UNIVERSITY OF CAPE TOWN

SKIN SYMPTOMS (ALLERGIC AND NON-ALLERGIC) PREDICTING THE DEVELOPMENT OF ALLERGIC RESPIRATORY OUTCOMES AND ASTHMA IN BAKERS

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A research report submitted to the School of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town in partial fulfilment of the requirement for the award of the degree of Master of Medicine (MMed) in Occupational Medicine

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March 2018

DECLARATION

Skin symptoms (allergic and non-allergic) predicting the development of allergic respiratory outcomes and asthma in bakers

I, Vânia Chongo-Faruk, hereby submit my dissertation for the degree of Master of Medicine (MMed) in Occupational Medicine. I declare that this is my original work (except where acknowledgements indicate otherwise) and that neither the whole work, nor any part of it, has been, is being, or is to be submitted for another degree in this or any other university.

Signed by candidate

Dr Vânia Chongo-Faruk March 2018

ACKNOWLEDGEMENTS

First and foremost, I would like to acknowledge and extend my heartfelt gratitude to people who provided me with academic support and have made this dissertation possible:

- My supervisor Professor Mohamed Jeebhay, School of Public Health and Family Medicine, University of Cape Town, for providing access to data and his inestimable guidance throughout the entire process, from protocol development, statistical analysis and critical comments on drafting this report;
- My Co-Supervisor Dr Roslynn Baatjies, Centre for Occupational and Environmental Health Research, School of Public Health and Family Medicine, University of Cape Town, for her valuable contribution and guidance with statistical analysis and critical comments on presenting results;
- Drs Amy Burdzik, Shahieda Adams and Dorothy Ngajilo, School of Public Health and Family Medicine, Division of Occupational Medicine, University of Cape Town, for their valuable input in the protocol development;
- Dr Francisco Mbofana, Department of Public Health of the Ministry of Health of Mozambique, for his support and valuable constructive criticism;
- Ms Faranaaz Bennett, Sharon Ferguson, and Carmen De Koker for assisting with administrative issues;
- My sponsors, the Irish Aid Fellowship program-Mozambique.

Preamble

Special and big thanks to my beloved friend and colleague Dr Dorothy for the continuous support ever since I joined the training, for believing in my ability to finish this dissertation, for your presence in my life beyond academics.

To my family, only you know how challenging and rewarding this journey has been. Without your unwavering support and prayers this would have been even more challenging and harder to endure. To my nephews and nieces, my beloved siblings (Ma Helena, Ilda and Aurelio), my dearest sister-in-law, Shabanam, my mother-in-law, Zarina, my goddaughter Neide; thank you all from the bottom of my heart.

To my love, Omar, words cannot begin to express my utmost respect for the love, support and care that you have given me throughout this journey in spite of the painful distance between us. Thank you for giving me two precious gifts that have been warriors in their own right. Adil and Naznin, you have simply been beyond amazing, my little angels, momy will forever be grateful for your love, maturity, and understanding over these past few years: you are my heroes!!!

Last, but not least, I would also like to express my heartfelt gratitude to the many friends and family without whom this journey would not have been possible. You are too many to name individually, however special thanks are given to Anita Mogutlal and her husband Manojcumar Arquissandas, whose support was crucial to start my training in occupational medicine. I am forever also grateful to Agostinho, your support and selflessness is highly appreciated.

DEDICATION

To Allah, my Creator and my Master;

To the memory of my parents (mamã e papá), Manuela and Armindo, who with so much love taught me perseverance. You are no longer here but your belief in me made me to strive for my dreams and enabled me to complete this dissertation. My love and respect for you shall live forever;

To my dear husband and friend Special and big thanks to my beloved friend and colleague Dorothy for the continuous support ever since I joined the training, for believing in my ability to finish this dissertation, for your presence in my life beyond academics., Omar;

To my beloved kids, Adil and Naznin;

To my siblings, Ma Helena, Ilda and Aurelio;

To my family and all my friends.

PUBLICATION

Parts of this dissertation has been published:

- Chongo-Faruk,V, Skin exposure, symptoms and asthma in occupational settings – is there a link? Curr Allergy Clin Immunol 2017,30: 251-257.

SKIN SYMPTOMS PREDICTING THE DEVELOPMENT OF ALLERGIC RESPIRATORY OUTCOMES AND ASTHMA IN BAKERS

ABSTRACT

Background: Recent studies have suggested that aside from the inhalational route, skin exposure may also play an important role in the sensitization to allergens, resulting in adverse allergic respiratory outcomes including asthma in workers exposed to these agents. This appears to be reported more commonly for low molecular weight agents such as isocyanates and some cleaning agents. This study investigated whether skin symptoms, in the presence or absence of allergic sensitization, can predict the development of allergic respiratory outcomes and asthma in bakery workers.

Methods: A cohort study investigated 263 bakery workers using a modified ECRHS questionnaire; immunological tests including skin prick tests for common local aeroallergens (ALK-Abello´ A/S, Horsholm, Denmark), Phadiatop and serum-specific IgE to bakery allergens (wheat, rye and fungal α-amylase); and pulmonological tests including spirometry, non-specific bronchial hyperresponsiveness, and fractional exhaled nitric oxide (FeNO), after a 4 year period.

Results: Workers' median age was 32 years (IQR: 26-38), 50% were female, 54% were ever smokers and 32% were atopic. At baseline, 26% of workers were sensitized to bakery allergens, skin symptoms were present in 22% and 11% reported work-related skin symptoms (WRSS).

While the incidence of general upper (19%) and lower (22%) respiratory symptoms over the follow-up period were very similar, work-related upper (29%) respiratory symptoms were higher than lower (20%) respiratory symptoms. However, the incidence of allergic sensitization to bakery allergens was only 8% and a new asthma diagnosis present in 4% over this period. In multivariate adjusted (gender, atopy and smoking status) regression models, having a history of skin symptoms was associated with an increased risk of developing work-related lower respiratory symptoms - WRLRS (RR=2.2, 95% CI: 1.03-4.83), while having clinically significant symptoms of eczema or urticaria was associated with an increased risk of reporting general upper respiratory symptoms (RR=5.5, 95% CI: 1.30-24.20) as well as WRLRS (RR= 4.8, 95% CI: 1.60-14.40). Furthermore, WRSS was associated with an increased risk of general upper respiratory symptoms (RR=5.1, 95% CI: 1.31-19.81), WRLRS (RR=4.1, 95% CI: 1.43-11.85) and elevated FeNO levels (FeNO>25ppb: RR=2.9, 95% CI: 1.19-7.28). The association between clinically significant skin symptoms or WRSS and new onset upper or lower respiratory symptoms were modified by use of dermal personal protective equipment. Infrequent or absent glove usage was associated with a higher risk (RR=5.3, 95% CI: 1.54-18.43) of having new onset WRLRS.

Conclusion: Skin symptoms, more so if work-related, appear to be associated with future development of general and work-related upper and lower respiratory symptoms and inflammatory markers suggestive of asthma in bakery workers.

Keywords: bakers, skin symptoms, asthma

ABREVIATIONS AND ACRONYMS

APS:	Aerosol Provocation System
ACD:	Allergic Contact Dermatitis
ALLSA:	Allergy Society of South Africa
ATS:	American Thoracic Society
CBD:	Chromium Beryllium lung Disease
FEIA:	Fluorescence Enzyme Immunoassay
DF:	*Dermatophagoides farinae*
ECRHS:	European Community Respiratory Health survey
ERS:	European Respiratory Society
FeNO:	Fractional exhaled Nitric Oxide
FLG:	Fillagrin
FEV1:	Forced Expiratory Volume in the 1st second
IgE:	Immunoglobulin E
MDI:	Methylene Diphenyl Diisocyanate
MI:	Methyl Isothiazolinone
MRC:	Medical Research Council
OA:	Occupational Asthma
OCD:	Occupational Contact Dermatitis
OVA:	Ovalbumin
PPE:	Personal Protective Equipment
PA:	Phthalic Anhydride

Ppb:	Parts Per Billion
RR:	Risk Ratio
SLS:	Sodium Laurel Sulphate
SPT:	Skin Prick Test
SC:	Stratum Corneum
Th2:	T helper cell type 2
TEWL:	Trans-epidermal Water Loss
TMA:	Tri-mellitic Anhydride
USA:	United States of America
WRLRS:	Work-related Lower Respiratory Symptoms
WRURS:	Work-related Upper Respiratory Symptoms

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SECTION A: PROTOCOL

INTRODUCTION

Background

Diverse immune responses have been associated with various environmental allergen exposures to the skin, resulting in activation of the adaptive immune response [1]. Some epidemiological studies and animal experiments have demonstrated positive associations between skin and respiratory symptoms and positive exposure-response relationships, while others have not been able to replicate this association [2–7].

One of the main issues highlighted by these observations has been the challenges in investigating skin exposure [8]. These challenges include the fact that skin exposure assessment methodologies are not as well developed as for inhalational exposures, and the limited exposure data and dermal exposure models that exist[9,10]. This is complicated further by the frequent variability and sporadic nature of skin exposure; the uncertainty regarding skin uptake; and the uncertainty that persists over the effectiveness of protective clothing in occupational settings [8]. Furthermore, most workers are exposed to mixtures of occupational agents, making it difficult to identify the specific exposure responsible for the health outcome of interest. For example, exposure to beryllium and isocyanates typically occurs in mixed exposure settings and these agents may be present in various physical or chemical forms, viz. metal particles, oxides, salts and alloys with copper and other metals [8].

With all the limitations for dermal exposure assessment, skin symptoms can be used as a proxy for skin exposure. Dermatitis in occupational settings presents with a primary lesion usually at

the site of contact with the causal agent, either allergic or irritant. However, when the agent is allergenic, secondary lesions can later flare in areas which never were in contact with the allergen [11]. Hence, skin symptoms implicitly suggest skin exposure and may be a route of sensitization and development of allergic respiratory disease including asthma.

Justification

Both high and low molecular weight contact allergens can lead to dermatological and respiratory health effects, such as allergic contact dermatitis, rhinitis, and asthma, causing a substantial health burden in occupational settings.

Inhalation is an obvious route for sensitization and its pathophysiologic mechanism is well defined. Additionally, improvement in occupational health standards in workplaces to minimize allergens inhalation exposure have been put in place. Despite these measures, the incidence of asthma has not dropped, but remains persistently high in some of the settings where workers are minimally exposed to allergen inhalation, for instance, industries using isocyanates. On the other side, several animal studies have shown that skin may be playing an important role in the sensitization and development of respiratory outcomes [3,5,12–14]. Hence, further research is needed to ascertain skin contact as an alternative route for sensitization.

The current study investigated whether skin plays a role as an entry route for sensitization to high molecular weight protein allergens, as it focused on skin symptoms as a predictive factor for later development of allergic respiratory symptoms and asthma, specifically in the bakery industry.

The results of the study will be used to update existing preventive measures for allergen exposure.

Purpose and benefits

Currently, the focus for preventing respiratory allergic disease is predominantly on the respiratory exposure. However, skin symptoms can be used as a proxy for skin exposure as it implicitly suggests skin contact as well as a likely route of exposure to allergens. Hence, preventive measures accounting for both routes would need to be put into place to protect high risk working populations in industries where allergens pose a health risk.

Research questions

1. Can initial onset of skin symptoms predict the future development of allergic respiratory outcomes in workers exposed to high molecular weight agents (e.g. flour allergens in bakers)?
2. Are there host and/or environmental risk factors that modulate this relationship?

Hypothesis

Skin symptoms, in the absence or presence of allergic sensitization, can predict the development of allergic respiratory symptoms (upper and lower) and asthma in bakers.

Aim

The aim of this study was to ascertain whether skin symptoms in the absence or presence of allergic sensitization could predict the development of allergic respiratory outcomes and asthma in bakers.

Objectives

1. To determine the prevalence of skin symptoms in the absence or presence of allergic sensitization in this group at baseline.
2. To determine the presence of new-onset *general* or *work-related* respiratory (allergic or irritant) symptoms and asthma, among bakers after four years follow up among those with and without skin symptoms at baseline.
3. To identify risk factors associated with the development of new-onset *general* or *work-related* respiratory (allergic or irritant) symptoms and asthma among bakers after four years follow up, based on the presence of skin symptoms at baseline.

METHODOLOGY

Study design

This retrospective cohort study analysed a subset of data previously collected in cross sectional surveys in 2003 and 2007. It encompassed 517 supermarket bakery workers from 31 bakeries

from a supermarket chain store in the Western Cape province of South Africa. The original study aimed to obtain baseline data of all workers prior to any interventions being done to reduce sensitization to flour dust allergens in these supermarket bakeries.

Study population

For the current analysis, 329 supermarket bakery workers who participated in both the baseline (2003) and follow up survey (2007) and have complete records were included.

Inclusion criteria:

For purposes of this study, the following criteria were applied for inclusion in the analysis:

1. Participation in the study at baseline (2003) and follow up (2007)
2. Complete information on the presence/absence of skin symptoms at baseline being available
3. Complete information on the sensitization status to flour allergens (IgE) at baseline and follow up being available
4. Complete information on the presence/absence of respiratory outcomes of interest (doctor diagnosed asthma, rhinitis, respiratory symptoms) at baseline being available
5. Spirometry (with or without bronchodilator use) or methacholine challenge test results at baseline being available
6. Complete information on respiratory symptoms (general and/or work-related) at follow up being available
7. Exhaled nitric oxide (FeNO) test results at follow up being available

Exclusion criteria:

Workers with the following criteria were excluded from the analysis:

1. Presence of doctor diagnosed asthma at baseline.
2. Presence of bronchial hyperresponsiveness (based on methacholine challenge and positive post-bronchodilator test) at baseline.

Sample size calculations

This study analysed data from all 329 subjects who participated in both surveys in 2003 and 2007. In this event no sample size calculation was applicable. However, since this was a retrospective analysis, information on the proportions of the outcome in subjects with and without the predictive factor was available. Hence, after applying exclusion criteria and using the actual proportion of asthma like symptoms in both groups, the power of the analysis was computed using STATA and found to be 0.69 and considered reasonable to proceed with the analysis.

Measurements

Data collection in the baseline and follow up, four years later, involved 517 participants from the main study[15] and used the following instruments:

a) Baseline assessment

As per Baatjies et al.[15], the following instruments were used in the baseline:

Respiratory health Questionnaire

The baseline questionnaire used was the standard European Community Respiratory Health Survey (ECRHS) questionnaire [16] with additional questions. It gathered information on demographic features, skin and respiratory symptoms, other allergic conditions, smoking status, domestic flour dust exposures (practice and frequency of baking activities in the home), health and safety education and training, and degrees of exposure to flour dust during previous and current employment. Occurrence of skin symptoms ("itchy/scratchy skin", "hives ("bommels")", "dry, scaly skin", "redness of the skin", "blisters or weeping skin", "burning skin"), its distribution ("hands/forearms" or "whole body") and its frequency in the last year were investigated for both the work and domestic environments. The presence of work-related skin symptoms, hands/fingers trauma at work and the frequency of hand washing were also assessed. Categorization of smoking status included the following groups: never-smokers (lifelong abstinence), ex-smokers (defined as having quit completely 1 month prior to the survey), ever smokers and current smoker. Upper and lower airway symptoms were deemed to be work-related if they were reported to worsen during the work shift and improve when away from work. The questionnaire was administered in English or in the language of the worker where appropriate.

Skin prick tests

Skin prick tests (SPT) were performed using the following standard common local aeroallergens (ALK-Abello´ A/S, Horsholm, Denmark): house dust mite (Dermatophagoides pteronyssinus), bermuda grass (Cynodon dactylon), rye grass (Lolium perenne), grass mix (Pollen III: Avena, Hordeum,Triticum, Secale), cockroach (Blattella germanica), cat (Felis domesticus), dog (Canis familiaris), mould mix (Cladosporium herbarum, Alternaria lternata, Fusarium) and Aspergillus (Aspergillus fumigatus). A positive SPT was regarded as a wheal read 15 min after testing that had a diameter (mean of two perpendicular measures) of 3 mm or more than the negative control. Areas of wheal were traced on clear tape and stored for later measurement. For the purposes of our study, atopy was considered to be present if the SPT to one or more common aeroallergens was positive. The presence of atopy in workers who did not undergo SPTs (n510) was defined by a positive Phadiatop*1* test (ImmunoCAP 100 System; Phadia, Uppsala, Sweden).

Allergen-specific immunoglobulin E

Serum-specific immunoglobulin E (IgE) levels to flour dust allergens were measured in 424 workers. Quantification of specific IgE antibodies to wheat (f4), rye (f5) and fungal α-amylase (k87) was performed using CAP-FEIA (fluorescence enzyme immunoassay) 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/European Respiratory Society guidelines [17]. Workers were required to refrain from smoking for 1 hour, from using short-acting b2-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.

Methacholine challenge test

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 [18]. The doses were delivered by the Jaeger APS MedicAid Side Stream APS-Nebulizer (Sensormedics, CA, USA) according to the manufacturer's instructions, commencing with the lowest dose of 0.026 mg and a maximum of 0.4 mg. In subjects in whom PD_{20} methacholine was contraindicated, such as those with acute asthma symptoms or a baseline FEV_1 <1.5 L or FEV1 <70% predicted, a bronchodilator (400 mg salbutamol dose) was administered instead. A change in FEV_1 of $\geq$12% 10 min after administration of bronchodilator was considered suggestive of bronchial hyperresponsiveness.

b) Follow up assessment

According to Baatjies et al. [15] the following instruments were used to collect data on workers for the follow up assessment:

Respiratory health questionnaire

All workers responded to the questionnaire, which collected information on demographics, general and work-related respiratory symptoms and several factors influencing FeNO levels, viz. smoking status, alcohol consumption, current medication, recent nitrate-containing food-intake (green vegetables), physical activity and lung function test.

Fractional exhaled nitric oxide (FeNO) test

A hand-held portable nitric oxide sampling device (NIOX MINO) was used to determine FeNO during the work shift in all workers. It was performed in a room distant from the bakery area during the work shift throughout the working week according to American Thoracic Society (European Community Respiratory Health survey)/European Respiratory Society (ERS) recommendations [19,20]. 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 one hour 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. A FeNO levels >50ppb was considered to indicate the presence of allergic airway inflammation, while levels from 25 to 50ppb considered to be elevated [19].

DATA MANAGEMENT AND ANALYSIS

In the data analysis, the following variables were studied in detail.

List and definition of variables

Table 1 below depicts the information that was studied at baseline and at 4 years follow up in order to generate the predictor and outcome variables and investigated the possible risk factors associated with the outcomes.

Table 1. Predictor and outcome variables

Baseline data (2003)	**Outcome data at follow up (2007)**
Questionnaire: - Doctor diagnosed asthma and/or rhinitis - Respiratory symptoms - Skin symptoms (pattern and distribution) *Immunological tests:* - Specific IgE to wheat/rye/alpha-amylase - Skin prick test/Phadiatop for atopy *Pulmonary function tests:* - Spirometry - NSBH (from methacholine challenge and positive post-bronchodilator test) *Risk factors:* - Host: age, gender, atopy, smoking, childhood eczema, pre-existing skin disease, trauma, hand washing activities - Environmental: employment/job duration, job type, personal protective equipment use	*Questionnaire:* Newly diagnosed asthma and/or rhinitis Respiratory symptoms (upper and lower) -Work-related -General *Immunological tests:* Specific IgE to wheat/rye/ α-amylase *Pulmonary function:* Exhaled nitric oxide (FeNO)

Predictor variables

The main predictor variables pertained to the presence of:

Skin symptoms in terms of:

- Clinical features
  - Itchy/scratchy skin
  - Hives (" bommels")
  - Dry, scaly skin
  - Redness of the skin
  - Blisters or weeping skin
  - Burning skin
  - Skin trauma (bruised, burnt or injured)
  - Composite skin variable (presence of itchy/scratchy skin, or hives -"bommels" or redness of skin)
- Distribution
  - Forearms/hands
  - Whole body

A*llergic sensitization* (elevated IgE of >0.35 KU/L to flour allergens: wheat, rye or α-amylase)

Atopy (SPT to one or more common aeroallergens was positive. The presence of atopy in workers who did not undergo SPTs was defined by a positive Phadiatop test, ImmunoCAP 100 System; Phadia, Uppsala, Sweden).

Outcome variables

The following outcome variables were generated using the primary data as outlined above to investigate the outcomes of interest:

- Newly self-reported asthma
- Newly prescribed treatment for asthma
- Newly prescribed treatment for rhinitis
- New-onset of two or more lower respiratory symptoms
- New-onset of work-related lower respiratory symptoms
- Newly self-reported rhinitis
- Newly reported work-related rhinitis
- Presence of high FeNO (>50ppb) – allergic airway inflammation
- Sensitization to any flour dust allergen (wheat/rye/α-amylase)

Data Analysis

STATA V.14 computer software (StataCorp, College Station, Texas, USA) was used to analyse the respiratory health questionnaires, immunological tests (skin prick tests and serum-specific immunoglobulin E for flour allergens), pulmonary function tests and fractional exhaled nitric oxide (FeNO). Association between skin symptoms and sensitization at baseline and subsequent development of allergic respiratory outcomes was investigated. The associations of interest were investigated in two groups (Figure 1): workers who reported skin symptoms and those without symptoms at baseline. The group with skin symptoms was further categorised into workers with and without sensitization.

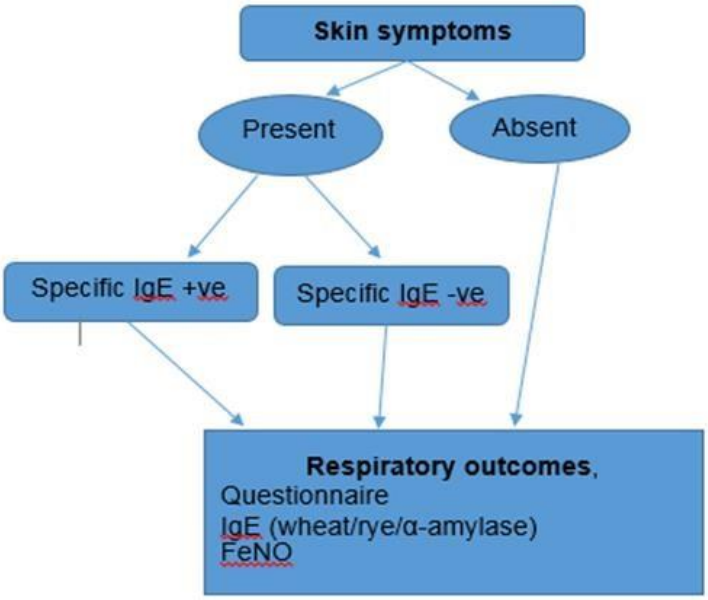

Figure 1. Flowchart for assessment of skin as a predictor of allergic respiratory outcomes

At follow up, information about allergic respiratory symptoms, specific IgE to flour dust allergens (wheat/rye/α-amylase) and abnormal FeNO results were analyzed to calculate the incidence of work-related and general new-onset allergic respiratory symptoms (upper and lower) and asthma. Bivariate analysis and multivariate logistic regression, were used to investigate associations between the predictor variables and the outcomes and to identify possible risk factors modulating the relationship.

Due to the fact that this study was based on secondary data analysis, one of the potential limitations was lack of power to identify real effect, as the sample size was predetermined. Other limitation was the healthy worker effect. There is a trend for workers who develop occupational disease to leave their jobs. Hence, in this cohort, it is possible that workers who developed new-

onset allergic respiratory outcomes and asthma may have left their employment. This could give the false impression that the active force is healthier than it actually is, leading to biased estimates. In this case, since loss to follow-up would have most likely be differential with respect to disease status (allergic respiratory outcomes), the measure of effect (Risk Ratio-RR) could have declined in magnitude.

ETHICS AND COMMUNICATION

This study involved secondary data analysis and no additional data was collected. Hence, there was no additional risk for original study participants. The original study was approved by the Research Ethics Committee of the University of Cape Town (reference no. 272/2002). The Declaration of Helsinki principles [21] were applied to the study:

Autonomy

The participants in the original study were informed about it being a voluntary study in terms of participation in the interviews, tests (skin, blood and pulmonary function) and the right to leave the study at any point in time. Moreover, all participants signed written informed consent.

Confidentiality

The data was recorded by patient number and the original patient records were not made available to the investigators. Hence, researchers were blinded regarding individual participant identity.

Beneficence

At the time of the original study at both time points, patients were given all test results with their respective interpretation (if not acknowledged otherwise) and advised to show the results to their doctor if any problems were identified. This supplementary analysis did not directly benefit the participants directly. However, the findings will eventually contribute to awareness and better working conditions and improved medical surveillance of at risk workers.

Non-maleficence

The original study presented some low risk (discomfort) due to invasive and non-invasive procedures performed (blood sample collection, skin prick test and pulmonary function and challenge tests). However, the possible risk was minimized by means of pre-test screening and the procedures took place under controlled conditions (with skilled medical personnel for any possible emergencies). Participants gave informed consent and no adverse events were finally reported in this study. For the present analysis, there was no additional risk for participants since access to them was not required.

Justice

This study was done on bakers who are a high-risk group of workers for allergic sensitization. I is envisaged that the findings of the study would lead to improvement of preventive measures accounting for both routes of exposure to allergens, inhalation and skin contact, which ultimately could lower the risk of occupational allergic disease in this group of workers.

Dissemination of research results

The analysis was performed for purposes of completion of the MMed degree and results will be disseminated through the MMed dissertation, a peer-reviewed publication in an appropriate journal and research forums.

Funding

Funding support for the original study was provided by research grants from the Medical Research Council of South Africa (Cape Town), National Research Foundation (Pretoria), Fogarty International Centre (Bethesda, MD, USA), the Allergy Society of South Africa (Cape Town) and University of Cape Town Research Committee (Cape Town) and the baking industry (Cape Town).

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PART B: LITERATURE REVIEW

SKIN EXPOSURE, SYMPTOMS AND ASTHMA IN OCCUPATIONAL SETTINGS – IS THERE A LINK?

ABSTRACT

Occupational contact with allergens through the dermatological and respiratory route can lead to various health effects, including allergic contact dermatitis, urticaria, rhinitis and asthma, which may result in a substantial disease burden in occupational settings. Inhalation is an obvious route for sensitization and its pathophysiologic mechanisms are relatively better defined. Recent studies have suggested that skin exposure may also play an important role in the sensitization and development of respiratory outcomes in exposed workers. The review found that the evidence for such an association was limited and the immune mechanisms not well understood. A better understanding of this association is required, more so for high molecular weight (protein) agents since the evidence is more scant in the literature, so as to identify important risk factors that may contribute towards existing preventive efforts in reducing the incidence of allergy and asthma in occupational settings.

INTRODUCTION

Diverse immune responses have been associated with various environmental allergen exposures to the skin, resulting in activation of the adaptive immune response [1]. In barrier-disrupted skin, type 2 lymphoid cells, mast cells and basophils are known to trigger pathogenic Th2 responses in murine models [2]. However, even when the skin barrier is intact; it still has properties that may allow, to some extent, permeability to some allergens. The “brick and mortar” model, a schematic explanation of the permeability of the stratum corneum, in which corneocytes are the bricks and the lipids are the mortar, presents the stratum corneum as a metabolically active structure with adaptive functions. This could be behind the mechanism in which some allergens

could be absorbed by an healthy skin [3].

Some epidemiological studies and animal experiments have demonstrated positive associations between skin and respiratory symptoms and positive exposure-response relationships, while others have not been able to replicate this [4–9].

One of the main issues highlighted by these observations has been the challenges in investigating skin exposure [10]. Methodologies to assess skin exposure are not as well advanced as for inhalational assessment and there is limited exposure data [11,12]. Additionally, airborne exposure to skin is variable and sporadic and there is uncertainty regarding the extent of skin uptake [10]. Furthermore, most workers are exposed to mixtures of occupational agents, making it difficult to identify the specific exposure responsible for the health outcome of interest. For example, exposure to beryllium and isocyanates typically occurs in mixed exposure settings and these agents may be present in various physical or chemical forms, viz. metal particles, oxides, salts and alloys with copper and other metals [10].

The main objective of this literature review was to assess the nature and extent of the associations between skin and respiratory symptoms following skin exposure to high and low molecular weight sensitizers. The review included all relevant English publications that were retrieved from PubMed/Medline and Google Scholar. The key search terms that were used in this review were terms used in other reviews and included “skin”, “asthma” OR “dermal” AND “high molecular weight” OR “low molecular weight” AND “sensitization” OR “dose-response” OR “link”. Other terms that were subsequently added included: allergen, allergy, atopy, occupational, work- related, respiratory, dermatological, dermatitis. Furthermore, some articles were retrieved using the functions “similar articles search” in PubMed and “related articles” in Google Scholar as well relevant articles that were cited in the references of these articles.

EPIDEMIOLOGICAL STUDIES

Co-existing or sequential development of dermal and respiratory outcomes

Workers in various occupations report both skin and respiratory symptoms. Table 1illustrates case study reports in which both dermal and respiratory outcomes, (diagnosed using patch tests and inhalation challenge tests, respectively) were observed in occupational settings with diverse exposures. These allergens can cause both occupational asthma (OA) as well as allergic contact dermatitis (ACD) [13]. To ascertain which health outcome precedes the other can be a challenge due to the nature of the study design used and the lack of a comparison group in such reports.

Arrandale [4] conducted an analysis of four cross-sectional pooled studies from a soda ash plant, softwood planing mill, embalming and cabinet making, in which workers were exposed to ammonia, softwood dust, formaldehyde and/or glutaraldehyde and hardwood dust, respectively. Altogether, both skin and respiratory symptoms were reported by 11% (26/236). The highest prevalence of both dermal and respiratory symptoms was seen among embalmers, with no statistical significance. Although this study does not show temporality, it reinforces evidence of co-occurrence of both respiratory and dermal symptoms in occupational settings [4]. Similarly, previous studies among sewage treatment and isocyanate workers reported concomitant occurrence of dermal and respiratory symptoms in exposed workers [14,15]. However, Bauer et al. [16] could not stablish correlation between occupational hand dermatitis and flexural dermatitis, respiratory atopy (allergic rhinitis and bronchial asthma), serum IgE ±100IU/ml or metal sensitization in their study in bakers.

Aside from the need to identify temporality, the co-existence of dermal and respiratory symptoms does not necessarily indicate that the same exposure is the trigger for both outcomes,

unless the exposure assessment specifically characterised the nature and route of the exposures in affected workers [13].

Table 1. Co-occurring occupational asthma (OA) and occupational contact dermatitis (OCD) – diagnosed using specific inhalation challenge and patch testing – case reports reported

Exposure	Occupation	Author (year)
2-hydroxyethyl methacrylate (HEMA)	Beautician	Moulin et al., 2009
Diglycidyl Ether of Bisphenol A (DGEBA)	Resin applier	Moulin et al., 2009
Diphenylmethane-4,4'- diisocyanate (MDI)	Manufacturing (Automotive Industry)	Valks et al., 2003
Potassium Dichromate	Cement Floorer	De Raeve et al., 1998
Aziridine Hardener	Painter and varnisher	Kanerva et al., 1995
Onion	Homemaker	Valdivieso et al., 1994
Nickel	Manual grinding of metal castings	Estlander et al., 1993
Spiramycin	Poultry breeder	Paggiaro et al., 1979

Reproduced from Arrandale 2012 [13]

Association between skin exposure, allergy specific sensitization and subsequent development of respiratory disease

Table 2 summarises the few key epidemiological studies that have investigated the role of skin exposure and symptoms and the subsequent development of respiratory symptoms including asthma in these workers.

Brisman et al. [16] have alluded to the association between bakers' asthma and eczema, without indicating whether sensitization to wheat flour was due to inhalation or due to contact with allergens through the skin (or both). In a study of bakers and auto body shop workers

(ABSWs) exposed to wheat and isocyanates respectively, Arrandale et al. [5] reported an association between skin and respiratory symptoms. Work-related itchy skin was associated with wheeze, asthma-like symptoms and work-related asthma symptoms in ABSWs but not bakers. The authors did, however, indicate, that the body shop workers had adhered to much stricter use of personal protective equipment, while such use of personal protective equipment had not been observed by the bakers [5]. A previous study by Arrandale et al. [4] also found that eczema increases the odds of concurrent work-related skin and respiratory symptoms [4]. It needs to be borne in mind that this not necessarily indicate that skin exposure is always predictive of respiratory outcomes.

Lynde et al. [18] investigated a group of predominantly male (84%) professional cleaners with 9.3% having a current rash and 18.6% reporting a rash in the last 12 months. The study found that cleaners with a current rash and those reporting a rash in the last twelve months were at significantly increased odds of reporting work-related respiratory symptoms compared to those without a rash. This suggested an association between the presence of work-related asthma symptoms and dermatitis among professional cleaners [18]. However, atopy was considered as a possible underlying mechanism for this association, and lack of PPE use could have also been another factor influencing this association [18].

Isocyanates, used in spray-painting and polyurethane foam products, have received considerable attention in relation to skin exposure and the resulting effects of asthma [5,7,10,20-21]. A key link for suggesting an association between allergic sensitization via transcutaneous route for isocyanates and asthma has been the improvement in occupational health standards in workplaces due to the use of respirators to prevent isocyanate inhalation. However, the incidence of isocyanate-induced asthma remains persistently high, particularly in settings where skin-

contact with isocyanates has not been well controlled [20]. A laboratory study by Karol et al. [22] reported that isocyanate exposure to the skin, particularly TDI, could induce pulmonary hypersensitivity in guinea pigs. Subsequent studies have shown that similar patterns of sensitization exist in humans [1,5,7].

Table 2. Studies of working populations investigating the association between skin exposure/symptoms and respiratory symptoms/asthma

Author & year	**Arrandale et al., 2013** [5]	**Arrandale et al., 2012** [4]	**Lynde et al., 2009** [18]	**Petsonk et al., 2000** [22]
Aim of study	To investigate associations between skin and respiratory symptoms in bakery and auto body shop workers (ABSW)	To identify predictors of reporting concurrent skin and respiratory symptoms in a clinical population	To compare the prevalence of occupational cutaneous symptoms among professional indoor cleaners to other building workers (OBW) and their association with exposures and respiratory symptoms	To evaluate the respiratory health of workers exposed to Methylene Diphenyl Diisocyanate (MDI)
Study design	Cross-sectional	Cross-sectional	Cross-sectional	Cohort
Population	723 bakers 473 ABSW	204 patients from the occupational health clinic	549 professional cleaners 593 OBW	214 wood product plant employees (144 completed initial, follow-up and occupational questionnaires)
Agent	Isocyanate and Wheat	Multiple agents (animal dander, cement, isocyanates, pesticides, wet work, , dust, fumes, paint)	Cleaning agents	MDI
Assessment tool/s	Questionnaire, IgE for common inhalants, specific challenge tests and personal airborne exposure measurements	Questionnaire	Questionnaire	Questionnaire, serial peak flow, spirometry, methacholine challenge, specific IgE
Skin symptoms prevalence (%)	Work-related itchy skin: ABSW - 9%; Bakers - 17%	Possible work-related skin disease: 82%	Current rash: cleaners - 10%, OBW 6%	Not reported

Author & year	**Arrandale et al., 2013** [5]	**Arrandale et al., 2012** [4]	**Lynde et al., 2009** [18]	**Petsonk et al., 2000** [22]
			Rash in the past 12 months: cleaners - 19%, OBW 16%	
Respiratory symptom prevalence (%)	Work-related asthma symptoms (WRAS): ABSW - 4%; Bakers - 2%	Possible work-related respiratory disease: 18%	In males with rash: • physician-diagnosed asthma - 19% • new onset asthma 14% • ≥3 respiratory symptoms: 77% • ≥2 WRAS: 63% • ≥3 WRAS: 40%	Among the 178 (who participated in at least 1 follow-up survey): • initial asthma-like symptoms - 11% • follow-up asthma-like symptoms - 20% • new-onset asthma-like symptoms - 12%
Association between skin exposure/ symptoms and respiratory symptoms/ asthma	Association between work-related itchy skin and respiratory symptoms in: ABSW: • Wheeze OR= 2.50 (95% CI 1.7–3.6) Asthma like symptoms OR=2.12 (95% CI 1.5–3.0) • WR asthma symptoms OR=3.61 (95% CI 1.4–9.4) Bakers: • Wheeze OR=1.60 (95% CI 1.1–2.3) • Asthma like symptoms OR=1.54 (95% CI 1.2–2.0) • WR asthma symptoms OR=2.15 (95% CI 0.7–6.3) Exposure-response relationship in ABSW	Eczema increases odds of concurrent work-related skin and respiratory symptoms: OR=3.68 (95% CI: 1.7–7.8)	Rash in the past 12 months associated with: • Physician diagnosed asthma OR=2.3 (95% CI: 1.1–4.5) • New onset asthma OR=3.0 (95% CI: 1.2–7.6) • ≥3 respiratory symptoms OR=2.6 (95% CI: 1.6–4.3) • ≥2 WRAS OR=3.2 (95% CI: 1.9–5.3) • ≥3 WRAS OR=4.0 (95% CI: 0 2.2–7.2)	52% of workers who reported MDI skin stains reported asthma-like symptoms

Author & year	**Arrandale et al., 2013** [5]	**Arrandale et al., 2012** [4]	**Lynde et al., 2009** [18]	**Petsonk et al., 2000** [22]
	• itchy/dry skin PR=1.55, 95 % CI: 1.2–2.0 • work-related itchy skin PR= 1.97 (95 % CI 1.2–3.3)			
Study limitations	• poor correlation between airborne and skin exposure for particulates • lack of information on other, potentially causal, exposures in the workplace • potential role of Type IV allergy or irritant mechanisms in symptom development not modelled • healthy worker effect due to fewer symptomatic subjects at higher exposure levels	• cross-sectional study – temporality cannot be ascertained • not generalizable to all workers due to the selective clinical population	• low response rate • outcomes (rashes) were self-reported and not clinically confirmed	• loss to follow up • lack of environmental exposure measurements f

PATHOPHYSIOLOGICAL CORRELATES

Several studies in children have suggested that skin exposure and sensitization precede the response in the airways. Dohi et al. [24] compared eight atopic dermatitis (AD) patients without previous report of asthma symptoms, and 8 mite-allergic asthmatic patients. These 2 groups were

subjected to bronchial inhalation challenges (non-specific with methacholine and specific with house dust mite). Results demonstrated that both IgE and anti-mite IgE antibody were higher in AD patients than mite-allergic asthmatic patients [24]. The response for methacholine in AD patients was from normal to asthmatic range. In a study by Lack et al. [25], peanut allergy did not show dependent association with intake of soymilk and soy formula. Peanut allergy was however associated with skin rash over the joints and flexures, crusted skin rash, and intake of soy milk and soy formula. In addition, use of peanut containing oils on the skin were associated with peanut allergy, suggesting that skin exposure could lead to generalised sensitization [25]. In more severe form, local skin contact with certain foods, medications, latex, metals and occupational allergens may result in generalised urticaria or systemic symptoms (angioedema, wheezing) [26].

It has also been suggested that beryllium sensitization in those suffering from chronic beryllium lung disease (CBD), may also have percutaneous origins. Tinkle et al. [27] observed that decreasing inhalational exposure had no effect on the incidence of the disease, suggesting that inhalation was not the only cause for the disease. The investigators suggested that following skin exposure to beryllium, the inhalational exposure to beryllium necessary to elicit an immune response and the formation of a CBD-related granuloma, was significantly reduced. In further support of this hypothesis, topical application of beryllium ointment to C3H/HeJ Heston mice showed an increase in beryllium sensitivity in the mice as determined through beryllium lymphocyte proliferation tests of lymph node and peripheral blood [27]. Furthermore, it has been shown that the stratum corneum (SC), the external layer of the skin, which although mechanically strong and resilient to stress and physical strain, may be penetrated by fine and ultra-fine beryllium particles [27].

The most refined models demonstrating the link between allergic sensitization and asthma from skin exposure, has been from murine experimental studies. Spergel et al. [28] applied the high-molecular weight molecule ovalbumin (OVA) via occlusive patch tests to tape stripped mice skin. This experiment showed an OVA epicutaneous sensitization and local allergic dermatitis. Later, when the sensitized mice was exposed to intravenous methacholine, the response was eosinophilia in the bronchoalveolar lavage fluid and airway hyperresponsiveness [28].

In murine models, it has also been demonstrated that dermal infiltration of eosinophils in response to dust mite allergens in skin that has been sensitized by barrier disruption is greater than sensitization through intact skin [28–31]. This suggests that there is a higher induction of Th2-dominant immunologic responses to environmental allergens through skin that has the skin barrier disrupted, as is experienced in patients with atopic dermatitis [32], and particularly following rubbing or scratching of skin, compared to intact skin. There is common agreement for Th2 response, that allergen exposure requires both the involvement of barrier disruption and an adaptive immune recognition in order to induce an allergic response [1,33].

PREDISPOSING FACTORS FOR ALLERGIC RESPIRATORY SYMPTOMS FOLLOWING SKIN EXPOSURE

Several predisposing risk factors could result in sensitization and to the subsequent development of allergic respiratory symptoms following skin exposure to occupational and environmental allergens.

Host risk factors

Pre-existing skin diseases

Atopic Dermatitis

The integrity of the skin barrier is intrinsic to an individual's ability to respond to dermal allergen exposure [34]. In AD both cellular immune abnormalities and skin barrier defects are known to be behind its pathophysiologic mechanism [35]. Various non-invasive biomarkers of epidermal permeability are used to identify increased risk for allergic sensitization through the skin. Trans-epidermal water loss (TEWL) has been directly, but not exclusively, associated with atopic dermatitis and the associated risk of respiratory allergy [36]. Kelleher et al. [37] found that new-borns with raised TEWL were at increased risk of developing atopic dermatitis at one year of age, as well as IgE associated food allergies, despite the absence of early-onset atopic dermatitis. Loo et al. [38] also demonstrated that children with eczema before 18 months exposed to inhalant allergen (house dust mite) were more likely to present with positive skin prick tests at 18 months [38].

Irritant Dermatitis

A damaged skin barrier, as is present in irritant dermatitis due to either physical, chemical or biological processes, is a potential route of entry for allergens [13]. Nielsen [39] demonstrated that skin treated with higher concentrations of sodium laurel sulphate (SLS), a known skin irritant, had greater overall penetration and a greater rate of penetration of chemical substances (pesticides with a wide range of solubility) compared of with undamaged skin [39].

Ichthyosis vulgaris

Bremmer et al. [34] demonstrated in a study of 491 patients with atopic dermatitis and ichthyosis vulgaris (IV) that those with higher severity of IV were more likely to report asthma, even after adjusting for atopic dermatitis severity, age, sex, and season of symptoms occurrence. He suggested that the presence of severe IV could be used as a marker for patients having a greater likelihood of developing allergic respiratory disease [34].

Trauma

Skin trauma is another risk factor for facilitating entry of contact allergens into the body. This may increase a person's risk of sensitization as has been observed in, for instance, seafood processing workers and animal handling workers (rats) resulting in the development of allergic respiratory symptoms [7,10,40].

Filaggrin gene mutations

One of the first-line factors associated with skin-barrier deficiencies are Filaggrin (FLG) defects [41], which typically occur due to inherent FLG gene mutations [42]. FLG is an important protein responsible for the strength and integrity of the SC, regulating the permeability of the skin to water and antigens, involved with the packing of keratin filaments in the epidermis, and maintaining the skin's normal acid pH. [1] Studies in the general population evaluating allergen exposure via skin, sensitization and respiratory outcomes have been reported [42–44]. Brough et al. [45] reported a positive association between FLG defects and peanut allergy. Filaggrin defects

have also been identified in atopic dermatitis patients, and there appears to be a correlation between the extent of FLG defects, the extent of allergen exposure through the skin, and the severity of atopic dermatitis [45]. It was reported that 50% of patients (in European and Asian populations) with moderate-to-severe atopic dermatitis have loss-of-function mutations in the gene encoding FLG. Additionally, these patients were reported to have an increased the risk of developing inhalant allergic sensitization, allergic rhinitis, asthma, and peanut allergy. In African-American populations this defect is rare [45,46].

Environmental risk factors

Various high molecular weight (generally proteins) and low molecular weight (generally chemicals) allergens are capable of stimulating the induction of IgE antibodies and result in sensitization and the development of allergic respiratory symptoms [7]. The extent to which they are able to do so will depend on the agent's physical properties, exposure intensity and duration.

Agent

Physical properties

Theoretically, liquid and solid allergens will facilitate skin contact and entry when compared to aerosolised substances. Petsonk et al. [23] found that after 2 years of working in a wood manufacturing plant, subjects who worked with liquid methylene diphenyl diisocyanate (MDI) had a relatively higher odd of reporting asthma-like symptoms than those who did not work with liquid MDI. Additionally, those who reported observing MDI skin stains at least once

(suggesting skin exposure) also had higher odds of reporting asthma-like symptoms compared to those who never observed such stains. However, the prevalence of asthma-like symptoms was more prevalent among workers who reported brief removal of respiratory personal protective equipment (PPE) while performing their routine tasks that included liquid MDI handling. The investigators concluded that although inhalation was an important route of exposure for development of the respiratory symptoms, skin exposure may have also played a role in these outcomes.

Chemical properties (molecular structure)

Transcutaneous chemical penetration also depends on chemical characteristics of agents. Haptens must be structurally able to bind with a protein as a pre-requisite to be recognized by the immune system. [39] While lipophilic properties facilitate skin permeability for allergens, [39] hydrophilic properties are also needed to allow for movement of the chemical from the SC into the dermis [47]. Hence, an efficient allergen, should be amphiphilic (both lipophilic and hydrophilic) [47]. Low molecular weight particles and molecules, such as nickel and poison ivy (urushiol) are known contact allergens that cause skin sensitization by their action of binding to host proteins in the skin [7]. As a result of their chemical reactivity with host proteins, these particles cause otherwise innocuous compounds to be converted into hapten-protein complexes that stimulate the adaptive immune response [1]. High molecular weight protein allergens such as peanut, dust mite, or water-soluble cat allergens, which range in size from 5,000 Da to 100,000 Da, are generally unable to pass through the skin's cutaneous permeability barrier due to their size [48]. In such instances, it is generally understood that sensitivity to such high molecular weight compounds is only possible when the integrity of the skin is to some extent

compromised [1].

Exposure intensity and duration (dose-response relationships)

The concentration of the agent on the skin surface and the duration of this contact, apart from all other conditions that interfere with the skin integrity, may influence the body's response to an allergen. Some studies in animal models have investigated trimellitic anhydride (TMA), phthalic anhydride (PA) and MDI and found that increasing sensitising intradermal doses did not increase a respiratory response. However, Arakawa et al. [49] found a dose-dependent response in guinea pigs for *Dermatophagoides farinae* (DF mite) and a dose-response relationship with increasing doses of intradermally administered TMA eliciting asthma-like symptoms.

Devos et al. [50] investigated the asthmagenic capacity of Methylisothiazolinone (MI), a known cause of allergic contact dermatitis, commonly used in cosmetics, household products as well as in different industries, in animal models. Fifteen days after dermal administration of MI, the investigators did not show a significant respiratory response (either airway hyperreactivity or inflammation). The study concluded that while MI was a dermal sensitizer and irritant, it was unable to elicit an asthma-like response. Paulunh et al. [9] also investigated the dose-response relationship of MDI exposure in animal models and lung response after primary skin exposure. Surface area or dose-to-body weight did not show specific associations. On the contrary, the magnitude of the respiratory response was dependent on the frequency of inhalation challenge doses administered instead of the previous cutaneous doses.

CONCLUSION

Skin is an important route of exposure to allergens leading to sensitization and the potential to cause allergic skin symptoms that could co-exist or precede respiratory symptoms, and other systemic health outcomes. There is, however, much that still needs to be investigated to better understand the modes of entry and sensitization in occupational settings. Particularly among workers exposed to high molecular weight protein allergens since the evidence for this is scant in the literature, there is a need to ascertain the pathophysiological mechanisms involved in skin exposure resulting in respiratory disease and other systemic effects. By addressing these issues, better interventions aimed at preventing occupational exposure to these allergens can be achieved.

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PART C: JOURNAL ARTICLE MANUSCRIPT

This manuscript has been prepared to be submitted for publication in the journal, Occupational and Environmental Medicine. The format of the article follows the journal's guidelines for authors (Appendix 12)

SKIN SYMPTOMS PREDICTING THE DEVELOPMENT OF ALLERGIC RESPIRATORY OUTCOMES AND ASTHMA IN BAKERS

Vânia Chongo-Faruk

ABSTRACT

Objective: The aim of this study was to ascertain whether skin symptoms could predict the development of allergic respiratory outcomes and asthma in bakers.

Methods: A cohort study investigated 263 bakery workers using a modified ECRHS questionnaire; immunological tests including skin prick tests for common local aeroallergens, Phadiatop and serum-specific IgE to bakery allergens (wheat, rye and fungal α-amylase); and pulmonological tests including spirometry, non-specific bronchial hyperresponsiveness and fractional exhaled nitric oxide (FeNO), over a four-year period.

Results: Workers' median age was 32 years (IQR: 26-38), 50% were female, 54% were ever smokers and 32% were atopic. At baseline, 26% of workers were sensitized to bakery allergens, skin symptoms were present in 22% and 11% reported work-related skin symptoms (WRSS). While the incidence of general upper (19%) and lower (22%) respiratory symptoms over the follow-up period were very similar, work-related upper (29%) respiratory symptoms were higher than lower (20%) respiratory symptoms. However, the incidence of allergic sensitization to bakery allergens was only 8% and a new asthma diagnosis present in 4% over this period. In multivariate adjusted (gender, atopy and smoking status) regression models, having a history of skin symptoms was associated with an increased risk of developing work-related lower respiratory symptoms - WRLRS (RR=2.2, 95% CI: 1.03-4.83), while having clinically significant symptoms of eczema or urticaria was associated with an increased risk of reporting general upper respiratory symptoms (RR=5.5, 95% CI: 1.30-24.20) as well as

WRLRS (RR= 4.8, 95% CI: 1.60-14.40). Furthermore, WRSS was associated with an increased risk of general upper respiratory symptoms (RR=5.1, 95% CI: 1.31-19.81), WRLRS (RR=4.1, 95% CI: 1.43-11.85) and high levels of FeNO (FeNO>25ppb: RR=2.9, 95% CI: 1.19-7.28). The association between clinically significant skin symptoms or WRSS and new onset upper or lower respiratory symptoms were modified by use of dermal personal protective equipment. Infrequent or absent glove usage was associated with a higher risk (RR=5.3, 95% CI: 1.54-18.43) of having new onset WRLRS.

Conclusion: Skin symptoms, more so if work-related, appear to be associated with the future presence of general and work-related upper and lower respiratory symptoms and increased inflammatory marker levels suggestive of asthma in bakery workers.

Keywords: bakers, skin symptoms, asthma

WHAT THIS PAPER ADDS

1. Skin symptoms can predict further development of adverse respiratory outcomes in bakers.
2. Bakers who develop work-related skin symptoms are at increased risk to further develop allergic airway inflammation, upper and lower respiratory symptoms.
3. Absent or infrequent use of dermal protection increases the risk of developing allergic airway inflammation and chest symptoms in bakers.

INTRODUCTION

Occupational contact with allergens through the dermatological and respiratory route can lead to various health effects, including allergic contact dermatitis, urticaria, rhinitis and asthma, which may result in a substantial disease burden in occupational settings. Inhalation is an obvious route for sensitization and its pathophysiologic mechanisms are relatively better defined. Recent studies have suggested that skin exposure may also play an important role in the sensitization and development of respiratory outcomes in exposed workers. The review found that the evidence for such an association was limited and the immune mechanisms not well understood. A better understanding of this association is required, more so for high molecular weight (protein) agents, so as to identify important risk factors that may contribute towards existing preventive efforts in reducing the incidence of allergy and asthma in occupational settings [1].

A few epidemiological studies and animal experiments have demonstrated positive associations between skin and respiratory symptoms and positive exposure–response relationships, whereas others have not been able to replicate this association [2–7]. One of the main issues highlighted by these observations has been the challenges in investigating skin exposure [8]. Methodologies for assessing skin exposure are not as well advanced as for inhalational assessment, and exposure data are limited [9,10]. In addition, airborne exposure to skin is variable and sporadic and there is an uncertainty regarding the extent of skin uptake [8]. Furthermore, most workers are exposed to mixtures of occupational agents, making it difficult to identify the specific exposure responsible for the health outcome of interest.

Several host and environmental factors are implicated in the pathophysiological process of sensitization and further development of allergic respiratory symptoms following skin exposure. Host factors such as pre-existing skin diseases, namely, atopic dermatitis, irritant dermatitis, ichthyosis vulgaris and trauma were shown to increase the risk of sensitization following dermal allergen exposure[1]. Filaggrin gene mutations were also reported as a risk factor to develop sensitization and respiratory outcomes in studies investigating dermal allergen exposure [11–15]. Environmental factors such as the agent's physical [16,17] and chemical properties [18–21] determine its likelihood to cross the skin barrier and to stimulate the induction of IgE antibodies resulting in sensitization. However, dose-response relationship may also have a crucial role to play in this process for some allergen agents [5,22,23].

In the bakery industry, very little is known regarding the role of skin exposure in the process of sensitization and subsequent development of respiratory disease. The aim of this study was to investigate whether skin symptoms in the presence or absence of allergic sensitization could predict the development of allergic respiratory outcomes and asthma in bakers over a four-year follow-up period.

MATERIALS AND METHODS

Study design, population and sampling

This retrospective cohort study analyzed a subset of data previously collected in cross sectional surveys in 2003 and 2007. It encompassed 517 supermarket bakery workers from 31 bakeries from a supermarket chain store in the Western Cape province of South Africa. The original study aimed to obtain baseline data of all workers prior to any interventions being done to reduce sensitization to flour dust allergens in these bakeries. The aim of the follow-up

study, encompassing 544 workers, was to document the emergence of newly acquired allergic respiratory outcomes.

For the current analysis, 329 supermarket bakery workers who participated in both the baseline (2003) and follow up survey (2007) and had complete records were included. However, further analysis was performed on only 263 subjects that met inclusion criteria. Study exclusion criteria comprised the presence of doctor diagnosed asthma or NSBH/significant airway reversibility at baseline.

Health outcome assessment

a) Baseline assessment

The following instruments were used in the baseline assessment as reported by Baatjies et al. [24]:

Respiratory health questionnaire

The standard European Community Respiratory Health Survey (ECRHS) questionnaire [25] with additional questions was used. It gathered information on demographic features, skin and respiratory symptoms, other allergic conditions, smoking status, domestic flour dust exposures (practice and frequency of baking activities in the home), and duration of employment, the bakery and job characteristics, including use of personal protective equipment. Occurrence of skin symptoms ("itchy/scratchy skin", "hives" ["bommels"], "dry, scaly skin", "redness of the skin", "blisters or weeping skin"," burning skin"), its distribution ("hands/forearms" or "whole body") and its frequency in the last year were investigated for both the work and domestic environments. The presence of work-related skin symptoms and the frequency of hand washing were also assessed. Smoking status was classified into the following three categories: never-smoker (lifelong abstinence), ex-smoker (defined as having

quit completely 1 month prior to the survey) and current smoker. Upper and lower airway symptoms were deemed to be work-related if they were reported to worsen during the work shift and improve when away from work. The questionnaire was administered in English and in the language of the worker where appropriate.

Skin prick tests

Skin prick tests were performed using the following standard common local aeroallergens (ALK-Abello´ A/S, Horsholm, Denmark): house dust mite (Dermatophagoides pteronyssinus), bermuda grass (Cynodon dactylon), rye grass (Lolium perenne), grass mix (Pollen III: Avena, Hordeum,Triticum, Secale), cockroach (Blattella germanica), cat (Felis domesticus), dog (Canis familiaris), mould mix (Cladosporium herbarum, Alternaria lternata, Fusarium) and Aspergillus (Aspergillus fumigatus). A positive SPT was regarded as a wheal read 15 min after testing that had a diameter (mean of two perpendicular measures) of 3 mm or more than the negative control. Areas of wheal were traced on clear tape and stored for later measurement. For the purpose of this study, atopy was considered to be present if the SPT to one or more common aeroallergens was positive. The presence of atopy in workers who did not undergo SPTs was defined by a positive Phadiatop*1* test (ImmunoCAP 100 System; Phadia, Uppsala, Sweden).

Allergen-specific immunoglobulin E

Serum-specific immunoglobulin E levels to flour dust allergens were measured on all workers. Quantification of specific IgE antibodies to wheat (f4), rye (f5) and fungal α-amylase (k87) was performed using CAP-FEIA (fluorescence enzyme immunoassay) 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/European Respiratory Society guidelines [26]. Workers were required to refrain from smoking for 1 hour, short-acting b2-agonist bronchodilators for 4 hours, and oral asthma medications for 8 hours prior to lung function testing. None of the workers were receiving treatment that included long-acting bronchodilators.

Methacholine challenge test

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 [27]. The doses were delivered by the Jaeger APS MedicAid Side Stream APS-Nebulizer (Sensormedics, CA, USA) according to the manufacturer's instructions, commencing with the lowest dose of 0.026 mg and a maximum of 0.4 mg. In subjects in whom PD_{20} methacholine was contraindicated, such as those with acute asthma symptoms or a baseline FEV_1 <1.5 L or FEV1 <70% predicted, a bronchodilator (400 mg salbutamol dose) was administered instead. A change in FEV_1 of ≥12% 10 min after administration of the bronchodilator was considered suggestive of bronchial hyperresponsiveness.

b) Follow up assessment

According to Baatjies et al. [24] the following instruments were used to collect data on workers for the follow up assessment:

Respiratory health questionnaire

An abbreviated ECRHS questionnaire, which collected information on demographics, general and work-related respiratory symptoms and several factors influencing FeNO levels, viz. smoking status, alcohol consumption, current medication, recent nitrate-containing food-intake (green vegetables), physical activity and lung function test.

Fractional exhaled nitric oxide (FeNO)

A hand-held portable nitric oxide sampling device (NIOX MINO) was used to determine FeNO during the work shift in all workers. 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) and European Respiratory Society (ERS) recommendations [28,29]. 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 one hour 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. A FeNO level >50ppb was considered to indicate the presence of allergic airway inflammation, while levels between 25-50pbp were considered to be elevated [28].

DATA ANALYSIS

The data was analysed using STATA V.14 computer software (StataCorp, College Station, Texas, USA). Descriptive statistics such as medians, interquartile ranges and proportions were used to summarize the data. The incidence of work-related and general allergic respiratory symptoms (upper and lower) and asthma was computed. Key associations of interest involved

investigating the association between skin symptoms at baseline and subsequent development of allergic respiratory outcomes. The associations of interest were investigated among two groups of workers, viz. those who reported skin symptoms and those without skin symptoms at baseline using the Chi-square and Fisher's exact tests where appropriate. These associations were further explored according to sensitization status. Unadjusted logistic regression was used to investigate the association between the incidence of respiratory outcomes and host factors (age, gender, atopy and smoking), environmental factors (job, personal protective equipment - PPE use) and skin symptoms at baseline. Multivariate logistic regression was used to further explore the association between skin symptoms at baseline and respiratory outcomes adjusting for atopy, gender and smoking. This multivariate regression analysis was further stratified by "glove use", as a measure of effect modification. A two-tailed p-value of <0.05 considered to be statistically significant.

RESULTS

Study population

The demographic characteristics of the 263 study subjects that participated in both baseline and the follow-up assessment are outlined in Table 1. Gender was well represented. Almost half of the study population was ever smokers (54% at baseline and 44% at follow-up) and current smokers at baseline had a 4-median pack-years smoking history. The most common job category among the participants was bakers and assistant bakers in both baseline (48%) and at follow-up (51%). The majority of workers (95%) reported using general personal protective equipment (aprons, gloves and masks) on a regular basis. However, only 32% reported using gloves and 2% used respirators. The majority of workers (90%) reported

washing hands six or more times per day and a few workers (4%) reported adverse reactions to grain products on ingestion.

Atopy was presented in 32% individuals at baseline. Sensitization to at least one bakery related allergen was found in 26% and 33% of workers, at baseline and follow-up, respectively. Among those with sensitization to flour dust allergens, wheat and rye were the most common allergens and presented more individuals with elevated IgE levels whilst alpha-amylase were less so (Table 1).

Table 1. Demographics and allergic sensitization characteristics of supermarket bakery workers

Subjects (N = 263)	**Baseline n (%)**	**Follow up n (%)**
Sex (Female- Male)	132-131	132-131
Age (median, IQR)	32 (26-38)	35 (24-41)
Smoking status (ever smokers)	142 (54)	115 (44)
History of current smoker's pack years (median, IQR)	3.8 (2-8)	*
Duration of employment in current bakery (median, IQR)	5.5 (3-8)	*
Duration of employment in current job post (median, IQR)	3 (2-5)	*
Occupation (~)		
Counter hands	54 (21)	29 (13)
Bakers and assistant bakers	126 (48)	111 (51)
Confectioners	31 (12)	28 (13)
Managers and supervisors	29 (11)	51 (23)
Others	23 (9)	44 (17)
General use of personal protective equipment on a regular basis	249 (95)	*
Use of respirator only on a regular basis	4 (2)	*
Use of gloves only on a regular basis	85 (32)	*
Hand washing frequency		
Less than six times per day	25 (10)	*
Six or more times per day	238 (900	*
Self-reported adverse reactions to grain products	10 (4)	*
Rye products	6 (2)	*
Whole-wheat products	3 (1)	*
White bread	0	*
Breakfast cereals	1 (0)	*
Baking activities at home	111 (42)	*
Eczema (childhood)	9 (3)	*
Atopy	85 (32)	85 (32)
Sensitization to flour allergens (IgE>0.35 kU/L) (†)		
Wheat	65 (25)	69 (32)
Rye	61 (23)	62 (28)
Alpha-amylase	5 (1)	5 (2)
To at least one flour dust allergen	68 (26)	72 (33)

(*) – Data not available at follow-up; (~) n=219 for follow-up; (†) N=262 at baseline, N=219 for follow-up

Skin symptoms were present in 22% of participants, with 13% reporting two or more episodes of skin problems in the last 12 months (Table 2). The skin problems commonly affected the hands more than the entire body. While skin trauma (bruises, burns and injury) was highly prevalent (78%), work-related skin symptoms were reported in 11% of subjects. Stratifying according to sensitization status, certain skin symptoms affecting hands were more prevalent at baseline. These included having itchy/scratchy skin, hives or redness of the skin. The prevalence of work-related skin symptoms among sensitized workers (18%) was also two-fold higher that non-sensitized workers (9%).

Table 2. Prevalence of skin symptoms of supermarket bakery workers at baseline stratified according to sensitization status

Skin symptoms	**Overall (N = 262) n (%)**	**Presence of sensitization (N = 68) n (%)**	**Absence of sensitization (N = 194) n (%)**	**Chi-square p-value**
Presence of skin symptoms ever	58 (22)	15 (22)	43 (22)	0.986
Two/more episodes of skin problems in the last 12 months	33 (13)	12 (18)	21 (11)	0.145
Symptoms affecting the hands				
- Itchy/scratchy skin	20 (8)	10 (15)	10 (5)	**0.011**†
- Hives (”bommels”)	10 (4)	7 (10)	3 (2)	**0.004***†
- Dry, scaly skin	15 (6)	6 (9)	9 (5)	0.227*
- Redness of the skin	16 (6)	8 (12)	8 (42)	**0.036***†
- Blisters or weeping skin	3 (1)	1 (1)	2 (1)	1.000*
- Burning skin	7 (2)	4 (6)	3 (2)	0.077*
- Composite skin variable (**)	23 (9)	11 (16)	12 (6)	**0.012**†
Symptoms affecting the entire body				
- Itchy/scratchy skin	16 (6)	5 (7)	11 (6)	0.569*
- Hives (”bommels”)	6 (2)	3 (4)	3 (2)	0.183*
- Dry, scaly skin	14 (5)	5 (7)	9 (5)	0.365*
- Redness of the skin	13 (5)	3 (4)	10 (5)	1.000*
- Blisters or weeping skin	0	-	-	-
- Burning skin	4 (2)	1 (1)	3 (2)	1.000*
Skin trauma (bruise, burn or injury)	205 (78)	55 (81)	149 (77)	0.486
Work-related skin symptoms (~)	30 (11)	12 (18)	18 (9)	0.062

Sensitization data available for N=262; (*) – Fisher’s exact test; (~)-unspecified body area, (**) – presence of Itchy/scratchy skin; or hives (”bommels”) or redness of skin; (†) $p<0.05$

From the general respiratory outcomes (Table 3), ocular-nasal symptoms were the most prevalent at both baseline (33%) and follow-up (36%). Lower respiratory symptoms (such as tight chest, wheeze, shortness of breath and cough) were lower at baseline (19%) than at follow-up (31%). The prevalence of asthma was however similar (8%) at both points of assessment. As expected, the incidence of work-related ocular-nasal symptoms (29%) was higher than lower respiratory symptoms (20%). The prevalence of allergic sensitization increased from 26% at baseline to 33% at follow-up with a cumulative incidence of 8% during this follow-up period.

Table 3. General and work-related allergic or irritant respiratory outcomes and asthma at baseline and follow up among supermarket bakery workers

Respiratory outcomes (N=263)	Baseline Prevalence n (%)	Follow up* Prevalence n (%)	Follow up** Incidence		
			N	N (at risk)	%
General outcomes					
Ocular-nasal symptoms (~)	87 (33)	95 (36)	34	176	19
Treatment for rhinitis	24 (9)	13 (5)	6	239	3
Two or more lower respiratory symptoms (tight chest/wheeze/shortness of breath/cough) (~)	50 (19)	81 (31)	47	213	22
Asthma	22 (8)	21 (8)	10	241	4
Treatment for asthma	11 (4)	10 (4)	6	252	2
Work-related outcomes					
Ocular-nasal symptoms	73 (28)	106 (40)	54	187	29
Lower respiratory symptoms (tight chest/wheeze)	37 (14)	64 (24)	45	222	20
Sensitization to at least one flour dust allergen	68 (26) (†)	72 (33) (†)	16	194	8

(*) subjects reporting current respiratory outcome at follow up (prevalence); (**) subjects reporting new onset respiratory outcome at follow up excluding those who reported at baseline (incidence); (~)-reported in the last 12 months; (†) n= 262 at baseline, n= 219 at follow-up

Further analysis demonstrated that the incidence of the various adverse respiratory outcomes (general and work-related symptoms) was not associated with the presence of skin symptoms at baseline (see Supplementary table 1), even after stratifying by sensitization status (see Supplementary table 2).

Host and environmental risk factors associated with respiratory outcomes

Among the host factors, atopy was significantly associated with new-onset work-related lower respiratory symptoms, allergic airway inflammation and sensitization to at least one flour dust allergen (see Supplementary table 3). Childhood eczema was significantly associated with work-related rhinitis and lower respiratory symptoms. As expected, smoking was associated with a decreased risk of having high levels of FeNO.

Among the environmental factors, being a manager or supervisor was significantly associated with an increased risk of developing ocular-nasal symptoms when compared to a counter hand (least exposed) (Supplementary table 4). Using general PPE on a regular basis was significantly associated with a decreased risk of developing ocular-nasal symptoms (RR=0.1, 95% CI: 0.01-0.49), work-related rhinitis (RR=0.1, 95% CI: 0.02-0.51) and elevated FeNO levels (FeNO>25ppb RR=0.2, 95% CI: 0.06-0.53).

Association between skin symptoms and the development of bakery respiratory outcomes

In unadjusted models, workers with a history of an itchy or scratchy skin affecting the hands were at increased risk of developing ocular-nasal (RR=4.6, 95% CI: 1.09-19.44) and work-related lower respiratory symptoms (WRLRS) (RR=3.9, 95% CI: 1.33-11.39) (Supplementary table 5). Similarly, the risk of WRLRS was increased among workers reporting hives (RR=17.2, 95% CI: 1.87-157.7) and redness of the skin (RR=4.4, 95% CI: 1.34-14.32), in both cases affecting the hands. Having clinically significant skin symptoms affecting the hands (itchy/scratchy skin, hives or redness), as defined by a composite skin variable, had an increased risk of developing WRLRS (RR=4.0, 95% CI: 1.50-11.6). A history of previous work-related skin symptoms was significantly associated with developing

ocular nasal symptoms (RR=3.9, 95% CI: 1.12-13.68), work-related respiratory symptoms (RR=3.6, 95% CI: 1.33-9.77) and allergic airway inflammation (RR=4.3, 95% CI: 1.83-10.38) (Supplementary table 5).

In multivariate logistic regression models (adjusting for gender, atopy and smoking status), having clinically significant skin symptoms affecting the hands was associated with an increased risk of developing ocular-nasal symptoms (RR=5.5, 95% CI: 1.30-24.20). A similar association was observed between having work-related skin symptoms and the development of ocular-nasal symptoms (RR=5.1, 95% CI: 1.31-19.81). For new onset WRLRS, an increased risk was associated with a past history of skin symptoms (RR=2.2, 95% CI: 1.03-4.83), having clinically significant skin symptoms affecting the hands (RR=4.8, 95% CI: 1.6-14.40), and having work-related skin symptoms (RR=4.1, 95% CI: 1.43-16.88). Furthermore, work-related skin symptoms increased the risk of developing having elevated FeNO levels of (FeNO>25ppb RR=2.9, 95% CI: 1.19-7.28) (Table 4).

Further stratification based on glove use in adjusted logistic regression models revealed that workers with significant skin symptoms in the absence of glove use, were at higher risk of developing ocular-nasal symptoms (RR=5.8, 95% CI: 1.10-30.8) than their counterparts. For work-related skin symptoms, an increased risk of developing WRLRS (RR=5.3, 95% CI: 1.54-18.4) and elevated FeNO levels (FeNO>25ppb RR=3.0, 95% CI: 1.07-8.45) was also observed (Table 5).

Table 4. Association between skin symptoms at baseline and development of new-onset bakery allergic or irritant respiratory symptoms and asthma in adjusted multivariate logistic regression models

	Adjusted risk ratio† (Confidence Interval)						
	Presence of skin symptoms ever	**Two or more skin symptoms in the last 12 months**	**Itchy/scratchy skin affecting the hands**	**Hives ("bommels") affecting the hands**	**Redness of the skin affecting the hands**	**Composite skin variable**	**Work-related skin symptoms**
Outcome							
New-onset self-reported ocular-nasal symptoms	1.0 (0.43-2.67)	0.26 (0.04-1.71)	**7.1 (1.51-32.92)**	~	**6.5 (1.16-36.50)**	**5.5 (1.30-24.20)**	**5.1 (1.31-19.81)**
New-onset self-reported work-related rhinitis	1.2 (0.55-2.81)	1.05 (0.23-4.80)	1.62 (0.36-7.27)	~	3.16 (0.58-17.03)	2.2 (0.56-9.10)	0.7 (0.15-3.88)
New-onset of 2/> lower respiratory symptoms	1.6 (0.73-3.45)	0.5 (0.13-2.20)	1.3 (0.25-6.67)	5.2 (0.70-39.41)	2.0 (0.36-11.20)	2.8 (0.76-10.60)	2.8 (0.94-8.63)
New-onset work-related lower respiratory symptoms	**2.2 (1.03-4.83)**	0.5 (0.11-2.21)	**4.4 (1.40-13.96)**	3.8 (0.99-14.61)	**4.7 (1.32-16.88)**	**4.8 (1.60 -14.40)**	**4.1 (1.43-11.85)**
FeNO >25ppb	0.9 (0.41-1.93)	0.6 (0.14-3.03)	1.2 (0.36-4.09)	2.1 (0.47-9.61)	1.2 (0.31-4.93)	1.4 (0.45-4.14)	**2.9 (1.19-7.28)**
FeNO 25-50ppb	1.1 (0.49- 2.73)	0.4 (0.06-2.17)	1.4 (0.39-5.44)	3.6 (0.84-15.40)	2.1 (0.54-8.37)	1.8 (0.54-5.80)	**5.7 (2.26-14.60)**
FeNO >50ppb	0.6 (0.15-2.10)	~	0.7 (0.08-6.01)	~	~	0.6 (0.07-4.87)	~
Sensitization to at least one bakery related allergen	1.2 (0.36-4.25)	0.6 (0.07-5.15)	~	~	~	~	0.9 (0.10-7.63)

(†) Each risk ratio represents a separate model adjusted for atopy, gender and smoking status; (~) Risk ratio indeterminable.

Table 5. Association between composite skin variable and work-related skin symptoms at baseline and development of new-onset bakery allergic or irritant respiratory symptoms and asthma in adjusted multivariate logistic regression models

Adjusted risk ratio† (Confidence Interval)						
	Composite skin variable			Work related skin symptoms		
	Overall	With gloves	Without gloves	Overall	With gloves	Without gloves
Outcome						
New-onset self-reported ocular-nasal symptoms	**5.5 (1.30-24.20)**	~	**5.8 (1.10-30.8)**	**5.1 (1.31-19.81)**	9.9 (0.40-243.9)	4.7 (0.85-26.26)
New-onset self-reported work-related rhinitis	2.2 (0.56-9.10)	5.5 (0.30-112.00)	1.8 (0.38-8.60)	0.7 (0.15-3.88)	~	1.2 (0.20-7.31)
New-onset of 2/> lower respiratory symptoms	2.8 (0.76-10.60)	9.2 (0.65-131.79)	1.5 (0.30-8.51)	2.8 (0.94-8.63)	3.9 (0.45-33.85)	2.3 (0.60-8.54)
New-onset work-related lower respiratory symptoms	**4.8 (1.60 -14.40)**	7.4 (0.80-68.23)	**4.1 (1.13-15.07)**	**4.1 (1.43-11.85)**	2.1 (0.30-16.86)	**5.3 (1.54-18.43)**
FeNO >25ppb	1.4 (0.45-4.14)	1.9 (0.17-22.76)	1.3 (0.39-4.69)	**2.9 (1.19-7.28)**	3.7 (0.50-27.37)	**3.0 (1.07-8.45)**
FeNO 25-50ppb	1.8 (0.54-5.80)	1.5 (0.14-17.46)	1.9 (0.48-7.53)	**5.7 (2.26-14.60)**	4.2 (0.60-29.38)	**7.6 (2.50-23.29)**
FeNO >50ppb	0.6 (0.07-4.87)	~	0.6 (0.07-5.46)	~	~	~
Sensitization to at least one bakery related allergen	~	~	~	0.9 (0.10-7.63)	~	1.2 (0.12-11.67)

(†) Each RR represents a separate model adjusted for atopy, gender and smoking status; (~) Risk ratio indeterminable.

DISCUSSION

The results of this study add to the growing body of evidence that skin symptoms can be predictive of future development of adverse respiratory outcomes, including asthma-like symptoms and allergic airway inflammation in workers exposed to allergens. The findings are similar to other studies in bakers, workers employed in auto body repair, wood product manufacturing exposed to isocyanates as well as professional cleaners [6,16,30]. In the current study, bakers who reported clinical manifestations suggestive of urticarial or eczema (itchy/scratchy skin, hives and redness) of the hands were at significantly increased risk of developing upper airway symptoms and work-related lower respiratory symptoms, at the fourth year of follow-up. Furthermore, should the skin symptoms be work-related, other than being at increased risk of developing upper airway and work-related lower respiratory symptoms, bakery workers were at increased risk of developing allergic airway inflammation.

The prevalence of skin symptoms in this current study (22%) was higher than that reported in bakers and confectioners (20% and 7%, respectively) [31], professional indoors cleaners (10%) and other building workers (6%) [30]. In some studies in the seafood-processing industry, the prevalence of skin symptoms was more than two-fold (43%) higher than the prevalence reported in the current study [32]. Additionally, Helaskoski et al. in a retrospective review of the patient information collected in a Finish occupational medicine clinic, reported a high prevalence of skin conditions due to high and low molecular weight agents (80% for contact urticaria and 20% for protein contact dermatitis), with flour, grains and animal feed being the most common causes implicated [33]. While 13% of subjects from the present study reported two or more episodes of skin symptoms in the last 12 months, Steiner et al. reported that 19% of workers in a Scottish bakery reported at least one skin

symptom in the previous 12 months [31]. Furthermore, professional indoors cleaners (19%) and other building workers (16%) reported similar figures for skin rash in the previous 12 months [30]. While 11% of workers in the current study reported work-related skin symptoms, work-related itchy skin was reported in 17% of bakers and 9% auto body shop workers in a previous study [6]. Additionally, Arrandale et al. reported that 63% of workers exposed to a variety of agents (animal dander, cement, isocyanates, pesticides, wet work, dust, fumes, and paint) reported possible work-related skin rash [2]. This high prevalence is probably due to the study population being patients attending an occupational medicine clinic. Overall, this current study found that skin symptoms in bakery workers are more likely to be allergic in nature. A similar trend was observed in another study of bakers, in which workers sensitized to wheat were more likely to have itchy/dry skin or work-related itchy skin than their counterparts [6].

The current study in bakery workers found a considerably high prevalence and incidence of both general (36% and 19%, respectively) and work-related (40% and 29%, respectively). upper respiratory symptoms Studies in British bakeries also reported a high prevalence of general upper respiratory symptoms (38%), of which 19% was work-related [34]. Likewise, this current study found a high prevalence and incidence of general symptoms (for 31% and 22%, respectively) and work-related (24% and 20%, respectively) lower respiratory symptoms). Comparable results were observed in the British bakeries reporting prevalence of 35% for one or more general upper respiratory symptoms of which 13% were work-related [34]. Lower figures have been reported in wood product plant employees exposed to Methylene Diphenyl di-Isocyanate (MDI), with a prevalence of 20% for asthma-like symptoms and an incidence of 12% [16].

Overall, the respiratory outcomes found in this study do not differ much in nature, in that almost similar proportions were found for allergic and irritant respiratory outcomes (Supplementary table 1). However, atopy and a history of childhood eczema were significant host factors associated with adverse respiratory outcomes. Atopy is regarded as a potent unmodifiable risk factor for sensitization to high molecular weight allergens in the workplace [35]. Furthermore, various other studies have demonstrated that the onset of atopic disease in childhood frequently occurs and manifests as an atopic dermatitis (AD) [37,38]. Laboratory studies have also demonstrated that percutaneous exposure to high-molecular weight allergens, such as ovalbumin, can lead to subsequent manifestations of the allergic respiratory response under conditions that trigger AD-like skin inflammation [35,39–41]. In this study, smoking status was associated with a decreased risk of having elevated FeNO levels (FeNO>25ppb RR=0.4, 95% CI: 0.24-0.82) as has been previously reported by Baatjes et al. [42] in the larger study of this group of workers.

Among the environmental risk factors, being manager or supervisor was associated with an increased risk of developing upper respiratory symptoms when compared to counter hands (least exposed) [43]. Arakawa et al. demonstrated that the allergic response to *Dermatophagoides farinae* mite was dose-dependent in guinea pigs and asthma-like symptoms were triggered by increased doses of intradermal Tri-mellitic Anhydride (TMA) [23]. Also evident in this study was that general PPE use of any sort (aprons, mask, and gloves) on a regular basis was associated with a decreased risk of developing allergic airway inflammation.

One of the key findings of this study was that the presence of skin symptoms at baseline was associated with future development of adverse respiratory outcomes. Helaskoski et al. also reported that 38% occupational rhinitis and 21% occupational asthma patients attending a

Finish occupational medicine clinic were concomitantly diagnosed with skin disorders [33]. Petsonk et al. investigated respiratory outcomes in workers exposed to low molecular weight agents (isocyanates) under strict conditions to prevent inhalational exposure [16]. He reported that 52% of workers with strong history of skin exposure (MDI stains) developed adverse respiratory outcomes [16]. Furthermore, in a recent review, 46% of occupational skin disorders occurred concomitantly with occupational airway disease caused by the same agent, suggesting a strong association between dermal exposure, sensitization and airway inflammation [33]. In the current study, a previous history of general skin symptoms or having clinically significant skin symptoms of urticaria or eczema affecting the hands, was strongly associated with the development of ocular-nasal and work-related lower respiratory symptoms. Furthermore, the presence of work-related skin symptoms at baseline was also strongly associated with an increased risk of developing allergic airway inflammation, ocular-nasal symptoms and work-related lower respiratory symptoms. Interestingly, the risk of developing work-related skin symptoms was modified by the use of dermal PPE (gloves). Bakers who reported clinically significant skin symptoms and did not use gloves had a higher risk of developing ocular-nasal symptoms (RR=5.8) and work-related lower respiratory symptoms (RR=4.1). Furthermore, those workers with work-related skin symptoms in the absence of regular glove use, also had a higher risk of developing allergic airway inflammation (RR=3.0) and work-related lower respiratory symptoms (RR=5.3).

The findings of this study suggest that skin exposure may play an important role in the process of sensitization and the future development of respiratory symptoms, including asthma. This has been reported in some studies investigating the link between skin exposure to allergens and the future development of sensitization and respiratory disease [2,7,17]. However, the current study was unable to demonstrate an increased risk of developing sensitization to flour dust in this group. Nevertheless, the study did demonstrate that skin

symptoms can predict allergic airway inflammation, which may imply allergic sensitization in bakers [33]. Baatjies et al. have shown that sensitization to wheat is the strongest predictor of increased FeNO in this group of workers [42]. However, this does not exclude the possibility of an irritant cause for the upper and lower respiratory symptoms observed in the current study, since a sizeable proportion of bakers with respiratory symptoms may not demonstrate sensitization [44–47].

The major strength of this study is its cohort design and the use of sensitive markers to demonstrate airway inflammation present in asthma. The inability to demonstrate a positive association between skin symptoms and sensitization to the bakery allergens may be attributed to the lack of power due to the relatively small sample size. Furthermore, only 8% (16/194) of workers developed new sensitization to bakery allergens at follow-up, which may suggest a healthy worker effect. De Zotti et al. reported a cumulative incidence of 10% for sensitization in apprentice bakers after 30 months [48] Another limitation of this study was the fact that concurrent sensitization via skin and respiratory (inhalation) routes cannot be excluded, since the respiratory route was not strictly or minimally protected and that only 2% (4/249) of workers using general PPE reported regular mask use. Finally, the absence of more conventional measures for airway reversibility and asthma, such as spirometry (with bronchodilator challenge) or non-specific bronchial hyperresponsiveness at follow-up, also posed as limitations. This was partially compensated by the use of markers of allergic airway inflammation (FeNO) and respiratory symptoms to detect the presence of asthma. Since there may be other causes of a rise in FeNO, only levels >50ppb were considered as being suggestive of airway inflammation as is present in asthma. Future studies should include more objective measurements to improve the specificity of the respiratory outcomes of interest, as well as include exposures to both high and other low molecular weight agents not previously studied using prospective study designs.

In conclusion, the present study has demonstrated that skin symptoms in workers exposed to high molecular weight protein allergens, such as cereal flour dust, may predict the presence of general and work-related upper and lower respiratory symptoms and increased inflammatory marker levels suggestive of asthma. Medical surveillance programmes should also consider for inclusion the presence and distribution of skin symptoms when administering asthma symptom questionnaires. Furthermore, both skin and respiratory protection should be equally promoted so as to decrease the likelihood of sensitization and the development of upper and lower airway disease, including asthma, in high risk working populations.

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SUPPLEMENTARY TABLES

Supplementary table 1. New-onset general allergic or irritant respiratory symptoms and asthma among supermarket bakers stratified according to the presence of allergic skin symptoms at baseline

Respiratory outcomes	Presence of skin symptoms	Absence of skin symptoms	Chi-square p-value
Overall (N = 262)	**n = 58**	**n = 204**	
New-onset self-reported ocular-nasal symptoms	7 (12)	27 (13)	0.816
Newly prescribed treatment for rhinitis	0	6 (3)	0.344*
New-onset of two or more lower respiratory symptoms	12 (21)	35 (17)	0.536
New-onset self-reported asthma	3 (5)	7 (3)	0.465*
Newly prescribed treatment for asthma	1 (2)	5 (2)	1.000*
FeNO >=25ppb	11 (19)	44 (21)	0.668
- FeNO 25-50ppb	8 (14)	26 (13)	0.834
- FeNO >50ppb	3 (5)	18 (9)	0.583*
With sensitization (N = 68)	**n = 15**	**n = 53**	
New-onset self-reported ocular-nasal symptoms	2 (13)	7 (13)	1.000*
Newly prescribed treatment for rhinitis	0	4 (8)	0.569*
New-onset of two or more lower respiratory symptoms	3 (20)	10 (19)	1.000*
New-onset self-reported asthma	2 (13)	7 (13)	1.000*
Newly prescribed treatment for asthma	0	5 (9)	0.579*
FeNO >=25ppb	6 (40)	24 (45)	0.716
- FeNO 25-50ppb	4 (27)	11 (21)	0.726*
- FeNO >50ppb	2 (13)	13 (25)	0.492*
Without sensitization (N= 194)	**n = 43**	**n = 151**	
New-onset self-reported ocular-nasal symptoms	5 (12)	20 (13)	0.780
Newly prescribed treatment for rhinitis	0	2 (1)	1.000*
New-onset of two or more lower respiratory symptoms	9 (21)	25 (17)	0.506
New-onset self-reported asthma	1 (2)	0	0.222*
Newly prescribed treatment for asthma	1 (2)	0	0.222*
FeNO >=25ppb	5 (12)	20 (13)	0.780
- FeNO 25-50ppb	4 (9)	15 (10)	1.000*
- FeNO >50ppb	1 (2)	5 (3)	1.000*

(*) – Fisher's exact test

Supplementary table 2. Presence of new-onset work-related allergic or irritant respiratory symptoms and asthma among bakers stratified according to the presence of skin symptoms at baseline

Work-related respiratory outcomes	**Presence of skin symptoms n (%)**	**Absence of skin symptoms n (%)**	**Chi-square p-value**
Overall (N = 258) *(†)*	**n=58**	**n=200**	
- New-onset self-reported work-related rhinitis (sneezy/itchy/runny nose or red/itchy/watery eyes)	11 (19)	43 (22)	0.676
- New-onset work-related lower respiratory (tight chest or wheeze)	14 (24)	31 (16)	0.127
With sensitization (N = 67)	**n=15**	**n=52**	
- New-onset self-reported work-related rhinitis (sneezy/itchy/runny nose or red/itchy/watery eyes)	2 (13)	12 (23)	0.431
- New-onset work-related lower respiratory (tight chest or wheeze)	5 (33)	13 (25)	0.495
Without sensitization (N = 191)	**n=43**	**n=148**	
- New-onset self-reported work-related rhinitis (sneezy/itchy/runny nose or red/itchy/watery eyes)	9 (21)	31 (21)	0.954
- New-onset work-related lower respiratory (tight chest or wheeze)	9 (21)	18 (12)	0.132

(†) N=258 due to missing data on work related symptoms for 4 participants at follow-up

Supplementary table 3. Host risk factors associated with the development of new-onset bakery allergic or irritant respiratory symptoms and asthma

Risk ratio (Confidence Interval)							
	Age	**Gender (male)**	**Smoking**	**Atopy**	**History of childhood eczema**	**Hand trauma**	**Hand washing frequency (>6 times per day)**
Outcome							
New-onset self-reported ocular-nasal symptoms	1.0 (0.94-1.03)	0.9 (0.43-1.94)	0.9 (0.41-1.84)	2.0 (0.91-4.58)	1.0 (0.11-9.66)	1.2 (0.49-3.04)	1.8 (0.38-8.09)
New-onset self-reported work-related rhinitis	1.0 (0.96-1.04)	1.2 (0.62-2.19)	1.1 (0.56-2.00)	1.8 (0.90-3.51)	**10.6 (1.15-96.78)**	1.1 (0.54-2.35)	0.6 (0.22-1.48)
New-onset 2/> lower respiratory symptoms	1.0 (0.95-1.03)	0.6 (0.34-1.25)	0.8 (0.41-1.51)	1.7 (0.87-3.40)	**7.6 (1.35-43.04)**	0.8 (0.37-1.76)	1.3 (0.42-4.07)
New-onset of work-related lower respiratory symptoms	1.0 (0.95-1.03)	0.6 (0.31-1.17)	1.3 (0.67-2.50)	**2.6 (1.35-5.19)**	4.1 (0.81-21.26)	1.0 (0.45-2.17)	0.7 (0.25-2.16)
FeNO >25ppb	1.0 (0.94-1.02)	1.4 (0.77-2.54)	**0.4 (0.24-0.82)**	**2.7 (1.49-5.06)**	1.9 (0.47-8.03)	1.4 (0.63-2.88)	0.6 (0.26-1.64)
FeNO 25-50ppb	1.0 (0.95-1.04)	1.2 (0.56-2.37)	0.6 (0.27-1.15)	1.6 (0.74-3.26)	0.8 (0.10-6.91)	0.9 (0.39-2.13)	0.8 (0.24-2.36)
FeNO >50ppb	1.0 (0.90-1.02)	1.7 (0.68-4.27)	0.4 (0.15-1.02)	**4.8 (1.87-12.44)**	3.5 (0.69-18.21)	2.9 (0.65-12.66)	0.6 (0.16-2.20)
Sensitization to at least one flour dust allergen	0.9 (0.90-1.03)	0.9 (0.34.2.67)	0.6 (0.23-1.80)	**4.4 (1.55-12.66)**	~	1.3 (0.36-4.92)	~

(~) Risk ratio indeterminable.

Supplementary table 4. Environmental risk factors associated with the development of new-onset bakery allergic or irritant respiratory symptoms and asthma

	Risk ratio (Confidence Interval)				
	Job type (bakers, confectioners and M&S) (†)	**Employment duration**	**General PPE use on a regular basis**	**Respiratory PPE use on a regular basis (mask)**	**Dermal PPE use on a regular basis (gloves)**
Outcome					
New-onset self-reported ocular-nasal symptoms	1.8 (0.57-5.88) 0.8 (0.13-4.63) **4.2 (1.04-16.73)**	1.0 (0.91-1.06)	**0.1 (0.01-0.49)**	~	0.5 (0.19-1.14)
New-onset self-reported work-related rhinitis	1.1 (0.45-2.52) 0.6 (0.17-2.23) 1.2 (0.35-3.81)	1.0 (0.89-1.03)	**0.1 (0.02-0.51)**	~	0.7 (0.38-1.48)
New-onset 2/> lower respiratory symptoms	1.06 (0.45-2.47) 1.00 (0.29-3.17) 2.25 (0.77-6.51)	1.0 (0.93-1.06)	0.8 (0.16-4.32)	~	0.8 (0.41-1.68)
New-onset work-related lower respiratory symptoms	0.5 (0.20-1.04) 0.4 (0.09-1.37) 1.6 (0.57-4.58)	1.0 (0.93-1.06)	0.50 (0.15-1.65)	~	1.5 (0.77-3.00)
FeNO >25ppb	1.0 (0.43-2.24) 1.1 (0.34-3.25) 1.1 (0.37-3.56)	0.9 (0.88-1.01)	**0.2 (0.06-0.53)**	1.25 (0.13-12.41)	1.0 (0.54-1.93)
FeNO 25-50ppb	0.6 (0.23-1.58) 0.6 (0.15-2.52) 0.9 (0.25-3.36)	0.9 (0.84-1.00)	**0.1 (0.04-0.37)**	2.29 (0.23-22.60)	1.3 (0.64-2.85)
FeNO >50ppb	2.5 (0.53-11.62) 2.8 (0.44-17.67) 1.9 (0.26-14.44)	0.9 (0.89-1.07)	1.1 (0.14-9.13)	~	0.6 (0.22-1.79)
Sensitization to at least one flour dust allergen	0.9 (0.30-3.42) 2.5 (0.56-11.09) ~	0.9 (0.89-1.10)	~	~	1.1 (0.37-3.08)

M&S = Managers and supervisors; (†) Counter hands as a reference category; (~) Risk ratio indeterminable.

Supplementary table 5. Association between skin symptoms at baseline and development of new-onset bakery allergic or irritant respiratory symptoms and asthma in unadjusted multivariate logistic regression models

	Risk ratio† (Confidence Interval)						
	Presence of skin symptoms ever	**Two or more skin symptoms in the last 12 months**	**Itchy/scratchy skin affecting the hands**	**Hives (" bommels") affecting the hands**	**Redness of the skin affecting the hands**	**Composite skin variable**	**Work-related skin symptoms**
Outcome							
New-onset self-reported ocular-nasal symptoms	1.1 (0.42-2.67)	1.9 (0.61-5.71)	**4.6 (1.09-19.44)**	~	4.5 (0.86-23.28)	3.6 (0.92-14.41)	**3.9 (1.12-13.68)**
New-onset self-reported work-related rhinitis	1.2 (0.55-2.72)	1.1 (0.37-3.43)	1.5 (0.35-6.53)	~	2.5 (0.50-13.05)	2.0 (0.53-8.00)	0.7 (0.14-3.44)
New-onset of 2/> lower respiratory symptoms	1.5 (0.70-3.20)	1.9 (0.66-5.31)	1.0 (0.20-5.03)	3.6 (0.50-26.60)	1.4 (0.27-7.62)	2.1 (0.60-7.55)	2.6 (0.86-7.58)
New-onset work-related lower respiratory symptoms	2.0 (0.98-4.28)	2.3 (0.92-5.91)	**3.9 (1.33-11.39)**	**17.2 (1.87-157.7)**	**4.4 (1.34-14.32)**	**4.0 (1.50-11.6)**	**3.6 (1.33-9.77)**
FeNO >25ppb	0.9 (0.41-1.79)	1.0 (0.42-2.49)	0.9 (0.30-2.94)	1.7 (0.41-6.63)	0.9 (0.24-3.15)	1.0 (0.37-3.00)	2.1 (0.91-4.77)
FeNO 25-50ppb	1.1 (0.47-2.58)	1.6 (0.61-4.22)	1.2 (0.33-4.36)	3.1 (0.75-12.49)	1.6 (0.43-5.96)	1.5 (0.50-4.62)	**4.3 (1.83-10.38)**
FeNO >50ppb	0.6 (0.16-2.00)	0.3 (0.04-2.53)	0.6 (0.07-4.61)	~	~	0.5 (0.06- 3.90)	~
Sensitization to at least one bakery related allergen	1.1 (0.36-3.89)	0.5 (0.06-4.20)	~	~	~	~	1.7 (0.07-5.07)

(†) Each RR represents a separate unadjusted regression model; (~) Risk ratio indeterminable.

PART D: APPENDICES

APPENDIX 1: ARTICLE - SKIN EXPOSURE, SYMPTOMS AND ASTHMA IN OCCUPATIONAL SETTINGS – IS THERE A LINK?

Allergies in the workplace

SKIN EXPOSURE, SYMPTOMS AND ASTHMA IN OCCUPATIONAL SETTINGS – IS THERE A LINK?

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ABSTRACT

Occupational contact with allergens through the dermatological and respiratory route can lead to various health effects, including allergic contact dermatitis, urticaria, rhinitis and asthma, which may result in a substantial disease burden in occupational settings. Inhalation is an obvious route for sensitisation and its pathophysiological mechanisms are relatively better defined. Recent studies have suggested that skin exposure may also play an important role in the sensitisation and development of respiratory outcomes in exposed workers. The review found that the evidence for such an association was limited and the immune mechanisms were not well understood. A better understanding of this association is required, more so for agents with a high molecular weight (protein), so as to identify important risk factors that may contribute to existing preventive efforts in reducing the incidence of allergy and asthma in occupational settings.

INTRODUCTION

Diverse immune responses have been associated with various environmental allergen exposures to the skin and these have resulted in the activation of the adaptive immune response.[1] In barrier-disrupted skin, type-2 lymphoid cells, mast cells and basophils are known to trigger pathogenic Th2 responses in murine models.[2] However, even when the skin barrier is intact; it still has properties that may allow, to some extent, permeability to some allergens. The 'brick-and-mortar' model – a schematic explanation of the permeability of the stratum corneum, in which corneocytes are the bricks and lipids are the mortar – presents the stratum corneum as a metabolically active structure with adaptive functions. This could be behind the mechanism in which some allergens could be absorbed by a healthy skin.[3]

Some epidemiological studies and animal experiments have demonstrated positive associations between skin and respiratory symptoms and positive exposure–response relationships, whereas others have not been able to replicate this.[4-9]

One of the main issues highlighted by these observations has been the challenges in investigating skin exposure.[10] Methodologies for assessing skin exposure are not as well advanced as for inhalational assessment and exposure data are limited.[11,12] In addition, airborne exposure to skin is variable and sporadic and there is uncertainty regarding the extent of skin uptake.[10] Furthermore, most workers are exposed to mixtures of occupational agents, making it difficult to identify the specific exposure responsible for the health outcome of interest. For example, exposure to beryllium and isocyanates typically occurs in mixed exposure settings and these agents may be present in various physical or chemical forms, namely, metal particles, oxides, salts and alloys with copper and other metals.[10]

The aim of this literature review is to assess the nature and extent of the associations between skin and respiratory symptoms following skin exposure to sensitisers with a high or a low molecular weight. The review includes all the relevant English publications that were retrieved from PubMed/Medline and Google Scholar. The key search terms that were employed in this review were terms used in other reviews; they included 'skin', 'asthma' or 'dermal', 'high molecular weight' or 'low molecular weight' and 'sensitisation' or 'dose-response' or 'link'. Other terms subsequently added included: 'allergen', 'allergy', 'atopy', 'occupational', 'work-related', 'respiratory', 'dermatological' and 'dermatitis'. Furthermore, some articles were retrieved using the functions 'similar articles search' in PubMed and 'related articles' in Google Scholar as well relevant articles that were cited in the references of these articles.

Figure 1: Bakery work handling various food proteins (high molecular weight agents)

EPIDEMIOLOGICAL STUDIES

CO-EXISTING OR SEQUENTIAL DEVELOPMENT OF DERMAL AND RESPIRATORY OUTCOMES

Workers in various occupations report both skin and respiratory symptoms. Table I illustrates case study reports in which both dermal and respiratory outcomes (diagnosed using patch tests and inhalation challenge tests respectively) were observed in occupational settings with diverse exposures. These allergens can cause both occupational asthma and allergic contact dermatitis.[13] To ascertain which health outcome precedes the other can be a challenge because of the nature of the study design used and the lack of a comparison group in such studies.

Arrandale[4] conducted an analysis of four cross-sectional pooled studies from a soda ash plant, a softwood planing mill, embalming and cabinet-making in which workers were exposed to ammonia, softwood dust, formaldehyde and/or glutaraldehyde and hardwood dust, respectively. Altogether, both skin and respiratory symptoms were reported by 11% (26/236). The highest prevalence of both dermal and respiratory symptoms was seen among embalmers, with no statistical significance.[13] Although this study does not show temporality, it reinforces evidence of the co-occurrence of both respiratory and dermal symptoms in occupational settings.[14] Similarly, previous studies among sewage-treatment and isocyanate workers reported a concomitant occurrence of dermal and respiratory symptoms in exposed workers.[15,16] However, no correlation was found between occupational hand dermatitis and flexural dermatitis, respiratory atopy (allergic rhinitis (AR) and bronchial asthma), serum IgE ± 100 IU/mL or metal sensitisation in the study of bakers by Bauer et al.[14]

Aside from the need to identify temporality, the co-existence of dermal and respiratory symptoms does not necessarily indicate that the same exposure is the trigger for both outcomes, unless the exposure assessment specifically characterised the nature and route of the exposures in affected workers.[13]

ASSOCIATION BETWEEN SKIN EXPOSURE, ALLERGY-SPECIFIC SENSITISATION AND SUBSEQUENT DEVELOPMENT OF RESPIRATORY DISEASE

Table II summarises the few key epidemiological studies that have investigated the role of skin exposure and symptoms and the subsequent development of respiratory symptoms, including asthma, in these workers.

Brisman et al[17,18] have alluded to the association between bakers' asthma and eczema, without indicating whether sensitisation to wheat flour was due to inhalation or due to contact with allergens through the skin (or both).

In a study of bakers exposed to wheat and autobody-shop workers (ABSWs) exposed to isocyanates, Arrandale et al[5] demonstrated an association between skin and respiratory symptoms. Work-related itchy skin was associated with wheeze, asthma-like symptoms and work-related asthma symptoms in ABSWs but not in bakers. The authors did, however, indicate that the autobody-shop workers had adhered to much stricter use of personal protective equipment, while such use of personal protective equipment had not been observed by the bakers.[5] A previous study by Arrandale et al[4] also found that eczema increases the odds

TABLE I: CO-OCCURRING OCCUPATIONAL ASTHMA (OA) AND OCCUPATIONAL CONTACT DERMATITIS (OCD) – DIAGNOSED USING SPECIFIC INHALATION CHALLENGE AND PATCH TESTING – CASE REPORTS REPORTED

EXPOSURE	OCCUPATION	AUTHOR, YEAR
2-hydroxyethyl methacrylate (HEMA)	Beautician	Moulin et al, 2009
Diglycidyl Ether of Bisphenol A (DGEBA)	Resin applier	Moulin et al, 2009
Diphenylmethane-4,4'-diisocyanate (MDI)	Manufacturing (automotive industry)	Vaiks et al, 2003
Potassium dichromate	Cement floorer	De Raeve et al, 1998
Aziridine hardener	Painter and varnisher	Kanerva et al, 1995
Onion	Homemaker	Valdivieso et al, 1994
Nickel	Manual grinding of metal castings	Estlander et al, 1993
Spiramycin	Poultry breeder	Paggiaro et al, 1979

Reproduced from Arrandale 2012[13]

TABLE II: STUDIES OF WORKING POPULATIONS INVESTIGATING THE ASSOCIATION BETWEEN SKIN EXPOSURE/SYMPTOMS AND RESPIRATORY SYMPTOMS/ASTHMA

AUTHORS, YEAR	ARRANDALE ET AL, 2013[5]	ARRANDALE ET AL, 2012[4]	LYNDE ET AL, 2009[10]	PETSONK ET AL, 2000[2]
Aim of study	To investigate associations between skin and respiratory symptoms in bakery and ABSW	To identify predictors of reporting concurrent skin and respiratory symptoms in a clinical population	To compare the prevalence of occupational cutaneous symptoms among professional indoor cleaners to other building workers (OBW) and their association with exposures and respiratory symptoms	To evaluate the respiratory health of workers exposed to methylene diphenyl diisocyanate (MDI)
Study design	Cross-sectional	Cross-sectional	Cross-sectional	Cohort
Population	723 bakers 473 ABSW	204 patients from the occupational health clinic	549 professional cleaners 593 OBW	214 wood product plant employees (144 completed initial, follow-up and occupational questionnaires)
Agent	Isocyanate and wheat	Multiple agents (animal dander, cement, isocyanates, pesticides, wet work, dust, fumes, paint)	Cleaning agents	MDI
Assessment tool(s)	Questionnaire, IgE for common inhalants, specific challenge tests and personal airborne exposure measurements	Questionnaire	Questionnaire	Questionnaire, serial peak flow, spirometry, methacholine challenge, specific IgE
Skin symptoms prevalence (%)	Work-related itchy skin: ABSW – 9%; Bakers – 17%	Possible work-related skin disease: 82%	Current rash: cleaners - 10%, OBW 6% Rash in the past 12 months: cleaners – 19%, OBW 16% (96)	Not reported
Respiratory symptom prevalence (%)	Work-related asthma symptoms (WRAS): ABSW – 4%; Bakers – 2%	Possible work-related respiratory disease: 18%	In males with rash: • physician-diagnosed asthma – 19% • new onset asthma 14% • ≥3 respiratory symptoms: 77% • ≥2 WRAS: 63% • ≥3 WRAS: 40%	Among the 178 (who participated in at least one follow-up survey): • initial asthma-like symptoms – 11% • follow-up asthma-like symptoms – 20% • new-onset asthma-like symptoms – 12%
Association between skin exposure/ symptoms and respiratory symptoms/ asthma	Association between work-related itchy skin and respiratory symptoms in: ABSW: • wheeze OR = 2.50 (95% CI 1.7–3.6) • asthma-like symptoms OR = 2.12 (95% CI 1.5–3.0) • WR asthma symptoms OR = 3.61 (95% CI 1.4–9.4) • Bakers: • wheeze OR = 1.60 (95% CI 1.1–2.3) • asthma-like symptoms OR = 1.54 (95% CI 1.2–2.0) • WR asthma symptoms OR = 2.15 (95% CI 0.7–6.3) Exposure-response relationship in ABSW: • Itchy/dry skin PR = 1.55, 95 % CI: 1.2–2.0 • work-related itchy skin PR = 1.97 (95 % CI 1.2–3.3)	Eczema increases odds of concurrent work-related skin and respiratory symptoms: OR = 3.68 (95% CI: 1.7–7.8)	Rash in the past 12 months associated with: • physician-diagnosed asthma OR = 2.3 (95% CI: 1.1–4.5) • new-onset asthma OR = 3.0 (95% CI: 1.2–7.6) • ≥3 respiratory symptoms OR = 2.6 (95% CI: 1.6–4.3) • ≥2 WRAS OR = 3.2 (95% CI: 1.9–5.3) • ≥3 WRAS OR = 4.0 (95% CI: 0 2.2–7.2)	52% of workers who reported MDI skin stains reported asthma-like symptoms
Study limitations	• Poor correlation between airborne and skin exposure for particulates • Lack of information on other, potentially causal, exposures in the workplace • Potential role of Type IV allergy or irritant mechanisms in symptom development not modelled • Healthy worker effect owing to fewer symptomatic subjects at higher exposure levels	• Cross-sectional study – temporality cannot be ascertained • Not generalisable to all workers because of the selective clinical population	• Low response rate • Outcomes (rashes) were self-reported and not clinically confirmed	• Loss to follow-up • Lack of environmental exposure measurements

of concurrent work-related skin and respiratory symptoms. It needs to be borne in mind, though, that this does not necessarily indicate that skin exposure is always predictive of respiratory outcomes.

Lynde et al[19] investigated a group of predominantly male (84%) professional cleaners, 9.3% of them having a rash currently and 18.6% reporting having had a rash in the past 12 months. The study found that cleaners with a current rash and those reporting a rash in the past 12 months were at significantly increased risk of reporting work-related respiratory symptoms compared to those without a rash. This suggested an association between the presence of work-related asthma symptoms and dermatitis among professional cleaners.[19] However, atopy was considered as a possible underlying mechanism for this association, and a lack of personal protective equipment (PPE) use could have also been another factor influencing this association.[19]

Isocyanates, used in spray-painting and polyurethane foam products, have received considerable attention in relation to skin exposure and the resulting effects of asthma.[5,7,10,20,21] A key link for suggesting an association between allergic sensitisation via transcutaneous route for isocyanates and asthma has been the improvement in occupational health standards in workplaces due to the use of respirators to prevent isocyanate inhalation. However, the incidence of isocyanate-induced asthma remains persistently high, particularly in settings where skin contact with isocyanates has not been well controlled.[20] A laboratory study by Karol et al[22] demonstrated that isocyanate exposure to the skin, particularly TDI, could induce pulmonary hypersensitivity in guinea pigs. Subsequent studies have shown that similar patterns of sensitisation exist in humans.[1,5,7,23]

PATHOPHYSIOLOGICAL CORRELATES

Several studies in children have suggested that skin exposure and sensitisation precede the response in the airways. Dohi et al[25] compared eight atopic dermatitis (AD) patients without a previous report of asthma symptoms and eight mite-allergic asthmatic patients. These two groups were subjected to bronchial inhalation challenges (non-specific with methacholine and specific with house-dust mite (HDM)). Results demonstrated that both IgE and anti-mite IgE antibody were higher in AD' patients than mite-allergic asthmatic patients. The response for methacholine in AD' patients was from normal to asthmatic range. In a study by Lack et al,[26] peanut allergy did not show dependent association with intake of soymilk and soy formula. Peanut allergy was, however, associated with skin rash over the joints and flexures, crusted skin rash, and intake of soy milk and soy formula. In addition, the use of peanut-containing oils on the skin was associated with peanut allergy, suggesting that skin exposure could lead to generalised sensitisation. In more severe form, local skin contact with certain foods, medications, latex, metals and occupational allergens may result in generalised urticaria or systemic symptoms (angioedema, wheezing).[27]

It has also been suggested that beryllium sensitisation in those suffering from chronic beryllium lung disease (CBD) may also have percutaneous origins. Tinkle et al[28] observed that decreasing inhalational exposure had no effect on the incidence of the disease, suggesting that inhalation was not the only cause for the disease. The investigators suggested that following skin exposure to beryllium, the inhalational exposure to beryllium necessary to elicit an immune response and the formation of a CBD-related granuloma was significantly reduced. In further support of this hypothesis, the topical application of beryllium ointment to C3H/HeJ Heston mice showed an increase in beryllium sensitivity in the mice as determined through beryllium lymphocyte proliferation tests of lymph node and peripheral blood.[28] Furthermore, it has been shown that the stratum corneum (SC), the external layer of the skin, which although mechanically strong and resilient to stress and physical strain, may be penetrated by fine and ultra-fine beryllium particles.[28]

The most refined models demonstrating the link between allergic sensitisation and asthma from skin exposure have been from murine experimental studies. Spergel et al[29] applied the high-molecular weight molecule ovalbumin (OVA) via occlusive patch tests to tape-stripped mice skin. This experiment showed an OVA epicutaneous sensitisation and local allergic dermatitis. Later, when the sensitised mice were exposed to intravenous methacholine, the response was eosinophilia in the bronchoalveolar lavage fluid and airway hyper-responsiveness.[29]

In murine models, it has also been demonstrated that the dermal infiltration of eosinophils in response to dust-mite allergens in skin that has been sensitised by barrier disruption is greater than sensitisation through intact skin.[29–32] This suggests that there is a higher induction of Th2-dominant immunological responses to environmental allergens through skin that has the skin barrier disrupted, as is experienced in patients with AD,[33] and particularly following rubbing or scratching of skin, compared to intact skin. There is common agreement about Th2 response that allergen exposure requires both the involvement of barrier disruption and an adaptive immune recognition in order to induce an allergic response.[1,34]

PREDISPOSING FACTORS FOR ALLERGIC RESPIRATORY SYMPTOMS FOLLOWING SKIN EXPOSURE

Several predisposing risk factors could result in sensitisation and to the subsequent development of allergic respiratory symptoms following skin exposure to occupational and environmental allergens.

HOST RISK FACTORS

A. Pre-existing skin diseases

Atopic dermatitis (AD)

The integrity of the skin barrier is intrinsic to an individual's ability to respond to dermal allergen exposure.[35] In AD both cellular immune abnormalities and skin-barrier defects are known to be behind its pathophysiological mechanism.[36] Various non-invasive biomarkers of epidermal permeability are used to identify increased risk for allergic sensitisation through the skin. Trans-epidermal water loss (TEWL) has been directly, but not exclusively, associated with AD and the associated risk of respiratory allergy.[37] Kelleher et al[38] found that newborns with raised TEWL were at increased risk of developing AD at one year of age, and also at higher risk of IgE-associated food allergies, despite the absence of early-onset AD. Loo et al[39] also demonstrated that children with eczema before 18 months exposed to inhalant allergen (HDM) were more likely to present with positive skin-prick tests (SPT) at 18 months.

Irritant dermatitis

A damaged skin barrier, as is present in irritant dermatitis as a result of either physical, chemical or biological processes, is a potential route of entry for allergens.[13] Nielsen[40] demonstrated that skin treated with higher concentrations of sodium laurel sulfate (SLS), a known skin irritant, had greater overall penetration and a greater rate of penetration of chemical substances (pesticides with a wide range of solubility) compared to undamaged skin.

Ichthyosis vulgaris

Bremmer et al[35] demonstrated in a study of 491 patients with AD and ichthyosis vulgaris (IV) that those with higher severity of IV were more likely to report asthma, even after adjusting for AD severity, age, sex and season of the occurrence of symptoms. Bremmer suggested that the presence of severe IV could be used as a marker for patients who have a greater likelihood of developing allergic respiratory disease.

Trauma

Skin trauma is another risk factor for facilitating the entry of contact allergens into the body. This may increase a person's risk of sensitisation, as has been observed, for instance, in seafood-processing workers and animal-handling workers (rats), resulting in the development of allergic respiratory symptoms.[7,10,41]

B. Filaggrin gene mutations

One of the first-line factors associated with skin-barrier deficiencies is Filaggrin (FLG) defects,[42] which typically occur as a result of inherent FLG gene mutations.[43] FLG is an important protein responsible for the strength and integrity of the SC, regulating the permeability of the skin to water and antigens, involved with the packing of keratin filaments in the epidermis, and maintaining the skin's normal acid pH.[1] Studies in the general population evaluating allergen exposure via skin, sensitisation and respiratory outcomes have been reported.[43–45] Brough et al[46] found a positive association between FLG defects and peanut allergy. Filaggrin defects have also been identified in AD patients, and there appears to be a correlation between the extent of FLG defects, the extent of allergen exposure through the skin and the severity of AD.[46] Loss-of-function mutations in the gene encoding FLG are present in up to 50% of patients with moderate-to-severe AD (in European and Asian populations) and have been shown to increase the risk of inhalant allergic sensitisation, allergic rhinitis (AR), asthma and peanut allergy. In African American populations this defect is rare.[46,47]

ENVIRONMENTAL RISK FACTORS

Various high molecular weight (generally proteins) and low molecular weight (generally chemicals) allergens are capable of stimulating the induction of IgE antibodies and resulting in sensitisation and the development of allergic respiratory symptoms.[7] The extent to which they are able to do so will depend on the agent's physical properties, exposure intensity and duration.

A. Agent

Physical properties

Theoretically, liquid and solid allergens will facilitate skin contact and entry in contrast to aerosolised substances. Petsonk et al[24] found that after two years of working in a wood-manufacturing plant, subjects who worked with liquid methylene diphenyl diisocyanate (MDI) had a relatively higher risk of reporting asthma-like symptoms than those who did not work with liquid MDI. In addition, those who reported observing MDI skin stains at least once (suggesting skin exposure) also had a higher risk of reporting asthma-like symptoms compared to those who had never observed such stains. However, the prevalence of asthma-like symptoms was more prevalent among workers who reported brief removal of respiratory PPE while performing their routine tasks, which included liquid MDI handling. The investigators concluded that although inhalation was an important route of exposure for the

Figure 2: Spray-painting work with isocyanates (low molecular weight chemicals)

development of the respiratory symptoms, skin exposure may have also played a role.[24]

Chemical properties (molecular structure)

Transcutaneous chemical penetration also depends on the chemical characteristics of agents. Haptens must be structurally able to bind with a protein as a prerequisite for being recognised by the immune system. While lipophilic properties facilitate skin permeability for allergens,[40] hydrophilic properties are also needed to allow for movement of the chemical from the SC into the dermis. Therefore an efficient allergen should be amphiphilic (both lipophilic and hydrophilic).[48] Low molecular weight particles and molecules, such as nickel and poison ivy (urushiol), are known contact allergens that cause skin sensitisation by their action of binding to host proteins in the skin.[7] As a result of their chemical reactivity with host proteins, these particles cause otherwise innocuous compounds to be converted into hapten–protein complexes that stimulate the adaptive immune response.[1] High molecular weight protein allergens such as peanut, dust mite or water-soluble cat allergens, which range in size from 5 000 Da to 100 000 Da, are generally unable to pass through the skin's cutaneous permeability barrier owing to their size.[49] In such instances, it is generally understood that sensitivity to such high molecular weight compounds is possible only when the integrity of the skin is to some extent compromised.[1]

B. Exposure intensity and duration (dose–response relationships)

Apart from all other conditions that interfere with the skin integrity, the concentration of the agent on the skin surface and the duration of this contact may influence the body's response to an allergen. Some studies involving animal models have investigated trimellitic anhydride (TMA), phthalic anhydride (PA) and MDI and found that increasing the sensitising intradermal doses did not increase a respiratory response. However, Arakawa et al[50] found a dose-dependent response in guinea pigs for Dermatophagoides farinae (DF mite) and a dose–response relationship with increasing doses of intradermally administered TMA eliciting asthma-like symptoms.

Devos et al[51] investigated the asthmagenic capacity of methylisothiazolinone (MI) – a known cause of allergic contact dermatitis commonly used in cosmetics, household products and in different industries – in animal models. Fifteen days after the dermal administration of MI, the subjects did not show a significant respiratory response (either airway hyperreactivity or inflammation). The study concluded that whereas MI was a dermal sensitiser and irritant, it was unable to elicit an asthma-like response.[51]

Paulunh et al[9] also investigated the dose–response relationship of MDI exposure in animal models and the lung response after primary skin exposure. Surface area or dose-to-body weight did not show specific associations. On the contrary, the magnitude of the respiratory response was dependent on the frequency of inhalation challenge doses administered instead of the previous cutaneous doses.[9]

CONCLUSION

Skin is an important route of exposure to allergens leading to sensitisation and the potential to cause allergic skin symptoms that could co-exist or precede respiratory symptoms and other systemic health outcomes. However, much still needs to be investigated to enable us to understand better the modes of entry and sensitisation in occupational settings. Particularly among workers exposed to high molecular weight protein allergens, there is a need to ascertain the pathophysiological mechanisms involved in skin exposure that result in respiratory disease and other systemic effects. By addressing these issues, better interventions aimed at preventing occupational exposure to these allergens can be made possible.

ACKNOWLEDGEMENTS

I would like to thank Dr Dorothy Ngajilo (Occupational Medicine) from University of Cape Town, Francisco Mbofana (MD, MIH) from MoH Mozambique, Dr Amy Burdzik (Occupational Medicine) and Professor Mohamed Jeebhay, both from University of Cape Town, for their contribution and comments in preparing this article.

DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict of interest.

This articles has been peer reviewed.

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APPENDIX 2: ETHICS APPROVAL

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

25 October 2017

HREC REF: 687/2017

Prof M Jeebhay
Department of Public Health & Family Medicine
Division of Occupational Medicine
Room 4.45, Level 4, Falmouth Building
FHS

Dear Pro Jeebhay

PROJECT TITLE: SKIN SYMPTOMS (ALLERGIC AND NON-ALLERGIC) PREDICTING THE DEVELOPMENT OF ALLERGIC RESPIRATORY OUTCOMES AND ASTHMA IN BAKERS (MMED CANDIDATE - DR V CHONGO-FARUK) SUB-STUDY LINKED TO 272/2002

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC)for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 October 2018.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr V Chongo-Faruk will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 687/2017

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC 687/2017

APPENDIX 3: CONSENT FORM

UCT OCCUPATIONAL ALLERGY AND ASTHMA STUDY AMONG BAKERY WORKERS IN THE WESTERN CAPE PROVINCE OF SOUTH AFRICA

ENGLISH CONSENT FORM

1. **Title of research project**

   Occupational risk factors and interventions for reducing the incidence of allergy and asthma among bakery workers in the Western Cape.

2. **Purpose of the research**

   The University of Cape Town is conducting this important study of the allergic effects of exposure to flour dust. This study is going to be done by researchers who are independent of the company. We will be studying a group of workers who have been involved with baking process. It is hoped that this study will provide greater insight into the risk factors for allergic sensitization among bakery workers and identify appropriate preventative strategies to be implemented in order to reduce the incidence of allergy and asthma among bakery workers.

3. **Description of the research project**

   If you agree to participate you will be asked to complete the following tests during working time:

   a) **Complete a questionnaire**. A member of our study team will interview you in privacy to complete the questionnaire. You will be asked questions about any breathing or chest problems; current and previous employment history, working with flour and dietary history.

   b) **Skin tests**
   Skin tests will be done to see whether you are allergic to any of the flour extracts or any other substance that commonly causes allergy in the Western Cape. A nurse will place a drop of liquid containing each type of flour allergen and the other substances on your forearm and then use a lancet to scratch the skin in that area.

   c) **Blood test**
   You will also be asked to undergo a blood test to check for allergies to specific flour allergens. Ten ml (about two teaspoons) of blood will be drawn once by a nurse.

   d) **Breathing tests**
   You will be asked to blow several times into a machine which measures how well your lungs are working. You will be asked to repeat the breathing test after you first breathe in a small amount of a chemical substance (methacholine). This test helps us find out if you may have a breathing problem like asthma. You may be asked to breathe in this substance and then blow into the machine several times.

4. **Confidentiality of information collected**

   Your name will not appear in any reports on this study. The records of skin tests, blood tests, questionnaires and breathing tests will be kept completely confidential and will be seen only by members of the study team.

5. **Risks and discomforts of the research**

a) **From the blood tests**. You will feel a single needle stick when the blood is taken. Sometimes a small bruise may occur from the needle stick, but this is minor and will heal quickly. The total amount of blood taken is quite small and your body will quickly replace it.

b) **From the questionnaire and breathing tests.** From the questionnaire and breathing tests. There are no risks from completing the questionnaire. There is a small chance that the initial breathing test could cause you to become light-headed or faint. Having you complete the test in a seated position under the observation of trained personnel greatly reduces the chance of your having such a problem. Part of the breathing test uses a chemical substance that can cause headache, cough, chest tightness, hoarse voice or a sore throat for a short time in some people. Very rarely it can cause severe breathing problems. Such breathing problems almost always can be treated successfully immediately with a different medication, which you breathe in. You will only be given the chemical substance if your simple breathing test is normal. This greatly reduces the chance of having a serious problem. These tests will be carried at the Lung Institute with medical personnel knowledgeable in the treatment of such problems immediately available.

c) **From the skin tests.** Itchiness can occur in some instances. Very rarely severe allergic reactions to skin tests (difficulty breathing or feeling faint and collapsing) may occur in people that are highly allergic. You will be asked questions before receiving the tests to help make sure you are not at any risk for such a problem. In addition, you will be at the Lung Institute, where nurses will be available to check you for any possible problems, for several hours after the test and have medications on hand to treat any such reaction. A doctor is also located nearby and ready to help if necessary.

6. **Expected benefits to you and to others**

You will be given a written copy of all your test results along with an explanation of what they mean, unless you tell us that you do not wish to receive this. You may wish to show these to your doctor if you are having any problems. These tests will help determine if you have an allergy to flour or other substances used in the skin tests. What we learn from this study will help to protect you, and those working with flour in South Africa and other parts of the world. We will learn how best to monitor worker's health and how to reduce workers' exposure to flour allergens.

7. **Costs to you resulting from participation in the study**

The study is offered at no cost to you. In the event a problem is discovered and you wish to be seen by a doctor for it, we can recommend to you who to see. However, the study cannot pay for these additional medical visits or treatments.

8. **Contact person.**

You may contact one of the following persons for answers to further questions about the research, your rights, or any injury you may feel is related to the study.

University of Cape Town Researchers:
Dr. Mohamed Jeebhay, Telephone No. (021) 406-6309
Roslyn Baatjies, Telephone No.: (021) 406-6665
University of Cape Town Research Ethics Committee:
Ms. Xolile Fula (Ethics Administrator) (021) 406-6492

UCT OCCUPATIONAL ALLERGY AND ASTHMA AMONG BAKERY WORKERS STUDY IN WESTERN CAPE OF SOUTH AFRICA

ENGLISH CONSENT FORM

STUDY NO. _____

9. **Consent of the participant**

I have read the information given above, or it has been read to me. I understand the meaning of this information, Dr./Mr./Ms.

_____

has offered to answer any questions concerning the study. By signing this form, I hereby consent to participate in the study. I also understand that I am free to withdraw from the study at any time without penalty.

10. **Documentation of the consent**

One copy of this signed document will be kept together with our research records for this study. A copy of the information sheet about the study will be given to you to keep.

_____	_____
Printed name of participant	Signature, Mark, or Thumb Print
_____	_____
Interviewer's name (Print)	Signature

DATE: _____

APPENDIX 4: ENGLISH QUESTIONNAIRE- BASELINE

UCT OCCUPATIONAL ALLERGY AND ASTHMA STUDY AMONG BAKERY WORKERS IN THE WESTERN CAPE PROVINCE OF SOUTH AFRICA-2003

ENGLISH QUESTIONNAIRE

Card 1

Survey Number _____ | | | | 1-3

A. IDENTIFICATION DATA

1. Surname _____

2. First name/s _____

3. Address _____

4. Work number _____ | | | | | | | 4-9

5. Date of birth: Day____Month_____Year____ | | | | | | | | 10-15

6. Gender: Male (1) Female (2) | | 16

7. Home Language: English (1) Afrikaans (2) Xhosa (3) Other (4) | | 17

8. Interviewer's initials _____ | | 18

9. Date of interview: Day___Month_____Year_____ | | | | | | 19-24

10. Bakery: _____ | | 25-26

11.Are you a casual or permanent worker?

Casual (1) ☐ 27

Permanent (2)

B.HEALTH PROBLEMS

Wheeze and tightness in the chest

1. Have you ever had wheezing or whistling in your chest in the past?

Yes (1) ☐ 28

No (2)

If YES, go on to Question 1.1
If NO, skip to Question 2

1.1 If yes, when was the first time you had these symptoms.

Date: Month_____Year _____ ☐☐☐☐ 29-32

1.2 Have you had wheezing or whistling in your chest at any time in the **last 12 months?**

Yes (1) ☐ 33

No (2)

If YES, go on to Question 1.2.1
If NO, skip to Question 2

1.2.1 Have you been short of breath when the wheezing noise was present?

Yes (1) ☐ 34

No (2)

1.2.2 Have you had this wheezing or whistling when you did not have a cold or flu?

Yes (1) ☐ 35

No (2)

2. Have you been woken up with a feeling of tightness in your chest at any time in the **last 12 months?**

Yes (1) ☐ 36

No (2)

Shortness of breath

3. Have you had an attack of shortness of breath that came on during the daytime when you were at rest at any time in the **last 12 months?**

Yes (1) ☐ 37

No (2)

4. Have you had an attack of shortness of breath that came on following running or exercise at any time in the **last 12 months?**

Yes (1) ☐ 38

No (2)

5. Have you been woken by an attack of shortness of breath at any time in the **last 12 months?**

Yes (1) ☐ 39

No (2)

Cough and phlegm from the chest

6. Have you been woken by an attack of coughing at any time in the **last 12 months?**

Yes (1) ☐ 40

No (2)

7. Do you usually cough first thing in the morning?

Yes (1) ☐ 41

No (2)

8. Do you usually cough during the rest of the day, or at night?

Yes (1) ☐ 42

No (2)

If YES, go on to Question 8.1
If NO, skip to Question 9

8.1 Do you cough like this on most days/nights for as much as three or more months in each of the last two years?

Yes (1) ☐ 43

No (2)

9. Do you usually bring up any phlegm from your chest first thing in the morning?

Yes (1) ☐ 44

No (2)

10. Do you usually bring up any phlegm from your chest during the day, or at night?

Yes (1) ☐ 45

No (2)

If YES, go on to Question 10.1
If NO, skip to Question 11

10.1 Do you bring up phlegm like this on most days/ nights for as much as three or more months in each of the last two years?

Yes (1) ☐ 46

No (2)

Breathing

11. Do you ever have trouble with your breathing? ☐ 47

Yes (1)

No (2)

If YES, go on to Question 11.1
If NO, skip to Question 12

11.1 Do you have this trouble: 48

Give all options at once
Insert a cross (X) next to one answer only

a) continuously so that your breathing is never quite right? _____

b) repeatedly, but it goes away completely between the times when it troubles you? _____

c) only rarely? _____

12. Are you disabled from walking by a condition other than heart or lung disease? 49

Yes (1)
No (2)

If YES, state the condition _____
and go on to Question 13
If NO, go to Question 12.1

12.1 Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill? 50

Yes (1)
No (2)

If YES, go on to Question 12.1.1
If NO, skip to Question 13

12.1.1 Do you get short of breath walking with other people of your own age on level ground? 51

Yes (1)
No (2)

12.1.1.1 Do you have to stop for breath when walking at your own pace on level ground? 52

Yes (1)

No (2)

Asthma

13. Have you ever had asthma?

Yes (1) ☐ 53

No (2)

If YES, go on to Question 13.1
If NO, skip to Question 13.8

13.1 If yes, was this confirmed by a doctor?

Yes (1) ☐ 54

No (2)

13.2 How old were you when you were told you have asthma? ☐ 55

Give all options at once
Insert a cross (X) next to one answer only

a) Only before you were 17 years old ____
b) Only at the age of 17 years or older ____
c) Both ____

The following references to "attack" of asthma refers to episodes of wheezing, shortness of breath, chest tightness or cough attributed to asthma

13.3.1 How old were you when you had your first attack of asthma?

_____years old ☐☐ 56-57

13.3.2 How old were you when you had your most recent attack of asthma?

_____years old ☐☐ 58-59

13.4.1-6 Which months of the year do you usually have attacks of asthma?

13.4.1 January/February

Yes (1) ☐ 60

No (2)

13.4.2 March/April

Yes (1) ☐ 61

No (2)

13.4.3 May/June

Yes (1) ☐ 62

No (2)

13.4.4 July/August

Yes (1) ☐ 63

No (2)

13.4.5 September/October

Yes (1) ☐ 64

No (2)

13.4.6 November/December

Yes (1) ☐ 65

No (2)

13.5 Have you had an attack of asthma in the last **12 months?**

Yes (1) ☐ 66

No (2)

If YES, go on to Question 13.5.1
If NO, skip to Question 13.6

13.5.1 How often have you had an attack of asthma in the **last 12 months?** ☐☐ 67

Give all options at once
Insert a cross (X) next to one answer only

a) Every day _____
b) More than 2 times a week _____
c) More than 1 time per month _____
d) 3 to 12 times in the whole year _____
e) 1 to 2 times in the whole year _____

13.6 Are your chest symptoms caused by, or made worse by any of the following:

Answer all questions

13.6.1 Contact with animals/pets

Yes (1) ☐ 68
No (2)

13.6.2 Grass or flowers

Yes (1) ☐ 69
No (2)

13.6.3 Heavy exercise

Yes (1) ☐ 70
No (2)

13.6.4 Breathing cold air

Yes (1) ☐ 71
No (2)

13.6.5 Dusts or sprays at work

Yes (1) ☐ 72
No (2)

13.6.6 Tobacco smoke

Yes (1) ☐ 73
No (2)

13.6.7 Change in the weather

Yes (1) ☐ 74

No (2)

13.7 Do your chest symptoms seem better or worse when you are away from work (for example, on weekends, off-shift and vacations)? ☐ 75

Give all options at once
Insert a cross (X) next to one answer only

a) Stay the same _____
b) Get better _____
c) Get worse _____

13.8 Does being at work ever make your tight chest or wheezy?

Yes (1) ☐ 76
No (2)

If YES, go on to Question 13.8.1
If NO, skip to Question 13.9

13.8.1 When did you first notice having problems with chest tightness or wheeze at work?

Date: Month_____Year _____ ☐☐☐☐ 77-80

13.8.2 Is there anything that you work with that causes you to have these chest symptoms? Card 2

Yes (1) ☐ 1
No (2)

If YES, go on to Question 13.8.3 (**specify wheat, rye &/or premix**) or any other substance
If NO, skip to Question 13.9

13.8.3 What do you think is causing these symptoms? ☐ 2

_____

13.9 Have you ever had to change or leave your work area, either temporarily or permanently, in this bakery

or any other bakery because of any chest symptoms?

Yes (1) ☐ 3

No (2)

If YES, go on to Question 13.9.1
If NO, skip to Question 13.10

13.9.1 What type of job were you doing when this happened?

☐☐ 4-5

13.9.2 Was this a job in this bakery?

Yes (1) ☐ 6

No (2)

If YES, go on to Question 13.9.2.1
If NO, skip to Question 13.10

13.9.2.1 What area/section did you move to?

☐☐ 7-8

13.9.2.2 What job did you do there?

☐☐ 9-10

13.9.2.3 Did your symptoms improve when you changed jobs?

Yes (1) ☐ 11

No (2)

13.10 Have you ever worked in a job or jobs that exposed you to vapours, gas, dust or fumes?

Yes (1) ☐ 12

No (2)

If YES, go on to Question 13.10.1.
List the jobs beginning with the most recent
If NO, skip to Question 13.11

13.10.1 What was or is this job? _____ ☐☐ 13-14

(if current job write 'current job')

13.10.2 Before that? _____ 15-16

13.10.3 Before that? _____ 17-18

13.11 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? 19

Yes (1)

No (2)

If YES, go on to Question 13.11.1.
If NO, skip to Question 13.12

13.11.1 What was or is this job? _____ 20-21

(if current job write 'current job')

13.12 Are you using any medicines, including inhalers/ pumps, nebulizers, syrups or tablets, for asthma or breathing problems? 22

Yes (1)

No (2)

If YES, go on to Question 13.12.1, showing examples of each
If NO, skip to question 13.13

13.12.1 Which medicines? 23 24 25

13.12.2 Do you take these medicines every day even when you do not have any trouble breathing? 26

Yes (1)

No (2)

13.13 Have you ever been treated for any of the following:

Answer all questions

13.13.1 Repeated chest infections as a child

Yes (1) ☐ 27

No (2)

UNK (3)

13.13.2 Tuberculosis (TB)

Yes (1) ☐ 28

No (2)

UNK (3)

13.13.3 Chronic bronchitis

Yes (1) ☐ 29

No (2)

UNK (3)

Nose and eye symptoms

14. Have you ever had any nose or eye problems or allergies such as hay fever?

Yes (1) ☐ 30

No (2)

If YES, go on to Question 14.1 Answer all questions
If NO, skip to Question 14.4

14.1 How old were you when you first noticed these symptoms?

_____years old ☐☐ 31-32

14.2 During the past 12 months have you had two or more episodes of:

14.2.1 sneezy, itchy or runny nose when you did not have a cold or flu?

Yes (1) ☐ 33

No (2)

14.2.2 red, itchy or watery eyes

Yes (1) ☐ 34
No (2)

14.2.3 Do you usually have the nose or eye symptoms at any particular time of the year?

Yes (1) ☐ 35
No (2)

14.2.3.1 If YES, which is the worst season? ☐ 36

Give all options at once
Insert a cross (X) next to one answer only

a) Winter _____
b) Spring _____
c) Summer _____
d) Autumn _____

If YES to any of the above in question 14.2, go on to Question 14.3
If NO, skip to Question 14.4

14.3 Do your nose or eye symptoms seem better or worse when you are away from work (for example, on weekends, off-shift and vacations)? ☐ 37

Give all options at once
Insert a cross (X) next to one answer only

a) Stay the same _____
b) Get better _____
c) Get worse _____

14.4 Does being at work ever cause you to have sneezy/ itchy/runny nose or red/itchy/watery eyes?

Yes (1) ☐ 38
No (2)

If YES to any one of the above, go on to Question 14.4.1
If NO, skip to Question 14.5

14.4.1 Since when have you been having these symptoms at work?

Date: Month_____Year ____ 39-42

14.4.2 Is there anything that you work with that causes you to have these symptoms?

Yes (1) 43

No (2)

If YES, go on to Question 14.4.3 (**specify wheat, rye &/or premix**) or any other substance

If NO, skip to Question 14.5

14.4.3 What do you think is causing these symptoms? 44

14.5 Are you using any medicines, including nose sprays, drops, tablets or injections, for any nose or eye symptoms at present?

Yes (1) 45

No (2)

If YES, go on to Question 14.5.1

If NO, go on to Question 14.6

Present a chart with different samples of allergy medicines (N.B. a worker might show you his/her medicines).

14.5.1 Which medicines? 46

47

14.6 Did you have hay fever (itchy or watery eyes/nose) as a child?

Yes (1) 48

No (2)

Skin symptoms

15. Have you ever had any kind of skin problem either at home or at work?

Yes (1) ☐ 49

No (2)

If YES, go on to Question 15.1
If NO, skip to Question 15.4

15.1 How old were you when you **first** noticed this skin problem?

_____years old ☐☐ 50-51

15.2 During the past **12 months** have you had any skin problems that occurred **2 or more times**?

Yes (1) ☐ 52

No (2)

If Yes, which of the following problems did you have?

Go through each option in the table below and circle the appropriate response.

	Forearms Hands	**Whole Body**	
15.2.1			
itchy or	Yes/No	Yes/No	☐ 53
scratchy skin			☐ 54
15.2.2			
hives	Yes/No	Yes/No	☐ 55
("bommels")			☐ 56
15.2.3			
dry, scaly	Yes/No	Yes/No	☐ 57
skin			☐ 58
15.2.4			
redness of	Yes/No	Yes/No	☐ 59
the skin			☐ 60
15.2.5			

blisters or	Yes/No	Yes/No	61
weeping skin			62
15.2.6			
burning skin	Yes/No	Yes/No	63
			64
15.2.7			
started within			
an hour of	Yes/No	Yes/No	65
contact with			66
a substance			
or food item			
			Card 3
15.2.8			1
Other?	Yes/No	Yes/No	2
Specify:			

If YES, to any of the above go on to Question 15.3
If NO, skip to Question 15.4

15.3 Do your skin problems seem better or worse when you are away from work (for example, on weekends, off-shift and vacations)? 3

Give all options at once
Insert a cross (X) next to one answer only

a) Stay the same _____
b) Get better _____
c) Get worse _____

15.4 Does being at work ever cause you to have any skin problems? 4

Yes (1)
No (2)

If YES, go on to Question 15.4.1
If NO, skip to Question 15.4.4

15.4.1 Since when have you been having these skin

problems at work?

Date: Month_____Year ____ 5-8

15.4.2 Is there anything that you work with that makes these skin problems worse? 9

Yes (1)

No (2)

If YES, go on to Question 15.4.3 (**specify wheat, rye &/or premix**) or any other substance

If NO, skip to Question 15.4.4

15.4.3 What do you think is causing these skin problems? 10

_____

15.4.4 Have you ever bruised, burnt or injured your fingers or hands while working in the bakery? 11

Yes (1)

No (2)

15.5 How many times do you wash your hands in the course of a day? 12

Give all options at once
Insert a cross (X) next to one answer only

0 _____

1 time _____

2-3 times _____

4-5 times _____

6 or more _____

15.6 Are you using any medicines, including any creams or ointments, for your skin problems at present? 13

Yes (1)

No (2)

If YES, go on to Question 15.6.1
If NO, skip to next question 15.7

15.6.1 Which medicines? ☐ 14 ☐ 15

15.7 Did you have eczema as a child?

Yes (1) ☐ 16

No (2)

Other allergic conditions

16. Are you allergic to insect stings or bites?

Yes (1) ☐ 17

No (2)

If YES, go on to Question 16.1
If NO, skip to Question 17

16.1.1-3 What kind of reactions do you have?

16.1.1 Breathing difficulty, feeling faint, fever?

Yes (1) ☐ 18

No (2)

16.1.2 Redness, itching or swelling at the sting site

Yes (1) ☐ 19

No (2)

16.1.3 Other: _____ ☐ 20

17. Have you ever had any difficulty with your breathing after taking medications or injections that you did not have before?

Yes (1) ☐ 21

No (2)

If YES, go on to Question 17.1
If NO, skip to 18.1

17.1 Which medicines? _____ ☐ 22

18.1-6 When you are near animals (such as cats, dogs or horses), near feathers (including pillows, quilts or duvets), near grass and flowers, or in a dusty part of the

house, do you ***ever***

18.1 Start to cough?

Yes (1)
No (2)

23

18.2 Start to wheeze?

Yes (1)
No (2)

24

18.3 Get a tight chest?

Yes (1)
No (2)

25

18.4 Start to feel short of breath?

Yes (1)
No (2)

26

18.5 Get a runny/stuffy nose or sneeze?

Yes (1)
No (2)

27

18.6 Get itchy or watery eyes?

Yes (1)
No (2)

28

18.7 Get itchy skin/rash?

Yes (1)
No (2)

29

19. Have you ever had an illness or trouble caused by eating a particular type of food/fruit?

Yes (1)
No (2)

30

If YES, go on to Question 19.1
If NO, skip to 20

19.1 What type of food/fruit was this?

31

19.1.1-6 Did this illness or trouble include:

19.1.1 Itchy skin or rash

Yes (1) ☐ 32

No (2)

19.1.2 Diarhoea or vomiting

Yes (1) ☐ 33

No (2)

19.1.3 Runny or stuffy nose

Yes (1) ☐ 34

No (2)

19.1.4 Severe headaches

Yes (1) ☐ 35

No (2)

19.1.5 Breathlessness/tight chest/wheeze

Yes (1) ☐ 36

No (2)

19.1.6 Other:_____ ☐ 37

19.2 Was the food canned or preserved?

Yes (1) ☐ 38

No (2)

UNK (3)

19.3 Do you experience these problems when you drink fizzy drinks also?

Yes (1) ☐ 39

No (2)

C. FAMILY HISTORY

1. Do/did any members of your family (blood relatives) ever have any kind of allergies? ☐ 40

Do not include relatives by marriage
If family history is completely unknown (subject is adopted, etc.), mark UNK and do not complete table. Move to next section

Yes (1)
No (2)
UNK (3)

If YES, complete table below. Insert a cross (X) in the appropriate block for each option

Type of Allergy	**NO ONE** in family	**YES**, present in the family			**Do Not Know**	
		Parent	Brother/ Sister	Child		
1.1 Hay fever	1	2	3	4	5	41
1.2 Eczema	1	2	3	4	5	42
1.3 Asthma	1	2	3	4	5	43
1.4 Flour related Allergy	1	2	3	4	5	44
1.5 Other allergy Specify:	1	2	3	4	5	45

D. SMOKING HISTORY

1. Have you ever smoked tobacco (cigarettes or pipe) for as long as a year?

'YES' means at least 20 packs of cigarettes or 360 grams of tobacco in a lifetime or at least one cigarette per day for one year

Yes (1) 46
No (2)

If YES, go on to Question 1.1
If NO, skip to Question 2

1.1 How old were you when you started smoking?

_____years old 47-48

1.2 Do you now smoke?

'YES' means smoking tobacco in the last month or more

Yes (1) ☐ 49

No (2)

If YES, go on to Question 1.2.1
If NO, skip to Question 1.3.1

1.2.1-2. How much do you now smoke on average?

1.2.1 Number of cigarettes per day _____ ☐☐ 50-51

1.2.2 Pipe tobacco in grams/week _____ ☐☐☐ 52-54

1.3. Have you stopped smoking completely?

Yes (1) ☐ 55

No (2)

If YES, go on to Question 1.3.1
If NO, skip to Question 1.4

1.3.1. How old were you when you stopped smoking completely?

_____years old ☐☐ 56-57

1.3.1.1 How many years in total did you smoke cigarettes? (Do not include the years you stopped before you started again)

_____years ☐☐ 58-59

1.3.2.1-2 On average of the entire time you smoked, how much did you smoke?

1.3.2.1 Number of cigarettes per day _____ ☐☐ 60-61

1.3.2.2 Pipe tobacco in grams/week _____ ☐☐☐ 62-64

1.4 Do you or did you inhale the smoke?

Yes (1)

No (2)

☐ 65

2. Have you been regularly exposed to tobacco smoke from other people smoking cigarettes or pipe in the last 12 months?

'Regularly' means on most days or nights

Yes (1)

No (2)

☐ 66

E. DIETARY HISTORY/DOMESTIC ACTIVITIES

1. How often have you eaten the following grain products in the last 12 months?

Go through each wheat product option and insert a cross (X) in the block for each option

Type of wheat product	**Daily**	**1 to 3 times a week**	**1 to 3 times per month**	**Never**	
					Card 4
1.1 White bread/Rolls	1	2	3	4	☐ 1
1.2 Brown bread/Rolls	1	2	3	4	☐ 2
1.3 Whole wheat bread/ rolls	1	2	3	4	☐ 3
1.4 Rye bread/ rolls	1	2	3	4	☐ 4
2. Pastries	1	2	3	4	☐ 5
3. Cereals	1	2	3	4	☐ 6
4. Biscuits containing wheat	1	2	3	4	☐ 7
5.Pasta containing wheat	1	2	3	4	☐ 8

6. Other	1	2	3	4
Specify:				

9

2.Have you changed your diet or avoided certain grain (eg. wheat/rye/soya) products because they do not agree with you when you eat them?

Yes (1) 10

No (2)

If YES, go on to Question 2.1
If NO, skip to Question 3

2.1 What grain products have you avoided? 11 12

3. Do you bake at home?

Yes (1) 13

No (2)

If YES, go on to Question 3.1
If NO, go to Question 4

3.1 How often do you do baking at home? 14

a) once a month _____
b) 2-3 times a month _____
c) 2-3 times per week _____
d) once a week _____
e) everyday _____

3.2 What do you bake?

a) bread/rolls _____ 15
b) cakes/biscuits _____ 16
c) tarts/pastries _____ 17
d) Other: _____ 18

Specify:_____

4. Does any one else bake at home?

Yes (1) 19

No (2)

F. HEALTH AND SAFETY EDUCATION AND TRAINING

1. What are the hazards associated with flour dust?

20
21

2. Have you had any health and safety training on how to protect yourself when working with flour dust?

Yes (1)
No (2)

22

G. WORK HISTORY IN THE BAKERY INDUSTRY

1. How long have you been working at this bakery?

_____years
_____months

23-26

Present job

2. How long have you been working in your current job?

_____years
_____months

27-30

3. In which area/section are you currently working?

31-32

3.1 What is your job in this area/section?

Job Title _____

33-34

get a short description of the job

3.2 What products do you produce:

a) doughs Yes (1)
No (2)

35

b) pastry	Yes	(1)	36
	No	(2)	
c) croissants	Yes	(1)	37
	No	(2)	
d) bread,rolls	Yes	(1)	38
	No	(2)	
e) cakes/tarts	Yes	(1)	39
	No	(2)	
f) biscuits	Yes	(1)	40
	No	(2)	
g) confectionary	Yes	(1)	41
	No	(2)	
h) other	Yes	(1)	42
	No	(2)	

Specify:_____

3.3 What ingredients do you work with?

a) Flour (wheat, rye)			43
	Yes	(1)	
	No	(2)	
b) Baking additives (premix)			44
	Yes	(1)	
	No	(2)	
c) Icing sugar			45
	Yes	(1)	
	No	(2)	
d) Nuts (peanuts, hazelnuts)			46
	Yes	(1)	
	No	(2)	
e) Seeds (sesame, lupine)			47

Yes (1)
No (2)

f) Other Yes (1) 48
No (2)

Specify:_____

3.4 Do you ever do other jobs during your shift on a regular basis (almost every day)?

Yes (1) 49
No (2)

If **Yes**, which jobs? _____ 50
51

3.5 How much dust would you say your current job produces: 52

Give all options at once
Insert a cross (X) next to one answer only

a) None _____
b) A little _____
c) An average amount _____
d) A lot _____

3.5.1 What aspect of your work would you say is very dusty?

a) Tipping/Dispensing 53

Yes (1)
No (2)
N/A (3)

b) Weighing 54

Yes (1)
No (2)
N/A (3)

c) Sifting 55

Yes (1)
No (2)
N/A (3)

d) Mixing

Yes (1)
No (2)
N/A (3)

56

e) brushing table

Yes (1)
No (2)
N/A (3)

57

f) dough handling

Yes (1)
No (2)
N/A (3)

58

g) other

Yes (1)
No (2)
N/A (3)

59

Specify:_____

3.5.1.1 What type of cleaning activities in your daily work are very dusty.

3.5.1.1.1 Cleaning work table surfaces?

Yes (1)
No (2)
N/A (3)

60

3.5.1.1.2 Sweeping floors?

Yes (1)
No (2)
N/A (3)

61

3.5.1.1.3 Cleaning equipment (mixers, cutters)

Yes (1)
No (2)
N/A (3)

62

3.5.2 How far do you work from the source of the dust?

63

Give all options at once
Insert a cross (X) next to one answer only

a) Right next to the source _____
b) About 1-2 metres away _____
c) More than 3 metres away _____
d) Does not apply _____

3.6 Do you use any personal protective equipment on a regular basis (almost every day) while doing your job?

Yes (1) ☐ 64
No (2)

If NO, skip to Question 4
If YES, continue with Question 3.6.1

3.6.1 Which of the following personal protective equipment do you use on a regular basis (almost every day)?

3.6.1.1 Goggles: Yes (1) ☐ 65
No (2)

3.6.1.2 Gloves: Yes (1) ☐ 66
No (2)

3.6.1.3 Mask: Yes (1) ☐ 67
No (2)

3.6.1.4 Aprons: Yes (1) ☐ 68
No (2)

3.6.1.5 Other: _____ ☐ 69

If NO to all of the previous questions, skip to Question 4
If YES to any one of the above questions, continue with Question 3.6.2.1

3.6.2.1 Goggles _____ years ☐☐ 70-71

3.6.2.2 Gloves: _____ years ☐☐ 72-73

3.6.2.3 Mask: _____ years | 74-75

3.6.2.4 Aprons: _____ years | 76-77

3.6.2.5 Other: _____ years | 78-79

Previous jobs in present bakery | Card 5

4. Before doing this job at this bakery, did you do a different job here?

Yes (1) | 1

No (2)

If NO, skip to question 5
If YES, continue with question 4.1

4.1 What other jobs did you do here?

Start with the first job and work forward, getting a one-line description of each job. If casual worker, denote each period of employment as a separate job. For continuous years of seasonal work consider as one job (provided no broken years service)

Job 1

4.1.1 Area/section _____ | 2-3

4.1.2 Job Title _____ | 4-5

get a short description of the job

_____

4.1.3 Permanent/casual: _____ | 6

4.1.4. How long did you work in this job? | 7-10

_____years

_____months

4.1.5 What products did you produce:

a) doughs	Yes	(1)	11
	No	(2)	
b) pastry	Yes	(1)	12
	No	(2)	
c) croissants	Yes	(1)	13
	No	(2)	
d) bread,rolls	Yes	(1)	14
	No	(2)	
e) cakes/tarts	Yes	(1)	15
	No	(2)	
f) biscuits	Yes	(1)	16
	No	(2)	
g) confectionary	Yes	(1)	17
	No	(2)	
h) other	Yes	(1)	18
	No	(2)	

Specify:_____

4.1.6 What ingredients did you work with?

a) Flour (wheat, rye)			19
	Yes	(1)	
	No	(2)	
b) Baking additives (premix)			20
	Yes	(1)	
	No	(2)	
c) Icing sugar			21
	Yes	(1)	
	No	(2)	
d) Nuts (peanuts, hazelnuts)			22
	Yes	(1)	
	No	(2)	

e) Seeds (sesame, lupine) ☐ 23

Yes (1)
No (2)

f) Other ☐ 24

Yes (1)
No (2)

Specify:_____

4.1. 7 How much dust would you say that this job produced: ☐ 25

Give all options at once
Insert a cross (X) next to one answer only

a) None _____
b) A little _____
c) An average amount _____
d) A lot _____

4.1.8 What aspect of your work would you say was very dusty?

a) Tipping/Dispensing ☐ 26

Yes (1)
No (2)
N/A (3)

b) Weighing ☐ 27

Yes (1)
No (2)
N/A (3)

c) Sifting ☐ 28

Yes (1)
No (2)
N/A (3)

d) mixing ☐ 29

Yes (1)
No (2)
N/A (3)

e) brushing table [ ] 30

Yes (1)
No (2)
N/A (3)

f) dough handling [ ] 31

Yes (1)
No (2)
N/A (3)

g) other [ ] 32

Yes (1)
No (2)
N/A (3)

Specify:_____

4.1.8.1. What type of cleaning activities in your daily work were very dusty.

4.1.8.1.1. Cleaning work table surfaces? [ ] 33

Yes (1)
No (2)
N/A (3)

4.1.8.1.2 Sweeping floors? [ ] 34

Yes (1)
No (2)
N/A (3)

4.1.8.1.3 Cleaning equipment (mixers, cutters) [ ] 35

Yes (1)
No (2)
N/A (3)

4.1.9 How far did you work from the source of the dust? [ ] 36

Give all options at once
Insert a cross (X) next to one answer only

a) Right next to the source _____

b) About 1-2 metres away _____
c) More than 3 metres away _____
d) Does not apply _____

4.1.10 Did you use any personal protective equipment on a regular basis (almost every day) while doing your job?

Yes (1) ☐ 37
No (2)

If NO, skip to Question 4.2.1
If YES, continue with Question 4.1.10.1

4.1.10.1Which of the following personal protective equipment did you use on a regular basis (almost every day)?

4.1.10.1.1 Goggles: Yes (1) ☐ 38
No (2)

4.1.10.2 Gloves: Yes (1) ☐ 39
No (2)

4.1.10.3 Mask: Yes (1) ☐ 40
No (2)

4.1.10.4 Aprons: Yes (1) ☐ 41
No (2)

4.1.10.5 Other: _____ ☐ 42

If NO to all of the previous questions, skip to Question 4.2.1
If YES to any one of the above questions, continue with Question 4.1.11.1

4.1.11.1 Goggles _____ years ☐☐ 43-44

4.1.11.2 Gloves: _____ years ☐☐ 45-46

4.1.11.3 Mask: _____ years ☐☐ 47-48

Section D: Appendices

49-50

51-52

53-54

55-56

_____ _____ 57

58-61

62

63

64

65

66

67

68

h) other Yes (1) 69
No (2)

Specify:_____

4.2.6 What ingredients did you work with?

a) Flour (wheat, rye) 70
Yes (1)
No (2)

b) Baking additives (premix) 71
Yes (1)
No (2)

c) Icing sugar 72
Yes (1)
No (2)

d) Nuts (peanuts, hazelnuts) 73
Yes (1)
No (2)

e) Seeds (sesame, lupine) 74
Yes (1)
No (2)

f) Other 75
Yes (1)
No (2)

Specify:_____

4.2.7 How much dust would you say that this job produced: Card 6 1

Give all options at once
Insert a cross (X) next to one answer only

a) None
b) A little
c) An average amount _____

d) A lot

4.2.8 What aspect of your work would you say was very dusty?

a) Tipping/Dispensing | | 2

Yes (1)
No (2)
N/A (3)

b) Weighing | | 3

Yes (1)
No (2)
N/A (3)

c) Sifting | | 4

Yes (1)
No (2)
N/A (3)

d) mixing | | 5

Yes (1)
No (2)
N/A (3)

e) brushing table | | 6

Yes (1)
No (2)
N/A (3)

f) dough handling | | 7

Yes (1)
No (2)
N/A (3)

g) other | | 8

Yes (1)
No (2)
N/A (3)

Specify:_____

4.2.8.1. What type of cleaning activities in your daily

work were very dusty.

4.2.8.1.1.Cleaning work table surfaces?

Yes (1) | 9
No (2)
N/A (3)

4.2.8.1.2 Sweeping floors?

Yes (1) | 10
No (2)
N/A (3)

4.2.8.1.3 Cleaning equipment (mixers, cutters)

Yes (1) | 11
No (2)
N/A (3)

4.2.9 How far did you work from the source of the dust? | 12

Give all options at once
Insert a cross (X) next to one answer only

a) Right next to the source _____
b) About 1-2 metres away _____
c) More than 3 metres away _____
d) Does not apply _____

4.2.10 Did you use any personal protective equipment on a regular basis (almost every day) while doing your job?

Yes (1) | 13
No (2)

If NO, skip to Question 4.3.1 or 5 if no other jobs
If YES, continue with Question 4.2.10.1

4.2.10.1Which of the following personal protective equipment did you use on a regular basis (almost every day)?

4.2.10.1.1 Goggles: Yes (1) | 14
No (2)

4.2.10.2 Gloves:	Yes	(1)	15
	No	(2)	
4.2.10.3 Mask:	Yes	(1)	16
	No	(2)	
4.2.10.4 Aprons:	Yes	(1)	17
	No	(2)	
4.2.10.5 Other:	_____		18
4.2.11.1 Goggles	_____	years	19-20
4.2.11.2 Gloves:	_____	years	21-22
4.2.11.3 Mask:	_____	years	23-24
4.2.11.4 Apron:	_____	years	25-26
4.2.11.5 Other:	_____	years	27-28

Job 3

4.3.1 Area/section	_____	29-30
4.3.2 Job Title	_____	31-32
4.3.3 Permanent/casual:		33

4.3.4. How long did you work in this job?

_____years | ☐☐☐☐ 34-37

_____months

4.3.5 What products did you produce:

a) doughs	Yes	(1)	☐ 38
	No	(2)	
b) pastry	Yes	(1)	☐ 39
	No	(2)	
c) croissants	Yes	(1)	☐ 40
	No	(2)	
d) bread,rolls	Yes	(1)	☐ 41
	No	(2)	
e) cakes/tarts	Yes	(1)	☐ 42
	No	(2)	
f) biscuits	Yes	(1)	☐ 43
	No	(2)	
g) confectionary	Yes	(1)	☐ 44
	No	(2)	
h) other	Yes	(1)	☐ 45
	No	(2)	

Specify:_____

4.3.6 What ingredients did you work with?

a) Flour (wheat, rye)			☐ 46
	Yes	(1)	
	No	(2)	
b) Baking additives (premix)			☐ 47
	Yes	(1)	
	No	(2)	
c) Icing sugar			☐ 48
	Yes	(1)	

No (2)

d) Nuts (peanuts, hazelnuts) ☐ 49

Yes (1)

No (2)

e) Seeds (sesame, lupine) ☐ 50

Yes (1)

No (2)

f) Other ☐ 51

Yes (1)

No (2)

Specify:_____

4.3.7 How much dust would you say that this job produced: ☐ 52

Give all options at once

Insert a cross (X) next to one answer only

a) None _____

b) A little _____

c) An average amount _____

d) A lot _____

4.3.8 What aspect of your work would you say was very dusty?

a) Tipping/Dispensing ☐ 53

Yes (1)

No (2)

N/A (3)

b) Weighing ☐ 54

Yes (1)

No (2)

N/A (3)

c) Sifting ☐ 55

Yes (1)

No (2)

N/A (3)

d) mixing ☐ 56

Yes (1)
No (2)
N/A (3)

e) brushing table ☐ 57

Yes (1)
No (2)
N/A (3)

f) dough handling ☐ 58

Yes (1)
No (2)
N/A (3)

g) other ☐ 59

Yes (1)
No (2)
N/A (3)

Specify:_____

4.3.8.1. What type of cleaning activities in your daily work were very dusty.

4.3.8.1.1.Cleaning work table surfaces? ☐ 60

Yes (1)
No (2)
N/A (3)

4.3.8.1.2 Sweeping floors? ☐ 61

Yes (1)
No (2)
N/A (3)

4.3.8.1.3 Cleaning equipment (mixers, cutters) ☐ 62

Yes (1)
No (2)
N/A (3)

4.3.9 How far did you work from the source of the dust? ☐ 63

Give all options at once
Insert a cross (X) next to one answer only

a) Right next to the source _____
b) About 1-2 metres away _____
c) More than 3 metres away _____
d) Does not apply _____

4.3.10 Did you use any personal protective equipment on a regular basis (almost every day) while doing your job? ☐ 64

Yes (1)
No (2)

If NO, skip to Question 4.4.1 or 5
If YES, continue with Question 4.3.10.1

4.3.10.1 Which of the following personal protective equipment did you use on a regular basis (almost every day)?

4.3.10.1.1 Goggles: Yes (1) ☐ 65
No (2)

4.3.10.2 Gloves: Yes (1) ☐ 66
No (2)

4.3.10.3 Mask: Yes (1) ☐ 67
No (2)

4.3.10.4 Aprons: Yes (1) ☐ 68
No (2)

4.3.10.5 Other: _____ ☐ 69

If NO to all of the previous questions, skip to Question 4.4.1 or 5
If YES to any one of the above questions, continue with Question 4.3.11.1

4.3.11.1 Goggles _____ years [ ][ ] 70-71

4.3.11.2 Gloves: _____ years [ ][ ] 72-73

4.3.11.3 Mask: _____ years [ ][ ] 74-75

4.3.11.4 Apron: _____ years [ ][ ] 76-77

4.3.11.5 Other: _____ years [ ][ ] 78-79

Job 4

Card 7

4.4.1 Area/section _____ [ ][ ] 1-2

4.4.2 Job Title _____ [ ][ ] 3-4

get a short description of the job

_____

4.4.3 Permanent/casual: _____ [ ] 5

4.4.4. How long did you work in this job?

_____years [ ][ ][ ][ ] 6-9

_____months

4.4.5 What products did you produce:

a) doughs Yes (1) [ ] 10
No (2)

b) pastry Yes (1) [ ] 11
No (2)

c) croissants Yes (1) [ ] 12
No (2)

d) bread,rolls Yes (1) [ ] 13
No (2)

e) cakes/tarts Yes (1) [ ] 14

	No	(2)	
f) biscuits	Yes	(1)	☐ 15
	No	(2)	
g) confectionary	Yes	(1)	☐ 16
	No	(2)	
h) other	Yes	(1)	☐ 17
	No	(2)	

Specify:_____

4.4.6 What ingredients did you work with?

a) Flour (wheat, rye)			☐ 18
	Yes	(1)	
	No	(2)	
b) Baking additives (premix)			☐ 19
	Yes	(1)	
	No	(2)	
c) Icing sugar			☐ 20
	Yes	(1)	
	No	(2)	
d) Nuts (peanuts, hazelnuts)			☐ 21
	Yes	(1)	
	No	(2)	
e) Seeds (sesame, lupine)			☐ 22
	Yes	(1)	
	No	(2)	
f) Other			☐ 23
	Yes	(1)	
	No	(2)	

Specify:_____

4.4.7 How much dust would you say that this job

produced: 24

Give all options at once
Insert a cross (X) next to one answer only

a) None _____
b) A little _____
c) An average amount _____
d) A lot _____

4.4.8 What aspect of your work would you say was very dusty?

a) Tipping/Dispensing 25

Yes (1)
No (2)
N/A (3)

b) Weighing 26

Yes (1)
No (2)
N/A (3)

c) Sifting 27

Yes (1)
No (2)
N/A (3)

d) mixing 28

Yes (1)
No (2)
N/A (3)

e) brushing table 29

Yes (1)
No (2)
N/A (3)

f) dough handling 30

Yes (1)
No (2)
N/A (3)

g) other

Yes (1)
No (2)
N/A (3)

Specify:_____

4.4.8.1. What type of cleaning activities in your daily work were very dusty.

4.4.8.1.1. Cleaning work table surfaces?

Yes (1)
No (2)
N/A (3)

4.4.8.1.2 Sweeping floors?

Yes (1)
No (2)
N/A (3)

4.4.8.1.3 Cleaning equipment (mixers, cutters)

Yes (1)
No (2)
N/A (3)

4.4.9 How far did you work from the source of the dust?

Give all options at once
Insert a cross (X) next to one answer only

a) Right next to the source _____
b) About 1-2 metres away _____
c) More than 3 metres away _____
d) Does not apply _____

4.4.10 Did you use any personal protective equipment on a regular basis (almost every day) while doing your job?

Yes (1)
No (2)

If NO, skip to Question 5
If YES, continue with Question 4.4.10.1

31
32
33
34
35
36

4.4.10.1Which of the following personal protective equipment did you use on a regular basis (almost every day)?

4.4.10.1.1 Goggles:	Yes	(1)	☐ 37
	No	(2)	
4.4.10.2 Gloves:	Yes	(1)	☐ 38
	No	(2)	
4.4.10.3 Mask:	Yes	(1)	☐ 39
	No	(2)	
4.4.10.4 Aprons:	Yes	(1)	☐ 40
	No	(2)	
4.4.10.5 Other:	_____		☐ 41

If NO to all of the previous questions, skip to Question 5
If YES to any one of the above questions, continue with Question 4.4.11.1

4.4.11.1 Goggles	_____	years	☐☐ 42-43
4.4.11.2 Gloves:	_____	years	☐☐ 44-45
4.4.11.3 Mask:	_____	years	☐☐ 46-47
4.4.11.4 Apron:	_____	years	☐☐ 48-49
4.4.11.5 Other:	_____	years	☐☐ 50-51

Previous work in other bakeries

5. Have you worked in any other bakeries in the past two years?

Yes (1) ☐ 52

No (2)

If NO, skip to question 6
If YES, continue with question 5.1

5.1 Why did you change jobs?

_____ ☐ 53

5.2 What is the total amount of time you have worked in the bakery industry before you started working in this bakery?

Years_____Months _____ ☐☐☐☐ 54-57

Previous work experience

6. Name all the previous workplaces that you have worked in, when not working in this bakery or before coming to work in this bakery:

Start with the first job and work forward (including all other bakeries and jobs done)

Name of Company	What did company make?	Job Title (what did you do?)	Date start (Year)	Date stop (Year)	Total (yrs)
					☐ 58
					☐ 59

THANK YOU FOR ANSWERING THE QUESTIONNAIRE

APPENDIX 5: ENGLISH QUESTIONNAIRE- FOLLOW UP

UCT OCCUPATIONAL ALLERGY AND ASTHMA STUDY AMONG BAKERY WORKERS IN THE WESTERN CAPE PROVINCE OF SOUTH AFRICA-2006

ENGLISH QUESTIONNAIRE

Survey Number _____

A. IDENTIFICATION DATA

1. Surname _____

2. First name/s _____

3. Work number _____

4. Date of birth: Day____Month_____Year____

5. Gender: Male (1)
Female (2)

8. Interviewer's initials _____

9. Date of interview:
Day____Month_____Year_____

10. Bakery: _____

11. Did you change your job since the last interview?
Yes (1)
No (2)
Not applicable (3)

11.1 If Yes or NA, what is your new job?
_____

12. Which shift have you been working today?
04:00-12:00 (1)
07:00-16:00 (2)
08:00-17:00 (3)
09:00-18:00 (4)
12:00-21:00 (5)

B.HEALTH PROBLEMS

Recent chest infections

1. Have you had the flu or sinusitis in the past 3 weeks?
Yes (1)
No (2)

2. Have you had any of the following symptoms in the past **12 months** (at night, with exercise, exposure to cold air, work exposures)?

2.1 chest tightness — Yes (1) / No (2)

2.2 shortness of breath — Yes (1) / No (2)

2.3 wheezing or whistling in your chest — Yes (1) / No (2)

2.4 dry cough — Yes (1) / No (2)

2.5 Asthma — Yes (1) / No (2)

3. Are you being treated for Tuberculosis (TB)?

Yes (1) / No (2)

3.1 If yes, for how long? _____months _____weeks

If YES, to question no 3, indicate to person that the tests will not be done today. Schedule another appointment in three months time since the start of TB medication.

Nose and eye symptoms

4. Have you ever had any nose or eye problems due to allergies and/or hay fever?

Yes (1) / No (2)

C. SMOKING HISTORY

1. Do you smoke?

Yes (1) / No (2)

1.1 If yes, have you smoked tobacco (cigarettes or pipe) for as long as a year?

Yes (1) / No (2)

1.2 If yes, how many cigarettes per day do you smoke or did you smoke?

1.3 Have you smoked (cigarettes/tobacco) in the last hour?

Yes (1) / No (2)

D. ALCOHOL CONSUMPTION

1. Do you drink alcohol?

Yes (1)
No (2)

1.1 If yes, when have you last consumed alcohol?

1-2 hours ago (1)
1 day ago (2)
1 week ago (3)

1.2 How much alcohol did you consume?

_____

E. MEDICATION USAGE (show booklet)

1. Are you taking any medicine/s from a doctor or clinic at the moment for asthma, and or hayfever?

Yes (1)
No (2)

1.1 If yes, what are you taking and when last did you take them?

Names No. of hours since last dose

_____ _____
_____ _____
_____ _____

F. GREEN VEGETABLE CONSUMPTION

1. How often do you eat the following vegetable products?

Type of product	**Daily**	**1 to 3 times a week**	**1 to 3 times per month**	**Never**
1.1 Green salad	1	2	3	4
1.2 Spinach & other green leafy vegetables	1	2	3	4

2. When did you last consume green salad and/or spinach/other green leafy vegetables?

1-2 hours ago (1)
1 day ago (2)
1 a week ago (3)

G. PHYSICAL ACTIVITY

1. Do you exercise?

Yes (1)
No (2)

2. When was the last time you exercised?

1-2 hours ago	(1)
1 day ago	(2)
1 week ago	(3)

H. SPIROMETRY/LUNG FUNCTION TEST

1. Have you ever had a spirometry/lung function test?

Yes	(1)
No	(2)

2. If yes, when last did you blow into a lung function machine?

1-2 hours ago	(1)
1 day ago	(2)
1 week ago	(3)
> a week ago	(4)

I. RECENT FOOD INTAKE

1. Did you have anything to eat or drink in the last hour?

Yes	(1)
No	(2)

If YES to above question, reschedule test for at least 1 hour later the same day or another date.

J. WORK-RELATED SYMPTOMS

1. Does being at work ever make your tight chest or wheezy?

Yes	(1)
No	(2)

2. Does being at work ever cause you to have sneezy/ itchy/runny nose or red/itchy/watery eyes?

Yes	(1)
No	(2)

APPENDIX 6: SKIN PRICK TEST PRETEST DATA COLLECTION SHEET

UCT OCCUPATIONAL ALLERGY AND ASTHMA STUDY AMONG BAKERY WORKERS IN THE WESTERN CAPE PROVINCE OF SOUTH AFRICA
SPT PRETEST DATA COLLECTION SHEET

Card

Record Number 1-3
Work number 4-9
Date 10-15
DAY MONTH YEAR

1. Do you have any allergies that you know of? YES [1] NO [2] ☐16

1.1 ***If Yes,*** what are you allergic to? (Examples: cats, dogs, dust, grasses or trees, etc.) Please list.

_____ ☐17

_____ ☐18

_____ ☐19

1.2 Have you ever had a severe allergic reaction to any of these (collapse, chest tightness, wheeze)?

YES [1] NO [2] ☐20

If YES, indicate to the person that the skin prick tests will not be done. Explain that a blood test will be done instead.

2. Have you ever had a severe allergic reaction to flour products (wheat/rye, premix, peanuts) (collapse, chest tightness, wheeze)?

YES (1) NO (2) ☐21

If YES, indicate to the person that the skin prick tests will not be done. Explain that a blood test will be done instead.

3. Do you currently have an active skin problem such as eczema?

YES (1) NO (2) ☐22

If present, indicate to the person that the skin prick tests will not be done. Explain that a blood test will be done instead.

1

4. Have you used any medicines or skin creams for allergies or flu in the past **3 days**?

1. YES 2.NO ☐23

4.1 ***If yes,*** which medicines?

_____ ☐24

_____ ☐25

_____ ☐26

If medicine contains antihistamines, indicate to the person that the skin prick tests will not be done. Reschedule another appointment in **one** week's time and counsel accordingly. Explain that a blood test will only be done today.

5. For Women:

5.1 Are you Pregnant? 1. YES 2.NO ☐27

5.2 Are you Breastfeeding? 1. YES 2.NO ☐28

If **Pregnant**, indicate to the person that the Skin-Prick Test will not be done today. Explain that a blood test will be done instead.
If **Breastfeeding**, proceed with Skin-Prick Testing.

6. Are you wheezing or having a tight chest today? 1. YES 2.NO ☐29

If YES, indicate to the person that the skin prick tests will not be done. Explain that a blood test will be done instead.

If answers to any of the above are NO, proceed with skin prick testing.

APPENDIX 7: SKIN PRICK TEST DATA COLLECTION SHEET

UCT OCCUPATIONAL ALLERGY AND ASTHMA STUDY AMONG BAKERY WORKERS IN THE WESTERN CAPE PROVINCE OF SOUTH AFRICA

SKIN PRICK TEST DATA COLLECTION SHEET NO.1

Card 1

Record Number ☐☐☐ 1-3

Work number ☐☐☐☐☐☐ 4-9

Date ☐☐☐☐☐☐ 10-15 (DAY MONTH YEAR)

Time started: _____

Read at (20 minutes after time started): _____

VOLAR LEFT LOWER ARM:

TOP (elbow)

Bermuda gr.	**H/dust mite**
Cockroach	**Rye grass**
Cat	**Mouldmix**
Dog	**Grassmix**
Aspergillus	**Anisakis**
- Control	**+ Control**

BOTTOM (wrist)

BERMUDA GRASS *(Cynodon dactylon)* ☐☐ 1st diam ☐☐ 2nd diam 16-19

HOUSE DUST MITE *(D. Pteronyssinus)* ☐☐ 1st diam ☐☐ 2nd diam 20-23

COCKROACH *(Blatella germanica)* ☐☐ 1st diam ☐☐ 2nd diam 24-27

RYE GRASS *(Lolium perenne)* ☐☐ 1st diam ☐☐ 2nd diam 28-31

CAT *(Felis domesticus)* ☐☐ 1st diam ☐☐ 2nd diam 32-35

MOULDMIX *(Cladosporium herbarum, Alternaria alternata, Fusarium)* ☐☐ 1st diam ☐☐ 2nd diam 36-39

DOG *(Canis familiaris)* ☐☐ 1st diam ☐☐ 2nd diam 40-43

GRASSMIX *(Pollen III - Avena, Hordeum, Triticum, Secale)* ☐☐ 1st diam ☐☐ 2nd diam 44-47

ASPERGILLUS *(Aspergillus fumigatus)* ☐☐ 1st diam ☐☐ 2nd diam 48-51

ANISAKIS *(Anisakis simplex)* ☐☐ 1st diam ☐☐ 2nd diam 52-55

\- NEGATIVE CONTROL (saline) ☐☐ 1st diam ☐☐ 2nd diam 56-59

\+ POSITIVE CONTROL (histamine) ☐☐ 1st diam ☐☐ 2nd diam 60-63

1. Other allergic symptoms/reactions during skin prick tests of left arm? (ring answer) Yes/No ☐ 64

If yes, specify? _____

2. General comment: (eg. reason test not done/ stopped, reaction to tape, dermographism) ☐ 65

_____ ☐ 66

3. FIELDWORKER INITIALS: _____

1

UCT OCCUPATIONAL ALLERGY AND ASTHMA STUDY AMONG BAKERY WORKERS IN THE WESTERN CAPE PROVINCE OF SOUTH AFRICA

SKIN PRICK TEST DATA COLLECTION SHEET NO.2

Card 2

Record Number 1-3

Work number 4-9

Date 10-15 (DAY MONTH YEAR)

Time started: _____

Read at (20 minutes after time started): _____

VOLAR RIGHT LOWER ARM:

TOP (elbow)

Wheat	**Rye**
Barley	**Soya**
A-amylase	**Corn flour**
Peanut	**Oats**
Storage mite	**Spider mite**
+ Control	**- Control**

BOTTOM (wrist)

WHEAT FLOUR: 1st diam, 2nd diam — 16-19

RYE FLOUR: 1st diam, 2nd diam — 20-23

BARLEY FLOUR: 1st diam, 2nd diam — 24-27

SOYA FLOUR: 1st diam, 2nd diam — 28-31

ALPHA-AMYLASE: 1st diam, 2nd diam — 32-35

CORN FLOUR: 1st diam, 2nd diam — 36-39

PEANUT (*Arachys hypogaea*): 1st diam, 2nd diam — 40-43

OATS: 1st diam, 2nd diam — 44-47

STORAGE MITE (Lepid. destructor): 1st diam, 2nd diam — 48-51

SPIDER MITE(*Tetranychus urticae*): 1st diam, 2nd diam — 52-55

\+ POSITIVE CONTROL (histamine): 1st diam, 2nd diam — 56-59

\- NEGATIVE CONTROL (saline): 1st diam, 2nd diam — 60-63

1. Other allergic symptoms/reactions during skin prick tests of right arm? (ring answer) Yes/No — 64

If yes, specify? _____

2. General comment: (eg. reason test not done/ stopped, reaction to tape, dermographism) — 65

_____ 66

3. FIELDWORKER INITIALS: _____

2

APPENDIX 8: LUNG FUNCTION TEST PRETEST DATA COLLECTION SHEET

UCT OCCUPATIONAL ALLERGY AND ASTHMA STUDY AMONG BAKERY WORKERS IN THE WESTERN CAPE PROVINCE OF SOUTH AFRICA

LFT PRETEST DATA COLLECTION SHEET

Card

Record Number 1-3

Work number 4-9

Date 10-15

DAY MONTH YEAR

1. Have you had a heart attack or stroke in the last 3 months? 1.YES 2. NO ☐16

2. Do you have epilepsy? 1.YES 2. NO ☐17

3. Have you had any recent operation (in the last 12 months)? 1.YES 2. NO ☐18

If ***Yes***, what type and how many months ago?

_____ _____ (months)

If YES, to any of the above, indicate to the person that the lung function tests will not be done. If NO, proceed with the rest of the screening questions

4. For Women:

4.1 Are you Pregnant? 1.YES 2. NO ☐19

4.2 Are you Breastfeeding? 1.YES 2. NO ☐20

If **Pregnant**, indicate to the person that the Lung Function Test will not be done today.
If **Breastfeeding**, proceed with Lung Function Test with Post-Bronchodilator. Proceed with the rest of the screening questions.

5. Have you had the flu or lung infection in the past 3 weeks? 1.YES 2. NO ☐21

If ***Yes***, how many days ago did it end? _____ days ☐☐22-23

6. Are you being treated for Tuberculosis? 1.YES 2. NO ☐24

If ***Yes***, for how long? _____ months _____ weeks ☐☐☐☐25-28

If YES, to either question No. 5 or 6, indicate to the person that the lung function tests will not be done today. Schedule another appointment in three weeks time since the end of their illness or since the start of TB medication. If NO, continue with the rest of the questions.

1

7. Did you drink coffee, tea or coca-cola in the last 6 hours?

1. YES 2.NO ☐29

8. Have you smoked in the last hour? 1. YES 2.NO ☐30

If YES to No. 8, reschedule the Lung Function Test test for later the same day (at least one hour since last cigarette) or another date. Other screening procedures can be done first.

9. Have you had asthma in the past? 1.YES 2. NO ☐31

9.1 Do you have asthma now? 1. YES 2. NO ☐32

10. Are you taking any medicine/s from a doctor or clinic at the moment for your lungs, any heart condition, or your eyes? 1. YES 2.NO ☐33

10.1 If ***Yes***, what are you taking and when did you last take them?

Names	No. of hours since last dose	
_____	_____	☐☐34-35
_____	_____	☐☐36-37
_____	_____	☐☐38-39

If short-acting beta-2-agonist or anti-cholinergic inhalers used in the last **4** hours or long-acting MDI or theophylline used in last **8** hours, reschedule and counsel accordingly.

11. Have you had any of the following symptoms in the past 12 months? ☐40
(at night, with exercise, exposure to cold air, viral infections, work exposures]

11.1	chest tightness	1.YES 2. NO
11.2	shortness of breath	1.YES 2. NO
11.3	wheezing or whistling in your chest	1.YES 2. NO
11.4	dry cough	1.YES 2. NO

12. Do you currently have any of these symptoms? 1. YES 2.NO ☐41

12.1 ***If Yes***, which ones?

_____ _____

_____ _____

APPENDIX 9: LUNG FUNCTION TEST DATA COLLECTION SHEET

UCT OCCUPATIONAL ALLERGY AND ASTHMA STUDY AMONG BAKERY WORKERS IN THE WESTERN CAPE PROVINCE OF SOUTH AFRICA
LUNG FUNCTION TESTS DATA COLLECTION SHEET

Card 1

Record Number ☐☐☐ 1-3

Work number ☐☐☐☐☐☐ 4-9

Date ☐☐ ☐☐ ☐☐ 10-15
DAY MONTH YEAR

1. Subject's blood pressure ☐☐☐ systolic

[DO NOT PROCEED WITH MCT IF BP >180/110] ☐☐☐ diastolic

2. Subject's age ☐☐ YEARS 16-17

3. Subject's gender ☐ MALE ☐ FEMALE 18

4.1 Subject's height ☐☐☐ CENTIMETRES 19-21

4.2 Subject's weight ☐☐☐ KILOGRAMS 22-24

5. When did you last work in the bakery? Date ☐☐ ☐☐ ☐☐ 25-30

BASELINE SPIROMETRY

6. **PREDICTED FEV_1** ☐☐☐ 31-33

7. **INITIAL FEV_1 and FVC**
(up to 8 attempts)

	FEV_1	FVC	
1	☐ ☐☐	☐ ☐☐	34-39
2	☐ ☐☐	☐ ☐☐	40-45
3	☐ ☐☐	☐ ☐☐	46-51
4	☐ ☐☐	☐ ☐☐	52-57
5	☐ ☐☐	☐ ☐☐	58-63

7.1 Number of rejected attempts ☐ 64

8. **Best INITIAL FEV_1 as % of predicted FEV_1** ☐☐☐ 65-67
(divide best results from No. 7 by results from No. 6)

IF BEST INITIAL FEV_1 IS:
A) less than 60% PREDICTED or
B) less than 1.5 LITRES or
C) BP > 180/110 or
D) Breastfeeding
the individual is:
GO TO BRONCHODILATOR CHALLENGE - DO NOT DO METHACHOLINE CHALLENGE

1

BRONCHODILATOR CHALLENGE ONLY

9. **FEV_1 and FVC**

	FEV_1	FVC	
9.1 Record Best two technically satisfactory Manoeuvres (up to 8 attempts)	☐☐ / ☐☐	☐☐ / ☐☐	68-73 / 74-79
9.2 Number of rejected attempts		☐	80

METHACHOLINE CHALLENGE TEST

10. **CONTROL FEV_1** following inhalation of diluent

Card 2

10.1 Record two technically satisfactory manoeuvres (up to 3 attempts)	☐☐☐ / ☐☐☐	1-3 / 4-6
10.2 Number of rejected attempts	☐	7

11. **BEST CONTROL (post-diluent) FEV_1 as % of INITIAL FEV_1** ☐☐☐ 8-10
(divide best results from No. 10 by best results from No. 7)

IF BEST CONTROL FEV_1 <90% OF BEST INITIAL FEV_1 STOP METHACHOLINE CHALLENGE AND

GO TO REVERSAL OF BRONCHOCONSTRICTION

Choice of methacholine short, medium, long protocol,standard

STOP METHACHOLINE CHALLENGE if FEV_1 falls to <80% of CONTROL FEV_1
(multiply no. 10 by 0.8)

80% of **CONTROL FEV_1** ☐ ☐☐

12. DID THE SUBJECT ANSWER 'YES' TO QUESTIONS 9, 11 & 12 OF THE LFT Pre-Test? NO ☐ YES ☐

12.1 Which protocol will the subject follow? ☐ 11
CODING: 1 Protocol 1 (short), 2 Protocol 2 (medium), 3 Protocol 3 (long), 4 Standard Protocol

13. METHACHOLINE BATCH NUMBER _____ ☐☐ 12-13

DOSE LEVEL	DOSE (mg of 32 mg/ml)	Best FEV_1	2nd Best FEV_1	Rejected attempts	
1	Diluent				14-20
2	0.0256				21-27
3	0.032				28-34
4	0.064				35-41
5	0.128				42-48
6	0.256				49-55
7	0.512				56-62
8	1.024				63-69
9	2.048				70-76

Card 3

14. Why was methacholine challenge stopped?

TICK ONE BOX ONLY

a) best CONTROL FEV_1 < 90% of best INITIAL FEV_1 ☐ 1
b) end of test reached (2.048mg of 32 mg/ml inhaled) ☐ 2
c) >/= 20% fall in FEV_1 occurred ☐ 3
d) subject asked to stop: reason; _____ ☐ 4
e) other: _____ ☐ 5

All participants will have a bronchodilator at the completion of the test with post-bronchodilator LFT results recorded below.

Reversal of bronchoconstriction

15. **FEV_1 and FVC**

	FEV_1	FVC	
15.1 Record Best two technically satisfactory manoeuvres (up to 3 attempts)			6-11 / 12-17
15.2 Number of rejected attempts			18

16. **Best POST-BRONCHODILATOR FEV_1 as % of initial FEV_1** ☐☐☐ 19-21
(divide best results from No. 14 by best results from No. 7)

	NO	YES	
17. Has subject's FEV_1 returned to within 10% of baseline spirometry?	☐	☐	22

IF 'YES' THE SUBJECT MAY LEAVE THE CENTRE
IF 'NO' ADMINISTER ANOTHER 4 PUFFS OF SALBUTAMOL AND WAIT ANOTHER 10 MIN, THEN PERFORM PFT'S TO RESTORE BASELINE LUNG FUNCTION

18. **FEV_1 and FVC**

	FEV_1	FVC	Card 3
18.1 Record Best two technically satisfactory manoeuvres (up to 3 attempts)	☐☐☐	☐☐☐	23-28 / 29-34
18.2 Number of rejected attempts		☐	35

19. **Best 2nd POST-BRONCHODILATOR FEV_1 as % of initial FEV_1** ☐☐☐ 36-38
(divide best results from No. 18 by best results from No. 7)

	NO	YES	
20. Has subject's FEV_1 returned to within 10% of baseline spirometry?	☐	☐	39

All participants to answer questions below. Tick the relevant box.

21. Did the subject experience any of the following symptoms during the challenge test?

	NO	YES	
21.1 Dry or sore throat / hoarse voice	☐	☐	40
21.2 Cough	☐	☐	41
21.3 Chest tightness/wheeze/shortness of breath	☐	☐	42
21.4 Headaches/dizziness	☐	☐	43
21.1 Other	☐	☐	44

Specify _____

22. General comments:

_____

_____

_____

23. Technologist initial's _____ ☐ 45

24. Room temperature: _____ ☐☐ 46-47
(degrees celcius)

	NO	YES	
25 Lung function record appended	☐	☐	48

APPENDIX 10: EXHALED NITRIC OXIDE PRE-TEST DATA COLLECTION SHEET

UCT OCCUPATIONAL ALLERGY AND ASTHMA STUDY AMONG BAKERY WORKERS IN THE WESTERN CAPE PROVINCE OF SOUTH AFRICA

EXHALED NITRIC OXIDE PRE-TEST DATA COLLECTION SHEET

Card 1

Survey Number _____ ☐☐☐ 1-3

A. IDENTIFICATION DATA

1.Surname _____

2. First name/s _____

3. Work number _____ ☐☐☐☐☐☐ 4-9

4. Date of birth: Day____Month_____Year____ ☐☐☐☐☐☐ 10-15

5. Gender: Male (1) ☐ 16
Female (2)

8. Interviewer's initials _____ ☐ 17

9. Date of interview:
Day____Month_____Year_____ ☐☐☐☐☐☐ 18-23

10. Bakery: _____ ☐☐ 24-25

11. Did you change your job since the last interview? ☐ 26
Yes (1)
No (2)
Not applicable (3)

11.1 If Yes or NA, what is your new job?
_____ ☐☐ 27-28

12. Which shift have you been working today? ☐ 29
04:00 - 12:00 (1)
07:00 - 16:00 (2)
08:00 - 17:00 (3)
09:00 - 18:00 (4)
12:00 - 21:00 (5)

B.HEALTH PROBLEMS

Recent chest infections

1. Have you had the flu or sinusitis in the past 3 weeks? ☐ 30
Yes (1)
No (2)

1

2. Have you had any of the following symptoms in the past **12 months** (at night, with exercise, exposure to cold air, work exposures)?

2.1 chest tightness	Yes	(1)	☐ 31
	No	(2)	
2.2 shortness of breath	Yes	(1)	☐ 32
	No	(2)	
2.3 wheezing or whistling in your chest	Yes	(1)	☐ 33
	No	(2)	
2.4 dry cough	Yes	(1)	☐ 34
	No	(2)	
2.5 Asthma	Yes	(1)	☐ 35
	No	(2)	

3. Are you being treated for Tuberculosis (TB)?

Yes	(1)	☐ 36
No	(2)	

3.1 If yes, for how long? _____months _____weeks ☐☐☐☐ 37-40

If YES, to question no 3, indicate to person that the tests will not be done today. Schedule another appointment in three months time since the start of TB medication.

Nose and eye symptoms

4. Have you ever had any nose or eye problems due to allergies and/or hay fever?

Yes	(1)	☐ 41
No	(2)	

C. SMOKING HISTORY

1. Do you smoke?

Yes	(1)	☐ 42
No	(2)	

1.1 If yes, have you smoked tobacco (cigarettes or pipe) for as long as a year?

Yes	(1)	☐ 43
No	(2)	

1.2 If yes, how many cigarettes per day do you smoke or did you smoke? ☐☐ 44-45

_____

2

1.3 Have you smoked (cigarettes/tobacco) in the last hour?

Yes (1)
No (2)

☐ 46

D. ALCOHOL CONSUMPTION

1. Do you drink alcohol?

Yes (1)
No (2)

☐ 47

1.1 If yes, when have you last consumed alcohol?

1-2 hours ago (1)
1 day ago (2)
1 week ago (3)

☐ 48

1.2 How much alcohol did you consume?

_____

☐☐ 49-50

E. MEDICATION USAGE (show booklet)

1. Are you taking any medicine/s from a doctor or clinic at the moment for asthma, and or hayfever?

Yes (1)
No (2)

☐ 51

1.1 If yes, what are you taking and when last did you take them?

Names	No. of hours since last dose	
_____	_____	☐☐ 52-53
_____ _____	_____	☐☐ 54-55
_____ _____	_____	☐☐ 56-57

F. GREEN VEGETABLE CONSUMPTION

1. How often do you eat the following vegetable products?

Type of product	Daily	1 to 3 times a week	1 to 3 times per month	Never	
1.1 Green salad	1	2	3	4	☐ 58
					☐ 59
1.2 Spinach & other green leafy vegetables	1	2	3	4	☐ 60

2. When did you last consume green salad and/or spinach/other green leafy vegetables?

1-2 hours ago (1)
1 day ago (2)
1 a week ago (3)

☐ 61

3

G. PHYSICAL ACTIVITY

1. Do you exercise?

Yes	(1)	62
No	(2)	

2. When was the last time you exercised?

1-2 hours ago	(1)	63
1 day ago	(2)	
1 week ago	(3)	

H. SPIROMETRY/LUNG FUNCTION TEST

1. Have you ever had a spirometry/lung function test?

Yes	(1)	64
No	(2)	

2. If yes, when last did you blow into a lung function machine?

1-2 hours ago	(1)	65
1 day ago	(2)	
1 week ago	(3)	
> a week ago	(4)	

I. RECENT FOOD INTAKE

1. Did you have anything to eat or drink in the last hour?

Yes	(1)	66
No	(2)	

If YES to above question, reschedule test for at least 1 hour later the same day or another date.

J. WORK-RELATED SYMPTOMS

1. Does being at work ever make your chest tight or wheezy? 67

Yes	(1)
No	(2)

2. Does being at work ever cause you to have sneezy/itchy/runny nose or red/itchy/watery eyes? 68

Yes	(1)
No	(2)

APPENDIX 11: EXHALED NITRIC OXIDE DATA COLLECTION SHEET

UCT OCCUPATIONAL ALLERGY AND ASTHMA STUDY AMONG BAKERY WORKERS IN THE WESTERN CAPE PROVINCE OF SOUTH AFRICA

EXHALED NITRIC OXIDE DATA COLLECTION SHEET

Date: _____

Time _____

Card 1

Ambient NO concentration (ppb) _____		1-3
Ambient temperature (degrees celcius) _____		4-5
Survey Number _____		6-8
1. Subject's blood pressure	systolic _____	9-11
	diastolic _____	12-14
2. Subject's age (in years) _____		15-16
3.1 Subject's height (in centimetres) _____		17-19
3.2 Subject's weight (in kilograms) _____		20-22
4. Gender:	Male (1)	23
	Female (2)	
5. Effort number (start) _____		24-26
6.1 FENo measurement (ppb) 1st effort _____		27-29
6.2 FENo measurement (ppb) 2nd effort _____		30-32
6.3 FENo measurement (ppb) 3rd effort _____		33-35

APPENDIX 12: GUIDELINES FOR AUTHORS FOR CHOSEN JOURNAL (OCCUPATIONAL AND ENVIRONMENTAL MEDICINE)

Authors

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- Confidence intervals should be reported for measures of association.
- P-values may be reported if necessary for tests such as trend tests or non-parametric tests etc but should be given as quantitative values e.g. $p=0.032$ rather than relative to a cut point e.g. $p<0.05$.
- Generally numerical findings should not be reported to more than 1 or 2 decimal places.
- The approach to carrying out any statistical modelling should be described, including strategies for selection of explanatory variables and goodness of fit. The models presented in the paper should be clearly described and justified, with appropriate references given.
- Results from observational studies (cohort, case-control, or cross-sectional designs) should be reported following the guidelines in the STROBE statement, results of randomised trials should be reported following the CONSORT guidelines, and systematic reviews and meta-analyses should follow the PRISMA guidelines.

Article publishing charges

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Please review the below article type specifications including the required article lengths, illustrations, table limits and reference counts. The word count excludes the title page, abstract, tables, acknowledgements, contributions and references. Manuscripts should be as succinct as possible.

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Authors should also provide key messages with original research submissions under the following headings:

1. What is already known about this subject?
2. What are the new findings?
3. How might this impact on policy or clinical practice in the foreseeable future?

Word count: up to 3,500

Structured abstract: up to 250 words; ‘Objectives’, ‘Methods’, ‘Results’, ‘Conclusions’

Tables/Illustrations: up to 5

References: up to 40

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The ICMJE Recommendations state that authorship credit requires:

Substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data.

Drafting the work or revising it critically for important intellectual content.

Final approval of the version published.

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Full name, department, institution, city and country of all co-authors.

Word count, excluding title page, abstract, references, figures and tables.

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Authors can usually opt to (or are required to) choose keywords relevant to the content of the manuscript during the submission process. This assists in the identification of the most

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Abstract, or a summary for case reports (Note: references should not be included in abstracts or summaries).

Main text separated under appropriate headings and subheadings using the following hierarchy: BOLD CAPS, bold lower case, Plain text, Italics.

Tables should be in Word format and placed in the main text where the table is first cited. Tables should also be cited in numerical order.

Acknowledgments, Competing Interests, Funding and all other required statements.

References. All references should be cited in the main text in numerical order.

Figures must be uploaded as separate files (view further details under the Figures/illustrations section). All figures must be cited within the main text in numerical order and legends should be provided at the end of the manuscript.

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Check journal abbreviations using PubMed

Check citation information using PubMed

Example references

Journal article

13 Koziol-Mclain J, Brand D, Morgan D, et al. Measuring injury risk factors: question reliability in a statewide sample. *Inj Prev* 2000;6:148–50.

Chapter in book

14 Nagin D. General deterrence: a review of the empirical evidence. In: Blumstein A, Cohen J, Nagin D, eds. Deterrence and Incapacitation: Estimating the Effects of Criminal Sanctions on Crime Rates. Washington, DC: National Academy of Sciences 1978:95–139.

Book

15 Howland J. Preventing Automobile Injury: New Findings From Evaluative Research. Dover, MA: Auburn House Publishing Company 1988:163–96.

Abstract/supplement

16 Roxburgh J, Cooke RA, Deverall P, et al. Haemodynamic function of the carbomedics bileaflet prosthesis [abstract]. *Br Heart J* 1995;73(Suppl 2):P37.

Electronic citations

Websites are referenced with their URL and access date, and as much other information as is available. Access date is important as websites can be updated and URLs change. The "date accessed" can be later than the acceptance date of the paper, and it can be just the month accessed.

Electronic journal articles

Morse SS. Factors in the emergency of infectious diseases. *Emerg Infect Dis* 1995 Jan-Mar;1(1). www.cdc.gov/nciod/EID/vol1no1/morse.htm (accessed 5 Jun 1998).

Electronic letters

Bloggs J. Title of letter. *Journal name* Online [eLetter] Date of publication. url eg: Krishnamoorthy KM, Dash PK. Novel approach to transseptal puncture. *Heart* Online [eLetter] 18 September 2001. http://heart.bmj.com/cgi/eletters/86/5/e11#EL1

Legal material

Toxic substances Contro Act: Hearing on S776 Before the Subcommittee of the Environment of the Senate Comm. on Commerce, 94th Congress 1st September (1975).

Washington v Glucksberg 521 US 702 (1997)

Law references

The two main series of law reports, Weekly Law Reports (WLR) and All England Law Reports (All ER) have three volumes a year.

For example:

Robertson v Post Office [1974] 1 WLR 1176

Ashcroft v Mersey Regional Health Authority [1983] 2 All ER 245

R v Clarence [1868] 22 QBD 23

Wimpey Construction UK Ltd v Poole (1984) Times, 3 May

There are good historical precedents for the use of square and round brackets. Since 1891, round ones have referred to the date of the report, square ones to the date of publication of the report. Apart from not italicising the name of the case, we use the lawyers' style; be careful with punctuation. Here are some more examples:

Caparo Industries plc v Dickman and others [1990] 1 All ER 568-608.

R v Clarence [1888] 22 QBD 23.

Finlayson v HMAdv 1978 SLT (Notes) 60

Block v Martin (1951) 4 DLR 121

Official Journal of the European Communities: at the top of the page it gives the No, vol, and page and, at the other side of the header, the date.

The abbreviation for the title is given in parentheses under the title. Jiggle these elements around to get, eg:

Council Directive of 14 June 1989. Offical Journal of the European Communities No L 1989 June 28:181/44-6. (89/831/EEC.

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Alwick K, Vronken M, de Mos T, et al. Cardiac risk factors: prospective cohort study. *Ann Rheum Dis*Published Online First: 5 February 2004. doi:10.1136/ard.2003.001234

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Vole P, Smith H, Brown N, et al. Treatments for malaria: randomised controlled trial. *Ann Rheum Dis*2003;327:765–8 doi:10.1136/ard.2003.001234 [published Online First: 5 February 2002].

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