Work related symptoms, sensitisation, and estimated exposure in workers not previously exposed to flour

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Abstract

Findings are presented from the initial cross sectional phase of a cohort study of employees exposed to flour in bakeries or mills. Of 401 eligible workers in seven sites 344 (86%) were surveyed; symptoms assessed by self completed questionnaire, and sensitisation measured by the response to skin prick tests, were related to intensity of exposure both to total dust and to flour aeroallergen. Among 264 subjects without previous occupational exposure to flour, work related symptoms which started after first employment at the site were related to exposure intensity, especially when exposure was expressed in terms of flour aeroallergen. The relations with eye/nose and skin symptoms were independent of atopic status and cigarette smoking. Positive skin test responses to mixed flour and to α amylase were also more frequent with increasing exposure intensity, although this was confounded by atopic status. There was only a weak association between symptoms and specific sensitisation.

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To examine the relation between sensitisation or allergic symptoms and exposure to aeroallergens we have undertaken a longitudinal study of two groups of workers at high risk of occupational asthma: those exposed to flour and those working with laboratory animals. In this paper findings from the initial, cross sectional phase of a cohort study of bakery and flour mill workers are described.

There are about 75 000 workers in the United Kingdom baking industry (unpublished data, Labour Force Survey) with some 24 000 in occupations where exposure to flour is probable (Federation of Bakers, personal communication). A smaller but unknown number are involved in milling and wheat processing. Results from the surveillance of work related and occupational respiratory disease (SWORD) project suggest an annual incidence of occupational asthma among bakery workers of at least one per 1000,[1] a figure that includes only those cases seen by consultant chest or occupational physicians. A high prevalence of work related respiratory symptoms or sensitisation among employees of a large British bakery has been reported previously, with evidence of a semiquantitative relation with dust exposure.[2] Like most epidemiological studies of occupational asthma to date, this was cross sectional and subject to survivor bias. The current longitudinal study was planned to consider these deficiencies and to investigate the detailed nature of the exposure-response relation.

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Methods

Three large, modern, British bakeries, a flour packing factory, and three mills where wheat was milled and flour packed were identified. All full time employees in occupational groups where exposure to flour was probable, who had started work at the site from 1 January 1986 onwards and had worked for at least one month, were invited to participate. Members of the cohort still employed at the sites have been studied at six-monthly intervals since 1990.

This paper describes the findings from the initial survey. Workers at six sites were surveyed over a six month period in 1990, during which time each site was visited twice, on the second occasion to contact workers who had been missed earlier. The seventh site, a large flour mill, was similarly surveyed in 1991-2. Of 401 eligible men and women, 344 (86%) agreed to participate; there was no important difference in this proportion between sites. Questionnaires were completed by 322 subjects (80%) and skin prick tests by 335 (84%). All tests were completed by 304 subjects (76%).

QUESTIONNAIRE

The following symptoms, if present since 1986, were recorded with dates of onset: 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. Symptoms were considered to be work related if they were stated to improve over weekends or on holidays of a week or more or if they were reported by the subject as being provoked by contact with flour. Symptoms reported to have started after first employment at the site were considered as new.

Full smoking histories were obtained but for the present analysis subjects were divided into those who had ever and those who had not smoked at least one cigarette a day for as long as a year, at least part of which had been during their employment at the site.

SKIN TESTS

Skin prick tests were carried out in a standard manner and considered positive if the mean wheal diameter was at least 3 mm greater than that of an inert control ("1908" Bencard). Subjects were defined as atopic if they had one or more positive tests to three common allergens ("B2 grass pollens 4100" Bencard, "cat fur 3204" Bencard and "*Dermatophagoides pteronyssinus* 2801" Bencard). Tests were also made with a prepared extract (10 mg/ml) of five Canadian and English wheat flours provided by the Flour Milling Bakers Research Association, with fungal α amylase (10 mg/ml, Novo Nordsk), and with the mite *Lepidoglyphus destructor* (Allergon).

EXPOSURE ASSESSMENT

A complete work history with job titles and dates was obtained from each subject by questionnaire, including information on occupational exposure to flour before their present employment.

Exposure measurements were made in a sample of workers in each occupational group over whole shifts with personal air samplers. Samples were then assayed gravimetrically for total dust, and for flour allergen by use of a rabbit antibody based competitive inhibition assay.[3] Details of the sampling and environmental measurements are described fully in the companion paper.[4]

For the present analyses exposure groups were aggregated into three roughly equal sized categories of intensity according to current concentration of either total dust or of flour aeroallergen.[4] Occupations in the highest dust category were those in which flour was often handled and included flour dispensing, mixing, and packing; medium exposure intensity jobs were those with less frequent or indirect contact with flour (such as wheat milling and roll production); persons employed in wrapping and packing were in the lowest category. Eight subjects who could not be classified were excluded from the analyses. In general, dust measurements correlated well with flour aeroallergen concentrations[4] with groups almost all in the same exposure category whether based on total dust or aeroallergen.

ANALYSIS

As our purpose was to describe the incidence of new work related symptoms in relation to exposure, those with previous occupational exposure to flour were excluded. Comparisons of continuous, non-normally distributed data were made by the Wilcoxon rank sum test, and proportions analysed by χ^2 (or Fisher's exact) test. Trends across exposure categories were assessed by the χ^2 test for trend. The main measure of dust or aeroallergen exposure used was intensity category, either at the time of interview or at the time of onset of symptoms. The effects of exposure intensity independent of age, sex, atopic state, and smoking were examined by stepwise logistic regression.

SUBJECT CHARACTERISTICS

Of the 344 participants, 56 (16%) reported prior occupational exposure to wheat or flour; for a further 24 (7%) this information was not available. Table 1 shows some characteristics of the remaining 264 employees. Men (median age 29 years) were on average older than women (26 years) and were three times as likely to be atopic (43% *v* 14%), a difference present for all three common inhalant allergens. Women (57%) were smokers as often as men (56%); even after adjustment for sex atopic workers were less likely to be cigarette smokers (all subjects, 46% *v* 62%). The exposure groups, assessed by dust or aeroallergen, were similar in age, duration of employment, and proportion of smokers but showed some evidence of correlation with atopy. Classification by aeroallergen tended to move subjects into a higher exposure category, and slightly affected the distributions by sex.

The 56 workers known to have had previous occupational exposure to flour were more often men (82%) and tended to be older (median age 34 years) but had a similar average duration of employment at the site (median 26 months). A higher proportion (41%) were atopic and fewer were smokers (46%).

Results

SYMPTOMS AND SKIN PRICK TESTS

Forty six (14%) of all surveyed employees reported work related chest symptoms, 92 (29%) eye/nose symptoms, and 27 (9%) skin symptoms. Positive skin tests to mixed flour were recorded in 17 (5%) subjects and to α amylase in 18 (5%). Fifty eight (17%) had a positive test to *L destructor*.

Of those without previous occupational exposure to flour, 58 (22%) reported at least

Table 1 Characteristics of participants by exposure intensity category at time of survey

	Dust (mg/m³)				*Aeroallergen (μg/m³)*		
	Total	*Low*	*Medium*	*High*	*Low*	*Medium*	*High*
Exposure intensity*		<1	1–5	>5	⩽100·9	101–215·3	⩾227·6
No	264	104	90	62	90	83	83
Men	181 (69)	60 (58)	62 (69)	51 (82)	47 (52)	70 (84)	56 (67)
Age (y)†	28	28	27	27	27	27	28
Employed† (months)	26	26	22	29	25	22	28
Atopic	87 (34)	26 (25)	30 (35)	30 (49)	20 (23)	33 (42)	33 (40)
Smoking	148 (57)	54 (52)	54 (61)	36 (58)	47 (52)	47 (57)	50 (61)

*Geometric mean exposure intensity.
†Median.
Figures in parentheses are percentages of column totals.

Table 2 Frequency of work related symptoms and positive skin tests by exposure intensity category at time of survey

	Dust					*Aeroallergen*			
	Total	*Low*	*Medium*	*High*	*Trend (p)*	*Low*	*Medium*	*High*	*Trend (p)*
New work related symptoms:									
Chest	16 (6)	5 (5)	3 (3)	7 (11)	0·126	4 (4)	3 (4)	8 (10)	0·143
Eye/nose	45 (17)	11 (11)	13 (15)	19 (31)	0·001	10 (11)	11 (14)	22 (27)	0·007
Skin	17 (7)	2 (2)	9 (10)	6 (10)	0·029	1 (1)	5 (6)	11 (13)	0·001
Positive skin test:									
Mixed flour	10 (4)	2 (2)	5 (6)	3 (5)	0·282	1 (1)	4 (5)	5 (6)	0·099
a Amylase	12 (5)	2 (2)	6 (7)	4 (7)	0·138	1 (1)	5 (6)	6 (7)	0·059
L destructor	42 (16)	15 (15)	15 (18)	12 (20)	0·401	12 (14)	17 (22)	13 (16)	0·680
Mixed flour or *a* amylase	17 (7)	3 (3)	8 (9)	6 (10)	0·066	2 (2)	7 (9)	8 (10)	0·052
Any	56 (22)	17 (17)	21 (25)	18 (30)	0·050	13 (15)	22 (28)	21 (26)	0·087

*For denominators see table 1.
Figures in parentheses are percentages of totals at risk in each column.

one new work related symptom. Eye/nose symptoms were most commonly reported (table 2), and were isolated in 30 (67%). Five (31%) of those with chest symptoms and eight (47%) with skin symptoms reported these symptoms alone; five employees reported all three symptoms.

In two subjects, new work related chest symptoms had started within one month after first employment at the site. The median duration of employment before onset in the remainder was 365 (range 30-1534) days. Fifteen with new eye/nose symptoms and five with skin symptoms reported an onset within one month; in the rest, the duration of employment before onset tended to be shorter than for chest symptoms: 229 (30-1216) days and 274 (31-1736) days respectively. Among those with more than one symptom there was no consistent sequence in the dates of onset of each type.

Among the 56 employees with previous occupational exposure to flour the prevalence of new work related eye/nose symptoms was higher (20%), although there was little difference in the frequency of either chest (7%) or skin symptoms (6%). Positive skin prick tests to mixed flour and to α amylase were more common among those with previous exposure (11% for each allergen). Forty two (16%) of those without, and 10 (18%) of those with previous exposure had positive tests to *L destructor*.

EXPOSURE INTENSITY

The frequency of new work related symptoms tended to increase with intensity of exposure at the time of survey (table 2). The trend was clearest for eye/nose symptoms and was present for both dust and allergen exposure categories. Positive skin tests to mixed flour or to *a* amylase, but not *L destructor*, were more common with increasing aeroallergen exposure intensities. Positive responses to *L destructor* were more common with increasing dust intensity.

Workers with new work related chest (38%) or skin (41%) symptoms were more likely to have moved between exposure intensity categories during employment at the site than those without new work related symptoms of any sort (12%); to a lesser extent this was also true for employees reporting new eye/nose symptoms (18%). In most cases these moves were to jobs in a lower intensity category. A similar analysis to that shown in table 2, but based on exposure intensity at time of onset, resulted in only small differences in distributions and trends. The patterns were also unchanged when subjects reporting onset of symptoms within one month of exposure were excluded.

Most subjects with positive skin tests to specific antigens reported no symptoms; of those with symptoms these were described equally as work related or not work related. Table 3 shows the association between new work related symptoms and skin test results. None of those reporting chest symptoms had positive tests to mixed flour or to *a* amylase.

ATOPY AND SMOKING

All new work related symptoms were more common among smokers but there was little difference between atopic and non-atopic subjects (table 4). The patterns of increasing symptom frequency with increasing aeroallergen exposure were maintained when atopic and non-atopic, and smoking and non-smoking subjects were examined separately. Positive skin tests, especially to *L destructor*, were strongly associated with atopy at all levels of exposure but were unrelated to smoking (table 5). After stratification there was little evidence of consistent exposure-response relations for positive skin tests.

Regression analysis failed to show an independent effect of exposure intensity at time of onset on new work related chest symptoms. New eye/nose symptoms, however, were independently related to high intensity aeroallergen exposures (odds ratio (OR) 3·1, 95% confidence interval (95% CI) 1·3-7·4); similar

Table 3 Skin prick test results by presence of new work related symptoms

	Chest		*Eye/nose*		*Skin*	
	+	−	+	−	+	−
Mixed flour						
+	0 (0)	9 (4)	2 (4)	8 (4)	2 (12)	8 (3)
−	16 (100)	227 (96)	43 (96)	200 (96)	15 (88)	228 (97)
a Amylase:						
+	0 (0)	10 (4)	1 (2)	10 (5)	1 (6)	10 (4)
−	16 (100)	226 (96)	44 (98)	198 (95)	16 (94)	226 (96)
L destructor:						
+	5 (31)	37 (16)	9 (20)	33 (16)	3 (18)	39 (17)
−	11 (69)	199 (84)	36 (80)	175 (84)	14 (82)	197 (83)

Figures in brackets are percentages of totals at risk in each column.

Table 4 Frequency of new work related symptoms by intensity category of flour aeroallergen exposure at time on onset of symptoms: by atopy and by smoking

	Intensity of exposure to flour aeroallergen							
Symptoms	*Total*	*Low*	*Medium*	*High*	*Total*	*Low*	*Medium*	*High*
			Atopic				*Non-atopic*	
Chest	6 (7)	0 (0)	2 (6)	4 (13)	10 (6)	3 (4)	3 (7)	3 (6)
Eye/nose	16 (19)	0 (0)	8 (23)	8 (25)	29 (17)	9 (13)	6 (14)	13 (27)
Skin	8 (9)	1 (5)	3 (9)	4 (13)	9 (5)	1 (2)	2 (5)	6 (13)
			Smoking				*Non-smoking*	
Chest	12 (8)	2 (4)	5 (11)	4 (8)	4 (4)	1 (2)	0 (0)	3 (10)
Eye/nose	29 (20)	5 (11)	9 (19)	15 (31)	16 (14)	4 (10)	5 (14)	6 (19)
Skin	12 (8)	1 (2)	4 (9)	7 (14)	4 (4)	1 (2)	1 (3)	2 (6)

Figures in parentheses are percentages of totals at risk in each column.

Table 5 Frequency of positive skin tests to specific antigens by intensity category of flour aeroallergen exposure at time of survey: by atopy and by smoking

	Intensity of exposure to flour aeroallergen							
Antigen	*Total*	*Low*	*Medium*	*High*	*Total*	*Low*	*Medium*	*High*
			Atopic				*Non-atopic*	
Mixed flour	8 (9)	1 (5)	4 (12)	3 (9)	2 (1)	0 (0)	0 (0)	2 (4)
α Amylase	8 (9)	1 (5)	4 (12)	3 (9)	4 (2)	0 (0)	1 (2)	3 (6)
L destructor	35 (40)	9 (45)	14 (42)	12 (36)	7 (4)	3 (4)	3 (7)	1 (2)
Mixed flour or α amylase	12 (14)	2 (10)	6 (18)	4 (12)	5 (3)	0 (0)	1 (2)	4 (8)
Any	44 (51)	10 (50)	18 (55)	16 (49)	12 (7)	3 (4)	4 (9)	5 (10)
			Smoking				*Non-smoking*	
Mixed flour	4 (3)	0 (0)	1 (2)	3 (6)	6 (5)	1 (2)	3 (9)	2 (6)
α Amylase	6 (4)	0 (0)	3 (7)	3 (6)	6 (5)	1 (2)	2 (6)	3 (9)
L destructor	22 (15)	7 (15)	10 (22)	5 (10)	20 (18)	5 (12)	7 (22)	8 (25)
Mixed flour or α amylase	8 (6)	0 (0)	3 (7)	5 (10)	9 (8)	2 (5)	4 (13)	3 (9)
Any	29 (20)	7 (15)	12 (27)	10 (20)	27 (25)	6 (14)	10 (31)	11 (34)

Figures in parentheses are percentages of totals at risk in each column.

values were found with dust measures. For skin symptoms the relation was confined to aeroallergen exposure at high intensity (OR 5·6, 95% CI 1·2-26·9). No independent effect of exposure intensity on the presence of a positive skin test to any of the three specific allergens was found. Atopy was significantly and independently associated with a positive response to each of the three specific allergens, but not with any new work related symptom. Smoking was not independently related to either symptoms or to a positive skin test.

Discussion

Unlike most cross sectional populations the present analysis was based on workers first employed after a specified date. The study is also unusual in the detailed nature of the dust and aeroallergen exposure measurements, although so far used only semiquantitatively. Workers with previous occupational exposure to flour, about which there can be less confidence, were excluded from this analysis and emphasis was placed on new cases of work related disease as the best measure of incident disease. None the less, the results presented here should be interpreted in the light of possible survivor bias. Movements between jobs of different exposure intensities were taken into account by examining symptoms in relation to exposures both at the time of onset and at the time of survey.

The relation between the frequency of work related symptoms and positive skin tests to flour or fungal α amylase was weak. There are possible explanations for this. Firstly, the symptoms described are unlikely to be wholly specific for IgE associated allergic disease and may also result from direct irritation, although if this was so then an equal relation with aeroallergen and dust exposure could be expected. It is also possible that the exposure-response relations found were due in part to a greater tendency for workers in high exposure jobs to ascribe non-specific symptoms to their work. This question will be examined at a later stage with information from serial peak flow measurements and from tests of non-specific bronchial hyper-responsiveness. Secondly, there are probably several agents responsible for work related symptoms in workers exposed to flour, including, among others, flour derived allergens,[5] fungal[6] and cereal[7] α amylase, and soybean allergens.[8] Employees with new work related chest symptoms in this study, none of whom had positive skin tests to flour or α amylase, may have been sensitised to an unidentified allergen. The lack of any relation between the presence of a positive skin test to *L destructor* and current exposure to flour aeroallergen, by contrast with that with dust exposure, supports the view that storage mites have little special significance in allergic responses among bakery workers.[9]

Although new work related symptoms were

more common in atopic workers and in those who smoked during the period of exposure, these relations were not statistically independent of intensity of exposure. This may reflect the small numbers of persons affected or the cross sectional nature of the analysis but underlines the need to separate the effects of potential modifying influences from the effects of exposure. On the other hand, after adjustment for the strong relation with atopy, no independent effect of exposure intensity on specific sensitisation (as measured by skin prick testing) was found. Antigenic cross reactivity (with grass pollen) may explain some of the association between a positive skin response to mixed flour and atopic state, but is unlikely to account for the relation with either α amylase or *L destructor*.[10]

These findings may be compared with those from a study of identical design that we have undertaken in employees exposed to laboratory animals.[11] In both groups, symptoms were shown to be associated with intensity of exposure, but by contrast with the laboratory workers, current exposure for the flour exposed group was as important as exposure at the time of onset of symptoms; also, the exposure-response relation was similar for dust and aeroallergen measures of exposure, and was unmodified by atopic state or by smoking. These features suggest that whereas the symptoms among laboratory workers reflect an allergic response to airborne antigens, many of those described by the flour workers have a predominantly non-allergic basis.

Despite shorter average durations of employment, the frequencies of symptoms among all employees in this study were at least as great as those seen in our earlier survey of British bakery workers.[2] In that study, where similar questionnaires were used, 13% of current employees reported work related chest symptoms (compared with 14% in the current study) and 19% nasal symptoms (compared with 29% reporting eye or nasal symptoms in the current study). In the earlier study work related chest or nasal symptoms (among all workers) were also related to exposure intensity. The current analyses have allowed examination of the relation of incident disease to measured exposures; this relation was slightly stronger when exposures at the time of symptom development were examined and, for both new work related symptoms and for positive skin responses to specific allergens, when exposures were analysed in terms of flour aeroallergen rather than total dust. The detailed nature of the relation between exposure expressed in terms of average and peak intensity, duration and timing, and varied types of response will be examined in the longitudinal phase of this cohort study.

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