



Assessing the health impact of interventions for baker's allergy and asthma in supermarket bakeries: a group randomised trial

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Abstract

Purpose To assess the impact of an intervention for baker's allergy and asthma in supermarket bakeries.

Methods A group randomised trial conducted in 31 bakeries ($n=337$ bakers) that were randomly assigned to one of two intervention groups ($n=244$ bakers) and a control group ($n=93$ bakers). Health data collected prior to and 1-year after the intervention included information obtained from an ECRHS questionnaire; tests for atopy and serum-specific IgE to cereal flours; fractional exhaled nitric oxide (FeNO). Data from the two intervention groups were combined to form one intervention group for purposes of the statistical analysis.

Results At 1 year of follow-up, the incidence and level of decline of work-related ocular–nasal and chest symptoms, sensitisation status and elevated FeNO (FeNO > 25 ppb) was similar in both intervention and control groups. The mean FeNO difference was also similar across both groups (2.2 ppb vs 1.7 ppb, $p=0.86$). In those with FeNO > 25 ppb at baseline, the decline was greater in the intervention compared to control group (16.9 ppb vs 7.7 ppb, $p=0.24$). Multivariate logistic regression models (adjusting for smoking, baseline sensitisation to cereal flour, baseline FeNO > 25 ppb) did not demonstrate an appreciable FeNO decline ($\geq 10\%$) in the intervention compared to control group. However, stratification by the presence of work-related ocular–nasal symptoms in bakers at baseline demonstrated a significant FeNO decline ($\geq 10\%$) in the intervention compared to the control group (OR 3.73, CI 1.22–11.42).

Conclusion This study demonstrates some evidence of an intervention effect on FeNO 1 year after an intervention, particularly in bakers with work-related ocular–nasal symptoms.

Keywords Bakers · Allergy · Asthma · Exhaled nitric oxide · Workplace interventions

Introduction

Work-related asthma accounts for at least 15% of adult asthma, resulting in significant morbidity and disability (Toren and Blanc 2009; Tarlo et al. 2017). Various strategies

have been developed to reduce the burden of the disease and improve the prognosis of workers with occupational asthma. One of the approaches that has been found to be beneficial is the reduction of exposure to the offending sensitiser (de Groene et al. 2011; Vandenplas et al. 2012). However, there are few studies that have evaluated the effectiveness of interventions aimed at reducing exposure to occupational sensitisers (de Groene et al. 2011; Rees and Phillips 2014). Only two studies reported objective measurements of the level of exposures encountered (Soyseth et al. 1995; Dresel et al. 2007; de Groene et al. 2011). Furthermore, most of studies have reported on asthma symptoms, lung function or non-specific bronchial hyperactivity (NSBH) in evaluating the outcome of exposure reduction measures. None of these studies have utilised the presence of airway inflammation as an objective outcome measure in assessing the effectiveness of exposure reduction in occupational settings.

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Fractional exhaled nitric oxide (FeNO) is regarded as an important marker of airway inflammation in asthma among both symptomatic and asymptomatic subjects. Whilst the predictors of baseline FeNO levels have been evaluated in several clinical and population-based studies, the evidence for various factors associated with longitudinal changes in FeNO need further investigation (Al Badri and Jeebhay 2017). Continued exposure and avoidance of exposure to occupational airborne allergens have been identified as the main determinants of longitudinal changes in FeNO (Al Badri and Jeebhay 2017).

In an earlier phase of this overall larger study, the effectiveness of a multi-faceted intervention to reduce exposure to flour dust in supermarket bakeries with high flour dust levels and a population with a high prevalence (13%) of baker's asthma was evaluated (Baatjies et al. 2009, 2010). The specially designed intervention strategy was found to be extremely effective in reducing airborne dust and allergen levels by 50–80% (Baatjies et al. 2014). The aim of this current study was to assess the health impact of this strategy using FeNO and other clinical endpoints for baker's allergy and asthma assessed 1 year after the intervention.

Methods

Study design and population

This group randomised trial involved the analysis of health data that were collected in 2011 as a part of a larger study conducted in 2003 (Baatjies et al. 2010). The original study identified 31 bakeries in the Western Cape province of South Africa as the potential study population. The study population consisted of workers from 18 bakeries of a large supermarket chain store in South Africa. Supermarket bakeries had an average workforce of 20 workers per bakery (range 6–42) with an average production output of ~10,000 bakery units per week per bakery (range 4360–18,346). Bakeries were stratified into small, medium, and large size based on the number of workers employed and the production output (bread, rolls, and cakes) of the bakery. The bakery size indices were derived using tertile values of the following variables as cut-off points—number of employees: ≤ 14 , 15–21, and ≥ 21 ; and production output in units per week: ≤ 7504 , 7505–10 868, and $\geq 10,868$. An equal number of bakeries were randomly selected from each stratum. These bakeries were randomly assigned to either of the two intervention groups or a control group (Fig. 1). Two intervention strategies were developed, using a bakery mixer tub lid and training, through a focused group discussion that involved bakery workers, managers and engineers (Baatjies et al. 2014). An assessment of baseline environmental exposure was initially performed using full-shift personal samples to measure the

level of exposure to flour dust in different job categories in the bakeries (Baatjies et al. 2010). This was followed by a baseline health survey of 424 participants investigating the presence of chest symptoms, ocular–nasal symptoms and work-related symptoms using a short questionnaire. Furthermore, serum-specific IgE to wheat, rye and α -amylase as well as FeNO were assessed prior to implementing the intervention (Baatjies and Jeebhay 2013). One year after implementation, the effectiveness of these interventions was assessed by measurement of flour dust levels that is reported elsewhere (Baatjies et al. 2014). Thereafter, a cross-sectional survey was conducted of 361 workers, among whom 337 were from the original cohort that participated in the earlier phase. In this phase, data were collected on work-related symptoms using the modified the European Community Respiratory Health Survey (ECRHS) questionnaire (Burney et al. 1994), specific IgE to wheat, rye and fungal amylase and FeNO during the work shift.

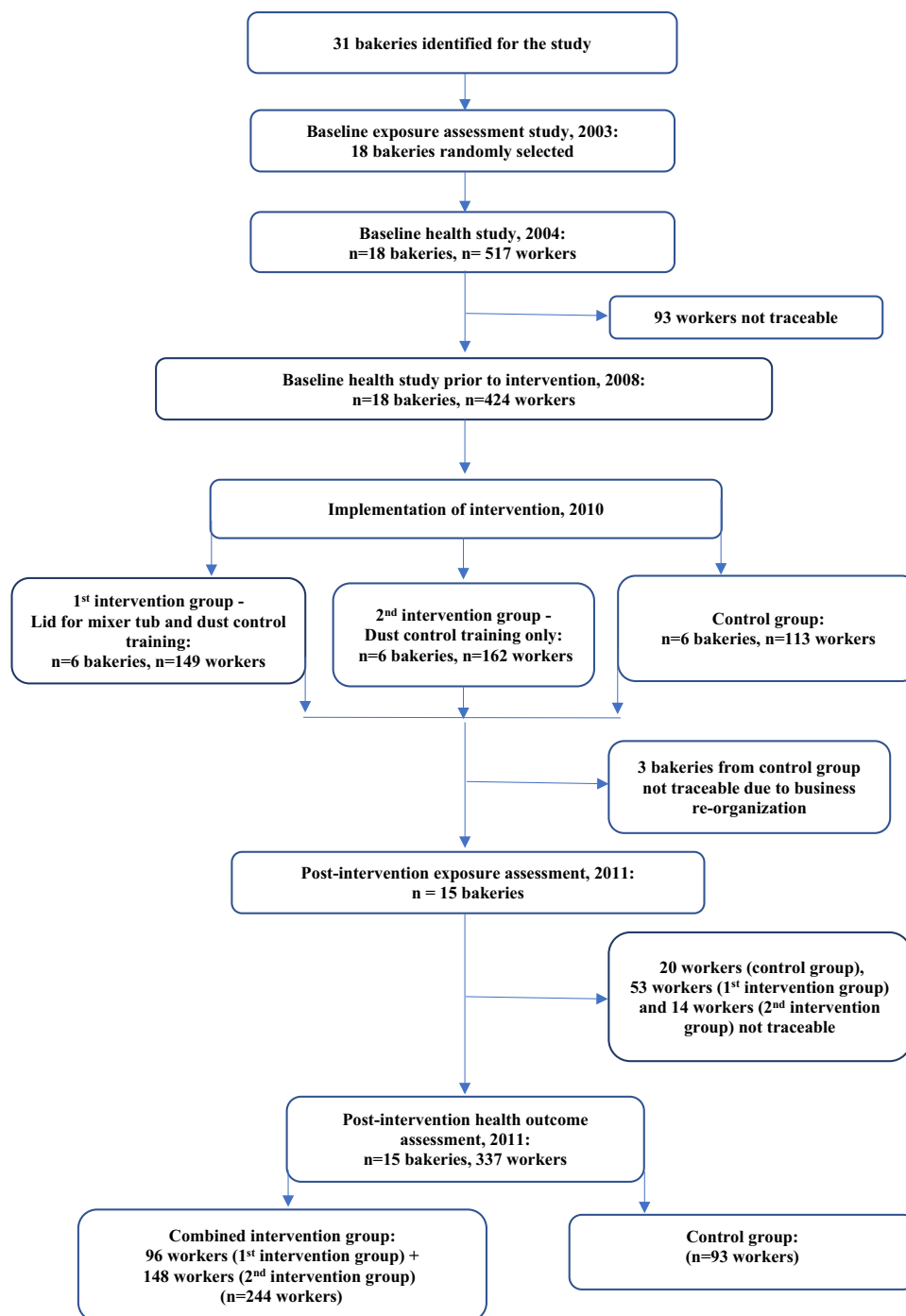
The required sample size calculated for the current study was computed to be 160 workers for each arm of the trial. However, 87 workers were not traceable for further evaluation due to various reasons (e.g. store closures due to re-organisation). To obtain sufficient power in the analysis, the data of both intervention groups (bakery mixer tub lid group and training group) were combined to form one intervention group, which was then compared to the control group. Fully complete data collected from 337 workers (244 from the two intervention groups and 93 from the control group) were subjected to further statistical analysis. This current cohort ($n = 337$) adequately represented the different job categories found in the bakery environment. The study received ethical approval from the University of Cape Town, South Africa (reference no. 272/2002).

Health outcome assessment

Skin prick tests

Skin prick test (SPT) results obtained from the initial sub-study as reported elsewhere were used (ALK-Abello' A/S, Horsholm, Denmark) to test for sensitization to common local allergens (Baatjies et al. 2009). In brief, reading of the tests was done 15 min after testing and areas of the wheal were traced on a clear tape. A wheal of ≥ 3 mm more than the negative control was considered positive. Atopy was defined as the presence of a positive SPT to one or more common aeroallergens. Since the data of skin prick tests (SPTs) were obtained from the previous sub-study, atopic data of some participants were not available.

Fig. 1 Flow diagram illustrating the study design investigation of the supermarket bakeries assessed pre-and post-intervention implementation



Respiratory questionnaire

A standard questionnaire designed based on the protocol for the European Community Respiratory Health Survey (ECRHS) (Burney et al. 1994) was administered to the participants in the follow-up study. It gathered information on acute and chronic respiratory and ocular-nasal symptoms and work-relatedness of these symptoms. It also covered information related to current and previous employment,

levels of exposure to flour dust and tobacco smoke. The modified questionnaire was administered in either English or Afrikaans.

Serum immunological tests

This method is also described in detail elsewhere (Baatjies et al. 2009). In brief, blood samples were obtained from the participants for serum-specific immunoglobulin IgE.

Sera were tested to determine the presence of atopy using Phadiatop[®] test (ImmunoCAP 100 System; Phadia, Uppsala, Sweden). The sera were also tested for specific IgE to flour dust allergens such as wheat (f4), rye (f5) and fungal α -amylase (k87) using fluorescence enzyme immunoassay (CAP-FEIA) according to the manufacturer's instructions (Phadia). Results were treated as a continuous or binary variable in which ImmunoCAP ≥ 0.35 kU/L) was considered positive.

Fractional exhaled nitric oxide levels

A hand-held portable nitric oxide sampling device (NIOX MINO) was used to determine FeNO during the work shift. It was performed in a room distant from the bakery area during the work shift throughout the working week, according to American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations (American Thoracic Society 2005; Dweik et al. 2011). The testing of workers had no particular variation with regard to time of testing for the different jobs. The average of three technically adequate FeNO measurements was determined. Workers were instructed to abstain from smoking, eating or drinking at least 1 h before the test. This was confirmed prior to testing, and those who did not follow the instructions were tested at a later stage after ensuring their full compliance with these instructions. Levels of FeNO were treated either as continuous variable (log-transformed), or binary variable FeNO > 25 ppb and FeNO > 50 ppb. A $\geq 10\%$ decline in FeNO was considered a significant reduction in airway inflammation post-intervention.

Statistical analysis

Data were analysed using STATA V.12 computer software (StataCorp, College Station, Texas, USA). Data are presented as proportions, means (geometric where appropriate) or median and the corresponding standard deviation (SD) or interquartile range (IQR). Chi-square test and an independent *t* test (or Fisher's exact test and Wilcoxon sum rank test where appropriate) were used to compare groups at baseline as well as to determine the effect of intervention on the incidence and decline of allergic and respiratory health outcomes at 1-year follow-up. Univariate linear regression was used to explore the determinants of longitudinal change in FeNO. Multivariate regression analysis was used to determine predictors of a $\geq 10\%$ decline in FeNO using the intervention and adjusting for the most important confounders which are current smoking, baseline FeNO > 25 ppb and sensitisation to cereal flour allergens. Further subgroup multivariate regression analysis stratified by the presence of work-related ocular–nasal symptoms was used to assess effect modification. A two-tailed *p* value of < 0.05 was considered to be statistically significant.

Results

The general characteristics of the 337 participants are presented in Table 1. The two groups were comparable with regard to age (32 vs 33 years), proportion of females (55% vs 57%) and smoking status (38% vs 40%). The intervention group had a significantly higher prevalence of workers with atopy compared to the control group (42% vs 25% $p=0.03$). The intervention group had a significantly higher baseline prevalence of workers with work-related chest symptoms (25%, $p=0.04$) and sensitisation to cereal flour allergens (35%, $p=0.04$) at baseline than the control group (15% and 23%, respectively). No significant differences were found for other allergic and respiratory health outcomes as shown in Table 1.

At 1 year of follow-up, the incidence and level of decline of work-related ocular–nasal and chest symptoms, sensitisation status and elevated FeNO was very similar in both groups as shown in Tables 2 and 3. The mean difference in FeNO was similar across the two groups (2.2 ppb vs 1.7 ppb, $p=0.86$). However, when stratifying according to baseline FeNO > 25 ppb, the FeNO decline was greater in the intervention group (16.9 ppb) compared to the control group (7.7 ppb), but this was not statistically significant ($p=0.24$) (Table 3). This was also evident when stratifying according to baseline FeNO > 50 ppb. FeNO decline approached borderline significance as the proportional level of decline increased when baseline FeNO > 25 ppb, such that 49% of the intervention group and 28% of the control group experienced a 40% decline in FeNO ($p=0.07$).

In the univariate linear regression analysis (Table 4), ocular–nasal symptoms and baseline FeNO were significant determinants of the percentage (%) longitudinal change in FeNO. Current smoking status and work-related ocular–nasal symptoms were borderline ($p=0.09$ for both predictors). However, intervention group, atopy, current use of steroids (for rhinitis/asthma) and duration of employment in the bakery industry were not significant predictors. Multivariate logistic regression models adjusting for smoking, baseline sensitisation to cereal flour and baseline FeNO > 25 ppb, did not demonstrate an appreciable decline in FeNO (> 10%) experienced by the intervention compared to the control group (Table 5). However, stratification according to the presence of work-related ocular–nasal symptoms at baseline demonstrated a significant decline (> 10%) in FeNO in the intervention group compared to the control group (OR 3.73, CI 1.22–11.42).

Discussion

This study is one of the few group randomised trials, and the first such trial in bakers, that evaluated the long-term health outcomes of a workplace intervention aimed at

Table 1 Baseline characteristics of supermarket bakery workers

Predictor	Intervention group			Control group			Chi square <i>p</i> value
	<i>n</i>	<i>N</i>	%	<i>n</i>	<i>N</i>	%	
Age, median (IQR)	33 (12)	244	–	32 (11)	93	–	0.58
Gender (female)	139	244	57	51	93	55	0.73
Weight, median (IQR)	74.5 (29)	244	–	74 (28)	93	–	0.53
Height, mean $\pm$ SD ^b	165 $\pm$ 8.2	155	–	166 $\pm$ 9.3	56	–	0.59
BMI, median (IQR) ^b	27.8 (9.5)	155	–	28.7 (10.6)	56	–	0.58
Current smoker	93	244	38	37	93	40	0.69
Atopy (skin prick test) ^b	65	155	42	14	56	25	0.03
Current steroid use for asthma and/or rhinitis	8	244	3	1	93	1	0.45 ^a
Current employment status (Permanent)	214	244	88	83	93	89	0.70
Current job with high exposure	161	222	73	54	83	65	0.20
Duration of employment in the bakery industry, median (IQR)	7 (7)	241	–	7 (10)	89	–	0.87
Ocular–nasal symptoms	83	244	34	31	93	33	0.91
Work-related ocular–nasal symptoms	92	241	38	34	93	37	0.78
Medication use for ocular–nasal symptoms	15	244	6	7	93	8	0.65
Asthma attack in the last 12 months	15	244	6	7	93	8	0.65
Work-related chest symptoms	61	241	25	14	93	15	0.04
Medication use for asthma	12	244	5	3	93	3	0.77 ^a
Specific IgE $\geq$ 0.35 kU/L							
Wheat	66	200	33	18	80	23	0.08
Rye	58	200	29	17	80	21	0.19
α -Amylase	2	200	1	1	80	1	1.00 ^a
Any one of the cereal flour allergens	70	200	35	18	80	23	0.04
Baseline FeNO, GM $\pm$ GSD	17.7 $\pm$ 2.3	244		17.8 $\pm$ 2.1	93		0.95
FeNO (ppb)							
< 25	179	244	73	67	93	72	0.81
25–50	34	244	14	18	93	19	0.22
> 50	31	244	13	8	93	9	0.29

^aFisher's exact test^bData obtained from a previous sub-study; Baatjies et al. (2009)

reducing the incidence of occupational allergy and asthma. It is also one of few occupational studies that evaluated the predictors of longitudinal decline in FeNO. The overall findings of this study demonstrate that workplace interventions aimed at reducing exposure to flour dust allergens can contribute towards suppression of allergic airway inflammation in exposed workers. This effect was more evident in workers with moderate to high airway inflammation (FeNO > 25 ppb) at baseline and those with pre-existing ocular–nasal symptoms.

The study, however, could not demonstrate significant differences in the incidence of asthma symptoms, ocular–nasal symptoms or medication use. This was probably due to the dilution effect on flour dust exposure as reported previously by Baatjies et al. (2014). Managers who were transferred to bakeries in the control group incorporated some elements of the intervention in their new bakeries. This resulted in dust exposures in the intervention group and the control group

being very similar post-intervention (GM 0.39 vs 0.44 mg/m³) (Baatjies et al. 2014).

Aside from the dilution effect, the findings of this study do demonstrate that persistent low-level exposure to airborne allergens can result in new onset or worsening of asthma as well as ocular–nasal symptoms as has been reported previously (Jolly Athena et al. 2015). Furthermore, these findings were similar to the overall findings of previous studies on the improvement in respiratory health outcomes following removal from exposure to airborne allergens (Dressel et al. 2007; Vandenplas et al. 2011; de Groene et al. 2011). A Cochrane systematic review identified only one prospective controlled before-and-after study that evaluated the health outcomes of a workplace intervention aimed at reducing exposure to airborne allergen in farmers (Dressel et al. 2007; de Groene et al. 2011). The authors reported a significant decline in respiratory symptoms in the intervention group 4–6 weeks after a 1-day educational training compared to its

Table 2 Incidence of allergic and respiratory health outcomes in supermarket bakery workers at 1-year follow-up

Predictor	Intervention group			Control group			Chi square <i>p</i> value
	<i>n</i>	<i>N^b</i>	%	<i>n</i>	<i>N^b</i>	%	
Ocular–nasal symptoms	41	161	25	15	62	24	0.84
Work-related ocular–nasal symptoms	41	149	28	15	59	25	0.76
Medication use for ocular–nasal symptoms	38	229	17	18	86	21	0.37
Asthma attack in the last 12 months	4	229	2	1	86	1	1.00 ^a
Work-related chest symptoms	29	180	16	18	79	23	0.20
Medication use for asthma	17	232	7	5	90	6	0.57
Specific IgE ≥ 0.35 kU/L							
Wheat	11	134	8	2	60	3	0.35
Rye	12	141	9	3	61	5	0.56
Specific IgE ≥ 0.35 kU/L							
α-Amylase	2	196	1	2	77	3	0.32
Any one of the cereal flour allergens	14	130	11	3	60	5	0.20
FeNO (ppb)							
25–50 ppb	17	179	10	7	66	10	0.80
> 50 ppb	10	213	5	1	83	1	0.30 ^a

^aFisher's exact test^bPopulation at risk free of the adverse health outcome of interest at baseline

baseline. However, the difference between the intervention group and the control group was not significant (risk ratio 7.62, 95% CI 0.47–124.22) (Dressel et al. 2007; de Groene et al. 2011). Furthermore, Vandenplas et al. in their systematic review found that only 17.6% of workers recovered fully after reduction of exposure, 60.1% showed improvement but 20.6% of subjects became worse after exposure reduction (Vandenplas et al. 2011). By comparison, the current study demonstrated 39% of workers demonstrated a decline in work-related chest symptoms and only 16% with new onset of work-related chest symptoms in the intervention group. This is also better than the systematic review by de Groene et al. (2011) which reported that only 24.8% of participants reported the absence of asthma symptoms after reduction of the exposure. On the other hand, Munoz et al. (2014) reported that asthma control questionnaire (ACQ) scores among those workers who avoided and those with continued exposure to airborne allergens were very similar.

In the current study, a higher prevalence of work-related chest symptoms and sensitisation was observed in the intervention group compared to the control group at baseline. This could have resulted in a potential bias, which could have contributed to the lack of demonstration of an intervention effect. It is unlikely that information bias could have been responsible since the assignment to the intervention and control groups was not based on exposure or the prevalence of adverse health outcomes of interest. However, it is possible that there may have been some form of selection bias that did not take into account other factors aside from bakery size (as determined by number of employees) and production output that could have resulted in an inability

to demonstrate a statistically significant decline in the incidence of the outcomes of interest.

The short duration of follow-up in this current study may also have contributed to the marginal findings of sensitisation and symptoms between the two groups. The participants in this study were assessed only 1 year after implementing the intervention, which may have been insufficient to demonstrate a significant difference between the two groups. Malo and Ghezzo reported that the maximum level of improvement of non-specific bronchial hyperresponsiveness (NSBH) was observed at 2.5–5 years post-cessation of exposure (Malo and Ghezzo 2004). Furthermore, Perfetti et al. demonstrated that NSBH improved in 48% of subjects evaluated only after 5 years of exposure cessation, whereas only 19% of workers evaluated at less than 5 years showed improvement (Perfetti et al. 1998). This long duration before symptom improvement could be explained by the presence of allergen-specific IgE, which can be detected in the sera from a few months to several years after cessation of exposure (Malo et al. 1988; Piirila et al. 2000; Park et al. 2002; Brant et al. 2006; Basketter et al. 2012). Previous studies have shown that the half-life of specific IgE to various allergens such as anhydrides, snow crab and detergent enzyme allergens can vary between 12, 20, and 21 months, respectively, after exposures to these allergens have been decreased (Bernstein et al. 1983; Malo et al. 1988; Brant et al. 2006). Furthermore, despite the effectiveness of the intervention in reducing flour dust exposures, participants in the intervention group may have still been exposed. This is based on the post-intervention inhalable flour dust exposures that ranged between 0.01 and 3.27 mg/m³, despite an overall reduction

Table 3 Relative decline in allergic and respiratory health outcomes in supermarket bakery workers assessed at 1-year follow-up

Predictor	Intervention group			Control group			Chi square <i>p</i> value
	<i>n</i>	<i>N</i>	%	<i>n</i>	<i>N</i>	%	
Work-related ocular–nasal symptoms	37	92	40	17	34	50	0.32
Medication use for ocular–nasal symptoms	4	15	27	3	7	43	0.63 ^a
Asthma attack in the last 12 months	6	10	60	2	5	40	0.61 ^a
Work-related chest symptoms	24	61	39	5	14	36	0.80
Medication use for asthma	3	12	25	0	3	0	1.00 ^a
Specific IgE change, median (IQR)							
Wheat	0.01 (0.06)	198		0.01 (0.05)	78		0.01
Rye	0.01 (0.06)	198		0.01 (0.05)	78		0.10
α -Amylase	0 (0.01)	198		0 (0.01)	78		0.311
Specific IgE ≥ 0.35 kU/L							
Wheat	9	64	14	0	18	0	0.19 ^a
Rye	8	57	14	1	17	6	0.67 ^a
α -Amylase	0	2	0	0	1	0	-
Any one of the cereal flour allergens	14	68	21	1	18	6	0.18 ^a
FeNO change, mean $\pm$ SD	2.2 $\pm$ 23.0	244		1.7 $\pm$ 14.5	91		0.86 ^b
Proportion decline in FeNO							
10% decline	125	244	51	40	91	43	0.18
20% decline	100	244	41	33	91	35	0.36
30% decline	75	244	31	24	91	26	0.37
40% decline	52	244	21	15	91	16	0.29
FeNO change if baseline > 25 ppb, mean $\pm$ SD	16.9 $\pm$ 35.2	63		7.7 $\pm$ 24.2	25		0.24 ^b
Proportion decline in FeNO if baseline > 25 ppb							
10% decline	44	63	70	16	25	64	0.60
20% decline	41	63	65	13	25	52	0.26
30% decline	36	63	57	9	25	36	0.07
40% decline	31	63	49	7	25	28	0.07
FeNO change if baseline > 50 ppb, mean $\pm$ SD	26.1 $\pm$ 45.5	31		11.5 $\pm$ 39.3	8		0.41
Proportion decline in FeNO if baseline > 50 ppb							
10% decline	22	31	71	5	8	63	0.68 ^a
20% decline	22	31	71	4	8	50	0.40 ^a
30% decline	21	31	68	3	8	38	0.22 ^a
40% decline	19	31	61	3	8	38	0.26 ^a

^aFisher's exact test^bWilcoxon sum rank test

in dust levels from baseline (Baatjies et al. 2014). This low-level flour dust exposure may have contributed towards persistence of flour-specific IgE in the blood and as well as respiratory symptoms. Future studies could investigate the half-life of flour-specific IgE and their utility in predicting ongoing allergic symptoms.

The results of this study suggest that airway inflammation, measured by FeNO, can be reduced by minimising exposure to airborne flour dust allergens. Although the difference in FeNO between the two groups following the intervention was not significant ($p=0.24$), the FeNO decline (among those with baseline FeNO > 25 ppb) was twofold greater in the intervention group (mean = 16.9 ppb) compared to the control group (mean = 7.7 ppb). Moreover, apart

from both groups having similar allergen exposures, the incidence of sensitisation was also similar. This may explain the non-significant difference in the FeNO decline in both groups since FeNO levels correlate with the level of allergen-specific IgE (Baatjies and Jeebhay 2013; Tsolakis et al. 2018). Although the effect of allergen avoidance on FeNO in paediatric studies has been inconsistent (Al Badri and Jeebhay 2017), a demonstrable association has been reported in the occupational setting. Dressel et al. demonstrated a significant decline in FeNO in the intervention group from its baseline after implementing a workplace intervention (Dressel et al. 2007). However, the difference between their intervention and control groups was not statistically significant. Furthermore, two case reports by Merget et al. of a

Table 4 Determinants of percentage (%) longitudinal change in fractional exhaled nitric oxide among supermarket bakery workers in univariate linear regression models

Predictor	Estimate (β_1)	p value
Gender	− 0.42	0.97
Age	0.59	0.39
Weight	− 0.09	0.73
Height	− 12.59	0.88
BMI	− 0.23	0.80
Current smoker	18.86	0.09
Current alcohol drinking	− 0.80	0.37
Current steroid use for asthma and/or rhinitis	5.36	0.87
Ocular–nasal symptoms	22.84	0.04
Work-related ocular–nasal symptoms	18.96	0.09
Current job with high exposure	− 2.01	0.87
Duration of employment in the bakery industry	0.82	0.34
Intervention vs control group	13.22	0.27
Atopy (skin prick test)	− 19.88	0.19
Specific IgE to wheat	− 0.17	0.75
Specific IgE to wheat ≥ 0.35 kU/L	16	0.23
Specific IgE to rye	− 0.01	0.97
Specific IgE to rye ≥ 0.35 kU/L	− 0.49	0.97
Specific IgE to α -amylase	− 7.07	0.18
Specific IgE to α -amylase ≥ 0.35 kU/L	− 81.33	0.17
Specific IgE to any one of the cereal flour allergens ≥ 0.35 kU/L	15.95	0.23
Baseline FeNO	− 0.71	<0.01
FeNO (ppb)		
> 25	− 50.04	<0.01
> 50	− 47.22	<0.01

baker and a farmer sensitised to wheat, rye and triticale demonstrated a decrease in FeNO after complete avoidance of potential allergens for two weeks (Merget et al. 2015, 2016). However, there was no objective measurement of the exposures before and after the intervention in these studies to confirm this. In the current study, the effect of occupational

intervention on FeNO decline was more prominent in workers with FeNO > 25 ppb as demonstrated by a strong association observed between a $\geq 10\%$ decline in FeNO and baseline FeNO > 25 ppb (OR 3.61, 95% CI 1.96–6.64), suggesting a beneficial effect in a subset of workers with above the cut-off level of normal range for FeNO (Bjermer et al. 2014).

Various approaches have been used to assess the longitudinal changes in FeNO over time. A decline of 10% in FeNO has been suggested previously for tapering oral corticosteroid in patients with severe asthma (Hashimoto et al. 2011). This 10% cut-off was used in the current study to evaluate the effectiveness of the intervention in reducing airway inflammation. Among the models explored, only baseline FeNO > 25 ppb ($\beta_1 = -50.04$) and ocular–nasal symptoms ($\beta_1 = 22.85$) were significantly associated with longitudinal changes in FeNO while smoking status and work-related ocular–nasal symptoms were of borderline significance in univariate models. In addition, baseline sensitisation to cereal flour allergens was added to the model due to it being strongly associated with FeNO in a previous study of bakers (Baatjies and Jeebhay 2013). The final model analysis demonstrated only a borderline association ($p = 0.09$) between a $\geq 10\%$ decline in FeNO and the intervention group (OR 1.62, 95% CI 0.93–2.81), suggesting a marginal intervention effect on airway inflammation post-intervention (Baatjies et al. 2014).

Allergic rhinitis (AR) and asthma frequently coexist in patients, and the presence of upper airway symptoms/AR is a significant predictor of occupational asthma (Foresi et al. 1997; Alvarez et al. 2000; Bousquet et al. 2008). In the occupational setting, there is a strong relationship between occupational asthma and occupational rhinitis, particularly in those workers exposed to HMW agents such as cereal flour dust (Moscato et al. 2008, 2012). Furthermore, it has been demonstrated that FeNO increases progressively in AR patients without lower respiratory symptoms (24.5 ppb, CI 18–31 ppb), those with lower respiratory symptoms without asthma (38 ppb, CI 27–49 ppb), and in patients with asthma (68 ppb, CI 45–92 ppb) (Rolla et al. 2007). These data

Table 5 Determinants of 10% or greater decline in FeNO among supermarket bakery workers in multivariate models

Predictor	Crude odds ratio			Bakers with work-related ocular–nasal symptoms			Bakers without work-related ocular–nasal symptoms		
	OR	95% confidence interval (CI)	p value	OR	95% confidence interval (CI)	p value	OR	95% confidence interval (CI)	p value
Intervention vs control group	1.62	0.93–2.81	0.09	3.73	1.22–11.42	0.02	1.62	0.56–2.25	0.75
Current smoker	0.92	0.56–1.52	0.75	0.99	0.42–2.39	0.99	1.00	0.52–1.92	0.99
Specific IgE to any one of the cereal flour allergens ≥ 0.35 kU/L	0.45	0.25–0.81	<0.01	0.43	0.16–1.17	0.10	0.69	0.31–1.53	0.36
Baseline FeNO > 25 ppb	3.57	1.94–6.59	<0.01	5.03	1.79–14.16	<0.01	3.02	1.35–6.77	<0.01

demonstrate a gradient continuum, which suggests that the total extent of airway inflammation depends on the degree of anatomical involvement of the airways from the nose to the small airways (Boulay et al. 2012). This relationship between the degree of anatomical involvement and extent of airway inflammation could explain the FeNO decline demonstrated when the data were stratified by the presence of work-related ocular–nasal symptoms at baseline. It demonstrated a significant ($p=0.02$) intervention effect on $\geq 10\%$ decline in FeNO (OR 3.73, 95% CI 1.22–11.42) in those with work-related upper airway symptoms. However, this effect modification by the presence of work-related ocular–nasal symptoms could also be attributed to the higher proportion of sensitised participants in those with work-related ocular–nasal symptoms compared to those that were asymptomatic (58% vs 42%, $p<0.01$). This suggests that the effect is most probably modified by the presence of flour dust allergic rhino-conjunctivitis.

This study has some important strengths including being the only prospective trial that measured workplace allergen exposures levels in relation to FeNO as an outcome measure to evaluate the effectiveness of a workplace intervention for occupational allergy and asthma. However, there were some limitations. First, some of the bakeries in the control group applied changes to their work practices as a result of rotation of the managers during the year that the implementation was being instituted, which diluted the strength of the effect estimates. Second, loss to follow-up was present in approximately 35% of the original cohort, which may have also affected the magnitude of the effect estimate. Third, the healthy worker effect may have introduced probable bias if there were differences among bakers that left the bakeries during this period, which may have also underestimated the effect. The use of other objective measures aside from FeNO such as NSBH could have further strengthened the findings, but the latter investigation was not done due to logistical considerations. Finally, the post-intervention period was not sufficiently long enough to detect an appreciable improvement in health outcome parameters such as sensitisation. The effect of intervention on new sensitization, ocular–nasal symptoms and asthma is more likely to be demonstrable if workers are evaluated at 2.5–5 years after the intervention.

In conclusion, this study suggests some evidence for an intervention effect on airway inflammation in bakers even after 1-year of follow-up, despite the limitations outlined. Furthermore, it suggests that FeNO could be a useful tool to monitor the effectiveness of workplace interventions for occupational allergy and asthma, particularly among those with pre-existing upper airway involvement and work-related ocular–nasal symptoms. Future studies should follow up participants after a longer duration to demonstrate an appreciable effect of workplace interventions on allergic respiratory

health outcomes. Assembling cohorts having exposure to different occupational allergens such as isocyanates, food and other animal allergens would be useful to demonstrate effectiveness in various high-risk contexts. Finally, studies should also consider using an expanded repertoire of objective tests (spirometry and non-specific bronchial hyper-responsiveness) beyond those used in the current study to evaluate the effectiveness of interventions on occupational allergic respiratory disease outcomes.

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Author contributions MFJ was responsible for the overall conceptualisation and design of the study, ensuring the development of the intervention. RB was responsible for overseeing the fieldwork, data management and analysis. FM was responsible for conducting the data analysis and preparing the manuscript under the supervision of MFJ and RB. All investigators contributed to and reviewed the manuscript prior to submission.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval The original study received ethical approval from the Research Ethics Committee of the University of Cape Town (reference no. 272/2002). Informed consent was obtained from all study subjects as per the protocol. The protocol can be accessed on-line (<https://1drv.ms/b/s!ApmArVMYxI4B4V-9TiBgKsTKGPMp>).

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