Determinants of asthma phenotypes in supermarket bakery workers

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Word count: 4549

ABSTRACT

Background: While baker's asthma has been well described, various asthma phenotypes in bakery workers have yet to be characterized. This study aims to describe the asthma phenotypes in supermarket bakery workers in relation to host risk factors and self-reported exposure to flour dust.

Methods: A cross-sectional study of 517 supermarket bakery workers in 31 bakeries used a questionnaire, skin prick tests, specific IgE to wheat, rye and alpha-amylase and methacholine challenge testing.

Results: The prevalence of probable occupational asthma (OA, 13%) was higher than atopic (AA, 6%), non-atopic (NAA, 6%) and work-aggravated asthma (WAA, 3%) phenotypes. Previous episodes of high exposure to dusts, fumes and vapours causing asthma symptoms were more strongly associated with WAA (OR=5.8, CI: 1.7 – 19.2) than OA (OR=2.8, CI: 1.4 – 5.5). Work-related ocular-nasal symptoms were significantly associated with WAA (OR=4.3, CI: 1.3 – 13.8) and OA (OR=3.1, CI: 1.8 – 5.5). Bakers with OA had an increased odds of reporting adverse reactions to ingested grain products (OR=6.4, CI: 2.0 – 19.8).

Conclusion: Occupational asthma is the most common phenotype among supermarket bakery workers. Analysis of risk factors contributes to defining clinical phenotypes, which will guide ongoing medical surveillance and clinical management of bakery workers.

Word count: 195

Key words: asthma phenotypes, bakery workers, determinants, risk factors, work-related asthma

It is well documented that exposure to flour dust increases the risk of respiratory diseases, particularly occupational asthma. Studies conducted among bakery workers have reported the prevalence of baker's asthma to be between 5-17%[1]. Asthma is commonly due to sensitization to wheat, rye and fungal alpha-amylase allergens present in flour.

Asthma is generally not considered a single disease but rather a syndrome comprising a common set of symptoms. Different phenotypes of asthma are distinguished by variations in clinical features, trigger factors and differences in immunological and pathophysiological characteristics [2]. Age of onset, high numbers of eosinophils in the airways, atopic status, family history of asthma, early exposure to allergens and exposure to inhalation accidents (exposure to high levels of vapors, gas, dust or fumes) are important predictors of adult asthma phenotypes [2,3]. While baker's asthma has been well described in various workplaces, phenotypes of asthma among bakery workers in a common workplace setting have yet to be characterized.

An evaluation of employment patterns in the baking industry worldwide over the past decade has demonstrated a significant rise in franchise (in-store) bakeries [4]. In South Africa in-franchise employment has risen from 20% of all employment in the baking industry in 1995 to 44% in 2002 [5]. This shift has increased the potential for workers to develop baker's allergy and asthma.

The aim of this paper is to describe various asthma phenotypes observed in supermarket bakery workers of a large chain store in relation to host risk factors and self-reported exposures to flour dust.

This study is part of a larger prospective intervention study aimed at reducing sensitization to flour dust allergens in supermarket bakers. A detailed baseline environmental exposure assessment study was also conducted and is the subject of a separate communication.

MATERIALS AND METHODS

Study design, population and sampling

A cross-sectional study was conducted on 517 workers currently employed in all 31 bakeries belonging to a supermarket chain store in the Western Cape province of South Africa during the period June 2003 to June 2004. All permanent (n=318) and casual workers (n=168) in the bakery and ex-bakers with asthma moved from bakery section two years prior to the study (n=31) were investigated. The protocol was approved by the University of Cape Town and the University of Michigan (IRB) prior to the study being conducted.

Questionnaire

Each worker completed the standard European Community Respiratory Health Survey questionnaire [6] designed for the investigation of asthma. Additional questions relating to current and previous employment and degrees of exposure to flour dust and tobacco smoke were included. Smoking status was classified into three categories viz. never-smoker (lifelong abstinence); ex-smoker (defined as having quit completely

more than one month prior to the survey); and current smoker. Self-reported high exposures were ascertained based on a positive response to the question: **"**Has there ever been an instance when you inhaled a large amount of vapour, gas, dust or fumes in any of these jobs that resulted in you developing a tight chest, wheeze or cough?". Also included were questions on domestic flour dust exposures, and in particular the practice and frequency of baking activities in the home. For purposes of this study ocular-nasal symptoms were defined as a positive response to the question: "Have you ever had any nose or eye problems or allergies such as hay fever?" Upper and lower airway symptoms were considered to be work-related if they were reported to worsen during the work shift and improve when away from work. Ingestion-related adverse reactions were assessed based on responses to the question: "Have you changed your diet or avoided certain grain products (e.g. wheat/rye/soya) because they do not agree with you when you eat them?"

Immunological tests

Skin prick tests (SPT)

Skin prick tests (SPT) were performed using the following standard common local aeroallergens (ALK-Abelló, A/S, Horsholm, Denmark): House dust mite (*D. pteronyssinus*), bermuda grass (*C. dactylon*), rye grass (*L. perenne*), grass mix (*Pollen III - Avena, Hordeum, Triticum, Secale),* cockroach (*B. germanica*), cat (*F. domesticus*), dog (*C. familiaris*), mould mix (*Cladosporium herbarum, Alternaria alternata, Fusarium*) and Aspergillus (*Aspergillus fumigatus*). Commercially available skin prick tests of flours (wheat, rye, oat grain, and barley grain) (Bencard), soya and corn flour (Leti Alergia), peanut and storage mite (*L. destructor*) and fungal

alpha-amylase (ALK-Abelló, A/S, Horsholm, Denmark) were also used. For the analysis of correlations between various allergens, SPT reactivity was expressed as the allergen histamine wheal ratio, i.e. the mean wheal diameter at the allergen site divided by the mean wheal diameter at the histamine site [7] A positive SPT was regarded as a wheal read 15 minutes after testing that had a diameter (mean of two perpendicular measures) of ≥ 3 mm more than the negative control. Areas of wheal were traced on clear tape and stored for later measurement. For purposes of this study atopy was considered to be present if the SPT to *one or more common* aeroallergens was positive.

Serum specific IgE

Serum specific IgE levels were measured on 513 workers. The presence of atopy in workers who did not undergo SPT (n=10) was defined by a positive Phadiatop® test (ImmunoCAP 100 System, Phadia, Uppsala, Sweden). Quantification of specific IgE antibodies to wheat (f4), rye (f5) and fungal alpha-amylase (k87) was performed using CAP-FEIA (fluorescence enzyme immuno assay) according to the manufacturer's instructions (Phadia). An ImmunoCAP result of >0.35 kU/L was regarded as positive.

Spirometry

Spirometry was performed using the Jaeger Aerosol Provocation System (APS) Pro apparatus according to American Thoracic Society (ATS) guidelines [8]. Workers were required to refrain from smoking for one hour, from using short-acting beta-2-agonist bronchodilators for 4 hours, and from using oral asthma medications for 8 hours prior to lung function testing. None were on long-acting bronchodilators. Pulmonary function reference values of the European

Community for Coal and Steel (ECCS) with lower limits corresponding to the 95th percentile were used where appropriate, and locally derived reference equation for South African university workers [9,10].

Methacholine challenge testing ($PD_{20}M$)

Methacholine challenge testing was performed on all workers by trained technologists according to an abbreviated protocol used in epidemiological surveys. The Medic Aid Pro Nebulizer dosimeter method involved a protocol of increasing numbers of breaths to achieve pre-defined cumulative doses of methacholine [11]. The doses were delivered by the Jaeger APS MedicAid Side Stream APS-Nebulizer according to the manufacturer's instructions, commencing with the lowest dose of 0.026 mg. The dose was increased to a maximum dose of 2.048 mg methacholine if a positive endpoint (fall in FEV_1 of 20% or more) was not obtained. The results of the methacholine challenge test were interpreted as follows: borderline defined as 0.4mg < $PD_{20}M$ <1.0 mg; mild = 0.08 mg > $PD_{20}M$ <0.4mg; moderate/severe = $PD_{20}M$< 0.08mg. Borderline values for $PD_{20}M$ were considered negative in the definition of NSBH. These cut-offs for the APS system were based on the results from a validation study performed on 40 hyper-responsive bakery workers. This study confirmed a satisfactory correlation between the APS cumulative $PD_{20}M$ method and the standard VMAX (Sensormedics) method [11].

In subjects in whom $PD_{20}M$ was contraindicated, such as those with acute asthma symptoms or a baseline FEV_1 <1.5L or FEV_1 < 70% predicted, a bronchodilator (400

μg salbutamol dose) was administered instead. A change in FEV_1 of ≥12 % ten minutes after administration of bronchodilator was considered suggestive of NSBH.

Among the 503 subjects who underwent normal spirometry, 422 performed interpretable $PD_{20}M$ results. Two subjects were unable to produce reproducible forced expiratory manoeuvers, 38 subjects underwent bronchodilator challenge (PBD) since $PD_{20}M$ was contraindicated, and 43 subjects had ≥10% decrease in FEV_1 after administration of saline diluent, and were therefore not considered for $PD_{20}M$. The $PD_{20}M$ was discontinued in 3 subjects; one requested the test to be stopped, and in two subjects because of technical problems.

Operational definitions of asthma phenotypes

1. *Atopic asthma*: Defined as either having an asthma attack *or* use of asthma medication in the past 12 months *or* presence of NSBH; *and* presence of atopy; *and* absence of sensitization to bakery dust allergens [3]
2. *Non atopic asthma*: Defined as either having an asthma attack *or* use of asthma medication in the past 12 months *or* presence of NSBH; *and* non-atopic; *and* absence of sensitization to bakery dust allergens
3. *Work-aggravated asthma*: Defined as either having an asthma attack *or* use of asthma medication in the past 12 months *or* presence of NSBH; *and* work-related chest symptoms, *and* absence of sensitization to bakery dust allergens
4. *Probable Occupational asthma*: Defined as either having an asthma attack *or* use of asthma medication in the past 12 months *or* presence of NSBH; *and* sensitization to bakery dust allergens [12]

Sensitisation to *bakery dust allergens* was defined as a positive SPT to any cereal allergen (wheat, rye, oats, barley, soya, corn) or elevated serum IgE to wheat, rye or alpha-amylase.

Statistical analysis

Statistical analysis was performed using STATA version 8 (StataCorp). Both continuous and categorical analyses were conducted. Key associations of interest were the relationships between host factor attributes (e.g. age, gender, smoking, past medical history, ingestion related reactions to grain products, adult-onset asthma), and self-reported occupational exposures with asthma phenotypes. Multivariate logistic regression models adjusted for age, gender and smoking was used to determine the relationship between individual asthma phenotypes and predictor variables.

RESULTS

Study population

A total of 517 workers, from all 31 stores participated in this study. The demographic characteristics of the study population are outlined in Table 1. Almost half the participants (47%) were current smokers, with an average of 5 pack-year smoking history. Of the currently employed workers 41% were bakers or assistant bakers, 27% counterhands and 10% confectioners. Among the workers with self-reported adverse reactions to grain products, a larger proportion (63%) attributed this to rye products.

Immunological characteristics

The prevalence of sensitization to common inhalants were as follows, house dust mite (*D. pteronyssinus)*: 33%, rye grass (*L. perenne)*: 20%, grass mix (*Pollen III)*: 18%, cockroach (*B. germanica)*: 11%, bermuda grass (*C. dactylon)*: 10%, dog (*C. familiaris)*: 8%, mould mix (*Cladosporium, A. alternate, Fusarium)*: 7%, cat (*F. domesticus)*: 4%, aspergillus (*A. fumigatus)*: 3%. The overall prevalence of atopy, defined as a positive SPT to one or more common aeroallergens, was 42%, while 12% were positive to more than three aeroallergens. The prevalence of sensitization to any of the bakery dust allergens was 33% (Table 2). The most common sensitizers on SPT were cereal flours wheat (16%) and rye (16%). However, higher proportions of workers (26% and 24% to wheat and rye flours respectively) had elevated IgE levels to flours but the prevalence of elevated IgE to alpha-amylase remained low (4%). A high degree of correlation was found for subjects sensitized between the various cereal flours, especially for wheat, rye, barley and corn flour (Spearmans r=0.67-0.75, $p<0.001$). Comparison of wheat SPT versus wheat IgE as well as rye SPT versus rye IgE, showed a high degree of correlation (Spearmans r =0.71 – 0.73, $p<0.0001$) between these two indices of allergic sensitization with the kappa statistic demonstrating moderate to substantial agreement (kappa = 0.55 – 0.64) between the tests. Workers sensitized to more than three aeroallergens were more likely to be sensitized to occupational allergens (OR=9.5, CI: 4.9 – 18.2).

Respiratory symptoms

The prevalence of work-related ocular nasal symptoms (31%) was higher than work-related chest symptoms (17%) (Table 3). Over half the workers with doctor diagnosed asthma (13%) reported adult onset asthma; and 38% of these reported current ocular-nasal symptoms. Thirty (6%) workers reported job changes prompted by work-related chest symptoms. Of these, 14 had worked as bakers/assistant bakers, 10 as counterhands, 4 as confectioners and 2 as supervisor/controllers *prior to being relocated*. A significantly higher proportion of women had shortness of breath (10%), current asthma treatment or attacks (9%) but a lower proportion (8%) reported symptoms associated with episodes of high exposure to flour dust. An evaluation of the sensitivity and specificity of the questionnaire to predict asthma and more specifically occupational asthma revealed that work-related chest symptoms were highly specific (89%) for both outcomes, but not very sensitive (31% – 43%) in accurately predicting the presence of non-specific bronchial hyperresponsiveness and occupational asthma respectively.

Pulmonary function and non-specific bronchial hyperresponsiveness

The results of pulmonary function and non-specific bronchial challenge tests are presented in Table 4. Using ECCS reference values, 17% of workers had a $FEV_1$of less than 80% of predicted values, while only 7% had evidence of airflow obstruction defined as a pre-bronchodilator FEV_1/FVC ratio of less than 0.70. Using an alternative set of reference values (Mokoetle et al), the prevalence of FEV_1 less than 80% predicted was 9%.A total of 22% of workers had evidence of bronchial hyper-responsiveness (19% positive on MCT ($PD_{20}M$ <0.4mg)), and 3% positive on the

basis of an increase in FEV_1 of ≥12% after bronchodilator), with a further 10% having 'borderline' results ($PD_{20}M \geq 0.4$mg and <1.0 mg).

Correlation between lung function and wheat and rye-specific IgE

There was a significant negative correlation between $PD_{20}M$ and IgE levels to wheat (Spearman r = - 0.30, p<0.001) and rye (Spearman r = - 0.28, p<0.001) flour. Stratifying the IgE data by atopic status, revealed similar inverse relationships between $PD_{20}M$ and IgE among atopics (Spearman r = - 0.26, p<0.001) and non-atopics (Spearman r= - 0.21, p<0.001) for wheat and rye. The degree of airway obstruction on baseline spirometry (FEV_1/FVC) was also inversely correlated with wheat IgE (Spearman r = - 0.15, p=0.001). However no correlation was observed between FEV_1 and wheat specific IgE (Spearman r = - 0.07, p=0.090). Similar patterns of association were observed for rye flour (data not shown).

Asthma phenotypes in relation to risk factors

Among the asthma phenotypes described, the prevalence of probable occupational asthma – OA (13%) was much higher than atopic asthma – AA (6%), non-atopic - NAA (6%) and work-aggravated asthma - WAA phenotypes (3%) (Table 5). A large proportion 55 / 60 (92%) of workers with OA had NSBH, whilst only 55 (12%) workers showed evidence of occupational rhinitis without asthma. In the multivariate logistic regression analysis, having recurrent chest infections as a child (OR=5.5) was significantly associated with WAA. Elevated odds ratios were demonstrated for the associations between atopy and OA, particularly in individuals with polysensitization to common aeroallergens. Previous episodes of high exposure that caused asthma symptoms were associated more strongly with WAA (OR=5.8) than probable occupational asthma (OR=2.8). Those with OA were significantly more likely to be supervisors or managers (OR=4.0) at the time of the study. There was a 6-fold increased odds (OR = 6.4) of self-reported ingestion-related adverse reactions to grain products in OA, and more so in the non-atopic subgroup. No association was found with baking at home and any of the asthma phenotypes. Using alternative definitions for probable occupational asthma, which included subjective work-related symptoms

in this definition decreased the prevalence to 7%. However, the significant association with predictors of this phenotype persisted and demonstrated higher odds ratios for ocular-nasal symptoms (OR = 13.0); previous episodes of high exposure causing asthma symptoms (OR=5.0); as well as self-reported ingestion-related adverse reactions to grain products (OR = 13.3).

DISCUSSION

This study of supermarket bakeries provides useful insights on the relative prevalence of and risk factors for different phenotypes of asthma among workers in this emerging and relatively poorly regulated industry. Asthma phenotypes were defined on the basis of clinical asthma, airway hyperresponsiveness, atopic status and sensitization to occupational allergens. This study has demonstrated that the prevalence of probable occupational asthma - OA (13%) in the industry is considerably higher than that of both atopic – AA (6%) and non-atopic asthma - NAA (6%) and the work-aggravated asthma phenotype - WAA (3%). Furthermore, the overall prevalence of AA in this cohort is at the lower end of the spectrum of adult asthma reported in developed countries (8-12%), but higher than the national average reported for South Africa (4%) [13,14]. The higher prevalence of asthma observed in this group may be attributed to these bakeries being located in a highly urbanized province (Western Cape), which has a higher population prevalence (8%) of adult asthma [15]. This study also demonstrated that 50% of the adult asthma phenotype is atopic as has been reported in previous studies [16].

The prevalence of probable occupational asthma (13%) in this study is at the upper end of the range of prevalence data (5-13%) reported by studies in industrial bakeries in which a similar definition of occupational asthma (bronchial hyper-responsiveness and sensitivity to flour) was used [17,18]. However, the prevalence was much higher

than that reported among British supermarket bakery workers (4%) even after using an alternative definition that included work-related asthma symptoms (7%) [4]. The potential underestimation that could arise due the healthy worker effect was partially minimised in this current study by the inclusion of ex-bakers in this study population. It should be noted that the inability to characterize the acute onset irritant-induced asthma phenotype in this study can be attributed to its low incidence in this setting as the production process in these bakeries mainly entail exposure to high molecular weight respiratory sensitizers in flour dust, although exposure to cleaning agents cannot be totally excluded [3].

In this study a high proportion (22%) of bakery workers demonstrated non-specific bronchial hyperresponsiveness (NSBH). Females, had a significantly higher prevalence than males (25% versus 18%), which is consistent with previous studies in which women comprised the major proportion of study subjects [19]. Given that a greater proportion (62-94%) of men were employed in the higher exposed jobs (baker, confectioner, manager) and women (98%) in the lower exposed jobs (counterhands), it is unlikely that the discrepancies observed are due to different job hiring practices for males and females. This gendered distribution of work does not totally explain the different patterns of NSBH observed in this study, suggesting other biological factors may play a role in the patterns observed [20].

It is well recognized that the most common flour dust allergens responsible for sensitization in the OA phenotype among bakers are cereal flours and synthetic enzymes [1]. This sensitization pattern has also been observed in the current study in which sensitization to wheat, rye and other related cereal flours on skin prick testing

was high (16%), but less so for fungal enzyme alpha-amylase (4%). Preliminary data from the detailed exposure assessment study conducted confirmed that bakers had the highest average (geometric mean) wheat allergen concentration (16.504 ug/m^3), followed by confectioners (7.307 ug/m^3), whilst counterhands the lowest exposures (0.84 μg/m^3). However, alpha-amylase concentrations for most job titles were below the limit of detection (1.083 ng/m^3). While sensitization to cereal flours were highly correlated (r=0.67-0.75), a very high degree of correlation (r = 0.92) was observed between wheat and rye. Interestingly, a large proportion (33 %) of workers reported work-related asthma symptoms specifically to rye flour despite this flour constituting a small proportion (<10%) of products handled in these bakeries. It has been suggested that cross-reactivity between grain cereal allergens could be a possible mechanism for these observations [21]. Cross-reactivity between rye flour allergens and rye grass allergens remains another possibility, although this is unlikely since a very low correlation was observed between sensitisation to these allergens (r = 0.37). While the response to rye may be immunologically mediated, the physical properties of rye flour may also produce an additional irritative effect as demonstrated by its ability to produce a greater bronchial response compared to wheat [22].

In this study a modest inverse correlation was demonstrated between $PD_{20}M$ and specific IgE levels to wheat and rye flour (Spearman r = - 0.30; - 0.28) which, as far as we can establish, has not been previously reported. However, there have been a few epidemiological studies among bakers that have reported an association between other markers of exposure (flour dust) and the degree of non-specific bronchial hyperresponsiveness following non specific challenge tests using methacholine. Prichard et al reported 41% of bakers versus 21% of controls (slicers/wrappers) had a

positive methacholine challenge test (PD_{20} <30 μmol producing a 20% fall in FEV_1) [23]. Similarly, Musk et al showed the proportion of bakers with a positive methacholine challenge test in less exposed bakers increased from 26% to 42% in the more exposed group [24]. Bohadana et al reported a significant dose-response relationship with the duration of exposure to flour dust, while Choudat et al demonstrated that flour dust exposure and smoking increase bronchial responsiveness as measured by the slope of the dose response curve to methacholine [25,26].

Atopy was identified as an important contributor to non work-related asthma (WRA) in this population in that half these subjects were atopic. This is corroborated by the very high prevalence (54%) of self-reported family history of atopy in the overall study population. Subjects with polysensitization to common aeroallergens also had a six-fold higher odds of presenting with atopic asthma (AA). Among the WRA phenotypes, atopy was significantly associated (OR=4.1) with probable occupational asthma (OA) but not work-aggravated asthma (WAA). This association between atopy and occupational asthma due to high molecular weight sensitizers such as bakery allergens has been well documented in the literature [27]. Polysensitized workers were also more likely to be sensitised to occupational allergens (OR=9.5) and present with OA (OR=5.5). This is consistent with the findings of studies among subjects with non-WRA in adults as well as children in which only a small proportion of mono-sensitized individuals become symptomatic, when compared to the majority of symptomatic individuals that are polysensitized to common inhalant allergens [28].

In this study of bakery workers self-reported history of recurrent chest infections in childhood was a significant predictor (OR=5.5) only of the WAA phenotype. The

association between childhood infections and asthma has been previously demonstrated by Arshad et al, in their study of children of 10 years of age with wheeze and asthma [29]. A more recent study by Tennant et al among adults has also demonstrated that frequent lower respiratory tract infections in childhood is a significant contributory factor in predicting FEV_1 decrements in adulthood [30]. Our findings therefore suggest that a history of recurrent infections in childhood could be used as an indicator in identifying workers requiring more intensive surveillance, and might be at increased risk of developing WAA. The possibility of recall bias in our study cannot however be excluded.

Upper airway symptoms and more specifically, work-related ocular-nasal symptoms were also significant predictors of AA and OA phenotypes in this study. Previous studies have shown that overall 11.5% of subjects with occupational rhinitis develop OA, and specifically 11.6% of those exposed to flours, grains and fodders [31]. Co-morbid rhinitis or rhino-conjunctivitis has been reported in a greater proportion (45-90%) of subjects suffering from IgE-associated OA and has been attributable to various sensitizers including flour dust [27]. Interestingly, work-related ocular-nasal symptoms also appear to be an important risk factor for WAA in this study, which, as far as we can establish, has not been previously reported. The cross-sectional nature of our study does not permit conclusions about the temporal relationship of ocular-nasal symptoms and the development of asthma. Overall, these findings are however consistent with other reported studies in the literature that rhinitis is a significant risk factor for adult-onset asthma, in both work-related and non-work-related disease outcomes and that the appearance of ocular-nasal symptoms could be used to identify workers at greater risk of developing occupational asthma [31,32,33].

Self-reported work exposures, particularly episodes of high exposures, can be a useful marker in predicting recent onset adult asthma. In this study, past history of episodes of high exposure to dusts, fumes and vapors causing asthma symptoms was a significant predictor for WAA and OA phenotypes among bakery workers. Interestingly, a stronger association was observed in workers with WAA (OR=5.8) than those with OA (OR=2.8). This finding is consistent with results from Finland in which 21% of respondents reported work-aggravated symptoms on a weekly basis in the past month in response to a number of factors including airborne dusts, gases or fumes [34]. A recently published ECRHS study also demonstrated an increased asthma risk (OR=3.3) among subjects following acute symptomatic inhalation accidents [3]. These findings suggest that high exposures to sensitizers can contribute substantially to new-onset asthma and workers with inhalation accidents should therefore be monitored closely over a longer period of time to identify this entity at an early stage. However, it needs to be borne in mind that the definition used in this study as outlined in the ECRHS protocol has its limitations as it does not specifically differentiate between flour dust and irritants.

In this study current job status was a significant predictor of OA in that workers with OA were more likely to be supervisors/managers (OR= 4.0). Although elevated odds ratios were obtained for bakers (OR=1.6), this association was not significant. This is highly indicative of selection effects as our pilot environmental exposure studies have shown that bakers have much higher exposures to inhalable dust than supervisors/managers. Since the response rate of individual bakeries in our study was high (90% -100%), it is unlikely that non-response bias may have affected the results.

The “healthy worker effect” is a more likely explanation, in that we have noted that bakers with occupational asthma are more likely to be transferred from their high exposure jobs to less exposed jobs (supervisors/managers) rather than the least exposed jobs (counterhands). This is due to the company policy on placement of workers that ensures these bakers, often having the longest service are retained in the bakery work environment due to their experience, which is then utilised in supervisory and managerial duties.

One of the intriguing findings of this study was the strong association (OR=6.4) between self-reported ingestion-related adverse reactions to grain products and OA phenotype, which was particularly pronounced amongst non-atopics. The evidence for an association between wheat-related food allergy and baker’s asthma is inconclusive. Some studies suggest that inhalant wheat allergy is caused by water-soluble proteins (albumins and globulins) whereas ingestion-related wheat allergy is related to non-water-soluble, thermo-resistant gluten fractions [35]. Other studies have suggested that similar allergens are responsible for symptoms following both ingestion and inhalation of cereals [36]. Mittag et al demonstrated that subjects with baker’s asthma and adults with food allergy had intense IgE-reactivity to both the albumin/globulin and glutenin fraction of wheat proteins [37]. While this may explain the association in the atopic group in our study, it is possible that the stronger associations observed in the non-atopic group may be due to other factors such as water-insoluble proteins (wheat gliadins) [38] or non immune reactions such as gluten intolerance. Further studies are currently being conducted to evaluate this differential response between atopics and non-atopics with OA and ingestion-related reactions to grain products as this may have important implications for dietary counselling of workers with OA.

In conclusion, this study has demonstrated that occupational asthma is the most common asthma phenotype among supermarket bakery workers in this region and an important evolving trend globally. Analysis of risk factors contributes towards differentiating between these various phenotypes. Defining various clinical phenotypes using specific clinical criteria is important for decisions regarding medical surveillance and clinical management of this high-risk group. Medical surveillance programmes in bakeries can therefore use these criteria to identify persons at risk at an early stage and intensify surveillance and other workplace interventions. Furthermore, in view of the increase in baking activities in supermarkets globally measures to monitor and reduce exposures remain an important priority.

Table 1. Demographic characteristics of supermarket bakery workers

Demographic characteristics (n = 517)	
Age (yrs)	32±9
Gender (%F:M)	51:49
Smoking status:	
- Current smokers	47%
- Ex-smokers	10%
- Never-smokers	43%
Pack-year history of current smokers (pack-years)	5
Occupation:	
- Bakers/assistant baker	41%
- Counterhand	27%
- Confectioner	10%
- Manager	6%
- Supervisor	6%
- Ex-baker*	6%
- General worker	3%
- Cleaner	1%
Duration of employment in bakery (yrs)	6±5
Duration of employment in current job (yrs)	4±4
Past history of lung disease (self-reported):	
- Repeated childhood chest infections	5%
- Previous treatment for tuberculosis	7%
- Previous treatment chronic bronchitis	5%
Family history of atopy[#]	54%
Self-reported adverse reactions to grain products (n=16)	3%
- Rye products	63%[†]
- Whole-wheat products	19%[†]
- White bread	12%[†]
- Breakfast cereals	6%[†]
Baking activities at home	38%
Training received on health risks of flour dust	8%

* Removed from the bakery in the last 2 years due to baker's asthma

[#] Family history of atopy – Defined as positive answer to the question: Does any member of your family (blood relatives) have any kind of allergies (e.g. hay fever, eczema, asthma)

[†] As a proportion of sub-group (n=16)

Table 2. Allergic sensitization profiles for potential occupational allergens among supermarket bakery workers

Occupational allergen	Overall (n=507)	Atopic (n=213)	Non-atopic (n=294)
Skin prick test (n = 507)			
Wheat flour	79 (16%)	52 (24%)	27 (9%)
Rye flour	82 (16%)	55 (26%)	27 (9%)
Corn flour	73 (14%)	51 (24%)	22 (7%)
Barley	59 (12%)	40 (19%)	19 (6%)
Soya	42 (8%)	32 (15%)	10 (3%)
Oats	41 (8%)	31 (15%)	10 (3%)
Storage mite (*Lepidoglyphus destructor*)	73 (14%)	67 (31%)	6 (2%)
Peanut	30 (6%)	28 (13%)	2 (1%)
Fungal alpha-amylase	17 (3%)	13 (6%)	4 (1%)
Specific IgE (n=513)*			
Wheat flour	134 (26%)	90 (42%)	44 (15%)
Rye flour	123 (24%)	81 (38%)	42 (14%)
Fungal alpha-amylase	21 (4%)	15 (7%)	6 (2%)
At least one bakery dust allergen** (any cereal or amylase)	172 (33%)	113 (52%)	59 (20%)

* Serum specific IgE>0.35 kU/l
**Positive on SPT and/or elevated IgE
Note: Chi-square $p<0.0001$ except for fungal alpha-amylase $p<0.01$

Table 3. Upper and lower respiratory symptoms among supermarket bakery workers

Symptom	Prevalence (%) (n=517)
Asthma history	
Doctor diagnosed asthma	67 (13%)
- < 17 years	30 (6%)
- ≥ 17 years	37 (7%)
Current use of asthma medication	36 (7%)
Asthma attack in the past year	31 (6%)
Work-related asthma symptoms	
Episode of high exposure causing tight chest, wheeze or cough	67 (13%)
Work-related chest symptoms	86 (17%)
Job change due to work-related chest symptoms	30 (6%)
Upper airway symptoms	
Ocular-nasal symptoms	196 (38%)
Work-related ocular-nasal symptoms	162 (31%)

Table 4. Pulmonary function indices among supermarket bakery workers

Pulmonary function indices‡	Overall (n=503)	Males (n=243)	Females (n=260)	p-value
FEV_1 (litres)	3.16 ± 0.77	3.63 ± 0.71	2.72 ± 0.52	-
FVC (litres)	3.83 ± 0.88	4.45 ± 0.71	3.25 ± 0.57	-
FEV_1 % predicted	92 ± 14	91 ± 14	93 ± 14	0.002*
FVC % predicted	95 ± 13	94 ± 12	97 ± 13	0.055*
FEV_1/FVC	83 ± 9	81 ± 10	84 ± 8	0.019*
No. with FEV_1/FVC <70%	33 (7%)	20 (8%)	13 (5%)	0.144§
No. with FEV_1<80% predicted	84 (17%)	42 (17%)	42 (16%)	0.107§
No. with FEV_1<80% predicted[#]	43 (9%)	25 (10%)	18 (7%)	0.177§
No. with bronchial hyper-responsiveness				
No. with ≥12% FEV_1 increase post-bronchodilator (n_c=38)	16 (3%)	7 (3%)	9 (3%)	0.086**§**
No. with ≥10% FEV_1 decrease post saline diluent (n_c=465)	43 (9%)	18 (7%)	25 (10%)	0.269**§**
Methacholine challenge test: $PD_{20}M$<0.4mg (n_c=419)	94 (19%)	37 (15%)	57 (22%)	0.012**§**
Non-specific bronchial Hyper-responsiveness[†] (n_c=457)	110 (22%)	44 (18%)	66 (25%)	0.030**§**

Continuous variables – mean ± S.S; Categorical variables – number (%), n_c: number completed test
‡ Pre-bronchodilator values unless stated otherwise
*Two-sample t-test
§ Chi-square test with 1 degree of freedom
[†] Non-specific bronchial hyperresponsiveness defined as any of two criteria; $PD_{20}M$ <0.4 or ≥12% increase in FEV1 after administration of a bronchodilator.
[#] Using locally derived reference equation for South African university workers, Mokoetle KE

Table 5. Risk factors associated with asthma phenotypes among supermarket bakery workers in multivariate models

	Atopic asthma	Non-atopic asthma	Work-aggravated asthma	Probable Occupational asthma	Probable Occupational asthma	
					Atopic	Non-atopic
Prevalence (%)	**29/457 (6%)**	**29/457 (6%)**	**13/457 (3%)**	**60/457 (13%)**	**42/188**	**18/269**
Determinants						
Family history of asthma	1.53 (0.55 – 4.26)	0.76 (0.22 – 2.65)	1.91 (0.50 – 7.33)	1.06 (0.49 – 2.28)	0.95 (0.37 – 2.42)	0.95 (0.20 – 4.43)
Atopy	-	-	1.23 (0.41 – 3.76)	4.15 (2.29 – 7.53)[§]	-	-
Polysensitization (> 3 aeroallergens)	6.28 (2.72 – 14.52)[§]	-	2.54 (0.65 – 9.93)	5.54 (2.78 – 11.03)[§]	-	-
Past medical history						
- childhood onset (<17 years) asthma	2.20 (0.68 – 7.11)	1.81 (0.49 – 6.75)	2.75 (0.54 – 13.95)	2.13 (0.81 – 5.62)	2.08 (0.69 – 6.27)	-
- pulmonary tuberculosis	0.57 (0.07 – 4.46)	2.06 (0.64 – 6.62)	4.07 (0.99 – 16.64)	1.92 (0.77 – 4.79)	2.90 (0.80 – 10.51)	1.53 (0.31 – 7.51)
- chronic bronchitis	1.81 (0.39 – 8.40)	2.59 (0.69 – 9.74)	4.47 (0.89 – 22.49)	2.01 (0.71 – 5.70)	1.94 (0.46 – 8.22)	2.44 (0.46 – 12.84)
- recurrent childhood chest infections	1.21 (0.27 – 5.55)	2.91 (0.89 – 9.53)	5.46 (1.02 – 29.17)*	0.81 (0.23 – 2.77)	2.27 (0.48 – 10.66)	-
Upper airway symptoms						
- Ocular-nasal symptoms	2.44 (1.12 – 5.29)*	0.51 (0.21 – 1.25)	2.91 (0.92 – 9.20)	6.02 (3.26 – 11.11)[§]	4.48 (1.97 – 10.23)[§]	7.11 (2.39 – 21.09)[§]
- Work-related ocular-nasal symptoms	1.56 (0.72 – 3.39)	0.73 (0.30 – 1.78)	4.30 (1.34 – 13.77)*	3.13 (1.78 – 5.49)[§]	2.51 (1.21 – 5.19)*	3.53 (1.27 – 9.81)*
Age of first exposure to flour dust allergens	1.16 (1.01 – 1.33)*	0.99 (0.91 – 1.09)	1.01 (0.89 – 1.16)	1.00 (0.94 – 1.07)	0.99 (0.92 – 1.08)	1.00 (0.91 – 1.10)
- 21-30 years[#]	1.93 (0.70 – 5.31)	1.64 (0.56 – 4.82)	8.66 (0.97 – 77.28)	1.04 (0.51 – 2.12)	1.08 (0.45 – 2.62)	1.23 (0.28 – 5.42)
- >30 years	3.09 (0.51 – 18.71)	1.72 (0.34 – 8.78)	1.30 (0.05 – 34.96)	0.65 (0.20 – 2.04)	0.46 (0.10 – 2.22)	0.99 (0.13 – 7.59)
Previous episodes of high exposure causing asthma symptoms	1.43 (0.51 – 4.00)	2.33 (0.87 – 6.22)	5.77 (1.74 – 19.15)[♦]	2.80 (1.43 – 5.52)[♦]	2.70 (1.07 – 6.83)*	3.61 (1.15 – 11.30)*
Current job status[δ]:						
- Baker	0.37 (0.11 – 1.18)	0.50 (0.17 – 1.46)	0.10 (0.01 – 1.18)	1.57 (0.66 – 3.74)	2.14 (0.78 – 5.88)	1.68 (0.14 – 20.77)
- Confectioner	0.29 (0.05 – 1.74)	0.49 (0.09 – 2.65)	0.93 (0.11 – 8.20)	1.12 (0.27 – 4.60)	0.51 (0.06 – 4.56)	4.86 (0.30 – 78.05)
- Supervisor/Manager	-	0.39 (0.06 – 2.35)	0.34 (0.02 – 5.98)	4.01 (1.28 – 12.59)*	5.41 (1.26 – 23.15)*	7.48 (0.49 – 115.05)
Self-reported ingestion- related adverse reactions to grain products	-	-	-	6.35 (2.03 – 19.83)[♦]	2.66 (0.56 – 12.65)	13.43 (2.23 – 80.83)[♦]
Baking activities at home	0.53 (0.22 – 1.28)	0.46 (0.19 – 1.13)	0.73 – 0.22 – 2.44)	1.11 (0.63 – 1.94)	1.63 (0.79 – 3.34)	0.72 (0.26 – 2.02)

Note: *p<0.05; ♦p<0.01; §p<0.001
Each odd ratio (OR) is a separate regression model adjusted for age, gender and smoking status
[#] Age category ≤20 years used as reference category
δ Counterhands used as reference group

ACKNOWLEDGEMENTS

We would like to acknowledge the special contribution of the following individuals and institutions. Prof Rodney Ehrlich and Jonny Myers and support staff of the Occupational and Environmental Health Research Unit in the School of Public Health and Family Medicine at the University of Cape Town. Research assistant, Ms Nadia Viljoen and Sisters Leonie Ritchie and Faieza Omar in conducting the fieldwork. Ms Verne Barnard, Alta Olckers and technologists from the Department of Respiratory Medicine and Lung Institute of the University of Cape Town Lung Institute for the pulmonary function and methacholine challenge testing. Ms Jhurien van Niekerk for data entry and management and Mr Rauf Sayed and Prof Francesca Little, from the Departments of Public Health and Statistical Sciences at the University of Cape Town for statistical advice and support. The contents of this report are solely the responsibility of the authors and do not necessarily reflect the official views of these agencies. We would also like to acknowledge the staff and employees of the bakeries that participated in this study.

Declaration of funding:

Funding support provided by the research grants from the Medical Research Council of South Africa, National Research Foundation, Fogarty International Centre, the Allergy Society of South Africa and University of Cape Town Research Committee and the baking industry.

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