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Allergen and Dust Exposure as Determinants of Work-Related Symptoms and Sensitization in a Cohort of Flour-Exposed Workers; a Case–control Analysis

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Objectives: To estimate the incidence of specific IgE sensitization and allergic respiratory symptoms among UK bakery and flour mill workers; and to examine the roles of flour aeroallergen and total dust exposures in determining these outcomes.

Methods: A cohort of 300 new employees, without previous occupational exposure to flour, were followed prospectively for a median (range) of 40 (1–91) months. Cases—defined as those developing work-related symptoms or a positive skin prick test to flour or α-amylase during follow up—were compared with controls, matched for duration of employment. Exposures to flour aeroallergen and total inhalable dust were estimated using a questionnaire and personal sampling techniques.

Results: Incidence rates for work-related eye/nose and chest symptoms were 11.8 and 4.1 cases per 100 person years (py), respectively. Fewer employees developed positive skin prick tests to flour (2.2 cases per 100 py) or α-amylase (2.5 cases per 100 py). Positive skin tests to occupational allergens were more common among those with new work-related symptoms. There were clear relationships between the risks of developing work-related symptoms or a positive skin prick test and three categories of estimated exposure to total dust or flour aeroallergen. Atopic employees were more likely to develop a positive skin prick test—but not work-related symptoms. These findings were unaffected by age, sex or cigarette smoking.

Conclusions: In this population, many work-related symptoms which develop after first employment in modern UK bakeries or flour mills were not accompanied by evidence of IgE sensitization to flour or α-amylase. Although average dust exposures were within current occupational standards, the risks of development of upper and lower respiratory symptoms and of specific sensitization were clearly related to total dust and/or flour aeroallergen exposure. The incidence of work-related chest symptoms in the presence of a positive skin test to flour or α-amylase in this setting was approximately 1 case per 100 py.

Keywords: sensitization; asthma; flour; α-amylase; bakers' asthma

INTRODUCTION

Occupational asthma among bakers and millers remains an important problem; reporting rates to the United Kingdom national surveillance scheme ('SWORD') suggest that this occupational group has a risk second only to coach painters and sprayers, with an estimated annual incidence of about 1.0 per 1000 (McDonald *et al*., 2000). Although most bakers' asthma reported by specialist physicians to SWORD is attributed to flour (Ross *et al*., 1997), the role of powdered baking additives, notably fungal α-amylase, has been increasingly recognized.

In 1990 we embarked upon a prospective study of employees in modern UK bakeries and flour mills

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Table 1. Exposure categories used in analysis

	Flour allergen ($\mu g\ m^{-3}$)		Inhalable dust ($mg\ m^{-3}$)	
	GM[a]	95% CI	GM[a]	95% CI
Low	65.0	57–74	0.58	0.5–0.7
Medium	144.0	124–167	1.17	1.0–1.4
High	296.1	257–340	4.37	3.8–5.1

[a]Geometric mean.

with the aim of establishing risk factors for the development of occupational asthma. We have previously reported the findings from the initial, cross-sectional survey of this cohort (Cullinan *et al*., 1994); among 264 employees without previous occupational exposure to flour there was a trend of increasing work-related symptoms and IgE sensitization across three categories of flour allergen or total dust exposure. Similar trends were found when a specific exposure–response analysis of α-amylase sensitization was undertaken (Nieuwenhuijsen *et al*., 1999). This paper describes a case–control analysis of the longitudinal phase of the same cohort.

METHODS

Subjects

We studied employees at three large bakeries, two flour mills and a flour packing station in the United Kingdom. In 1990 we identified a cohort of all workers who had been first employed at these sites after 1 January 1986 and who had worked for at least one month in a job with exposure to flour. At six-monthly intervals between 1990 and 1993 all cohort members still employed at the site were surveyed—a total of seven visits to each workplace.

In this analysis we have included only those employees who had never previously worked in baking or flour milling; a total of 300 workers who were followed for a median of 40 months (range 1–91 months). Sixty employees were surveyed only once; 47, 29, 36, 47, 29 and 52 were seen two to seven times, respectively; these figures represent approximately 80% of eligible employees at each time point.

Health information

At each survey visit, employees completed a questionnaire recording the presence and date of onset of the following symptoms: chest tightness, wheeze or difficulty in breathing ('chest symptoms'), itching of the eyes or nose, running or blockage of the nose or sneezing ('eye/nose symptoms'), and itchy skin rash ('skin symptoms'). Symptoms were considered to be work-related if they improved over a weekend or holiday or if employees reported them to be provoked by contact with flour. In this analysis we have included only those (incident) work-related symptoms which started after first employment at the study site. Information on smoking was also collected, and employees classified as smokers if they had smoked at least one cigarette daily for a year while employed at the site.

At every visit we carried out skin prick tests in a standard manner using positive and negative control solutions, three common inhalant allergens (Bencard 'B2 grass pollens', 'cat fur 3204' and '*Dermatophagoides pteronyssinus* 2801'), a prepared extract of five Canadian and British wheat flours (10 mg ml^{-1}—Flour Milling Bakers Research Association) and fungal α-amylase (10 mg ml^{-1}—Novo Nordisk). A positive test was one with a mean weal diameter at least 3 mm greater than that of the negative control (saline—Bencard '1908'). Employees were classified as atopic if they produced a positive response to at least one common allergen solution.

Workplace exposures

The details of our exposure assessments are published elsewhere (Nieuwenhuijsen *et al*., 1994). Briefly, at the initial survey we obtained a complete work history from each employee by questionnaire; changes were identified by a shorter questionnaire at each subsequent survey. Personal measurements of exposure to flour allergens and to inhalable dust were made in a representative sample of workers in each occupational group over a whole shift using personal air samplers.

For these analyses, we created three approximately equal-sized categories of exposure to flour aeroallergen and, separately, to inhalable dust (Table 1). We have previously described the variable correlation between inhalable dust and flour aeroallergen exposures in this population (Nieuwenhuijsen *et al*., 1995). Employees with average exposures in the lowest category included bread wrappers, confectioners (without direct contact with flour) and despatch and quality control staff. The middle category included bread and roll makers, cleaners and other confectioners. Those directly handling flour and mixing or braking doughs were included in the highest exposure category.

Analysis

Within the cohort defined above we carried out a case–control analysis. Cases were identified as those employees who developed work-related chest, eye/nose or skin symptoms—or a positive skin prick test to flour or α-amylase—after starting work at the site. Where a positive skin prick test was identified at an employee's first survey visit, the date of its onset was arbitrarily set at the midpoint of the interval between the date of first employment and the date of the survey visit.

Table 2. Characteristics of cases and controls

	Case type											
	Any symptoms		Chest symptoms		Eye/nose symptoms		Skin symptoms		+ Skin test: flour		+ Skin test: α-amylase	
	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
n	106	208	36	72	86	169	31	60	21	42	24	48
Age (median)	27	29	27	28	27	30	26	26	27	32	31	28
Male (%)	75	67	89	65	78	74	61	70	86	74	92	71
Atopic (%)	38	35	43	34	40	31	42	35	81	24	75	28
Smoke (%)	56	54	64	61	56	54	57	50	47	50	50	62
Exposure[a] category (%)												
Low	18	39	22	44	22	50	19	37	14	43	17	58
Medium	33	40	25	35	29	30	29	33	33	30	38	12
High	49	21	53	21	49	20	52	30	52	27	46	31

[a]Flour aeroallergen.

Two matched controls for each case were selected at random from those members of the cohort who:

1. during the period of the study did not develop work-related symptoms or a positive skin test to flour or α-amylase;
2. were working at the time the case was identified;
3. had been employed at the site for a similar duration (within six months).

Control subjects could be selected more than once. A case's exposure was defined by their job at the time of developing symptoms or at the date of onset of a new positive skin test; for the matched controls we used their exposure status at the time of identification of their control status. Odds ratios with 95% confidence intervals were estimated for each exposure category and outcome using conditional logistic regression (EGRET statistical software); included in the regression were age, sex, atopy and cigarette smoking as potential confounding exposures.

RESULTS

Incidence of work-related symptoms

One hundred and six symptomatic cases, with median ages ranging from 27 to 31 years, were identified (Table 2). Work-related eye/nose symptoms [$n = 86$: incidence 11.8 cases per 100 person years (py)] were more common than either chest ($n = 36$: 4.1 cases per 100 py) or skin ($n = 31$: 3.5 cases per 100 py) symptoms. Fifty-nine per cent of cases with eye or nose symptoms reported these in the absence of other symptoms; chest (31%) and skin (33%) symptoms were the sole complaint in fewer cases.

Cases were slightly more likely to be atopic than their matched controls but there were no important differences in smoking rates.

Incidence of positive skin prick tests to work-specific allergens

Twenty-one employees developed positive skin tests to flour (2.2 cases per 100 py) and 24 to α-amylase (2.5 cases per 100 py) allergens; nine had a positive response to both. Cases with new positive skin tests were more often atopic, but not smokers, than their matched controls (Table 2).

The accumulation of cases by time since first employment is displayed in Fig. 1. For each outcome, this was highest during the first 12 months of employment but approximately 50% of incident symptoms and positive skin tests to the work-related allergens developed after 24 months of employment.

Work-related symptoms and positive skin tests

Positive skin tests to flour or α-amylase were more frequent among those with symptoms than those without but the differences were small (Table 3). One quarter (nine employees) of those with chest symptoms also had a positive skin prick test to flour or α-amylase; this proportion was higher than among cases with other symptom types. For each symptom, cases more frequently had a positive test to α-amylase than to flour.

Exposure–response relationships

The odds ratios of developing each symptom type increased with higher intensities of exposure to flour, particularly for those employees in the highest exposure category (Table 4). Similar but steeper relationships were seen for the development of positive skin tests to each work-specific allergen. We did

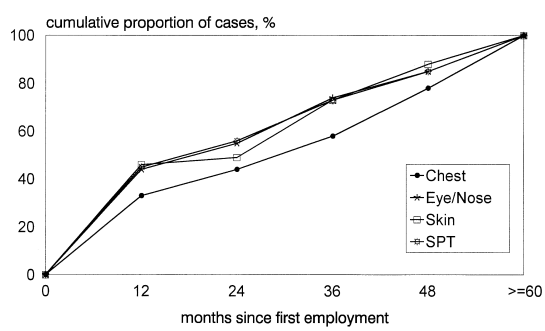

Fig. 1. Accumulation of cases by time since first employment (SPT = positive skin prick test to flour or α-amylase).

Table 3. Association between work-related symptoms and positive skin prick tests to specific allergens

			Positive SPT[a]		
		n	Flour or α-amylase (%)	Flour (%)	α-Amylase (%)
Chest symptoms	Yes	36	25	11	19
	No	264	10	6	6
Eye/nose symptoms	Yes	87	17	10	13
	No	213	10	6	6
Skin symptoms	Yes	33	18	9	15
	No	267	11	7	7
Any symptoms	Yes	109	15	9	11
	No	191	10	6	6

[a]Skin prick test.

Table 4. Mutually adjusted odds ratios and 95% confidence intervals derived from logistic regression analysis. Analysis using flour aeroallergen and total dust exposure categories are presented separately

Flour aeroallergen exposure	Case type											
	Any symptom		Chest symptoms		Eye/nose symptoms		Skin symptoms		+ Skin test: flour		+ Skin test: α-amylase	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Low	1		1		1		1		1		1	
Medium	1.8	0.9–3.6	2.1	0.6–8.2	3.1	1.4–7.2	1.6	0.5–5.3	5.0	0.4–58	16	1.0–265
High	6.1	2.8–13	7.7	1.8–33	9.6	3.7–25	3.5	1.0–12	21	1.2–363	20	0.3–1540
Atopy	0.8	0.4–1.4	1.0	0.4–2.9	1.0	0.5–1.8	1.9	0.6–5.8	–[a]		4.1	0.4–47
Smoking	0.9	0.5–1.6	2.1	0.7–6.1	0.7	0.4–1.4	1.4	0.5–4.0	0.5	0.1–3.5	0.1	0.0–2.1
Sex (♂)	1.6	0.9–3.0	3.2	0.8–12	0.7	0.3–1.5	0.4	0.1–1.5	3.7	0.3–47	0.5	0.0–15
Age	0.97	0.95–1.0	0.96	0.91–1.01	0.98	0.95–1.0	0.99	0.94–1.0	0.95	0.87–1.03	1.07	0.96–1.21
Total dust exposure	Any symptoms		Chest symptoms		Eye/nose symptoms		Skin symptoms		+ Skin test: flour		+ Skin test: α-amylase	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Low	1		1		1		1		1		1	
Medium	1	0.5–1.9	1.1	0.3–4.1	1.4	0.7–3.2	1.1	0.4–3.5	6.1	0.5–71.0	13	0.8–209
High	3.1	1.5–6.2	5.2	1.3–21	4.5	2.0–10.0	2	0.6–6.5	14.0	1–199	23	0.3–182
Atopy	0.8	0.5–1.4	1.1	0.4–3.2	1.1	0.6–2.0	1.7	0.6–5.0	–[a]		5.7	0.5–64
Smoking	1	0.6–1.8	1.9	0.7–5.4	0.9	0.5–1.6	1.4	0.5–3.9	0.5	0.1–3.0	0.1	0–2.4
Sex (♂)	1.6	0.9–2.9	2.8	0.8–10	0.8	0.4–1.8	0.5	0.2–1.6	3.3	0.3–35	0.5	0–13
Age	0.97	0.95–1.0	0.97	0.92–1.01	0.98	0.95–1.0	0.99	0.94–1.0	0.95	0.88–1.03	1.1	0.97–1.2

[a]Not calculable.

not find any consistent or statistically significant independent associations between atopy, cigarette smoking, age or sex and any of the symptom types. All those with a new positive skin test to flour in the low exposure group were atopic; atopy was also strongly—but not significantly—associated with the development of a positive test to α-amylase (OR 4.1). There was no evidence of a positive, independent effect of smoking on the development of a positive skin test.

An analysis using total inhalable dust (in place of flour aeroallergen) exposure produced very similar results. Odds ratios for each symptom type were significantly raised among workers in the highest exposure category.

DISCUSSION

In a cohort of new employees of large, modern bakeries and flour mills in the United Kingdom we observed a high annual incidence—approximately 12%—of work-related eye and nasal symptoms; and much lower rates of work-related chest and skin symptoms. Most of these were not, over the period of follow-up, accompanied by evidence of IgE-associated sensitization to two work-specific allergens; we observed nine cases with both work-related chest symptoms and a positive skin test to either flour or α-amylase allergens. The rates of development of each outcome were similar, about half developing two years or more after first occupational exposure in these settings. Employees with higher intensities of exposure to flour or inhalable dust were at increased risk of developing both work-related symptoms and positive skin tests independent of their age, sex or atopic state and of cigarette smoking.

We believe this to be the first prospective study of bakery and flour mill workers to employ direct measurements of exposure. No systematic process of pre-employment screening was undertaken at any of the sites. Within the cohort, we used a (nested) case–control analysis and generated odds ratios using conditional logistic regression. Mindful that the dates of onset of some outcomes might have been approximate, we selected our controls from among those who remained free of work-related symptoms or specific sensitization throughout the period of study, rather than from the population of employees free of such outcomes at the time of case identification. These approaches may have had the effect of overestimating the effects of exposure within each category and we suggest that the odds ratios are not considered as estimates of absolute risk. At each survey visit we failed to see approximately one fifth of the eligible cohort; if there was a process of selection by which those with (more severe) work-related symptoms were less likely to be surveyed before or after 1990 (Gordon *et al*., 1997), then this would have resulted in our incidence rates being artificially low. No information on specific sensitization among those employees who left employment at the sites between surveys is available. Perhaps a more serious limitation is the relatively short period of follow-up, an average of about 3.5 years. 'Bakers' asthma' is commonly believed to have an unusually long latency although it is worth noting that in a five-year longitudinal study of baking apprentices (albeit with a high loss to follow-up) approximately 80% of incident positive skin tests to flour occurred within three years of first occupational exposure (Herxheimer, 1973).

The apparent absence of sensitization to recognized allergens—and of an increased risk among atopic employees—suggests that a high proportion of the work-related symptoms did not have an allergic basis. This is consistent with the results of an initial, cross-sectional analysis of this population (Cullinan *et al*., 1994) and with the results of a similar study from the Netherlands (Houba, 1996), implying that many reported symptoms reflect an irritant or inflammatory response to airborne dust. In many, but not all, areas of these bakeries and flour mills there was a close correlation between levels of airborne dust and flour allergen (Nieuwenhuijsen *et al*., 1995). In this analysis the intensity of exposure to total dust in the highest category was, on average, 4.4 mg m^{-3} suggesting that work-related symptoms occur at dust concentrations below the current exposure limit of 10 mg m^{-3}.

A relatively small proportion of cases developed work-related symptoms in association with specific IgE antibodies to flour or α-amylase allergens, consistent with an allergic or hypersensitivity mechanism. None the less these represent annual incidence rates of approximately 1%. We are not aware of any comparable published studies from this or other countries but it is worth noting that the production processes in our study sites were highly mechanized with relatively low individual exposures to work-specific allergens. Specific IgE antibodies to fungal α-amylase were a little more frequent than to flour in our cohort; as in other countries (Quirce *et al*., 1992; Houba *et al*., 1996) sensitization to this additive may be a more important problem than traditional 'bakers' asthma' caused by allergy to flour proteins.

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