologic tests.

Methods: Asymptomatic adults with positive skin prick test results for birch (n = 15), nonatopic control subjects (n = 25), and birch pollen-allergic patients (n = 6) were followed through use of daily diary cards during 3 consecutive birch pollen seasons. At inclusion and at the 3-year follow-up visit, conjunctival and nasal challenges, intradermal late-phase reaction evaluation, and measurement of specific IgE were performed.

Results: Asymptomatic sensitized subjects defined a clinically significant phenotype between nonatopic and allergic subjects in terms of specific IgE levels and susceptibility to conjunctival provocation testing. Sixty percent (n = 9) of the asymptomatic sensitized subjects developed clinical allergy. This was associated with an initial birch skin prick test weal diameter of ≥ 4 mm, a positive conjunctival provocation test result, and specific IgE of $\geq$ CAP class 2, as well as with the presence of other allergies. Specific IgE of $\geq$ CAP class 2 was 87.5% predictive for allergy development, whereas a negative conjunctival provocation test result was 100% negatively predictive. Nasal provocation testing possessed no additional prognostic information. No changes in clinical phenotype were seen in nonatopic or birch-allergic subjects.

Conclusion: Asymptomatic skin sensitization is a risk factor for later allergy development. At risk is any subject with target organ sensitivity, an elevated specific IgE level, and/or a skin prick test weal diameter of >4 mm. (J Allergy Clin Immunol 2003;111:149-54.)

Key words: Rhinitis, asymptomatic sensitization, symptom development, challenge tests, skin prick test, late-phase reaction, birch pollen, specific IgE, histamine release

Abbreviations used

CPT: Conjunctival provocation test
LPR: Late-phase reaction
NPT: Nasal provocation test
NPV: Negative predictive value
PPV: Positive predictive value
s-IgE: Specific IgE
SPT: Skin prick test

The skin prick test (SPT) is considered a valid, safe, low-cost, and easy-to-perform method of demonstrating IgE sensitization toward an aeroallergen, and the SPT is recommended as the "test of choice" in clinical diagnostics as well as clinical and epidemiologic allergy research.¹ The presence of asymptomatic skin sensitization (a positive allergen skin test result without a suggestive history of allergy) was reported in parallel to the introduction of routine skin testing,² and it was later reported in 7.5% to 19% of schoolchildren.^{3,4} Asymptomatic skin sensitization has been theorized to be an intermediate clinical entity between nonatopy and manifest allergy and to imply an increased risk of allergy development; this has been supported by findings in 3 follow-up studies.⁵⁻⁷ In these studies, sensitization was defined as a positive scratch test result,⁵ a positive intradermal test result,⁶ or the combination of a positive SPT result and the presence of serum-specific IgE.⁷ The latter definition was used in a series of in vivo studies on allergen-stimulated PBMCs in which sensitization was shown to be related to elevated IL-4 levels and symptoms to elevated IL-5 levels.⁸⁻¹⁰ A clinical study in a hospital-based, SPT-positive sample showed that allergen challenge could elicit clinical symptoms in 38% of asymptomatic subjects.¹¹ Neither of these studies presented clinical follow-up. Identification of prognostic parameters for later allergy development is essential to avoid unnecessary secondary prevention that might have both social and economic consequences.¹² To our knowledge, there are no published, prospective, population-based, follow-up studies that have included symptom diaries to confirm clinical states. Neither has there been a clinical characterization of asymptomatic SPT-sensitized subjects or of the allergy developers in this group.

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The aim of the present study was to characterize clinically and then follow a community-based cohort of subjects with asymptomatic SPT sensitization. As a model for sensitization and allergy to a common inhalation allergen, we used birch pollen, which is a widespread cause of allergy in Europe, Northern America, and certain areas of the southern hemisphere.¹³

METHODS

Study population

Participants were recruited in February 1999 from a screening of approximately 1000 students and employees at universities in Copenhagen, Denmark. Each member of a subpopulation of volunteers was assigned to 1 of 3 groups on the basis of history of allergy (positive if there were self-reported symptoms of rhinoconjunctivitis and/or asthma during relevant allergen exposure) and SPT reactions to a commercially available standard panel of inhalation allergens (see the paragraph on skin tests below). The groups were defined as follows:

NA—the nonatopic group (n = 32): no history of allergy/atopy and a negative SPT to the standard panel

BA—the birch pollen—allergic group (n = 7): positive history of birch pollen allergy for at least 2 consecutive seasons and a positive SPT reaction to birch

AS—the asymptomatic, birch pollen–sensitized group (n = 19): negative history of birch pollen allergy and a positive SPT reaction to birch.

Exclusion criteria in all groups were as follows: perennial rhinitis or asthma, pregnancy or lactation, malignancy or other severe systemic disease. Sensitization to other allergens was not an exclusion criterion in the AS and BA groups. Clinical and paraclinical examinations were performed twice, each visit being preceded by at least 7 days without medication intake; visit A was the inclusion visit, which took place during the preseason (February/March) in 1999, and visit B was the follow-up, which took place in October/November 2001. The study was approved by the local ethics committee of Copenhagen, Denmark, and written, informed consent was obtained from all participants before admission into the study.

Allergen extracts

We used only commercially available aqueous solutions of birch (Soluprick [SPT] and Aquagen [all other clinical tests], ALK-Abellø, Hørsholm, Denmark), produced according to international guidelines for allergen preparation.¹ All extracts were kept at 4°C and handled as recommended by the manufacturer. All vials were discharged when expired; this led to a batch shift of Soluprick for SPTs between visit A and visit B, whereas all other tests were performed with the same allergen batch throughout the study. According to the manufacturer, the amount of the major birch allergen Bet v 1 was 12.5 µg in 10 histamine-equivalent pricks with birch Soluprick and in 100,000 standard quality units of birch Aquagen. Potency is expressed in micrograms of Bet v 1 per milliliter.

Skin tests

Both SPTs and intradermal tests were performed on the volar surface of the antebrachium. SPTs were done in duplicate with a commercially available panel of inhalation allergens: birch (*Betula verrucosa*), grass (*Phleum pratense*), mugwort (*Artemisia vulgaris*), horse dander, dog dander, cat dander, house dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*), and molds (*Alternaria alternata*, *Cladosporium herbarum*). The skin reaction was recorded after 10 minutes. A negative control and a positive control (histamine dihydrochloride 10 mg/mL) were

included, and positivity was defined as a mean weal diameter of ≥ 3 mm.¹ In the AS and BA groups, allergen-induced eosinophil inflammation was demonstrated by the size of the intradermal late-phase reaction (LPR).¹⁴ The weal-and-flare diameter was read 18 to 24 hours after monoplicate, intradermal injection of 0.05 mL of 125-ng Bet v 1/mL; there was a negative control on the opposite arm. The LPR reaction was positive if the allergen mean weal diameter minus the negative control exceeded 5 mm.¹

Challenge tests

Clinical susceptibility to allergen was examined with titrated challenges of the conjunctivae (conjunctival provocation test [CPT]), and the nasal mucosa (nasal provocation test [NPT]) through use of birch Aquagen in logarithmic steps from 12.5 ng to 12.5 µg Bet v 1/mL (titers 1 through 5) or until a positive test result was obtained.^{15,16} In participants without seasonal symptoms and with no symptoms at lower concentrations, the CPT and NPT included the concentration 125 µg Bet v 1/mL, corresponding to the application of 6.25 µg Bet v 1 by CPT (1 drop = 0.05 mL), and of 12.5 µg Bet v 1 by NPT (1 puff = 0.1 mL). Each result was expressed as the highest dose not eliciting symptoms; accordingly, a negative test result was defined as no significant clinical symptoms at any allergen concentration administered.

Paraclinical investigations

Specific IgE (s-IgE) in serum was measured through use of the CAP System (Pharmacia Diagnostics, Uppsala, Sweden), and a CAP class of ≥ 2 was considered positive. Total IgE was measured through use of a microparticle enzyme immunoassay (IMX System, Abbott Diagnostics, Abbott Park, Ill). Blood eosinophils were counted on a Sysmex SE9000 (Sysmex, Kobe, Japan). Birch pollen–induced basophilic histamine release was measured according to the method of Skov et al.¹⁷ The titer giving 50% of the maximal response was registered.

Symptom registration

All participants completed daily diary cards on symptoms and medication use from March through late May (covering the local birch pollen season) in 1999, 2000, and 2001. Symptoms from nose, eyes, and lungs were graded on a 0-to-3 scale (0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe). The symptom score was calculated as the sum of daily scores during the season. Medication was scored as follows: acrivastine 8 mg/capsule, 2 points; levocabastine eyedrops 0.5 mg/mL or nasal spray 50 µg/dose, 1 point; salbutamol inhalations 200 µg/dose, 1 point. The medication score was calculated as the sum of medications consumed daily.¹⁶ To avoid abolishment of possible symptoms, no local or systemic steroid use was permitted.¹⁶ The individual symptom score and the medication score were summed to a total symptom load score, comprising the area under the curve of symptoms and medication usage.¹⁸ Symptoms were considered to indicate birch pollen allergy if they lasted ≥ 7 days or if symptoms were repeatedly elicited when pollen counts exceeded a certain (individual) level.

Pollen counts and season

Pollen grains were collected by means of a standard Burkard Volumetric 7-Days Spore Trap in Copenhagen, Denmark (at 55° 43' N, 12° 34' E) 15 m above ground level. Pollen grains were counted daily (each count being expressed as the number of grains per cubic meter of air) by the Danish Meteorological Institute, Copenhagen,¹⁹ and the birch pollen season was defined as the period including the mid 90% of the total birch pollen count.¹⁶ Because birch pollen symptoms persist weeks after the decline in pollen count,¹⁶ the season in which symptoms were attributable to birch pollen was pragmatically defined as the period starting on the first day on which birch pollen levels were

>10 grains/m³ and ending on the first day on which grass pollen levels were >10 grains/m³.²⁰ The local grass pollen season runs from May through July.¹⁹ The accumulated seasonal exposure to Bet v 1 averages 0.3 µg Bet v 1 (the calculation being tidal volume [m³] × respiration frequency [minutes⁻¹] × 1440 [minutes/day] × mean average daily birch pollen count [grains/m³] × days of average birch pollen exposure [days] × Bet v 1 concentration [ng/grain]).^{13,21,22}

$$0.0005 \times 15 \times 1440 \times 200 \times 20 \times 0.006 = 260 \text{ ng Bet v 1}.$$

Statistical analysis

Statistical software was used for data analysis (SPSS for Windows, version 10.0.7) and post-hoc power calculation (R, version 1.1.1 [available at www.r-project.org]).²³ Continuous variables were analyzed through use of the Mann-Whitney *U* test and the Friedman test; categorical variables were analyzed through use of the Fisher exact test and with odds ratios. Statistical significance was reached when the *P* value was less than .05.²⁴ Positive and negative predictive values were calculated according to the method of Altman.²⁴ If more than 10% of data were missing in the diaries, data analysis was considered inconclusive. Missing data were omitted from data analysis; thus, no fitted values were constructed. Participants who did not attend visit B were excluded from the final calculations. Data were statistically analyzed in terms of minimum, maximum, and median values and frequency distributions.

RESULTS

Subjects

Forty-six participants (female/male by group: AS, 5/10; BA, 2/4; NA, 9/16) with a median age of 23 years (range, 20–41 years) completed the study, whereas 11 subjects attended visit A only and 1 subject missed visit B. The nonattenders were evenly distributed among the groups, and there were significant demographic differences neither between attenders and nonattenders nor among the 3 subgroups. Each of 8 subjects (BA, *n* = 3; AS, *n* = 5) reported having another allergy, which was grass pollinosis (Table I). Diaries contained less than 7% missing data, and no diary contained information on medicine intake without concomitant symptom registration.

Characterization of AS group at inclusion

Table I depicts clinical and paraclinical parameters for all 3 groups at inclusion. In addition, the size of the histamine SPT reaction and the blood eosinophil count did not differ between the groups (*P* > .1; Mann-Whitney *U* test).

Seasonal pollen exposure

The seasons varied in duration and pollen counts (Fig 1); each was designated as being of low (1999), intermediate (2000), or high (2001) pollen exposure.²² The season prior to the study (1998) had lasted 25 days and had a high pollen load: 8147 grains/m³ in total pollen count. The pollen exposure in all seasons in the study sufficed to induce nose and eye symptoms in all subjects in the BA group. No symptoms were reported in the NA group, and no lung symptoms were reported by any of the study participants.

Debut of allergy

As shown in Fig 1, 9 AS subjects (60%) developed birch pollen symptoms during the study period, there

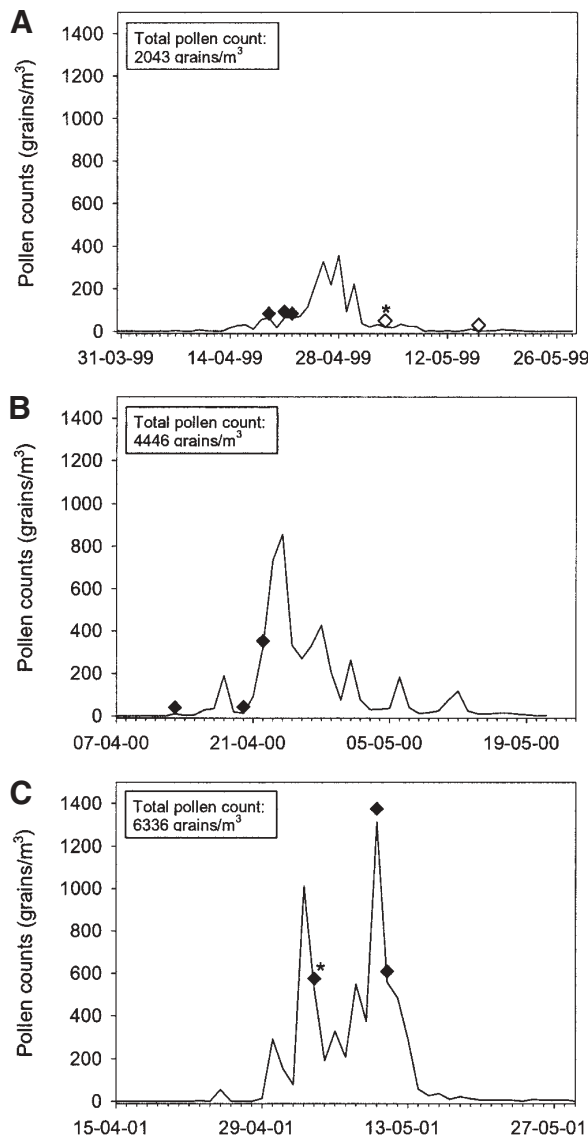


FIG 1. Numbers of pollen grains and onset of allergic symptoms in subjects in the AS group. **A**, 1999 season (duration, 19 days). **B**, 2000 season (duration, 24 days). **C**, 2001 season (duration, 14 days). *Identical subjects. Each black diamond indicates debut of birch pollen allergy; each white diamond indicates symptoms not suggestive of pollen allergy.

being a constant incidence of 3 subjects per season. During the 1999 season, 2 participants reported symptoms that failed to fulfill the definition of birch pollen allergy.

Characterization of allergy developers

Development of symptoms had no significant relation to age or sex (both: *P* > .25; data not shown). Significant differences between allergy developers and persistently asymptomatic subjects were present at inclusion (visit A) in several parameters (Table II). At neither visit were the 2 groups significantly different with respect to histamine SPT weal diameter, NPT titer, total IgE, basophil histamine release titer, or blood eosinophil count (*P* > .1). In

TABLE I. Clinical and paraclinical characterization at visit A of birch pollen susceptibility in the asymptomatic, sensitized group (AS) and statistical comparison with the nonatopic (NA) and birch pollen-allergic (BA) control groups

	Group			P value	
	AS (n = 15)	NA (n = 25)	BA (n = 6)	AS vs NA	AS vs BA
SPT (range) in mm	5.0 (3.5-8.5)	0 (0-0)	6.5 (4.0-10.0)	<.0001	>.3
LPR (range) in mm	0 (0-13.0)	ND	23.5 (0-96.0)	—	<.005
CPT titer (range)	10 ⁴ (10 ² -10 ⁵)	10 ⁶ (10 ⁶ -10 ⁶)	10 ³ (10 ¹ -10 ³)	<.0001	>.2
NPT titer (range)	10 ⁵ (10 ³ -10 ⁶)	10 ⁶ (10 ⁶ -10 ⁶)	10 ³ (10 ² -10 ⁴)	<.0001	>.8
HR titer (range)	2 (0-3)	0 (0-0)	3 (2-3)	<.002	>.1
CAP class (range)	2 (0-3)	0 (0-0)	3 (2-4)	<.05	<.05
Total IgE (range)	95 (13-1095)	19 (1-94)	54.5 (25-65)	<.05	>.2
CPT+: n (%)	12 (80)	0 (0)	6 (100)	<.0001	>.5
CAP+: n (%)	8 (56)	0 (0)	6 (100)	<.0001	.06
SPT ⁺ stand: n (range)	2 (1-7)	0 (0-0)	3 (2-4)	<.0001	>.5
Other allergies*: n (%)	5 (33)	0 (0)	3 (50)	<.005	>.6

Statistical analyses: Fisher exact test (categorical data) and Mann-Whitney *U* test (continuous data).

SPT, Skin prick test; LPR, late-phase reaction; ND, not done; CPT, conjunctival provocation test; NPT, negative predictive value; HR, basophil histamine release; CAP+, CAP class ≥ 2 ; SPT⁺ stand, positive SPT reactions to standard panel of 10 allergens.

*Grass pollinosis.

TABLE II. Clinical and paraclinical characterization of birch pollen susceptibility in allergy developers and persistent asymptomatic subjects (nondevelopers) at visits A and B

	Visit A			Visit B		
	Developers (n = 9)	Nondevelopers (n = 6)	P value	Developers (n = 9)	Nondevelopers (n = 6)	P value
SPT (range) in mm	6.0 (4.5-8.5)	4.5 (3.5-5.5)*	<.05	5.5 (3.0-8.0)	0 (0-4.0)	<.005
LPR (range) in mm	0 (0-13.0)*	0 (0-0)	>.7	49.0 (0-67.0)	0 (0-67.5)	>.05
CPT titer (range)	10 ⁴ (10 ² -10 ⁵)	10 ⁵ (10 ⁴ -10 ⁶)	<.05	10 ⁴ (10 ² -10 ⁵)	10 ⁶ (10 ⁴ -10 ⁶)	<.02
NPT titer (range)	10 ⁵ (10 ³ -10 ⁶)	10 ⁵ (10 ⁵ -10 ⁶)	>.1	10 ⁴ (10 ³ -10 ⁶)	10 ⁶ (10 ⁵ -10 ⁶)	>.2
CAP class (range)	2 (0-3)	0 (0-2)	.05	3 (0-4)	0 (0-2)	<.05
CPT+: n (%)	9 (100)	3 (50)	<.05	9 (100)	2 (33)	<.02
CAP+: n (%)	7 (78)	1 (17)	<.05	8 (89)	2 (33)	>.05
SPT ⁺ stand: n (range)	3 (1-7)	1.5 (1-4)	>.2	3 (2-5)	1 (0-2)	<.005
Other allergies: n (%)	5 (56)	0 (0)	<.05	5 (56)	0 (0)	<.05

Statistical analyses: Fisher exact test (categorical data) and Mann-Whitney *U* test (continuous data). For meanings of abbreviations, see footnotes to Table I.

*Significant difference ($P < .05$) between results at visits A and B (paired Mann-Whitney *U* test).

TABLE III. Median symptom load (range) in initially asymptomatic (AS) and symptomatic (BA) subjects during 3 consecutive seasons

	Season			P value*: 1999 vs 2001
	1999	2000	2001	
AS	29 (16-68)	62 (6-217)	46 (4-202)	<.03
BA	137 (24-859)	137 (69-983)	124 (30-842)	>.4
P value†	>.2	>.2	>.3	—

*Friedmann test.

†Mann-Whitney *U* test.

comparison with the BA group, allergy developers differed at visit B insignificantly in all of the investigated parameters (exception: higher levels of total IgE; $P = .050$) and in symptom load score (Table III). The Friedman test, as shown in Table III, suggested that the symptom load of allergy developers increased throughout the study, but no significant interseasonal differences were apparent ($P > .1$). The persistently asymptomatic subjects differed insignificantly from the NA group in all

parameters except in SPT birch diameter and by having more SPT-positive reactions ($P < .001$) and higher levels of total IgE ($P < .05$). All 5 subjects with grass pollinosis developed birch pollen allergy ($P < .05$), 3 of them having their debuts in the first season.

Prognostic values of clinical parameters at inclusion

For clinical tests at inclusion, the positive predictive value (PPV) for allergy development was 100% for LPR; the negative predictive value (NPV) was 43%. Both a negative CPT result and an SPT weal diameter of ≤ 4 mm precluded allergy development (100% NPV), the PPVs being 75% and 69%, respectively. Replacement of CPT with NPT or increment of cutoff limits weakened both the PPV and the NPV. For the presence of s-IgE of $\geq$ CAP class 2, the PPV was 87.5% and the NPV 71%, and the odds ratio for allergy development was significantly increased (17.5 [95% CI, 1.2-250]).

Statistical power

A post-hoc power calculation revealed that with the present number of cases (Table I), an error rate (alpha) of

0.05, a power (1-beta) of 0.8, and a pooled standard deviation of 30%, a between-groups difference of at least 30% would be detectable in a 1-tailed *t* test. To identify a difference in proportions of 2 groups (p_1 and p_2), a p_1 of 0.3 required a p_2 of at least 0.7. For smaller proportions, a p_1 of 0.01 required a p_2 above 0.3, and for larger proportions a p_1 of 0.5 required a p_2 above 0.95.²⁴

DISCUSSION

This study shows that adults with asymptomatic skin sensitization to birch pollen had an increased risk of developing hay fever during a 3-year follow-up period, supporting findings in previous studies.^{5-7,25,26} Neither nonatopic subjects nor patients with manifest birch pollen allergy changed with respect to clinical phenotype during the study.

Allergic sensitization was a clinically distinct entity separate from both nonatopy and manifest birch pollen allergy (Table I). Most asymptomatic subjects (80%) were positive to CPT with supraphysiologic concentrations of allergen (6.25 μ g in CPT vs 0.3 μ g Bet v 1 in vivo exposure). Pastorello et al¹¹ found lower levels of allergen responsiveness with challenge procedures and doses identical to those of the present study, but they reported the same tendency of CPT to be superior to NPT. Interstudy differences in extract potency cannot be ruled out. The presence of unspecifically positive test results are less likely, inasmuch as no nonatopic subject reacted to either test. Thus the CPT was a highly sensitive tool by which to demonstrate clinical susceptibility. At inclusion, asymptomatic sensitized subjects had elevated basophil histamine release and positive immediate challenge test results but negative late-phase reactions (Table I). This suggests that both s-IgE and effector cells are present in target organ mucosa but that under physiologic conditions they are few and/or opposed by dampening mechanisms.²⁷ At follow-up, the allergy developers and the manifest allergic subjects had comparable cutaneous LPR diameters. These clinical observations support in vitro findings that symptoms were associated with elevated expression of IL-5 but not of IL-4 or IFN- γ in allergen-stimulated PBMCs.^{8,9} Whereas IL-4 and IFN- γ affect IgE synthesis, IL-5 attracts, differentiates, and activates eosinophils, the predominant cell type in the LPR.^{9,14} IL-5 control seems crucial in maintaining the asymptomatic phenotype. Anti-IL-5 treatment has been promising in alleviating asthma symptoms in animal models, but further studies are needed to clarify whether it is useful as regards active secondary prevention of allergy development in asymptomatic sensitization.²⁸

The use of diaries allowed symptoms to be related to relevant pollen exposure (Fig 1) which in the first season (1999) resulted in 3 debuts of birch pollen allergy. It can be argued that these subjects simply had neglected or misinterpreted their birch pollen allergy in previous seasons. We deem this to be unlikely, inasmuch as these subjects were all familiar with seasonal allergic symptoms in the grass pollen season (May-July). Furthermore, the

pollen load had been much higher during the preceding season (1998) than in the 1999 season.

The association between pollen exposure and symptom severity is well established. How pollen exposure affects the prevalence of pollen allergy has been less vigorously investigated.²⁰ In a cross-sectional study, children were more often sensitized when living in areas with high birch pollen exposure, whereas the allergy prevalence was unaffected.²⁹ Likewise, in our study the magnitude of seasonal pollen exposure did not affect the incidence of pollinosis (Fig 1). However, our cohorts were small, making the possibility for a type II error apparent.²⁴ Nevertheless, the between-groups differences were generally larger than required (according to the post-hoc power calculations) to detect a statistical difference if one existed. However, the current findings need confirmation in a large-scale study. Late in the first season, 2 subjects reported symptoms that were disqualified from identification as birch pollen-induced. A possible bias of over-registration in the risk group and under-registration in the negative control group is difficult to avoid without reducing the amount of information given to participants or blinding the SPT results. Both options raise ethical considerations.

Several parameters obtained at inclusion possessed high predictive values for later allergy development. The presence of other allergy (grass pollinosis), detectable s-IgE, and/or a birch SPT diameter of >4 mm were positively associated with later development of birch pollen allergy, whereas a negative CPT precluded allergy development. Secondary prevention aims at preventing allergy development in sensitized subjects at risk—eg, birch pollen-sensitized foresters or wood industry employees in whom inhalation allergy could lead to chronic disease or be hazardous when heavy machinery is being operated.³⁰ However, secondary prevention can have major implications on social, economic, and occupational life,¹² and the present study shows that further allergy testing could avoid unnecessary preventive attempts by a few supplementary allergologic tests. The widespread use of SPTs makes research on their diagnostic and prognostic potential essential.¹

Our data support earlier prospective investigations that used other definitions for sensitization than a positive SPT result; one of these was a retrospective 2- to 24-year follow-up study using intradermal skin test to ragweed in 68 subjects aged 0 to 57 years,⁶ another was a prospective 23-year follow-up study of 105 adults having positive scratch test results to at least 1 of 15 allergens (12 aeroallergens, egg white, cow's milk, and wheat),⁵ and yet another was a prospective 4-year follow-up study of 114 children having positive SPT results and a RAST-class of ≥ 2 to mite, grass, mugwort, and/or birch.⁷ The incidence of allergy in asymptomatic subjects in these investigations (range, 43% to 53%) was very stable, despite interstudy differences.

In conclusion, we have shown that asymptomatic adults who were birch SPT-positive had an increased risk of developing allergy during a 3-year period; this

was predicted by the presence of s-IgE and the development of an LPR, and it was precluded by a negative CPT. Studying the immune responses of asymptomatic sensitized subjects might contribute to our understanding of mechanisms involved in symptom control and thus provide possible targets for future therapeutic intervention.

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