

Atopy and contact allergy to fragrance: allergic reactions to the fragrance mix I (the Larsen mix)

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Background: The relationship between an atopic diathesis and contact sensitization to fragrances is unclear.

Objective: To investigate whether there is an association between atopy and allergy to fragrance mix I (FM I).

Patients/Methods: The computerized files of patients patch tested to FM I at St John's Institute of Dermatology (1980–2004) were reviewed. Demographic details recorded for all patch-tested patients included age, sex, date of testing, history of current or previous atopic eczema (AE), history of current or previous asthma nor hay fever (A/HF), family history (FH) of any type of atopy, and any positive patch tests.

Results: About 8.4% of females (1713/20 338) and 6.6% of males (903/13 734) were allergic to FM I. About 8.95% (101/1129) of females with AE were allergic to FM I versus 8.63% (619/7171) of females who had neither AE and A/HF nor FH (non-atopics) ($P = 0.72$). About 5.6% (40/710) of males with AE were positive to FM I versus 6.9% (427/6201) of male non-atopics ($P = 0.23$). There was a striking increase in AE and A/HF during this 25-year period ($P < 0.0001$).

Conclusions: We found no association between atopy and allergy to FM I. There has been a marked increase in atopy in individuals referred for patch testing in the past 25 years.

Key words: asthma; atopic eczema; fragrance allergy; hay fever. © Blackwell Munksgaard, 2008.

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The role of atopy in the induction of allergic contact dermatitis has been widely debated. As patients with atopic eczema (AE) frequently undergo patch testing, dermatologists may have the impression that atopy is a risk factor for allergy to common sensitizers such as nickel and fragrance.

Previous studies have addressed the possibility of a link between atopy and sensitization to a number of common contact allergens. DeGroot found that in adult patch test patients, atopics were less likely to be sensitized to common contact allergens than non-atopics (1). Ingordo et al. found no significant difference in the likelihood of sensitization to common allergens in a group of patients with AE versus non-atopics (2). A previous study

from this institute showed that in hairdressers with hand eczema, there was no significant difference in the likelihood of sensitization to hairdressing allergens or to nickel between atopics and non-atopics (3). Recent study has identified mutations in the filaggrin gene, which may explain 50% of severe cases of atopic dermatitis, and shown an association between filaggrin deficiency and contact sensitization to nickel but not with other contact allergens (4, 5).

The published data on the relationship between allergy to fragrance mix I (FM I) and atopy have been conflicting. In a German multicentre study of 59 298 patients undergoing patch testing, there was no difference in the proportion of those who were atopic between all patients tested and those

who were allergic to FM I (17.2% versus 17.3%) (6). In another German study from the same authors, the frequency of type IV sensitizations to FM I was statistically significantly increased in patients with AE versus patients of similar age without AE (10.6% versus 9%) (7). In a previous study from this institute of 989 patients, which took place in 1990, those with AE were equally likely to be allergic to FM I (9.4%) as were non-atopics (9.0%) or those with asthma and/or hay fever (A/HF) (9.5%) (8).

FM I continues to be used in the baseline European series of contact allergens as a useful marker of fragrance allergy, detecting up to 85% of fragrance-allergic patients, although in 2006 a second fragrance mix II was added (9). In this study, we have investigated any link between allergy to FM I and an atopic tendency in a large patch-test population from a single centre.

Patients and Methods

This was a retrospective anonymized study of all patients tested to the European baseline patch test series between 1980 and 2004 at St John's Institute of Dermatology, London, UK. Trolab™ (Trolab Hermal, Reinbek, Germany) allergens in Finn Chambers® on Scanpor™ (Epitest Ltd OY, Rannankouku, Tuusula, Finland) tape were used with two-dimensional occlusion and readings were taken on D2/3 and D4/5. A database records demographic data on all patients tested. This includes information on age, sex, current or previous history of AE, current or previous history of A/HF, a family history (FH) of AE and/or A/HF, and any positive patch test reactions. A history of AE was determined by flexural involvement, childhood involvement, and itching. A search of the database identified all patients tested between 1980 and 2004 and, of them, the numbers who reported themselves to have AE, A/HF, or FH. Those patients who reported none of the three were defined as 'non-atopics' and those who had at least one were defined as 'atopics'. The pooled data for all years were grouped by the presence of

one or more of AE, A/HF, or FH and subdivided by sex and by whether or not patients were allergic to FM I (Table 1). Data for each individual year were also analysed to look at time trends (Table 2).

A two-sample statistical test for equality of proportion was used to compare the percentage rates of allergy to FM I in non-atopics versus atopics. The rate of allergy to FM I in non-atopics was compared specifically with the individual rates in those with AE alone, A/HF alone, and FH alone. The percentage of all patients tested each year who had AE, A/HF, or FH was calculated and a Cochran–Armitage test used to look for any increase in the number of atopy cases during the period of the study.

Results

34 072 patients were tested during this period (20 338 females and 13 734 males). 8.4% of females (1713/20 338) were allergic to FM I versus 6.6% of males (903/13 734) ($P < 0.0001$). About 13 372 of all patients tested were non-atopics (7171 females and 6201 males), and 1046 of them (7.8%) were allergic to FM I versus 7.6% (1570) of 20 700 atopics (13 167 females and 7533 males) ($P = 0.43$). About 7.8% of non-atopics (1046/13 372) were allergic to FM I versus 7.7% of patients with AE alone (141/1839) ($P = 0.85$), 6.9% of patients with A/HF alone (181/2639) ($P = 0.09$), and 8.0% of patients with FH alone (465/5840) ($P = 0.74$). In females, 8.6% of non-atopics (619/7171) were allergic to FM I versus 9.0% of those with AE alone (101/1129) ($P = 0.72$), 7.6% of those with A/HF alone (112/1473) ($P = 0.2$), and 8.4% of those with FH alone (310/3688) ($P = 0.69$). In males, 6.9% of non-atopics (427/6201) were allergic to FM I versus 5.6% of those with AE alone (40/710) ($P = 0.23$), 5.9% of those with A/HF alone (69/1166) ($P = 0.22$), and 7.2% of those with FH alone (155/2152) ($P = 0.62$) (Table 1).

Of all 34 072 patients tested, 9357 (27.4%) had AE, 30% of females ($n = 6110$) and 23% of males ($n = 3247$); 10 692 (31.4%) had A/HF, 33% of

Table 1. Results of 34 072 patients tested between 1980 and 2004, categorized by sex, positive patch test reactions to FM I and atopic subgroup

	Total	Non-atopics	AE alone	A/HF alone	FH alone	AE + A/HF	AE + FH	A/HF + FH	AE + A/HF + FH	All AE	All A/HF	All FH
Number of females tested	20 338	7171	1129	1473	3688	999	1575	1896	2407	6110	6775	9566
Number of males tested	13 734	6201	710	1166	2152	622	754	968	1161	3247	3917	5035
FM I-positive females	1 713	619	101	112	310	81	133	162	195	510	550	800
FM I-positive males	903	427	40	69	155	44	48	66	54	186	233	323
FM I-negative females	18 625	6552	1028	1361	3378	918	1442	1734	2212	5600	6225	8766
FM I-negative males	12 831	5774	670	1097	1997	578	706	902	1107	3061	3684	4712

AE, atopic eczema; A/HF, asthma and/or hay fever; FH, family history of atopy; FM I, fragrance mix I.

Table 2. Results of 34 072 patients tested between 1980 and 2004, categorized by year of testing and atopic subgroup

Year	F total	F AE	F AE %	F A/HF	F A/HF %	F FH	F FH %	M total	M AE	M AE %	M A/HF	M A/HF %	M FH	M FH %	All atopic	F total	M total
1980	179	44	24.6	38	21.2	74	41.3	113	24	21.2	24	21.2	55	48.7	169	105	64
1981	210	52	24.8	42	20	88	41.2	131	29	22	20	15.3	49	37.4	184	119	65
1982	1113	269	24.2	256	23	532	47.8	782	168	21.4	152	19.4	274	30.7	1084	688	396
1983	1025	267	26	271	26.4	436	42.5	845	172	20.4	222	26.3	273	32.3	1039	610	429
1984	1064	290	27.3	334	31.4	498	46.8	802	159	19.8	185	23.1	276	34.4	1087	678	409
1985	1125	307	27.3	317	28.2	530	47.1	747	160	21.4	205	27.4	258	34.5	1100	699	401
1986	1140	306	26.8	340	29.8	494	43.3	741	169	22.8	206	27.8	264	35.6	1083	689	394
1987	1017	301	29.6	319	31.4	488	48	753	153	20.3	205	27.2	286	38	1051	655	396
1988	1079	279	25.9	335	31	489	45.3	770	149	19.4	214	27.8	264	34.3	1040	660	380
1989	1060	279	26.3	318	30	509	48	725	131	18.1	188	25.9	275	37.9	1049	670	379
1990	871	263	30.2	296	34	394	45.2	625	127	20.3	156	30	238	38.1	920	579	341
1991	1012	287	28.4	347	34.3	475	46.9	674	129	18	185	27.4	236	35	979	633	346
1992	988	253	25.6	298	30.2	419	42.4	668	144	21.6	189	28.3	237	35.5	939	578	361
1993	916	258	28.2	323	35.3	456	49.8	597	119	18.4	181	30.3	220	36.9	912	593	319
1994	706	199	28.2	256	36.3	345	48.9	469	113	24.1	143	30.5	197	42	747	469	278
1995	613	209	34.1	220	35.9	271	44.2	475	161	33.9	142	29.9	172	36.2	678	401	277
1996	814	349	42.9	288	35.4	426	52.3	574	196	34.1	183	31.9	218	38	957	605	352
1997	861	292	33.9	318	36.9	436	50.6	592	171	28.9	175	29.6	244	41.2	953	611	342
1998	734	257	35	298	40.6	368	50.1	430	127	29.5	157	36.5	178	41.4	769	511	258
1999	701	228	32.5	293	41.8	366	52.2	421	117	27.8	152	36.1	154	36.6	738	490	248
2000	734	275	37.5	299	40.7	351	47.8	400	128	32	147	36.8	165	41.3	758	508	250
2001	734	266	36	310	42.2	362	49.3	402	109	27.1	146	36.3	166	41.3	775	518	257
2002	623	229	36.8	244	39.2	307	49.3	371	102	27.5	130	35	146	39.4	660	427	233
2003	613	195	31.8	247	40.3	264	43.1	403	119	29.5	142	35.2	126	31.3	631	400	231
2004	401	156	38.9	168	41.2	188	46.9	224	71	31.7	68	30.6	64	28.6	395	271	124

AE, atopic eczema; A/HF, asthma and/or hay fever; All atopic, M and F with AE and/or A/HF and/or FH; F, female; FH, family history of atopy; F total, F with AE and/or A/HF and/or FH; M, male; M total, M with AE and/or A/HF and/or FH; %, percentage of those tested in that year.

females (6775) and 28% of males (3917); and 14 601 (42.8%) had a FH of atopy, 9566 (47%) of females and 5035 (36.7%) males. Of 2616 patients with positive reactions to FM I (1713 females and 903 males), 696 (26.6%) had AE: 29% of females ($n = 510$) and 20% of males ($n = 186$); 783 (30%) had A/HF: 550 (32%) of females and 233 (25%) of males; and 1125 (43%) had a FH of atopy: 800 (46.7%) of females and 323 (35.8%) of males (Table 2).

There was a striking increase in AE and A/HF in both sexes during this 25-year period ($P < 0.0001$) (Figs 1–3).

Discussion

Patients with AE not infrequently report that they cannot tolerate certain cosmetic items, which cause a stinging sensation or a rash. The cosmetic industry specifically markets ‘unperfumed’ and

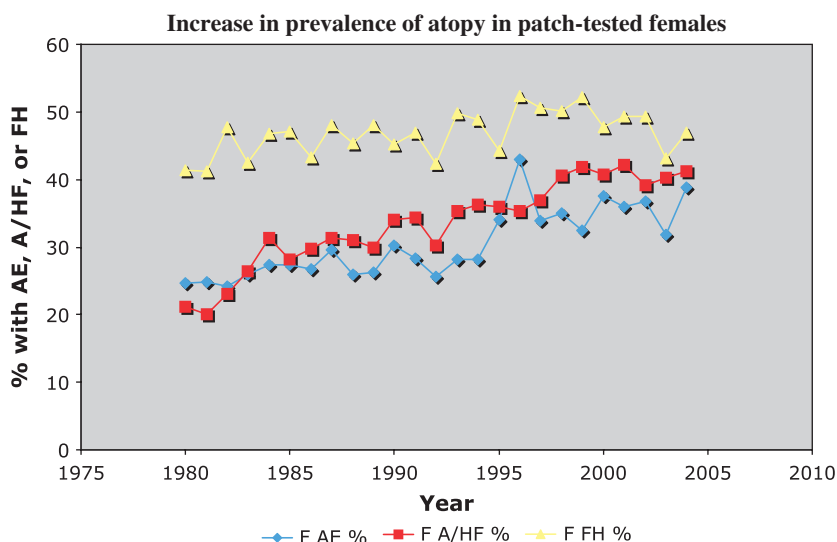
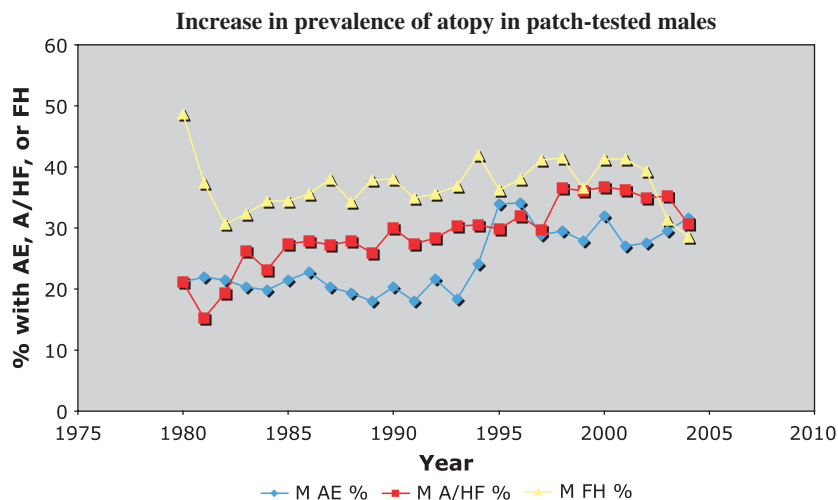


Fig. 1. Increase in prevalence of atopy in females attending for patch testing between 1980 and 2004. F AE %, percentage of all patch-tested females who had AE; F A/HF %, percentage of all patch-tested females who had A/HF; F FH %, percentage of all patch-tested females who had a FH of atopy. AE, atopic eczema; A/HF, asthma and/or hay fever; FH, family history of atopy.

Fig. 2. Increase in prevalence of atopy in males attending for patch testing between 1980 and 2004. M AE %, percentage of all patch-tested males who had AE; M A/HF %, percentage of all patch-tested males who had A/HF; M FH %, percentage of all patch-tested males who had a FH of atopy. AE, atopic eczema; A/HF, asthma and/or hay fever; FH, family history of atopy.

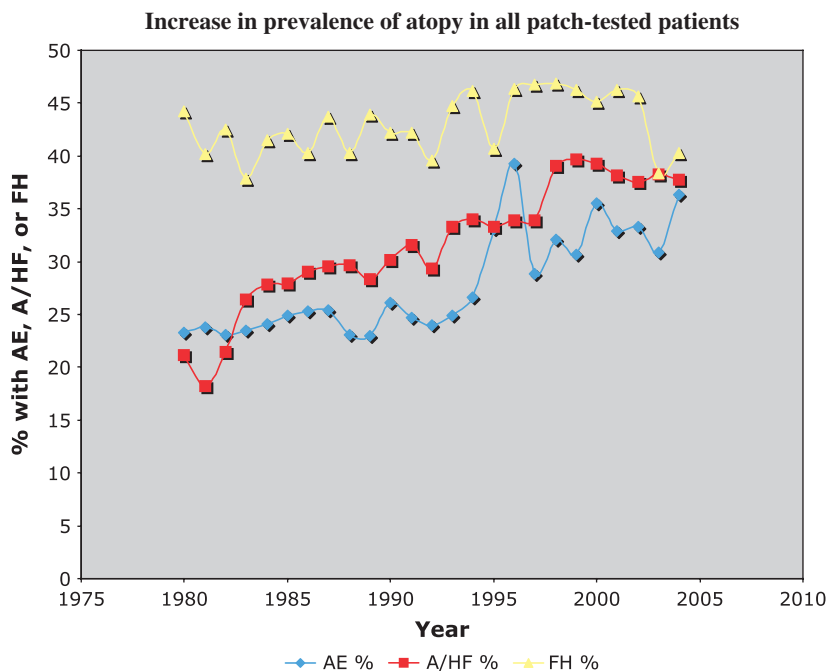


‘fragrance-free’ products to ‘people with sensitive skin’. Some patients with AE go on to develop chronic hand dermatitis in adulthood, especially those in high-risk occupations for irritant hand dermatitis such as metalworkers and healthcare workers whose hands are also regularly exposed to fragrances (10, 11). Aerosolized fragrances can cause eye and respiratory symptoms, associated with histamine release from peripheral blood basophils (12). However, this bronchial hyper reactivity is not immunoglobulin E mediated and is not associated with atopy (13). A high proportion (>50%) of the patients patch tested at our clinic are atopic, reflecting clinical suspicion of allergic contact dermatitis in this group. In this selected group of patients in whom patch testing

was indicated, we have assessed whether cutaneous delayed-type hypersensitivity to fragrances is more likely to affect atopic individuals than non-atopics.

The data in this study, collected in a single centre over more than two decades, show clearly that there was no difference in the likelihood of allergy to FM I between patients who reported no type of atopy and patients who reported themselves to have AE, mucosal atopy or a FH. This finding was true for both sexes, so exposure to a higher number and concentration of fragrance chemicals, such as is found in women’s perfumes (14), does not appear to increase the chance of sensitization in atopic females. Additionally, despite the gradual increase in prevalence of both AE and A/HF in

Fig. 3. Increase in prevalence of atopy in all patients attending for patch testing between 1980 and 2004. AE %, percentage of all patch-tested patients who had AE; A/HF %, percentage of all patch-tested patients who had A/HF; FH %, percentage of all patch-tested patients who had a FH of atopy. AE, atopic eczema; A/HF, asthma and/or hay fever; FH, family history of atopy.



those referred for investigation, the rate of allergy to FM I remained steady during this period (15).

The increase in all types of atopy that occurred in the 25-year period up to 2004 was a striking finding. More than a quarter of the patients in this study reported AE, almost one-third A/HF and almost one half a FH of atopy. Worldwide, there has been a noteworthy increase in atopy in recent decades. In a Norwegian study of school children aged 9–11 years, the prevalence of self-reported AE increased from 13.4% in 1985 to 20.8% in 2000; asthma from 9.3% to 13.8%, and hay fever from 16.5% to 26.6% (16). Among Italian children, there was an increase in allergic rhinitis of 5.2% in 6–7 year olds and 4.1% in 13–14 year olds between 1994 and 2002, while the prevalence of AE increased by 4.4% and 2.1%, respectively (17). There is a relative dearth of information about similar trends in adults where the prevalence rates of all types of atopy are less. In a recent US and European population-based study of adults, the mean prevalence of AE was 7.1% (with a range between countries of 2.2–17.6%) (18). In adults, atopy is strongly associated with urbanization and 'Western' lifestyles (19).

The reasons for this recent increase in atopy are unclear. Associations include increased prosperity, reduced overcrowding, higher standards of infant hygiene, early antibiotic treatment, improved parental education, increased maternal employment, and reduced parental smoking. Socioeconomic advantage and smaller family size are strongly linked with AE, both for reported and examined dermatitis (20). In Indian, Pakistani and Bangladeshi populations in the UK, children born in the UK and those who immigrated before the age of 5 years are significantly more likely to develop asthma versus those aged 5 years or more at the time of immigration (21). About 15% of black Caribbean children living in London had AE compared with 5.6% of similar children living in Jamaica (20).

There is no reason to believe that dermatologists are more likely to label a patient scheduled for patch testing as being atopic than 10 or 20 years ago as the questions we use are standardized and have not changed during this period. It is possible that family doctors are more inclined to give a specific diagnosis of 'asthma' or 'eczema' to a patient than two decades ago when the patient might have been told that they had 'cough', 'bronchitis', 'rash', or other non-specific conditions. In this study, females were slightly more likely to report any type of atopy than males, which could reflect a lower threshold for seeking healthcare advice, 'add-on' consultations when bringing a child or elderly relative to primary healthcare,

reading of health-related articles in women's magazines, or a true increase. Prevalence studies of childhood also show atopy to be slightly more frequent in females (20).

A recent study showed that a positive patch test to FM I did not impair the prognosis of dermatitis in adults with AE, except for those with facial dermatitis. During a follow-up period of 16 years, many became symptom free, possibly because of allergen avoidance or possibly because of the immunological effect of occasional skin exposure to an allergen keeping a beneficial T-cell population activated in the skin (22). The patch test reaction pattern of patients with AE may differ from that of non-atopics; patients with AE are more likely to have a strongly positive patch test to FM I at D3, presumably because of an irritant effect augmenting the allergic response, but they are less likely to have crescendo reactions gradually increasing in intensity from D1 to D3 (23).

The 8% FM I consists of a mixture of eight different chemicals (cinnamic alcohol, cinnamal, *Evernia prunastri*, isoeugenol, eugenol, geraniol, hydroxycitronellal, and alpha amyl cinnamal), each tested at 1% in petrolatum, with sorbitan sesquioleate as an emulsifier. It has been a robust method of detecting the majority of fragrance-allergic patients, but cannot detect allergy to individual fragrance chemicals. Thus, the data presented in this study reflect only the lack of an association between atopy and positive reactions to this mixture. It is possible that there may be an association between atopy and allergy to the individual fragrance chemicals, which we will address in a future study.

We have found that both AE and A/HF have been gradually and steadily increasing in patients undergoing patch testing in an urban population in the UK. The present study clearly shows no general association between atopy and fragrance allergy, in keeping with the findings of a recent comprehensive review (24). However, there is an association between AE and nickel allergy (5); differing associations between atopy and reactions to single perfume chemicals cannot be excluded.

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