THE INFLUENCE OF SOCIO-ECONOMIC STATUS ON THE PREVALENCE OF FOOD SENSITISATION AND FOOD ALLERGY IN CHILDREN 12 TO 36 MONTHS IN URBAN CAPE TOWN, SOUTH AFRICA

By

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PREAMBLE

DECLARATION

I, Lelani Hobane, declare that the work on which this dissertation is based 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.

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SIGNATURE: Signed by candidate

DATE: 15th August, 2016

DEDICATION

To my sisters for all the sacrifices and holding my hand through all my studies, thank you. My siblings for the unfailing confidence and belief in my abilities thank you for encouraging me on. To my sweetest Dad for all the motivation and constant reminder that there is no mountain higher. In loving memory of my dearest Mum, you are and will always be my inspiration through it all, this is for you.

PREAMBLE

ACKNOWLEDGEMENTS

Firstly, thank you to my supervisor Associate Professor Michael E. Levin, for allowing me the opportunity to do this dissertation under the on-going main research project. Thank you for all the effective oversight in the design, analysis and write up of the dissertation. Your invaluable comments played a major role in guiding me through the path of scholarly writing and understanding the field of public health and research. Thank you for your timely input on methodological and administrative issues relating to the primary study. Thank you to Associate Professor Christopher J Colvin for co-supervising my thesis write-up and for the guidance in academic writing. Doctor Claudia Grey thank you for your input in guiding the overall write up of the thesis.

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To my dearest friends and colleagues who helped me go through my studies with smiles and laughter in bumpy rides.

To God almighty for making it all possible against all odds.

PREAMBLE

ABSTRACT

Background:

Globally, food allergies (FAs) have become a public health concern with research suggesting a rising prevalence. FAs affect both the individual and their family advocating for a need to understand the extent of the problem. Allergies have increasingly been recognised as diseases of life-style resulting from interaction between genes and the environment in both the pre and post-natal periods. Various factors including socio-economic status (SES) have been identified from studies as risk factors that are associated with FAs in children. Generally higher SES has been correlated with improved health outcomes, however, in respiratory allergies higher SES may be associated with higher prevalence. With regards to SES as a risk factor for food allergy development, literature has indicated evidence of a relationship between SES and allergies but with conflicting results of both high and low SES postulated as risk factors.

Methodology:

This study is a sub-study of the South African Food sensitisation and Food Allergy (SAFFA) study, an on-going cross-sectional, observational study of IgE-mediated food allergy in an unselected population of children aged 12-36 months. The aim is to explore the influence of SES on food sensitisation and food allergy prevalence in children. We used a variety of measures of SES including household size, parental education, employment status and household income to investigate the association between SES and food allergy prevalence using sensitisation, self-reported respiratory and skin allergy and challenge proven food allergy data from children across the urban Cape Town Metropole. Associations between the SES variables and sensitisation/allergy were assessed using the Z-test for proportions and Chi-square/Fisher's exact.

Part A comprises the protocol which describes the methodology of the research. Part B is the review of literature on food allergy prevalence and risk factors associated with food allergy development. Section

C presents the "journal ready" manuscript according to the requirements of the Annals of Allergy, *Asthma & Immunology Journal (Appendix 3).*

Results:

The prevalence of low level sensitisation (at Skin Prick Test (SPT) ≥1mm) to any food was 12.3%, medium level (at SPT≥3mm) was 9.6%, high level (at SPT≥7mm) was 4.5% and challenge proven IgE mediated FA was 2.4%. Of the total 739 participants in the sample, 91 were sensitised to 1 or more foods. A trend of increased sensitisation at SPT≥1mm, ≥3mm, ≥7mm and proven food allergy in children of parents with tertiary education was observed (14.8%, 11.9%, 5.8% and 2.9%) compared to parents who attained primary/secondary education (10.5%, 7.9%, 3.5%, and 2.1%) respectively though these results did not reach statistical significance. Highest risk for food sensitisation (FS) and FA were in children with parents who are employed (p=0.03) and in children who are from homes with higher household income (p=0.02). Household size showed no association with FS and FA. No significant differences in sensitisation patterns were noted between ethnic groups.

Conclusion:

The analysis showed an existing burden of IgE mediated FAs in South African children advocating for diagnosis and management. SES is associated with food allergy in young children with a positive relationship to parental employment status and income.

LIST OF ACRONYMS AND ABBREVIATIONS

AD	Atopic Dermatitis
CCFs	childcare facilities
CDCs	Childhood development centres
CI	Confidence interval
DBPCFC	Double Blind Placebo-Control Food Challenge
FA	Food Allergy
FS	Food Sensitisation
HREC	Human Research Ethics Committee
IgE	Immunoglobulin E
IQR	Inter-quartile range
ISAAC	International Study on Asthma and Allergies in Childhood
OFC	Oral Food Challenge
PID	Participant identification
PPV	Positive Predictive Value
RCWMCH	Red Cross War Memorial Children's Hospital
SD	Standard Deviation
SES	Socio-economic Status
sIgE	Specific Immunoglobulin-E
SPT	Skin Prick Test
UCT	University of Cape Town
UK	United Kingdom
USA	United States of America

PREAMBLE

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SECTION A: PROTOCOL

The influence of socio-economic status on the prevalence of food sensitization and food allergy in children 12 to 36 months in urban Cape Town, South Africa

BACKGROUND

1. INTRODUCTION

Globally, food allergies (FAs) have become a public health concern as research suggests that its prevalence is rising (1). FA affects both the individual and their family and there is a need to understand the extent of the problem, both what causes it and also how it can be avoided or managed to enhance quality of life. It is key to identify, modify and or control these risk factors in order to reduce food allergy development (2). Researchers have made progress in examining environmental and genetic factors postulated to predispose children to develop FA (2), such as diet during infancy, the mother's diet when pregnant and during lactation, caesarean section birth, tobacco smoke exposure, supplementation of multivitamins, and ingestion of antacids just to mention a few (2). However, investigating food allergies is complex with problems associated with measuring and understanding the true risk factors and prevalence of FA stemming from poor methodologies and/or poor objective assessments (3). Yet, researchers have undoubtedly recognised the unprecedented rise of this problem especially in children.

FOOD ALLERGIES: A GLOBAL PERSPECTIVE

There is little reliable prevalence data on FA globally and many countries publish prevalence data based on self-reported survey data without the use of oral food challenges (OFC) to objectively confirm true allergies in the population (4,5). Generally, the common foods that children are allergic to include hen's egg, peanuts, tree nuts, shell-fish, cow's milk, soya, and wheat (6). The few available data from most studies suffer methodological limitations and researchers advocate for well-designed, challenge-based future studies (7). A systematic review by Burks et al (3) showed a rise in FA prevalence over several years and many studies stress on the importance of various environmental and life style exposures during infancy in the development of atopy and allergic disease (2). Similar to other allergic diseases such as atopic dermatitis (AD) and asthma, FA is also believed to be strongly influenced by both genetics and environmental factors (5).

The few studies available of confirmed FA through OFCs show an average of 1% and 2.5 % prevalence in adults and children respectively (8). A telephonic survey conducted in the USA revealed a tripling rise in the prevalence of peanut and tree nut allergy measured between 1997 and 2008 (1). Australia has experienced a 10 fold rise in food allergy referrals as well as a more than 5 fold rise in hospital referrals for cases of food allergy related anaphylaxis between the period of 1995 and 2006 (9). Osborne et al (6) conducted the large "Health Nuts" prevalence study in healthy 12 months old Australian children. The study found high rates of food sensitisation (18%) and a challenge proven food allergy prevalence of 10%.

However, studying the influence of socio-economic factors on FA has been challenging because of difficulties in conceptualising and measuring these variables (10). Studies worldwide have found differences in the prevalence of asthma and its severity between different groups in populations defined by self-reported ethnicity, race or socio-economic status (SES). In general poor health has been associated with low SES usually shown by low education, low income and or type of employment (11). Much of what is known about allergies and food allergies is cited from studies carried out in developed countries like UK, Australia and the USA wherein ethnicity, for example, has been found to have an influence on sensitization and/or food allergy rates (12).

Interestingly, a systematic review of literature in the USA on racial disparities in food allergies conducted by Greenhawt et al., (7) could not confirm racial/ ethnic disparities in FA. The study nonetheless reported that USA Black children had an increased risk of food allergy that was self-reported and these children were more sensitised with more clinical-based diagnoses of FA compared to white children (7). However, another USA birth cohort study examining the risk of sensitization to food allergen according to genetic ancestry or race, found higher rates of IgE-mediated sensitization to various foods in African American subjects compared to other races (13). Bergmann et al., (14) in Germany found that parents of high SES had a higher prevalence of sensitisation to inhalant allergens but their children were protected from developing symptomatic atopic disorders (allergic rhinitis and asthma), perhaps because of protective life-styles.

A Swedish birth cohort study found that higher parent's educational level was associated with reduced risk for atopic disease development (15). Parents who had more education were less likely to be smokers compared to those with a short education which may have mediated their children's protection from the development of atopic disease (15). Gupta et al., (16) conducted a population-based, electronic cross-sectional survey of children in the USA, tracking the severity, and distribution of childhood food allergy. The study found an 8% prevalence of FA with considerable disparities in the disease diagnosis according to race and income. More recently Liu et al, (17) found an estimated overall 2.5% prevalence of clinically proven allergy to peanut, egg, milk and fish with an increased risk in black non-Hispanic children (odds ratio, 3.06; 95% CI, 2.14-4.36), compared to non-Hispanic white children in the USA. FA was recognised as a risk factor potentially exacerbating asthma in these children.

ALLERGIES AND FOOD ALLERGY IN SOUTH AFRICA

Africa suffers a generally high burden of diseases and according to Pawankar at el., (18) allergy prevalence in the African population is estimated to be between 20 to 30%. South African research shows a pattern of a rising prevalence in respiratory allergies similar to the changes in global prevalence that happened about 30 years ago in developed countries (19). Most of the available data has also reported differences in the prevalence of eczema, respiratory allergies and aeroallergen sensitisation across socio-economic classes and in different ethnicities reflecting possible diverse environmental exposure, influences of genes or epigenetic phenomena (20).

The International Study on Asthma and Allergies in Childhood (ISAAC) assessed environmental factors that influence eczema development and allergic rhinitis in young children from many countries including those from developing countries (21). As an environmental exposure, SES represented by social, economic or work status has widely been used as a composite measure for making associations with disease outcomes (22). South Africa has a unique political and historic dispensation for which race/ethnicity (which are social constructs) have in many occasions been associated with differences in health outcomes and SESs. Hence self-reported race may be a significant confounder for SES in the context of South African research (22).

Studies conducted in South Africa contributing to knowledge on allergies in children have highlighted a possible difference in prevalence of allergies in children of different ethnic and socio-economic backgrounds (23). Respiratory allergies are more prevalent in urban environments than in rural areas, however respiratory allergies are increasing in both environments. The rise in rural environments has been more than the rise in urban environments leading to a narrowing of the urban-rural gradient (20). Repeatedly, SES has been indicated as an important risk factor for those conditions (21). Ehrlich et al. (24) investigated childhood wheezing and asthma risk factors and found a strong association between maternal education and smoking and asthma/wheeze in their children. It was shown that a mother's level of education affected exposure to smoke around her child in her house and this was also apparent to other members in the family all of which contributed to wheezing or asthma development (24). Similarly, Poyser et al., (25) found an increased prevalence of asthma in South African young adolescents from higher SES backgrounds. For this group of children, the incidence of severe asthma was reported more in children from low-income communities which were associated with poverty (25). Thus, fatal and near-fatal asthma was correlated with low SES in a South African study and poor access to care exacerbated these high rates (19,20).

Mercer et al., (26) found a positive association between SES and allergic rhinitis in a selected urban adolescent population. Gray et al., (27) investigated food allergy prevalence in a selected population of South African children with atopic dermatitis. There was a high prevalence of FA in children suffering from AD similar to that found in developed countries. In this selected population sample, there were ethnic differences in food allergy and sensitisation (27). Sensitization was higher in Black African subjects but with relative protection leading to less conversion to true FA (27).

The South African population is diverse ethnically and socio-demographically and there is thus a need to explore whether environmental or socio-economic factors have contributed to the rise in FA prevalence. To date, there is no prevalence data of food sensitization and food allergy in an unselected population of South African young children exploring the influences of SES. This study therefore seeks to explore the socio-economic factors associated with allergy outcomes in children and to explore any ethnic disparities in this population.

RATIONALE

Knowledge of demographic and socioeconomic factors associated with food allergy in children allows optimisation of prevention measures to identified sub-groups of the population. In South African children, little is known about modifiable or non-modifiable risk factors that are associated with food allergies and this study will therefore investigate this gap in knowledge.

RESEARCH QUESTION

Is there an association between socio-economic factors and food allergies in unselected population of children 12 to 36 months old in the urban Cape Town Metropole South Africa?

HYPOTHESIS

Null hypothesis: **There is no difference** in SES as measured by parental educational attainment, income and employment status between sensitized versus non-sensitized children and between proven (food) allergic versus proven non-allergic unselected children in urban Cape Town South Africa.

Alternative hypothesis: **There is a difference** in SES as measured by parental educational attainment, income and employment status between sensitized versus non-sensitized children and between proven (food) allergic versus proven non-allergic unselected children in urban Cape Town South Africa.

OBJECTIVES

The objectives of the study are as follows:

- To describe food sensitisation (FS) and challenge proven food allergy (FA) prevalence.
- To describe the possible association between SES (as measured by parental highest level of formal education, income, and employment status) and food allergy outcomes (FS and FA) in 12 to 36 month old children in the urban Cape Town Metropole South Africa through a secondary analysis of the South African Food sensitisation and Food Allergy (SAFFA) study, an on-going cross-sectional, observational study of IgE-mediated food allergy in an unselected population of South African children aged 12-36 months.
- To explore ethnic disparities in FS and FA.

2. METHODOLOGY

RESEARCH DESIGN

This is a descriptive quantitative prevalence study analysing secondary data from the SAFFA study. Detailed methodology and results of the pilot of the parent study have been described elsewhere in detail (28). Questionnaire data on ethnic and socio-economic factors include; self-reported ethnicity, parental level of education, employment status and income.

ANALYSIS OF DATA

Analysis of this data will comprise statistical investigation of the associations between the different variables i.e. disease status (allergy/sensitization) and exposure (different ethnicities/SES measured by household size, total household income, parental employment status and education). The initial piloting of the questionnaire was done before data collection commenced. Data were collected using the participant questionnaire (Appendix 5).

STUDY POPULATION

The population under study is of crèche/ childhood development centres (CDCs) attending children between the ages of 12 to 36 months in the Cape Town metropole of the Province of South Africa. Only

children with mothers or caregivers who provided informed consent, demographic information, SES and other epidemiological data will be included for this study.

SAMPLING STRATEGY

The study comprises of children from crèches/CDCs that were randomly selected as study sites. Recruitment of the locally registered crèches was done via random selection of crèches/CDCs registered with the Department of Social Development. The list was available online. Microsoft Excel number generator was used to generate a sampling frame to randomly select those particular crèches/ CDCs. The principal/manager was contacted for permission to carry out the study at their crèche facility/ CDCs. The principal/owner would then invite the parents of the eligible children to come to the facility for participation in study. Further consent was sought from parents who came to the crèche/ CDCs after the fieldworker explained the study procedures including SPT and potential risks and benefits involved. Once they agreed to participate by signing the written consent, the fieldworker went through the questionnaire with them collecting the required information.

SAMPLE SIZE ESTIMATION

The parent SAFFA study is aiming to enrol 1200 children in total. The initial pilot data for the study population reflected the demographics of Cape Town with similar 2011 demographics census data for children in the 0-4 age group; 46% black African, 42.4% Mixed Ancestry and 11.6% Caucasian (29). To date there is no prevalence data available that can be used in calculating sample size estimation in South Africa. The current study will use available data completely collected on the unselected population of 739 children in the urban cohort that was undertaken before a break was taken mid-year to embark on data collection for the rural cohort of the SAFFA study.

DATA COLLECTION

PARTICIPANT QUESTIONNAIRE

Once the parents agreed to participate in the study by signing the consent form, they were asked to answer questions in the study questionnaire in their most comfortable language and their child was examined physically together with a skin prick test (SPT) conducted by trained staff (see Appendix 5).

In cases where a child recently took antihistamine, the SPT was carried out on another day after a suitable washout period. In addition, an oral food challenge (OFC) was performed at the Red Cross War Memorial Children's hospital (RCWMCH) for children who reacted to any of the foods tested in the SPT and with whom tolerance was not evident on a history of consumption of a full age-appropriate portion without any reactions. To address potential selection bias, a short non-participant questionnaire was completed physically or telephonically comprising information regarding the child's age, diet, history of allergies and the family's history of allergy (see Appendix 6).

Household information was collected through an interviewer administered structured questionnaire by trained staff and the data was captured centrally using ACCESS software. Data collected by the questionnaire included the following:

- Age, ethnic origin (self-reported)
- Socioeconomic class (parental employment, education and total household income)
- Number of siblings/children living in the house
- Duration of breastfeeding
- History of dietary consumption of cow's milk, hen's egg, wheat, soy, fish, peanut and tree nuts
- Detailed history of allergic reactions to the above foods or any other foods
- Food consumption history (fast foods, fructose, fruit and vegetables, fried/microwaved meat, dietary recall)
- Family and child history of allergic diseases (asthma, eczema or allergic rhinitis)
- Other medical problems and current medication

Anthropometric measurements were carried out on each participant (weight, height, abdominal circumference and skin fold thickness).

SKIN PRICK TESTING

SPTs were carried out by trained medical/nursing staff. Children who did not have a history of any food reaction were tested at the selected crèche facilities/(CDCs). Standardised solutions from ALK Abello (Thermo FisherTM) and ALK lancets were used for testing food allergens including: egg white

extract, cow's milk, soya, wheat (flour), fish (cod), peanut, hazelnut, positive control and negative control. The procedure included placing droplets of the proteins for the specific foods being tested on the child's arm and using the lancets to push each the foods under the skin. Sensitisation was measured and recorded after 15 minutes as mean wheal-diameters in millimetres.

ORAL FOOD CHALLENGING

A sensitized child showing SPT results ≥ 1mm > the negative control qualified for an incremental food challenge if they were not tolerant on history to that particular food. If it happened that a child showed sensitisation to more than one allergen, multiple food challenges on different days were required and arranged for. The protocol for the OFC is attached in Annexure 2.

DATA MANAGEMENT

As this study involves the analysis of secondary data, no additional data will be collected. All data for this study will be derived from the South African Food sensitisation and Food Allergy (SAFFA) study dataset.

EXPOSURE VARIABLES

The exposure variables for SES include; self-reported ethnicity, parental education, employment status, total household income and educational levels for the parents of all eligible children.

EDUCATION

Parents/caregivers were asked to report their highest level of education which was reported as a categorical nominal variable, namely, grade completed in school and higher education attainment. For this study parental education was categorized into primary, secondary and tertiary or college level.

EMPLOYMENT STATUS

Employment status will be coded as a binary variable: employed or unemployed.

TOTAL HOUSEHOLD INCOME

The total household income was captured as a continuous variable to allow mothers to report the approximate total household income earned. A Shapiro-Wilk test will be used to determine whether the data (and log transformed data) is normally distributed. If it is normally distributed the mean and standard deviation (SD) will be used as the appropriate measures with the estimation: 95% CI for a population mean. A one sample t-test will be applied for hypothesis testing. If the data has a skewed distribution and cannot be log transformed, non-parametric data analysis will be performed.

ETHNICITY

Similar to the census, the questionnaire captured self-reported data on ethnicity which is a nominal variable. The parents or guardians self-reported the child's ethnicity based on the dominant population groups in South Africa (Stats SA population groups) i.e. Black African, White/Caucasian, Coloured/ Mixed race and Indian/Asian.

OUTCOME VARIABLES

For this study, the outcome variables are:

1. Sensitization as defined by one or more positive skin prick tests at differing levels of significance (i.e. low level ≥1mm, moderate level ≥ 3mm, and high level ≥ 7mm).
2. Proven food allergy.

Table 1. Definition of variables considered in the study

Variable	Scale	Options/Values
Population demographic variables		
Age	Numerical-continuous	12-36 months
Sex	Categorical-binary	Male, Female coded as (1/0)
Ethnic origin	Categorical-nominal	Black African, White/Caucasian, Coloured/Mixed race Indian/Asian.
Environmental socio-economic exposure variables		
Size of household	Numerical discrete	Total number of people living together in the household e.g. 4.
Highest level of education attained - **Primary** - **Secondary** - **Tertiary**	Categorical-nominal	Coded as factor variables (1, 2, 3)
Employment status - **Employed** - **unemployed**	Categorical-binary	Employed Unemployed
Household income (per month) Percentiles will be derived after testing the distribution.	Numerical (Continuous)	For analysis, income will be categorised into quintiles based on the income.
Outcome variables		
SPT Result	Numerical- continuous	≥0mm
Sensitization	Categorical-Binary	Yes/ no, (coded as 1/0) based on SPT levels low level ≥1mm moderate level ≥ 3mm high level ≥ 7mm
Allergy	Categorical-binary	Yes/ no, (coded as 1/0) based on positive FC
Family history of food allergy	Categorical binary	Yes/ no,(coded as 1/0)
Family history of any allergy	Categorical-Binary variable	Yes/ No

DATA ANALYSIS

This study seeks to investigate the influence between SES and food sensitization/food allergy in Cape Town urban children. The main outcomes of interest are the number of participants sensitised/truly allergic to a particular food as a proportion of the study sample. The risk factors (parental education, total household income, employment status, and concomitant allergy status) will be associated with the different proportions of participants that are either sensitised/truly allergic in order to extrapolate the influence of SES. The methodological approaches to statistical analysis: univariate and bivariate will be applied using the software package STATA version 14.1 (30).

UNIVARIATE ANALYSIS

The study will have univariate exploratory data analysis which will be summarized using frequency tables and histograms for categorical and continuous data. For continuous data that is normally distributed, mean and standard deviation (SD) will be used and for non-normally distributed data the median and interquartile range (IQR) will be used. Proportions and 95% confidence intervals (CI) will be used to summarize categorical data.

BIVARIATE DATA ANALYSIS

The study will also carry out bivariate exploratory data analysis using scatter plots for continuous variables, the chi-square statistic for categorical variables and the box and whisker plots for continuous and categorical variables.

RELIABILITY AND VALIDITY

The parent SAFFA study ensured reliability and validity, of the study questionnaire by piloting it to improve its reliability, validity and general utility (31). To ensure face validity, a pilot study was conducted for the acceptability and relevance of the study (28). In collecting the data, the study trained and employed a team of field workers, including doctors and 2 nurses to ensure quality in the data collected. Training of the staff on standardized interviewer question techniques was done to minimise bias and errors in collecting the data. Supervision and planning meetings were held in order to address other general information relating to improvement and validity of exposure and outcome variables of the study. Supervision also addressed data collection processes, in which the questionnaire was

consistently assessed for misinterpretation and it was adjusted to ensure clarity and minimal confusion (based on participant answers). The questionnaire was kept simple and concise to make sure that each variable in the questionnaire would be utilised in statistical analysis. In addition, all questionnaires were checked manually in a quality control session with the field workers to check and ensure completeness just after the field visit to ensure timely correction for discrepant and/ missing information.

For content and criterion-related validity, the study ensured that measurements utilized in the questionnaire for assessing food allergy were consistent with the most recent big prevalence study (The Health-nuts study, Australia (32). The SAFFA study further dealt with construct validity by defining multiple cut-off points for sensitization rather than using internationally derived cut-off points that may not be applicable in this setting. Further construct validity was ensured by adapting a set of sensitive and specific questions (e.g. total household income) through field-testing them and also asking the participants to write it down themselves to ensure comfort in answering the questions. Lastly, sampling bias was the main threat to obscuring the validity of the study findings. Therefore, it was addressed by randomly selecting the crèche facilities/CDCs and also having a set of non-participant questionnaires done in all the selected crèches/CDCs (done telephonically with the parents of legible children who could not participate at the crèche/CDCs).

3. ETHICAL CONSIDERATIONS

CONSENT

The parent SAFFA study attained ethical approval from the Faculty of Health Sciences Human Research Ethics Committee of the University of Cape Town (see attached Ethics Approval Letter Appendix 1). This study will seek ethical approval from the Human Research Ethics Committee of the University of Cape Town.

Parents/legal guardians gave informed consent by signing a consent form after everything about the study was explained to them in their language of choice; English, Xhosa or Afrikaans. The consent included all procedures of the study i.e. recording dietary and allergy history, conducting SPTs, performing oral food challenges if indicated, and for reporting and collection of data. The process of

consenting involved an in-depth description of the study verbally as well as signing the consent and information sheet handed out to the parent (see Appendix 4 and Appendix 7 for Oral food Challenges). Where required, trained translators assisted in interpreting to ensure full understanding and free consenting before the study commenced.

CONFIDENTIALITY

The raw data collected was stored in a specified securely locked cupboard at Red Cross Children's Hospital in the paediatric allergy department for which only the Principal Investigators and named study staff could access it. Each participating child was allocated a distinctive study identification number (PID) which was used in capturing the data into the study database. There were no names or hospital numbers in the data entry process in order to protect the identity of the participants. Documents correlating the study number and the respective names of the participants were kept in separate databases accessed only by the named study staff. Confidentiality was upheld at all times in the study ensuring that there were no names, hospital numbers, addresses, telephone numbers, or any other direct personal identifiers to the participants in the study records and were only meant to be extracted in cases required by law.

PRIMARY RISKS IN THE PARENT (SAFFA) STUDY

For this study, there are no new risks to study participants. There were risks in participating in the parent SAFFA study mainly in skin prick testing, the oral food challenges and to venepuncture.

SKIN PRICK TESTING RISKS

Theoretically, SPTs can potentially cause sensitization and severe allergic reactions including anaphylaxis both of which are extremely rare. Recently a Swedish study (33) reviewed findings from a sample of 5908 children 18 and younger who underwent SPTs. The results showed 0.12% of the participants who mostly had a generalised skin reaction only. Also for those reactions, the risk factors were age (children < 1 year) and eczema. In overall, the study did not find any cases of severe anaphylaxis reported, although two participants needed adrenalin but no further medical attention or treatment (33). SAFFA study subjects experienced short-lived reactions of itching and burning which were easily treated with oral antihistamines and topical cold compresses (28).

THE RISKS OF FOOD CHALLENGES

Oral food challenging involves giving gradually increased amounts of food allergen which may possibly provoke allergic reactions that can be treated quickly with appropriate medical therapy (34). A study reviewed allergic reactions in a retrospective study of 584 children, 28% experienced severe reactions all of which were respiratory (35). None of the reactions were cardiovascular or required hospitalisation. All of the reactions responded to antihistamines, β-agonists, adrenalin or corticosteroids. A report compiling over 120 oral food challenges conducted at RCHPAC in the past 2 years recorded no severe reactions and so far no one suffered anaphylaxis or needed adrenaline or hospitalisation (36). The SAFFA study minimised risks by performing supervised oral food challenges in a hospital setting that had all necessary resuscitation equipment operated by qualified medical staff who followed a standardised protocol for the study (28). Mild allergic reactions responded to antihistamines while more severe ones required intramuscular adrenaline treatment.

THE RISKS RELATED TO VENEPUNCTURE

Venepuncture is potentially painful and the SAFFA study ensured safety for children in performing this procedure by applying a local anaesthetic cream before drawing blood on the area to allow numbness. Further risk in infection development was minimised by using standard sterile procedures.

BENEFITS FOR PARTICIPATING

Participants that had positive food challenges received a food allergy diagnosis that was conclusive. This enabled appropriate counselling for strict food avoidance, risk reduction of unintended exposures, reduction of anxiety of the unknown and validated the family for their efforts in avoiding those allergenic foods. There were also benefits in a negative allergy tests and oral food challenges as parents/ guardians were reassured and advised to expand the diet of their child with those concerned foods to improve the child's nutrition and overall quality of life.

NO FAULT INSURANCE

All participants for this study were covered by the no-fault insurance which was offered by the University of Cape Town. All participants' parents or guardians were informed in detail of this in the consenting process and they were also given written information sheets detailing this no-fault insurance.

4. LOGISTICS

BUDGET

All funding for the study was obtained by the principal investigator mainly from grants. This particular analysis will be based on secondary data of the parent SAFFA study. Access to bibliographic references, scientific support and supervision will be provided by UCT as part of its Master of Public Health degree programme, for which this dissertation constitutes a requirement for the degree.

TIME FRAME

This study is projected to take 10 months as shown below.

Table 2. Time frame of the study

Time Frame 10 months							
	2015-2016						
	November	December	January	February	March	April, May June	July, August
Ethics paper work, proposal draft and supervisor paper work and final proposal hand in							
Literature search							
Literature review write up							
Literature review write up and beginning of analysis and data cleaning							
Data analysis and write up							
Writing of manuscript							
Submission of dissertation and dissemination of findings							

5. DISSEMINATION OF RESEARCH FINDINGS

The proposed study will be submitted in partial fulfilment of the requirements for the Master of Public Health (General) degree at the University of Cape Town. Families of the participants are the immediate beneficiaries of the information yielded from participating in the study. Findings will be disseminated in the form of a preliminary report, seminars in the School of Public Health, UCT and presentations at appropriate meetings and conferences. An article will be submitted to a peer-reviewed journal (the Annals of Allergy, Asthma & Immunology Journal).

From this analysis, the publication of results will be guided by the UCT publication guidelines after review by the UCT approved post-graduate student supervisors and other peer reviewers before the study findings are communicated to the public. The published article will also be available through UCT library and its respective online platforms.

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PART B: STRUCTURED LITERATURE REVIEW

The influence of socio-economic status on the prevalence of food sensitisation and food allergy in children 12 to 36 months in urban Cape Town South Africa.

1. 1. LITERATURE REVIEW OBJECTIVES.

- To highlight key features of the global, and South African FA prevalence.
- To summarize literature on the association between socio-economic status (SES) and FS/FA.
- To profile key risk factors, summarizing key epidemiological determinants of FS/FA.
- To identify opportunities for further research relating to SES and FS/FA.

1.2 . LITERATURE SEARCH STRATEGY

Our search was conducted in Ebsco Host in databases such as Academic search premier, General Science Abstracts, CINAHL, and Medline Health Source. We also searched Pubmed, Embase (Scopus) and Google Scholar. There were no strict limitations on publication dates as narrowing the search produced very few studies especially in African literature. Animal studies were excluded. Key words used included: "risk factors for food allergies in children", "socio-economic status" AND "infant allergy", "income" "food allergy prevalence" "epidemiology", "social status/class", "employment/status" "education and food allergy in children". Abstracts were screened using key words then articles were examined for relevance to exclude non-relevant articles. In addition references were examined to obtain unidentified relevant articles (snow-balling).

1.3. INTRODUCTION

Hypersensitivity describes adverse reactions that occur in individuals at a dose of a trigger that is usually tolerated by individuals who are not susceptible. An allergy is a type of hypersensitivity response instigated by immunologic mechanisms that are specific to an allergen exposure, and can be either anti-body-mediated or cell-mediated (1). Food allergy (FA) describes an adverse reaction to a food mediated by the immune system, whereas reactions not mediated by the immune system are best termed non-allergic food hypersensitivity (1). Allergic food reactions can be "immediate type" initiated by blood antibodies (IgE antibody) and occur immediately after eating the food, or can be "delayed type" in

reactions mediated by the cells (T-cells) in one's immune system and reactions may be delayed for variable periods after eating the food (2).

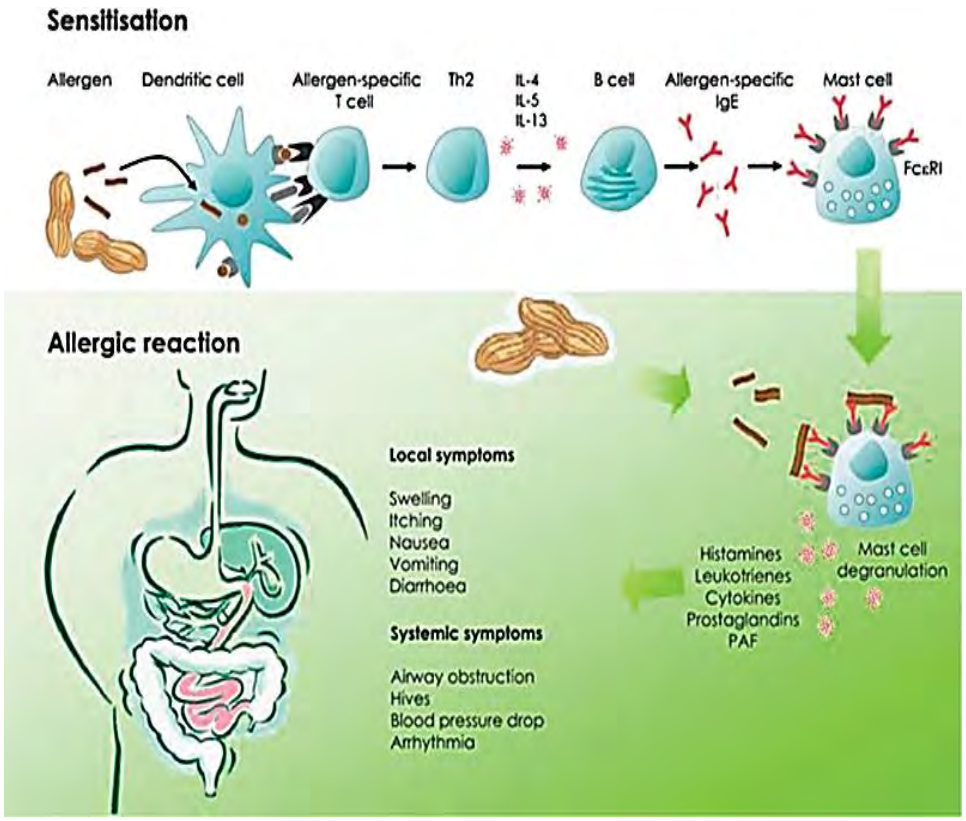
Food sensitisation (FS) refers to the production of specific IgE antibodies by the immune system to that particular food yielding a positive skin prick test (SPT) or ImmunoCAP blood test (3). Sensitisation is a precursor and prerequisite for "immediate type" IgE mediated food allergy, however individuals with sensitisation may either be truly allergic and experience adverse reactions to the ingested foods or may have "innocent sensitisation" without food allergy, in which case the food is tolerated by that individual (4). Management of food allergy sensitisation may require an oral food challenge (OFC) to clearly identify those individuals who are sensitized but are tolerant from those people who are truly allergic (5).

FOOD ALLERGY DEVELOPMENT AND EFFECTS

Food ingestion and processing through the intestinal tract ensures that nutrients are extracted and intact protein molecules are usually prevented from entering the body (1). At infancy these processes are immature putting the baby at risk of allergens entering the blood stream. Those allergens that do penetrate are usually processed by the immune system to induce a state of tolerance, however, these normal mechanisms may fail resulting in food sensitisation or food allergy (6).

In IgE mediated food allergy, the body produces food-specific IgE antibodies in the process of allergen sensitisation. Subsequent exposure in truly allergic individuals may result in cross linking of antibodies binding to mast cells resulting in histamine release that leads to clinical symptoms in the skin, gastrointestinal, and cardiovascular system (see Figure 1) (7). The food reactions can last an hour or persist for days or weeks affecting the quality of life. Day to day effects of dealing with food allergies can be challenging as this may involve avoiding certain foods, limiting certain activities and in severe cases needing hospitalisation. Patients may become socially isolated which leads to possible mental health problems (8).

Figure 1. **Food Allergy symptoms and process of sensitisation adapted from Fardous** (7)



Skin/ mucus membrane food allergic symptoms
- Urticarial
- Angio-oedema
- Rhinitis
- conjunctivitis

Respiratory food allergic symptoms
- Asthma
- hoarseness

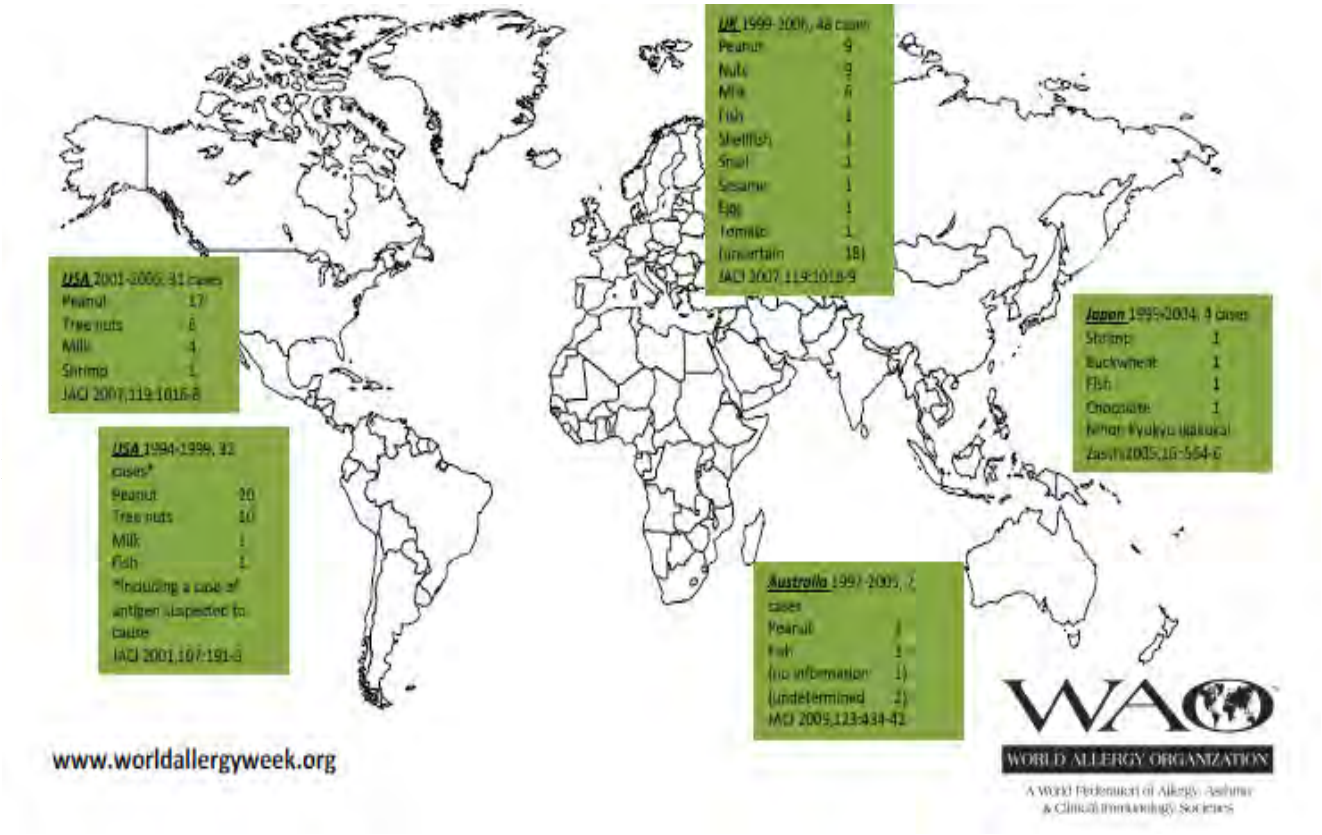
Cardiovascular food allergic symptoms
- Anaphylactic shock

Gastrointestinal food allergic symptoms
- Abdominal pain
- Vomiting
- diarrhoea

GLOBAL PREVALENCE OF FOOD ALLERGY

Prevalence of conditions such as allergic asthma, eczema and hay-fever has increased three fold in developed countries across the world. Similarly, food allergy prevalence has increased and most evidence comes from developed countries. This has been noted in children aged below 5 years of age especially towards eggs, cow's milk, fish (sea-food) and peanuts; with regional differences in prevalence (9,10). However, the true global prevalence of food allergy is unknown. There is an estimation of prevalence of food allergy thought to be between 1% to 10% and a dearth of quality data in many regions (10). Figure 2 shows prevalence of food allergy in a meta-analysis conducted by Rona et al. (11).

Figure 2. Country reports of anaphylaxis cases (11)



FOOD ALLERGIES IN DEVELOPING COUNTRIES

There is limited data on food allergy in developing countries and uncertainties on possible food allergy health effects in these populations (12). Recent studies from China show a progressively increasing prevalence of allergy (13). In a challenge-proven food allergy study from China the prevalence of FA in infants was reported to be 3.8%; with 2.5% allergic to egg and 1.3% to cow's milk (14). A review conducted by Boye identified emerging data from Asia, Middle East, Africa and South America (see Table 1 below) (12). In these countries, information on community prevalence of FA is not robust since most studies are case reports or tertiary clinic reports in selected populations which do not reflect true population prevalence. Boye's review highlighted the need for comprehensive data on prevalence rated of FA in developing countries (12). In addition, Kung et al (2014) reviewed FA prevalence data from 11 African countries. Most studies did not use objective, rigorous diagnostic approaches; since they used self-reported outcomes although these studies noted FA to be an emerging public health problem (15).

Table 3. Studies on FA found from different developing regions adopted from Boye (12)

Geographic region	Number of papers found	Specific countries in geographic region
Africa	27	Botswana, Egypt, Ghana, Morocco, Mozambique, Nigeria, South Africa, Togo, Zimbabwe
Asia	21	China, Hong Kong. India, Indonesia. Malaysia, Philippines, Singapore, South Korea, Taiwan, Thailand
South America	15	Argentina, Brazil, Chile Mexico
Middle East	8	Iran, Israel, Saudi Arabia

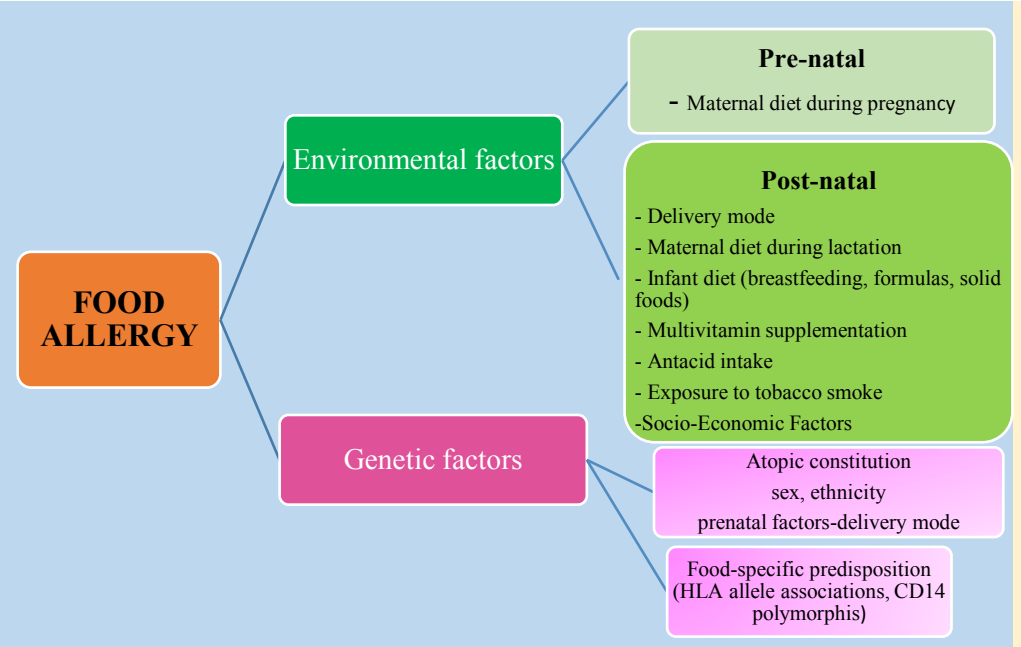
ALLERGY AND FOOD ALLERGY PREVALENCE IN SOUTH AFRICA

Allergy data in African children is informed by studies conducted in South African selected and unselected hospital populations. A study of FA in high risk children with severe AD found high rates of FS and FA similar to those seen in other selected populations in developed countries (16). Older research mainly explored respiratory allergies whereas more recent research has explored food allergies. Although respiratory allergies are more prevalent in urban than rural areas, studies have shown an increasing prevalence of respiratory allergies in both settings (17). The only study to date, which is still on-going, that explored food sensitisation and food allergy among a heterogeneous or unselected population of South African children aged 1-3 years has reported an overall sensitisation rate to common foods of 11.6%; with the sensitisation rate to eggs at 1.4% and to peanuts 1.1% (18).

2. RISK FACTORS FOR FOOD ALLERGIES IN CHILDREN

Like many illnesses and diseases, the aetiology of food allergy is multi-factorial involving both pre and post-natal periods and includes both genetic and environmental factors classified broadly as; microbial exposures, dietary factors, and lifestyle and environmental factors (see Figure 3) (23). The formative years of development of children are the most critical for food tolerance development, hence the need to identify these risk factors for timely intervention (24).

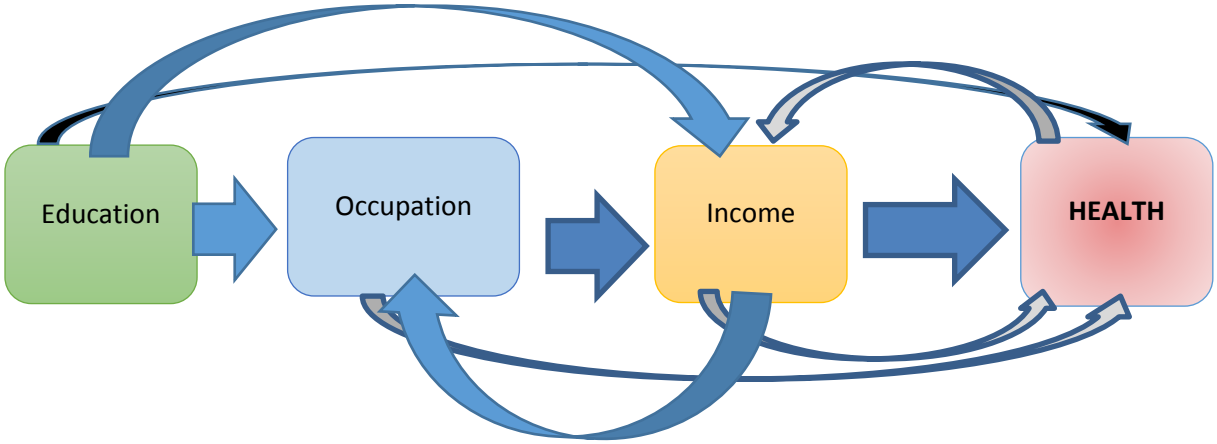
Figure 3. Risk factors for FA (adapted from Ezendam & van Loveren (19)**, Kaza et al** (20)



2.1. SOCIO-ECONOMIC STATUS

Socioeconomic status (SES) has been identified as an important risk factor for morbidity and mortality. SES was defined by Grotto et al as socially derived economic factors that have an influence on the positions held by people or groups within a stratified society (21). Despite extensive research on SES, researchers have not come to a consensus on a standard way to measure or quantify it. The commonly used measures of SES include; individual, household or contextual income, highest level of educational attainment, employment status, type of occupation, poverty or wealth measures (such as asset quintiles or deciles) and other proxies such as expenditure and housing (rural or urban dwellings) (21). Specific to South African history and political legacy, race and informal housing have been used as proxies of SES to monitor social change and equitable distribution of resources (21).

Figure 4. Relationship between socioeconomic determinants of health (22)



In general poor health has been associated with low socio-economic status (SES) shown by indicators such as short education, low income and or type of employment (Figure 4) (23). Although the schematic conceptual model is simplistic in showing the socio-economic determinants to health, it shows how education is assumed to be acquired first over the life course and how it contributes to occupational class and through this to income. Education effect on income is assumed to be mediated mainly through occupation, however greater income also facilitates greater educational attainment and how one's health status can be a determining factor for the ability to work in certain occupations. These relationships are rather complex and are not reflected by the diagram in Figure 4 (23). Environmental factors are highly associated with SES which in turn has a strong effect on allergic sensitisation development and this is thought to be the same for food allergies (24–26).

2.2. RELATIONSHIP BETWEEN SES AND ATOPIC DISEASE

Assessing SES in allergy studies is not uniformly done and in allergy research, some studies have used Gross National Product (GNP), some geographical social ranking indexes, and the common SES indexes (income, occupation and education (24,27–30). Stewart et al., found a significant positive association between asthma symptoms and high GNP and in both 13-14 year olds and 7-8 year olds there was a positive association between eczema and GNP (27). Even though the study has methodological limitations, it points out importance of environmental influences to allergy development. Braback et al., conducted a survey to assess the association over time between social class and the disease outcomes allergic rhinitis and asthma. The findings showed a negative interaction with a significant increased prevalence rate of asthma and allergic rhinitis in low socio-economic status conscripts which occurred over a period of 3 decades (28).

A German cohort study looked at SES influences to FA (measured by parental highest education and income) on parents with atopic phenotypes to assess if these had an impact on their children (24). Parents of high SES had a higher prevalence of inhalant allergies but their children were protected from developing atopic disorders. This may have reflected reverse causation as the parents adopted protective

life-styles. For the parents, education seemed to be an indicator of SES in their children's early life whereas income was a strong disease determinant in adulthood (24).

A UK study looked at the association between peanut allergy prevalence and SES measured by the level of deprivation on a Townsend Index (based on household assets, number of people and occupation status) (30). A strong negative relationship was recorded on the prevalence of peanut allergy in association with SES ($P < .001$) and a higher doctor-recorded peanut allergy prevalence was found in boys than girls and in children from affluent families (30).

Basagaña et al., used a combination of income, employment and education in young adults as SES measures to explore their associations with asthma prevalence investigating both individual and country SES simultaneously in 25 countries within 32 centres (29). A negative relationship was found with asthma prevalence higher in low SES groups for both education and social class (OR 1.28; 95%CI and 1.51; 95%CI). It was also apparent that regardless of individual SES, people who lived in areas that suffered lower education levels were at higher risk of asthma and it was concluded that the community influences of living in areas with low educational levels had a strong association with asthma independently of individuals' own educational level and social class (29). In these studies different results were found depending on the SES index employed.

2.3. RELATIONSHIP BETWEEN EDUCATION AND FA

Education in health is important and research has been conducted extensively to ascertain the influence of education on health behaviours and lifestyle or behaviours that contribute to ill-health (31). Similarly, education has been associated with prevalence of atopy and in a number of studies it presents as a potential risk factor (32). A Swedish study found that parent's educational level was associated with the risk factors for atopic disease development (32). Parents who had long education were less likely to be smokers compared to those with a short education which markedly protected their children from the development of atopic disease (32). Although threatened by selection bias, this study highlights the importance of educational level and lifestyle for different socio-economic groups as most risk factors

for atopy presented in children who came from households short of education showing a strong negative association (32).

Another study by Dom et al evaluating the relationship between parents' education and atopic sensitisation, recurrent wheezing and eczema at first year of life confirmed atopic sensitisation using specific serum IgE (31). This study found a positive association between parental education and the prevalence of atopic sensitisation and eczema but a negative association with recurrent wheezing. With adjusted models the study found that high maternal education was an important factor that played a role in atopic disease development (31).

Generally education influences the outcome of many studies in that knowledge about disease is linked to the reporting behaviours on the disease and it influences the lifestyle adopted by a household (33). For example, Ben-Shoshan et al., conducted telephone survey exploring the demographic correlations with peanut, fish, tree nut, sesame and shell fish allergy (33). The study found a positive association with higher prevalence of food allergies in individuals with more education and more shellfish allergy in participants from urban settings than those from rural settings. It was suggested that higher education level may be associated with increased risk of FA possibly mediated via family's lifestyle changes leading to increased environmental cleanliness/ sterility as proposed by the hygiene theory (33).

In Japanese 4 to 5 year olds, a study investigated the associations between parental education and childhood allergy (mainly self-reported as well as doctor-confirmed asthma and eczema) (34). This study found increased risk of self-reported wheeze and asthma associated with higher maternal education while paternal education was positively associated with self-reported eczema although these positive associations could not be confirmed for atopic eczema diagnosed by the doctor. The study did not find any relationship between mother's employment, type of job, household income and the investigated allergy outcomes (34). The results from this study could have been affected by selection bias as the researchers confirmed that in their follow-up survey fewer participants responded and most were from higher SES. A diagnosis of allergy was based on parents' self-reporting and allergy outcomes were not clinically proven (34).

2.4. RELATIONSHIP BETWEEN INCOME AND FA

In consistency with the hygiene theory, income as a socio-economic variable has been seen to be a risk factor to allergy development in which higher income is positively associated with allergy outcomes (24,35,36). The hygiene hypothesis asserts that lack of early childhood exposure to infectious agents, parasites and symbiotic micro-organisms increases the chance for allergic diseases through interfering with the development of immune tolerance (19). Supportive of this theory is research that has shown that environments with hygienic conditions and high-living standards are associated with an increased risk of allergic disease (37).

Ben-Shoshan et al., investigated the associations between socio-demographic and lifestyle factors with FA (38). It was shown that factors that influenced higher risk of allergy were: personal eczema history within 2 years of life, siblings or parents' FA allergy history and high income in the household. In overall, the study showed that in within the first 2 years of a baby's life, eczema is consistently a risk factor for FA development to peanut, egg, tree-nuts and fish (38).

In the USA, Gupta et al., showed significant associations between age, race, income, and geographic regions with observed disparities reported on the diagnosis of food allergy according to race and income (36). The results showed a positive association with disparities on the reported allergies and children with allergies were more likely to come from households with higher income (odds ratio of 0.5 (0.4–0.7 95% CI)). Meanwhile children from low income households were less likely to have odds of confirmed FA and if they reported having an allergy, they also were less likely to have (36). Results from this study are notable as it has a large sample size and for this study having high income influenced health seeking behaviours as people from high income backgrounds presented more for treatment. The main weakness of this study is that food allergy diagnosis and reaction history were self-reported by the participants and there was no validation of the survey or objective tests of allergen sensitisation or food allergy (36).

Income and education become more important as risk factors when combined. Pawlinska-Chma et al., observed more allergies in children who came from higher socio-economic status (high education and

high income) families(39). The authors regarded SES not as a direct risk factor but rather as an indicator of living conditions and lifestyle encompassing nutrition habits, access to medical care, housing conditions and exposure to allergens (39). Other studies have recorded negative associations between income and allergy. For example, a USA National Health and Nutrition Examination Survey showed that households with people living in poverty (measured by poverty income ratio) had higher food sensitisation prevalence compared to higher income households (40).

2.5. RELATIONSHIP BETWEEN EMPLOYMENT AND FA

Education, income and occupation may be combined in studies to reflect SES indexes. Level of education may affect the occupation attained by a parent which also influences their income. A Swedish study explored the relationship between socio-economic status and asthma, allergic diseases and sensitisation (26). There was a decreasing risk of asthma and rhinitis with increasing SES measured by parent occupation (26). The same negative association was observed as a risk factor for sensitisation to food allergens which decreased with increasing SES (OR 0.65 (0.41–1.02)). Low SES was a risk factor for the development of allergy though these results were speculated to be related to additional uncontrolled differences in the environmental exposures and life style between the groups (26).

Research in South Africa has shown that asthma in childhood is associated with socio-economic status in a complex fashion. Asthma has been found to be more common in people from higher socio-economic status households and in urban rather than rural communities (35). In both urban and rural communities, asthma prevalence is increasing although this is happening faster in rural than urban environments leading to a decrease in the urban: rural gradient.

Despite prevalence being driven by factors associated with improved SES, severity is influenced by poverty associated factors (35). In the Poyser et al. study, the incidence of severe asthma was reported more in children from low-income communities which were associated with poverty (35). Thus, fatal and near-fatal asthma was correlated with low SES in a South African Study and poor access to care exacerbated these high rates (2,41). Within the South African context this study highlights important

health outcome trends associated to SES although the methodology of self-reported cases may lead to over-estimation of association between the main variables; SES and asthma (2, 48).

Table 4. Summary of reviewed studies and their associations between SES and Allergy/FA

Key: "Positive association" refers to a direct where people with higher SES are found to be at higher risk of allergy/FA compared to people with low SES. For a "negative association", people with lower SES are at greater risk of allergy/FA compared to the individuals with higher SES; "No association" denotes findings that did not show any significant relationship between SES and allergy/FA.

-Study -publication year	**-Population -Sample size**	**Study design**	**SES measure used**	**Nature of association with FA/Allergy**
a) Positive association studies between SES and Allergy/FA				
Poyser et al (2002)	4706 13-14 year olds	Cross-sectional survey	Residential location of schools socio-politically defined 10 category scale	Positive
Dom et al., (2009	690 children birth cohort up to 1year	Aetiological study	Parental highest education (maternal and paternal education combined)	Positive
Gupta et al (2011) (2009-2010)	38480 birth cohort to 18 years old	Electronic randomised cross-sectional survey	Household income	Positive
Miyake et al., (2012).	480 mother-child pairs		maternal employment status, maternal job type, household income, maternal and paternal education	positive
Nwaru et al (2014)	Children and adults	Systematic review-meta analysis	Not mentioned	Positive
Ben-Shoshan et al (2012) 2008-2009	9667 Households Children and adults	Telephonic cross-sectional study	Income Location rural/urban Education level Immigration status	Positive
Pawlinska-Chmara (2008)	301 4-9 year olds	Cross-sectional study	Parent education Self-reported economic situation	Positive
Bergmann et al (2000)	1314 birth cohort up to 4 years and their parents	Prospective observational cohort study	Parental occupation Income	Positive
Stewart et al (2001)	6-7, 13-14 year olds	Ecological study	Gross National Product (GNP) per capita GDP and household income	Positive
Lee et al (2016)	75,643 adolescents (aged 13–18yrs grades 7–12)	Cross-sectional study	Family Affluence Scale (FAS) based on assets, parental education levels	Positive

b) Negative association studies between SES and Allergy/FA				
Lui et al (2010) (2005-2006)	8203 Adults and children	Cross-sectional survey	Income using poverty Income ratio (PIR) Household highest education	Negative
-Study -publication year	**-Population -Sample size**	**Study design**	**SES measure used**	**Nature of association with FA/Allergy**
Braback et al (2005)	1,247,038 male conscripts in aged 17-20	Retrospective survey	Occupation, educational, occupation level, type of production and the position at work of the head of the household	Negative
Lannero et al., (2002)	cohort of 4089 neonate children and their mothers	a prospective birth cohort study	educational level, profession and type of work	Negative
Kotz et al (2011)	29 583 66 patients 0 to 90+	Longitudinal retrospective case-control	Deprivation quantiles (Townsend Indexes based on household with no car, over-crowed households, households not owner occupied, unemployed persons)	Negative
Basagaña et al., (2004) 1991-1992	10971 20-44 year olds	Cross-sectional study	Occupation Education European Community SES groups classification	Negative
Almqvist et al (2005)	408 Families with children born 1994–1996	prospective birth cohort study	Parental occupation	Negative
c) No association studies between SES and Allergy/FA				
Koplin et al (2012)	5276 11-15 months children	Population based cross sectional study	Home post code and Area SES Indexes (SEIFA) - SES advantage/disadvantage - Economic resources - Education - Occupation characteristics	No association
Du Toit et al (2008)	10786 Jewish children from Israel and UK 4-18 year olds	Comparison nested case-control	Parental education (UK Occupation classification system)	No association
Osborne et al (2010) 2006-2009	2171 0ne year olds	Prevalence cross-sectional study	Area SES Indexes: - Economic resources - Education - Occupation	No association P<.01
Martin et al (2013)	4972 infants 11- 15 months	Population-based cross-sectional study	Local area SES using socio-economic indexes for areas (SEIFA) measures: -SES advantage and disadvantage, -economic resources (income, assets and expenditure) -educational, -occupation	No association

Some studies have however found no associations between income and allergy outcomes. Martin et al. investigated the relationship between eczema in infancy and socio-demographic risk factors. They found the strongest risk factors for eczema to be: maternal asthma and eczema history, being male and ethnicity (East Asian) and no association with household annual income or the parent's age and childhood eczema risk (47). Similarly in Australia, Osborne et al., (42) conducted a prevalence study assessing prevalence of IgE-mediated food allergies amongst 12 months-old infants. There were no associations found between socio-economic indices (derived from participant immunization location and combining economic resources), parental education and occupation (42).

Most studies have shown a positive association between SES and allergies in support of the hygiene hypothesis. A case of reporting bias amongst people with higher SES can possibly explain these positive associations in studies with self-reported allergy data which may be influenced by more health seeking behaviours in this group compared to those with low SES. SES is an important proxy measure for lifestyle features and characteristics including dietary habits, access to health care, family size, allergen exposure and other environmental factors relevant for enquiry in allergy research (43).

3. OTHER RISK FACTORS ASSOCIATED WITH FA PREVALENCE

3.1. PRENATAL FACTORS, GENETICS AND FA

Intrauterine trans-placental sensitisation and mother's diet during pregnancy have been postulated as possible pathways of exposure to allergens (44). As gestation is a very complex stage of development, it is believed that the developing foetus interacts with the gestational environment through the placental interface (45). Nutritional factors may affect immunity, or through epigenetic changes result in foetal programming that modifies risk of atopic disease development (44). In this case, SES becomes relevant as it affects affordability or unaffordability of certain foods in a families diet.

Allergic disease presence in parents and siblings of a neonate is a risk factor for atopy development and research has revealed various genes that influence IgE specific responses to particular antigens (3,44). A review conducted by Marrs et al., found some evidence from different studies that illustrated the

influence of microbial exposure to the development of FA in children (46). Genetic studies have demonstrated atopic heritability for asthma and other allergic disorders. It is believed that atopic phenotypes are a result of polygenic inheritance coupled with a complex interaction between environmental and genetic factors (47).

Age and sex

In a USA National Health and Nutrition Examination Survey age and sex were important risk factors for sensitisation and food allergy. The life-time peak of symptomatic food allergy has been observed more in children under the age of 3 wherein sensitisation happens mostly within the age of 1 year (17,36,48,49). Male children compared to females are five times more likely to have food allergy and studies have suggested a reversal of the male/female ratio for FA after adolescence and at adulthood which suggests that the expression of allergy is influenced by sex through endocrine processes (6). Some studies have however not found the association between sex and food allergy (37).

3.2. ETHNICITY

American studies have reported an increased risk of both self-reported and clinically diagnosed FA in black children compared to white children (36,50). Other studies have demonstrated higher food sensitisation rates in black children suggesting presence of either unidentified environmental factors or a possible genetic predisposition in black children that increases sensitisation (51,52).

A South African study conducted on Xhosa children revealed a 5.4% sensitisation rate to common foods but no cases of allergy (53). It was postulated that a cultural difference in peanut exposure with early introduction of peanuts was protective in these children (53). A prospective, observational study of 100 patients with atopic dermatitis showed an equivalent sensitisation rate for peanuts in black African children (41%) and children of mixed black and Caucasian ancestry (50%). However, challenge-proven IgE mediated peanut allergy rates were higher in children of mixed ancestry compared to black children (38% in mixed race vs. 15% in blacks: $p=0.01$) (54). This study revealed ethnic differences in allergy rates in Black Africans compared to other races because even though sensitisation was higher in Black

African children clinically proven FA was lower. Thus different factors may affect sensitisation and the risk of manifestation as food allergy. These factors may be mediated by genes, the environment or both through epigenetic modification (54).

3.3. ENVIRONMENTAL FACTORS POST-NATAL FACTORS

3.3.1. DELIVERY MODE, MATERNAL DIET DURING LACTATION AND BREAST FEEDING

Diet, breast-feeding habits, solids introduction and supplementation may be influenced by SES in the post-natal periods of a child's development. Diet manipulation during and after pregnancy is currently controversial but studies have proposed a window of opportunity to prompt tolerance through timing of food exposure orally (37). However, for children who are at risk of atopic development, studies have pointed that exclusive breast-feeding for at least 4 months is protective against atopic dermatitis development (55). Conflicting results in a systematic review revealed a protective effect of exclusive breastfeeding on food allergy development in some studies, while other studies showed an increased risk or no effect (19).

Formula feeding is widely used as an alternative to breastmilk. Hydrolysed infant formulas have been manufactured with reduced but not absent allergenicity (19). Von Berg et al found low allergic disease incidence in high risk children (with a family history of allergy) in those fed partially or extensively hydrolysed formula compared to those fed intact cow's milk formula (56). The benefits of hydrolysed formula in allergy prevention have since been refuted (57).

3.3.2. ALLERGENIC FOOD AVOIDANCE

Early studies found benefits in delaying the introduction of solid foods for lowering food allergy (58) but not for egg allergy (59). The American Academy of Paediatrics (AAP) and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommended solid food initiation at 4 to 6 months with exclusive breast-feeding prior to this (and in cases where breast-feeding

is not possible in high-risk infants, hydrolysed formula were advised) in order to prevent allergic disease and cow's milk allergy (60).

Results from a randomised control trial study by Du Toit et al., showed that early peanuts introduction to children at risk (atopic dermatitis and/or existing egg allergy) significantly improved their immune response to the peanuts and prevented peanut allergy later (51). The EAT study found no significant effect of early food introduction in the intention-to-treat analysis probably because of poor adherence to the dietary protocol. Per protocol analysis showed lower peanut and egg allergy rates in those with early introduction (43).

3.3.3. VITAMIN AND PRE-PROBIOTIC SUPPLEMENTATION

In a Swedish study subjects from anthroposophic households (i.e. homes with a lifestyle of restricted use of antibiotics, vaccinations, antipyretics and strict dietary habits), were found to have low food sensitisation sIgE rates (9%) compared to those who were not (16%) (61). Adding pre/probiotics to baby formula as a way of reducing food allergy development has been a subject of inquiry, with conflicting results found, perhaps due to the different dosing schedules and type of pre/probiotic used (62). In a recent review, approximately half of all studies of probiotics showed a beneficial effect, mostly on eczema but also some on food sensitisation (62).

For specific vitamins, studies have shown some positive influences of vitamin D for allergy. Camargo et al., (2014) showed that giving vitamin D supplements to high risk children most likely to suffer vitamin D deficiency in winter improved winter-related AD (63). Another study demonstrated that vitamin D deficiency increased the risk of sensitisation to food allergens and children with vitamin D deficiency had more severe atopic dermatitis (64). Recently, Weisse et al., (2013) argued against vitamin D supplementation by finding that high vitamin D levels taken at pregnancy and at birth are associated with higher risks of food allergy development (50). Ezendam & Van Loveren, (2010) could not make any conclusions about the effects of vitamin D on food allergy development in a review that showed conflicting results in different studies (19).

4. IDENTIFICATION OF GAPS OR NEEDS FOR FURTHER RESEARCH.

The true global prevalence of food allergy is unknown. There is an estimation of prevalence of food allergy and a dearth of quality data in many regions. Studies worldwide have found differences in the prevalence of food allergy, asthma and atopic diseases between different groups in populations defined by self-reported ethnicity, race or socio-economic status. In general poor health has been associated with low SES usually shown by low education, low income and or type of employment.

Much of what is known about allergies and food allergies is cited from studies carried out in developed countries like UK, Australia and the USA. Most studies used self-reported data on allergy prevalence and associations with SES, the few with confirmed diagnoses suffered from inherent weaknesses due to having small samples of data collected from predetermined groups of clinical patients which introduces selection bias.

Furthermore, studying the influence of socio-economic factors on FA has been challenging because of difficulties in conceptualising and measuring these variables. In the reviewed literature, SES categorization and measurement differed from study to study as different proxies were employed. It is clear that household income and highest parental education are the most predominant SES measures used in most studies. It could be useful to employ standardized or similar measures of SES in order to make cross-country comparisons easier. In addition, most studies employed logistical regression models to control for SES as a confounding variable rather than as an independent variable.

5. CONCLUSION

Undoubtedly the prevalence of food allergies in children is rising and this is attributed to various risk factors concomitant with different levels of socioeconomic development in young children. The risk factors stem from pre and postnatal environmental exposures and as postulated by the hygiene hypothesis allergies are seen more in children from affluent families/environments. Nonetheless, SES is a proxy measure for lifestyle features and characteristics including dietary habits, allergen exposure and other environmental factors and it is an important risk factor for atopic dermatitis, rhinitis and food

allergy. In the reviewed literature there were variations of associations between allergic diseases and SES; most studies showed a positive association between SES and allergies though most studies relied on self-reported data. Measuring and quantifying SES is also not uniform across studies conducted in different countries and there is need for more exploration of the effects of SES on food allergy. In overall, there are many factors that may contribute to associations between SES and allergy and more rigorous research is needed on this.

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PART C: JOURNAL ARTICLE MANUSCRIPT

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Article in line with ***Annals of Allergy, Asthma & Immunology Journal***

Socio-economic status and food sensitization, food allergy in Cape Town children

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ABSTRACT

Hobane, L.

Socio-economic status and food sensitization, food allergy in Cape Town children

Background: Health outcomes are known to be influenced by socio-economic status (SES), however, there is limited data exploring the relationship between SES and food sensitization (FS) or food allergy (FA) in children.

Objectives: To describe FA prevalence and explore associations between SES (i.e. household size, parental education, household income, and employment status) and FA outcomes (FS and FA) in urban Cape Town Metropole children.

Methods: Prevalence of FS and FA was assessed in the South African Food Sensitisation and Food Allergy study of 739 children 12-36 months attending randomly selected crèches/Childhood development centres (CDCs). Skin prick testing (SPT) was done on all eligible children. Associations between SES and FS/FA were assessed using the Z-test and Chi-square/Fisher's exact. Sensitized children not tolerating particular foods underwent oral food challenging.

Results: FS prevalence at SPT≥1mm to any food was 12.3%, at SPT≥3mm 9.6%, at SPT≥7mm 4.5% and challenge proven IgE mediated FA was 2.4%. In 739 sampled participants, 91 were sensitised to 1 or more foods. A non-significant trend of increased sensitization at SPT≥1mm, ≥3mm, ≥7mm and proven allergy in children of parents with tertiary education was observed (14.8%, 11.9%, 5.8% and 2.9%) compared to parents who attained primary/secondary education (10.5%, 7.9%, 3.5%, and 2.1%). Highest risk for FS and FA were in children with employed parents (p=0.03) and in children from homes with higher household income (p=0.02). Household size showed no association with FS and FA. No differences in sensitization and allergy patterns were noted between ethnic groups.

Conclusion: SES is associated with food allergy in young children with a positive relationship to parental employment status and income.

Key words: Socio-economic status, food allergy, food sensitization, skin prick test, children, Africa.

INTRODUCTION

Food allergy (FA) prevalence data on unselected populations is mostly from developed countries (1,2). FA has been dubbed the ‘‘second wave” of allergy disease after respiratory allergy and is recognised as a public health concern which affects both the individuals and their family (3). The food industry and health care professionals are affected by the rise in FA and therefore understanding the extent of the problem, what causes it and how it can be managed to enhance quality of life is paramount (4). Progress has been made in identifying the prevalence as well as risk factors associated with food sensitization (FS) and FA but gaps still remain as many studies suffer from poor methodologies, small sample sizes and/or poor objective assessments (5–8).

Studies from developed countries such as USA, UK, have found differences in the prevalence of allergies and their severity between different groups in populations defined by self-reported ethnicity, race and socio-economic status (SES) (9–11). Correlations between SES and socio-demographic variables and allergic diseases have mainly been investigated in asthma, rhinitis or atopic dermatitis (12–17). Few studies have explored correlation between SES and FS or FA in children. In general poor health has been associated with low SES shown by short education, low income and or type of employment (18).

The hygiene hypothesis views allergies as lifestyle diseases and may explain why allergy seems to be more prevalent in children from urban societies and high SES households (19). According to the hygiene hypothesis, reduced exposure to microbial components that are believed to be protective against allergy development results to an imbalance of the immune system with a predisposition to the allergic disorder development. These complex gene–environment interactions seem to be associated with modern lifestyle wherein high standards of living and hygiene conditions are seen to be associated with an increased risk to the development of an allergic disease (1,4). The relationship between SES and food allergies in children has been studied in different ways yielding varied results (i.e. negative, positive, no associations). There is limited epidemiological data on food allergies in Africa with most studies based on case reports or on selected populations (20).

Early studies exploring the association between SES and the prevalence of allergy have mainly explored aero-allergen sensitization and either asthma or allergic rhinitis for example the International Study on Asthma and Allergies in Childhood (ISAAC) which assessed environmental factors that influence eczema development and allergic rhinitis in young children from developing countries (13). Respiratory allergies in South Africa have increased in a similar pattern to that observed in developed countries with different rates of sensitizations and respiratory allergy observed in different SES and ethnic groups. This may reflect the effect of different environmental exposures and or their epigenetic interaction with genetic differences (21). As the South African population is diverse ethnically and socio-demographically, there is a need to explore whether socio-economic factors are associated or have contributed to the rise in FA prevalence. This study aimed to explore the socio-economic factors associated with FA and FS in children and also to explore any ethnic disparities in this population using prevalence data from a food sensitization and food allergy study of South African children.

METHODS

DESIGN

This study was a descriptive secondary analysis study of the South African Food sensitisation and Food Allergy (SAFFA) study; which is an on-going cross-sectional study of IgE-mediated food allergy in an unselected population of South African children aged 12-36 months. The study was conducted from February 2013 in childcare facilities (CCFs)/(CDCs) in the Cape Town urban Metropolis. Detailed methodology and results of the pilot of the parent study have been described in detail (22).

SUBJECTS, SETTING AND SAMPLING

The population of our study were 739 children aged 12-36 months attending crèche/(CDCs) in the Cape Town metropole. They were selected using a method based on equal probability mirroring the source Cape Town population of children from different ethnic backgrounds. Locally registered crèches/(CDCs) were recruited from the Department of Social Development online crèche/(CDCs) register. A Microsoft Excel number generator was used to create a sampling frame for randomly selecting the particular crèches/(CDCs) across the Cape Town urban metropolis. With permission from

the principal/manager to carry out the study at their facility, the principal/owner would then invite the parents of the eligible children to come and participate in the study. Further consent was sought from the parents who came to the crèche/ (CDCs) after the fieldworker explained the study procedures including SPT, and potential risks and benefits involved (see Appendix 4 and 7). Once consent was given, the fieldworker went through the questionnaire with them collecting demographics and allergy information.

INTERVENTIONS

Each participant was examined for hayfever, asthma and eczema. A non-participant questionnaire with demographics and allergy information was completed by non-participants to assess for selection bias (see Appendix 6).

SKIN PRICK TEST AND ORAL FOOD CHALLENGES

Using the standardised solutions from ALK Abelo (Thermo Fisher^{TM}) and ALK lancets, SPTs were conducted testing on egg white extract, peanut, wheat (flour), soy, hazelnut, cow's milk, fish (cod) and negative (saline) and positive (10mg/mL histamine) controls. For modified SPTs, fresh raw egg, milk and peanut butter were used. The forearm skin was pricked through a drop of the food extract and the SPT results were read after 15 minutes recording the average wheal size diameter in millimetres. SPT sensitization results ≥ 1mm > the negative control qualified the participant for an incremental food challenge if they were not clearly tolerant to a full age-appropriate portion on history or had never been exposed to that particular food. Those with a recent (4 months for all foods except 2 months for peanut) severe (World Allergy Organisation definition of anaphylaxis) reaction with SPT higher than previously published 95% PPVs (>24 months old: milk ≥8mm, egg ≥7mm & peanut ≥8mm and <24 months old milk ≥6mm, egg ≥5mm & peanut ≥4mm) were not challenged and were classified as allergic. However, no children fell into this category; all children identified as FA were diagnosed as such due to a food challenge (23). Sensitisation to more than one allergen required multiple food challenges on different days, conducted at Red Cross War Memorial Children's Hospital (RCWMCH). A pre-set standardised grading system for positive reactions was used see (22).

MARKERS OF SOCIO-ECONOMIC STATUS

The questionnaire captured demographic and socio-economic details of the participants. Epidemiological studies have used many socio-economic measures that may affect health in different pathways. We applied the widely used proxy variables that indicate SES including; parental highest education level, total household income, and employment status. Parental education was captured under primary, secondary and tertiary or college level with the highest level captured between the parents or guardians. Further educational classification was done into primary/secondary school and higher education qualification for analysis. Mothers reported the total household income earned, the total number of people living in the household as well as their employment status. Parents self-reported the child's ethnicity based on the dominant population groups in South Africa (Stats SA population groups) i.e. Black African, White/Caucasian, Coloured/ Mixed race and Indian/Asian.

MAIN OUTCOMES

Both participants and non-participants were asked about a history of current or past allergy to capture "self-reported comorbid allergic conditions". Subjects with evident clinical signs of allergy were captured as "confirmed clinical comorbid allergy" and those falling into either of the two groups were reported as having "any form comorbid allergy".

Definitions of food sensitisation and food allergy in the SAFFA study and for this study

- Low level sensitisation: 1 or more SPT with wheal size ≥1mm greater than negative control.
- Moderate level sensitisation: 1 or more SPT with wheal size ≥3mm greater than negative control.
- High level sensitisation: 1 or more SPT with wheal size ≥7mm greater than negative control.
- FA IgE mediated: positive SPT or a history of recent anaphylactic reaction to food with high SPT greater than the previously published 95% PPV or a positive OFC.

ETHICS

Ethical approval for this study was attained from the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee. Signed informed consent was obtained from the participants' parent/guardian to participate in the study as well as for the OFC where required.

DATA HANDLING & ANALYSIS

A Microsoft Access database was utilized to capture the questionnaire data collected from the participants and non-participants. Pivot tables were used to clean the data which was analysed using STATA version 14.1 (24) with statistical data conducted according to variable type (continuous or categorical). Chi-square test/Fisher's exact and the Z-tests were used to determine statistical difference between variables and proportions respectively with a P-value of ≤ 0.05 denoting statistical significance.

RESULTS

PARTICIPANT CHARACTERISTICS

The sample analysed 739 children from a total of 764 possible eligible children. The remaining 25 were either absent in the childcare facilities on the study day or not approached by study staff which could have contributed to possible selection bias in the sample. There was a high participation rate of 96.7% (739/764) with 19 completed non-participant questionnaires and 6 incomplete participant questionnaires added to the non-participant list. In the completed 739 participants, the median age was 26 months (IQR 21; 31 months). Half (394/739; 53%) were male. Between participants and non-participants regarding a history of a first-degree relative (i.e. mother, father and siblings), there was no significant difference in asthma (120/739 vs. 2/25: p=0.25), hay-fever (256/739 vs. 7/25: p= 0.51), eczema (111/739 vs. 3/25: p= 0.68), FA (34/739 vs. 2/25: p= 0.42) or any allergy (348/739 vs. 8/28: p=0.14).

The population demographics are displayed in Table 1. The median number of people in a household is 4. Grouping into tertiles revealed most households (45.2%) had 4-5 total people in a household. Most

parents of the participants attained secondary and tertiary education (416/739 (56.3%) & 310/739 (42%)) compared to 8/739 (1.1%) and 5/739 (0.7%) with primary and no formal education respectively. Most parents were employed (63.9%) with more fathers (81.6%) compared to mothers (73.9%). The study also analysed sensitization as a continuous variable that was generated to be an addition of all the SPT results per participant giving a cumulative SPT result from sensitized individuals.

174 **Table 1: Participants demographics**

Variable	(n = 739)	(%)	
Median Age (yrs.)	26; IQR (21-31)		
Sex	F: 345 M: 394	46.7 53.3	
Ethnic origin - Black African - Coloured/Mixed race - White/Caucasian	 387 278 74	 52.4 37.6 10	
Number of occupants in the household - 2-3 people - 4-5 people - 6 & more people	Median 4 196 334 209	IQR (3-6) 26.5 45.2 28.3	
Highest level of Parental Education - No formal education - Primary education - Secondary education - Tertiary education	 5 8 416 310	 0.7 1.1 56.3 42	
Maternal employment status - Student - Unemployed - Employed - Don't know	 51 135 546 7	 6.9 18.3 73.9 1.0	
Paternal employment status - Student - Unemployed - Employed - Don't know	 24 72 603 40	 3.2 9.7 81.6 5.4	
Combined Parental Employment status - Both Unemployed - One Unemployed - None Unemployed	 24 146 525	 3.5 21.0 75.5	
Monthly household income distribution - R1 - R1600 - R1601 - 3200 - R3201 -6400 - R6401 - 12800 - R12801 - 25600 - R25601 - 51200 - R51201 - 102400 †Minimum R310 , Max 100000, median R6100 IQR R2700-R17000	 121 111 140 127 139 84 17	 16.4 15.0 18.9 17.2 18.8 11.4 2.3	
Prevalence of sensitization & Food Allergy		%	95% CI
- SPT 1 - SPT 3 - SPT 7 - Oral Food Challenge Positive	91 71 33 18	12.3 9.6 4.5 2.4	10.0-14.9 7.6-12.0 3.1-6.2 1.4-3.8

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SENSITIZATION PREVALENCE

There was a significantly higher prevalence of sensitization in male infants at SPT≥1mm (14.7%; p=0.03), ≥3mm (12.2%; p=0.01) and ≥7mm (5.8%; p=0.05) than in female infants (9.6%, 6.7% and 2.9% respectively). Although more males (13; 72.2%) were likely to have positive OFC than females (5; 27.8%), the differences were not statistically significant p=0.10. Of the total 739 participants in the sample, 91 were sensitised to 1 or more foods, with 648 negative for all foods (87.7%). A proportion of 12.3%, 9.6% and 4.5% participants were sensitized at SPT≥1mm, ≥3mm and ≥7mm degree of sensitization respectively (Table 2). Only egg, peanut and cow's milk were detected at 7mm with most sensitization noted (27 participants: 3.7%; 95% CI 2.4-5.3) to fresh hen's egg. There were no adverse reactions to the skin prick tests observed in any of the participants.

FA PREVALENCE

All children with FS and no exposure or not clearly tolerant on history underwent OFCs. No subjects were defined as food allergic on the basis of a recent severe reaction with FS greater than the previously published 95% PPV. The overall food allergy prevalence confirmed with positive oral food challenges was 2.4% (18/739; 95% CI 1.4-3.8) of which 12 were allergic to 1 food, 3 allergic to 2 foods and 3 allergic to 3 foods. Of the food allergic children most reactions were to egg 14/739 (1.9%), 7 allergic to peanuts (0.9%) and 1 (0.1%) to cow's milk and fish.

193 **Table 2: Prevalence of Sensitization and Food Allergy**

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Food tested	**Prevalence sensitisation SPT (n=739)**		**Prevalence sensitisation SPT (n=739)**		**Prevalence sensitisation SPT (n=739)**		**Positive OFC IgE Mediated food allergy (n=739)**
	Any sensitization ≥1 mm		**≥3mm**		**≥7mm**		
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	**n (%) 95% CI**
Fresh egg	54 (7.3)	5.5-9.4	45 (6.1)	4.4-8.1	27 (3.7)	2.4-5.3	**14 (1.9)**
Egg white	45 (6.1)	4.5-8.1	29 (3.9)	2.6-5.6	2 (0.3)	0.0-1.0	
Peanut	37 (5.0)	3.5-6.8	26 (3.5)	2.3-5.1	8 (1.2)	0.5-2.1	**7 (0.9)**
Fresh peanut	29 (3.9)	2.6-5.6	19 (2.6)	1.6-4.0	9 (1.2)	0.6-2.3	
Fresh cow's milk	17 (2.3)	1.3-3.7	14 (1.9)	1.0-3.2	3 (0.4)	0.1-1.2	
Cow's milk	16 (2.2)	1.2-3.5	4 (0.5)	0.1-1.4	0	0-0.5	
Soya	16 (2.2)	1.2-3.5	6 (0.8)	0.3-1.8	0	0-0.5	**0**
Wheat	13 (1.8)	0.9-3.0	2 (0.1)	0-1.0	0	0-0.5	**0**
Fish	10 (1.4)	0.7-2.5	3 (0.4)	0.1-1.2	0	0-0.5	**1 (0.1)**
Hazelnut	10 (1.4)	0.7-2.5	3 (0.4)	0.1-1.2	1 (0.1)	0-0.8	**0**
Overall	91 (12.3)	10-15	71(9.6)	7.6-12	33 (4.5)	3.1-6.2	**18 (2.4) 1.4-3.8**

HOUSEHOLD SIZE VS SENSITIZATION AND FA

The household size ranged from 2 to 15 people with the median number of people in a household of 4. Household size did not have a particular trend or any significant relationship with sensitization at any level of SPT reactivity. Table 3 shows some differences in sensitizations that did not reach statistical significance by the use of the Pearson's Chi-square test. Cumulative skin prick test did not show any significant relationship with household number (K-Wallis chi-squared p=0.9).

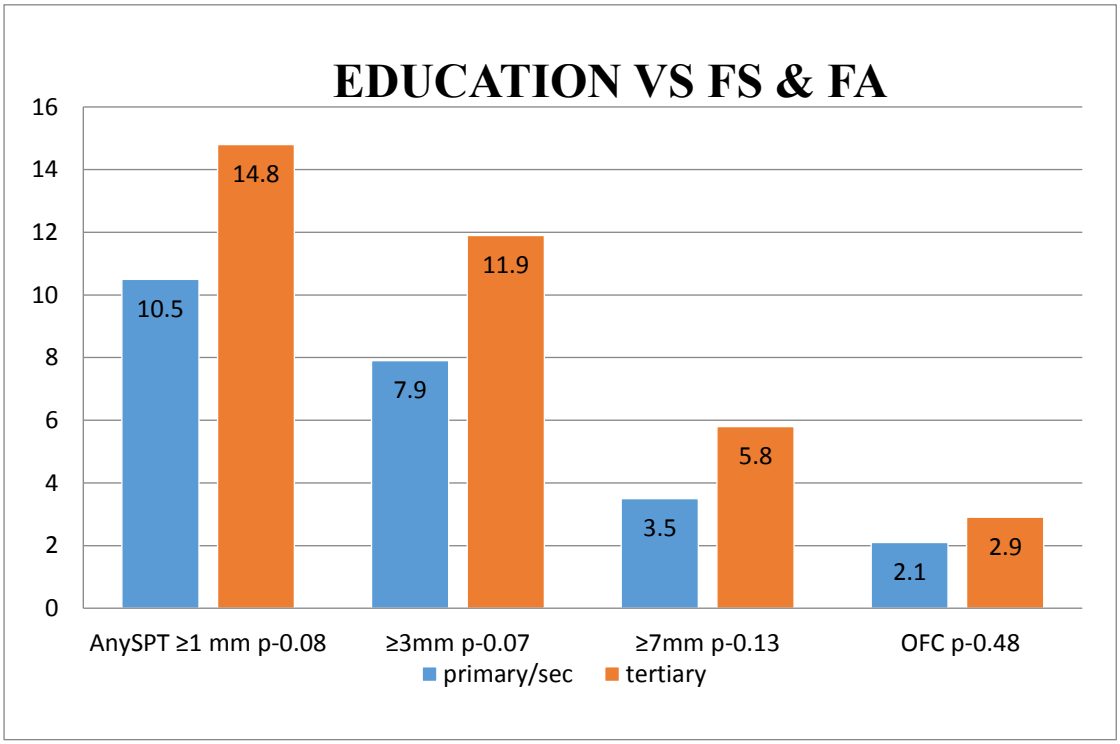
Table 3: Household number of people vs sensitization and FA

Number of people in a household	Any Sensitization ≥1 mm n (%)	≥3mm n (%)	≥7mm n (%)	Positive OFC n (%)
2-3 people n=(196)	26 (13.3)	22 (11.2)	8 (4)	3 (1.5)
4-5 people n=(334)	37 (11.1)	27 (8.1)	16 (5)	10 (3.0)
6 & more people (n= (209)	28 (13.4)	22 (10.5)	9 (4)	5 (2.4)
Total (n=739)	91 (12.3)	71 (9.6)	33(4.5)	18 (2.4)
Chi2 for trend P value	**0.95**	**0.83**	**0.92**	**0.59**

PARENTAL EDUCATION VS SENSITIZATION & PROVEN ALLERGY

Children with parents who have attained higher education had higher prevalence of sensitization compared to those with a lower education. A higher prevalence of sensitization at SPT≥1mm, ≥3mm and ≥7mm was apparent in children with parents who attained tertiary education (14.8%, 11.9%, 5.8% and 2.9%) compared to parents who attained primary/secondary education (10.5%, 7.9%, 3.5%, and 2.1%) respectively. However, these results did not achieve statistical significance (reported using the p values) see Figure 1. Cumulative skin prick test was not significantly associated with parental education (p=0.2 Wilcoxon rank-sum test).

Figure 1: Parental Education vs sensitization & proven food allergy



PARENTAL EMPLOYMENT VS SENSITIZATION & PROVEN FA

MATERNAL AND PATERNAL EMPLOYMENT STATUS VS SENSITIZATION & FA

The prevalence of sensitization seemed to be lower in children with maternal or paternal unemployment compared to both employed and student parents (Table 4). However, in all SPT levels together with the challenge proven cases none reached statistical significance using the Fishers Exact test (p=0.29, p=0.22, p=0.74 and p=0.28).

COMBINED PARENTAL EMPLOYMENT STATUS VS SENSITIZATION & FA

When assessing the effect of unemployment as a combined variable (i.e. both parents' unemployment status), the trend for all measures of FS and FA could be seen but was only significant for low level of sensitization (p=0.03) (Table 4). Cumulative skin prick test was not significantly associated with parental employment status (mother employment status p= 0.1, father employment status p= 0.3, and combined employment status p=0.1 Ranksum test).

225 **Table 4: Parental Employment status vs sensitisation and FA**

Mother Employment status	**SPT1 n (%)**	**SPT3 n (%)**	**SPT7 n (%)**	**OFC Positive n (%)**
Student **(n=51)**	7 (13.7)	4 (7.8)	1 (2.0)	3 (5.9)
Unemployed **(n=135)**	9 (6.7)	8 (5.9)	4 (3)	2 (1.5)
Employed **(n=546)**	75 (13.7)	59 (10.8)	28 (5.1)	13 (2.4)
Total **(n=732)**	91 (12.4)	71 (9.7)	33 (4.5)	18 (2.5)
Fishers **Pr Chi2**	**0.08**	**0.22**	**0.51**	**0.18**
†Expected values below 5 except for anySPT1, *there were 7 dropped were employment status was unknown				
Father Employment status	**SPT1 n (%)**	**SPT3 n (%)**	**SPT7 n (%)**	**OFC Positive n (%)**
Student **(n=24)**	4 (16.7)	3 (12.5)	0	1 (4.2)
Unemployed **(n=72)**	5 (6.9)	3 (4.2)	2 (2.8)	0
Employed **(n=603)**	74 (12.3)	58 (9.6)	28 (4.6)	15(2.5)
Total **(n=699)**	83 (11.9)	64 (9.2)	30 (4.3)	16 (2.1)
Fishers	**0.29**	**0.22**	**0.74**	**0.28**
† All expected values below 5, *of the 40 dropped, 2 had positive OFC reducing results to 16 instead of the usual 18 participants				
Combined Employment status				
Both Parents Employment status	**SPT1 n (%)**	**SPT3 n (%)**	**SPT7 n (%)**	**OFC Positive n (%)**
Both unemployed **(n=24)**	0	0	0	0
One unemployed **(n=146)**	12 (8.2)	9 (6.2)	6 (4.1)	2 (1.2)
None unemployed **(n=525)**	71 (13.5)	55 (10.5)	24 (4.6)	14 (2.7)
Total **(n=695)**	83 (11.9)	64 (9.2)	30 (4.3)	16 (2.3)
Fishers	**0.03**	**0.08**	**0.81**	**0.74**
†The total decreased after combining because 44 participants were excluded for cases of parent employment unknown †There were 3 people whose both parents employment was unknown.				

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HOUSEHOLD INCOME VS SENSITIZATION & PROVEN FA

Household income was treated as a continuous variable. Those with low level sensitization had a higher median monthly household income when compared those not sensitised (R8000 vs R6000 respectively). This difference is approaching statistical significance (Ranksum p-value 0.06). The difference achieved statistical significance at higher levels of sensitisation i.e. SPT>3mm (R9500 vs R6000: p-value = 0.02) and SPT>7mm (R12000 vs R6000: p-value = 0.02) (see Table 5).

Table 5: Monthly household income vs sensitization & proven FA

Sensitisation cut-offs	**Mean monthly income**		
	SPT≥1	**SPT≥3**	**SPT≥7**
Sensitisation ≥ than cut-off	R8000	R9500	R12000
Sensitisation ≤ than cut-off	R6000	R6000	R6000
Ranksum P value	**0.06**	**0.02**	**0.02**

No difference was observed in median monthly household income in children with FA (R 7500) than those without FA (R 6000) although the trend was in the same direction. Cumulative skin prick test tests were not significantly associated with monthly household income (Ranksum p-value= 0.4).

ETHNICITY VS SENSITISATION AND FA

There were no significant differences in sensitization patterns between ethnic groups (Table 6).

239 **Table 6: Sensitisation and food allergy patterns and ethnicity**

Ethnicity	Any Food N (%)	Egg N %	Fresh egg N %	Peanut N %	Fresh peanut N %	Cow's milk N %	Fresh cow's milk N %	Soya N %	Wheat N %	Fish N %	Hazelnut N %	Positive oral food challenge
	≥1 mm ≥3mm ≥7mm	≥1 mm ≥3mm ≥7mm	≥1 mm ≥3mm ≥7mm	≥1 mm ≥3mm ≥7mm	≥1 mm ≥3mm ≥7mm	≥1 mm ≥3mm ≥7mm	≥1 mm ≥3mm ≥7mm	≥1 mm ≥3mm ≥7mm	≥1 mm ≥3mm ≥7mm	≥1 mm ≥3mm ≥7mm	≥1 mm ≥3mm ≥7mm	
Black African (n=387)	45 (11.6)	24 (6.2)	32 (8.3)	19 (4.9)	15(3.9)	5 (1.3)	7(1.8)	7 (1.8)	5(1.3)	3 (0.8)	5 (1.3)	9 (2.3)
	35 (9.0)	14 (3.6)	27 (7.0)	13 (3.4)	12(3.1)	2 (0.5)	6(1.6)	4(1.0)	1(0.3)	0	2 0.51)	
	15 (3.9)	0	14 (3.6)	3 (0.8)	6(1.6)	0	1(0.3)	0	0	0	1(0.3)	
Mixed race (n=278)	40 (14.4)	17 (6.1)	18 (6.5)	17 (6.1)	13(4.7)	10 (3.6)	9(3.2)	9 (3.2)	8(2.9)	7 (2.5)	5(1.8)	8 (2.9)
	30 (10.8)	13 (4.7)	14 (5.0)	12 (4.3)	7(2.5)	2 (0.7)	7(2.5)	2 (0.7)	1(0.4)	3 (1.1)	1(0.4)	
	14 (5.0)	2 (0.7)	10 (3.6)	5(1.8)	3(1.1)	0	1(0.4)	0	0	0	0	
Caucasians (n=74)	6 (8.1)	4 (5.4)	4 (5.4)	1 (1.4)	1(1.4)	1 (1.4)	1(1.4)	0	0	0	0	1 (1.4)
	6 (8.1)	2 (2.7)	4 (5.4)	1(1.4)	0	0	1(1.4)	0	0	0	0	
	4 (5.4)	0	3 (4.1)	0	0	0	1(1.4)	0	0	0	0	
Total ≥1 mm	**91 (12.3)**	**45 (6.1)**	**54 (7.3)**	**37 (5.0)**	**29 (3.9)**	**16 (2.2)**	**17 (2.3)**	**16 (2)**	**13 (1.8)**	**10 (1.4)**	**10 (1.4)**	18 (2.4)
≥3mm	**71 (9.6)**	**29 (3.9)**	**45 (6.1)**	**26 (3.5)**	**19 (2.6)**	**4 (0.5)**	**14 (1.9)**	**6 (0.8)**	**2 (0.3)**	**3 (0.4)**	**3 (0.4)**	
≥7mm	**33 (4.5)**	**2 (0.3)**	**27 (3.7)**	**8 (1.1)**	**9 (1.2)**	**0**	**3 (0.4)**	**0**	**0**	**0**	**1 (0.1)**	
Difference betweeen ethnic groups by SPT category	0.29† 0.68† 0.65‡	1.00 0.75 0.33	0.55 0.60 0.92	0.25 0.56 0.41	0.48 0.38 0.70	0.12 1.00 1.00	0.52 0.73 0.33	0.22 1.00 1.00	0.21 1.00 1.00	0.15‡ 0.12‡ 1.00	0.72 1.00 1.00	0.83
SumSPT Ranksum p 0.4												

DISCUSSION

This study demonstrated that higher socio-economic status may be a risk factor for sensitization and food allergy in Cape Town children. Under the SAFFA study this secondary data analysis study is the first to investigate the relationship between socio-economic factors and the prevalence of FS and FA in an unselected population of African children. The study investigated household size, parental education, parental employment status, and total household income as proxy socio-economic variables. Highest risk for FS and FA was found in children with employed parents and in those from homes with higher household income. Household size showed no association with FS and FA. There were no significant differences in sensitization patterns between ethnic groups.

The overall sensitization prevalence in the study at SPT≥1mm to any food was 12.3%, at SPT≥3mm 9.6%, at SPT≥7mm 4.5% and challenge proven IgE mediated FA was 2.4%. Higher prevalence of sensitization was observed in male infants at SPT≥1mm (14.7%; p=0.03), ≥3mm (12.2%; p=0.01) and ≥7mm (5.8%; p=0.05) compared to female infants (9.6%, 6.7% and 2.9% respectively). Although not statistically significant, more males (72.2%) were likely to have positive OFC than females (27.8%). Sex is an important risk factor for FS and FA as reflected in our findings similar to previous studies (22,25,26).

This study's main strength lays in analysing the burden of disease at a point in time providing a snapshot of the prevalence of food allergies as well as the different exposures in young children across urban Cape Town. The sample involved in the study was reflective of the entire Cape Town infant population. Even though the sample was reflective of the Cape Town metropole population, our findings cannot be generalised to the entire South African children population. Due to the cross-sectional design of the study, the associations reveal a relationship between SES and the health outcome variables of interest but do not prove causality. The inverse social gradient in allergies seen in people of higher SES may be influenced by reporting bias as higher SES people have more resources to access health care and may be more likely to report allergies. However the outcome variables of FS and FA are clearly defined to exclude this explanation for the reporting bias.

The underlying premise of this study is that lower socio-economic status is protective from FS and FA development. Findings from a UK systematic review showed that lower socioeconomic position is associated with a higher prevalence of asthma but lower prevalence of allergies in general (27).

Parental education as a risk factor did not yield statistically significant results in this study although there was a trend showing a positive association. Children with parents who attained higher education had higher prevalence of sensitization compared to those with a lower education. A similar trend was observed in Italian children but focusing on comparing fathers' highest educational level between those with and without sensitisation (28). Our study however, captured highest parent education between the two parents/guardian and did not differentiate between parents' education.

Maternal education may be a better predictor for allergic outcomes in South African children. Feeding practices and food exposures are directly linked to a mother's SES (29), more so with education and possibly cultural influences in the South African context. Mothers are the usual primary care givers and their knowledge and awareness about perceived risks for food allergy might influence child rearing practices that could affect food sensitisation and allergy. Future research should look at the maternal education variable for associations with food allergy outcomes.

Household size showed no relationship with FS/FA. However, in this study; if the mechanism of household size is working through the hygiene hypothesis then the number of older siblings would be more important than the total household size (17,28,30). It is believed that the more siblings one has, the more exposure to infectious agents as proposed by the hygiene hypothesis(31). This analysis is still to be done in another sub-study of the SAFFA cohort.

Recent studies (28,32) have found higher FS and FA in higher socioeconomic classes with employment status and income showing trends of associations. Parents who are employed generally have high education which may mean more disease awareness and most likely more reporting. In this study most parents were employed (63.9%) with more fathers (81.6%) compared to mothers (73.9%). Employment showed significance at lower levels of sensitization with unemployment being the variable of interest. If employment is the main source of income within a household, unemployment may indicate having

less money which directly affects the family's diet. Less money changes one's dietary patterns leading to the consumption of diets with more carbohydrates and less protein, with less advanced glycation end-products (that may stimulate the innate immune system) and less junk food (27) which could have protective effects against FS and from having FA.

In this study, household income and employment status yielded a negative trend of influence making unemployment a variable of importance. Household income may be interlinked with employment. Less money potentially means poorer housing leading to increased exposure to more environmental allergens and less clean environments that are protective from having allergies as postulated by the hygiene hypothesis (17). In addition, without an income parents cannot afford child day care facilities resulting in children playing outdoors thereby spending more time in sunlight and increasing exposure to environmental factors that potentially protect them from FS and FA. These and other exposures or confounders will be explored in other sub analyses of the cohort.

There were no ethnic differences in sensitization patterns in the cohort. In the USA race was found to be a risk factor for FS and FA that may have been confounded by income (19). It is also important to note that there may or may not be environmental influence that has its effects via epigenetic mechanisms only in certain genotypes but in our study, environmental effects appeared far more important than ethnicity (30).

The South Africa black population is undergoing rapid urbanisation which means new 'westernised' diets and lifestyles, explaining the existing rise in FS/FA prevalence across the ethnic groups (7,13,22,33). It would therefore be important to investigate disparities and inequalities that exist in health care among children from different socioeconomic backgrounds in order to better understand and control FS and FA factors related to socio-economic status.

CONCLUSION

This study revealed a relationship between SES and FS and FA development. There was no relationship between household size and FS/FA. There was a relationship between education and FS/FA though the results did not achieve statistical significance. For employment status, unemployment was important showing a positive relationship which was further confirmed by income where significantly higher levels of sensitization appeared in children from homes with a higher median monthly income. Finally, there was no relationship between ethnicity and FS/FA. In this study, socio-economic status is not a direct cause for FS/FA, rather it indicates the influence of environmental factors at play to either reduce or increase risk. Future studies should prospectively explore which environmental factors influence susceptibility to FS/FA with in-depth analysis of phenotypic and exposure data.

AUTHOR'S CONTRIBUTION

Lelani Hobane was mainly involved in the SAFFA study data collection processes (participant recruitment), data cleaning and entry into the database, statistical analysis and drafting of manuscript.

AUTHOR'S INFORMATION

Lelani Hobane is a University of Cape Town Masters student in the department of School of Public Health and Family Medicine.

ACKNOWLEDGEMENTS

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Potential conflicts of interest-The author declares no competing interests.

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PART D: APPENDICES

APPENDIX 1: ETHICS APPROVAL FOR SAFFA STUDY

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

13 March 2012

HREC REF: 038/2012

Dr M Levin
Allergy Division
Red Cross War Memorial Children's Hospital

Dear Dr Levin

PROJECT TITLE: A PROSPECTIVE, DESCRIPTIVE STUDY OF IgE-MEDIATED FOOD ALLERGY IN AN UNSELECTED POPULATION OF SOUTH AFRICAN CHILDREN AGED 12-36 MONTHS.

Thank you for responding to the issues raised by the Faculty of Health Sciences Human Research Ethics Committee in your letter dated 1st March 2012.

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

Approval is granted for one year till the 30th March 2013.

Please submit a progress form, using the standardised Annual Report Form (FHS016), if the study continues beyond the approval period. Please submit a Standard Closure form (FHS010) if the study is completed within the approval period.

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

Please quote the HREC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

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) and Declaration of Helsinki 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.

APPENDIX 2: ETHICS APPROVAL LELANI HOBANE HREC/REF 846/5015

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

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
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Website: www.health.uct.ac.za/fhs/research/humanethics/forms

17 January 2016

HREC/REF: 846/2015

Prof M Levin
Allergy Division-5th Floor-ICH Building
Paediatrics & Child Health
Rondebosch

Dear Prof Levin

PROJECT TITLE: THE INFLUENCE OF SOCIO-ECONOMIC STATUS [SES] ON THE PREVALENCE OF FOOD SENSITIZATION AND FOOD ALLERGY IN CHILDREN 12 TO 36 MONTHS IN URBAN CAPE TOWN SOUTH AFRICA (Masters candidate- L Hobane) sub-study linked 038/2012

Thank you for your response submitted to the Faculty of Health Sciences Human Research Ethics Committee dated 07 January 2016.

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 January 2017.

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 following Masters Candidate Lelani Hobani will also be involved in this study.

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

Please quote the HREC REF in all your correspondence.

Yours sincerely

pp **PROFESSOR M BLOCKMAN**
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

846/2015

APPENDIX 3: ANNALS OF ALLERGY ASTHMA & IMMUNOLOGY JOURNAL INSTRUCTIONS

Annals
of Allergy, Asthma & Immunology
OFFICIAL PUBLICATION OF THE AMERICAN COLLEGE OF ALLERGY, ASTHMA & IMMUNOLOGY

Information for Authors

Article Types
The *Annals* publishes original articles, reviews, editorials, letters, correspondence, and many other categories of articles. Topics of interest include all subjects that relate to the practice of allergy-immunology. The most frequent published types are described herein.

Original Articles
Original articles should have a structured abstract of no more than 255 words with the following separate headings: Background, Objective, Methods, Results, and Conclusion. A maximum of 12 keywords, 60 references, and a combined total of 8 tables and/or figures are allowed. Text should not exceed 4,000 words and should be organized into the following separate headings: Introduction, Methods, Results, and Discussion.

Letters
Letters are the primary means for an author to communicate brief clinical or scientific observations to our readership. Letters should **NOT** begin with the salutation "To the Editor", are limited to 1,000 words, one figure **OR** table, and 10 references.

Correspondence
Correspondence are brief opinions about recently published articles in the *Annals* and other current topics of general interest to our readership. Correspondence may or may not have a response, should begin with the salutation "To the Editor" and are limited to 500 words and 10 references. Figures and tables are not allowed for this category. Correspondence submissions are reviewed in the Editorial Office and do not undergo outside peer review. Correspondence discussing a recently published *Annals* article will generally be considered only if it is received within 2 months of the article's publication date. Exceptions to this policy must have the approval of the Editor-in-Chief. The previously published article should be cited in the text.

Invited Articles
The following article types require approval by the Editor-in-Chief before invitation. Authors who have an idea for one of these manuscript types are encouraged to submit a brief description to the Editor-in-Chief via email (annallergy@uncedu). Only those proposals that are approved by the Editor-in-Chief can be submitted and considered for publication. Exceptions to the guidelines for these features (i.e. word count, references, etc) should be approved by the Editor-in-Chief prior to submission and be noted in the Author Comments section during the submission process.

Review Articles
Review articles address a specific question or issue that is relevant for clinical practice and provide an evidence-based, balanced, patient-oriented review on a focused topic, either clinical or basic science. Because of space limitations, the review is not intended to be exhaustive—it should be directed. These articles should focus on current advancements in the field, and should be based on the latest "cutting-edge" clinical, translational, or basic science.

Review Articles should have a structured abstract of no more than 255 words with the following headings: Objective, Data Sources, Study Selections, Results, and Conclusion. A maximum of 12 keywords and 60 references are allowed. Text should not exceed 4,000 words and should be organized into the following sections: Introduction and Conclusion.

Perspectives
On occasion, important topics of general interest to the readership are identified that warrant commentary and discussion by a specific expert. The Editor-in-Chief will invite such an expert to offer his/her perspective on a specific topic. Perspectives are limited to 2,000 words and 20 references. These articles do not have an abstract.

MOC-CME Review
MOC-CME Review articles offer physicians a process to keep skills and knowledge current in a changing field where vigilance is key to practicing state-of-the-art specialty medical care. These articles are designed to help fulfill the requirements for Continuing Medical Education (CME) credit required for the maintenance of certification (MOC) program by the American Board of Allergy and Immunology. Text should not exceed 2,000 words and should be organized into the following sections: Clinical Vignette (case presentation, up to 750 words), Introduction (a brief description of the pathophysiology fundamentals to the case, a clinical context of the case in terms of its uniqueness for the literature), and Conclusion (relevance to the practicing clinician including the principles of the case that would impact provider practice behavior). A maximum of 12 keywords and 20 references are allowed, and articles must include 2 "behaviorally" written learning objectives. A minimum of 5 multiple-part questions (with 5 answers each) related to the material must be included, along with a rationale and a maximum of 3 references for each question.

Editorials
Guest Editorials are usually solicited to accompany certain special articles, CME review articles, and original articles that are published in the *Annals*. Text should not exceed 1,000 words and 10 references. Guest Editorials should reference the previously published article in the *Annals*.

CME Review Articles
CME Review articles are offered as part of a CME endeavor and are intended to be directed rather than exhaustive reviews of a specific clinical topic. The intent is to synthesize an overview of that topic with reference to the most current literature to allow the reader to better understand for the ultimate goal of changing practice behavior. Text should not exceed 4,000 words and should be organized into the following sections: Introduction and Conclusion. A maximum of 12 keywords and 60 references are allowed, and articles must include 2 "behaviorally" written learning objectives. A minimum of 5 multiple-part questions (with 5 answers each) related to the material must be included, along with a rationale and a maximum of 3 references for each question.

Clinical Perspectives
Clinical Perspectives are evidence-based reviews of topics relevant to the practicing allergist/immunologist. Clinical Perspectives are limited to 2,000 words, 20 references, and a combined total of 8 tables and/or figures. Text should be organized into the following sections: Clinical Problem, Strategies and Evidence (to include evaluation and symptomatic versus specific therapy, when available), Areas of Uncertainty, Guidelines, and Conclusions and Recommendations. These articles do not have an abstract.

Clinical Pearls
Clinical Pearls focus on an unusual or unique physical finding, a diagnostic dilemma, or an unexpected clinical outcome. These are NOT classic case reports, rather a specific, point-by-point communication that should provoke further clinical thought by the reader. Clinical Pearls are limited to a maximum of 1,000 words, 10 references, and a combined total of 8 tables and/or figures.

Challenging Clinical Cases
Challenging Clinical Cases consider the step-by-step process of clinical decision making. Cases are presented in stages (in boldface type) to simulate the typical way such information emerges in clinical practice. The author responds (in regular type) as new information is presented, sharing his/her reasoning with the reader. Challenging Clinical Cases are limited to 2,500 words, 20 references, and a combined total of 8 tables and/or figures.

Book Reviews
Short reviews of recently published books of central interest to our readers are published only by invitation from the Editor-in-Chief. Review text should not exceed 250 words and must include the title of the book, the author, publisher and address, edition and year of publication, availability in hard or soft copy, the number of pages, the price and ISBN#. Books for review should be sent to the *Annals* Editorial Office located at University of Mississippi Medical Center, 2500 North State Street, N416, Jackson, MS 39216.

Manuscript Submission
Manuscripts should be submitted online via the *Annals of Allergy, Asthma & Immunology* online manuscript submission and peer review system. **NOTE:** Only manuscripts submitted through this medium will be considered for review.

APPENDIX 4: SAFFA PARENT INFORMATION SHEET AND CONSENT FORM

This Information Sheet has been written to help you decide if you would like you and your child to participate in the SAFFA Study. Please read this Information Sheet carefully and feel free to ask questions to any of the staff members or contact Dr Maresa Botha on 021 6585779 or 0766240860. By signing the *Consent Form*, you indicate that you have read and understood this Information Sheet and that you give consent for your child to take part in the SAFFA Study on the terms set out in this Information Sheet. You will be given a copy of this Information Sheet to keep as well as a copy of the consent you've signed.
Before you decide you need to understand why the research is being done and how you will be involved. Please read all the sections carefully and feel free to ask questions to members of staff if you wish. Your participation in the study is entirely voluntary and your child's care will not be affected if you decide not to take part.

Why is this study being performed?
Studies in other parts of the world, especially in Europe and the USA, have found that many children have allergies to certain foods. Food allergies are very common especially in children between 1-3 years. In some children food allergies may cause problems such as an itchy rash, breathing difficulties or even collapse soon after they eat the food they are allergic to. This can be a medical emergency. In other children, eating the food they are allergic to may cause their eczema to get worse many hours to days after eating the food. It is important to know about such food allergies so that the child can get the right feeding advice.

Previously we had thought that food allergies were *not* very common in the South African children, and especially rare in Black South African children. We are trying to find out how many South African children have food allergies, to see whether it is as common as in the overseas studies, or whether it is perhaps not common here, and what the factors are that may be associated with food allergy in this country.

Why has your child been invited to take part?
We are inviting 1200 children between 12 months and 3 years who attend crèches/Childhood development centeres(CDCs) in Cape Town to take part in the study**.**

Do you have to take part?
You are not in any way obligated to take part in our study. Taking part is entirely voluntary. Your child will only be entered with your permission and signed consent. Your child's medical care will not be affected in any way whatever you decide to do. If you say yes to be part of the study and later change your mind, you can do this without any consequences to your child or his/her medical care.

What will happen if you decide to take part?
1. We will describe the study to you and answer any questions you may have. . We will ask you to sign a consent form if you decide to take part.

2. Your child will be seen by one of the study team members and you will be asked questions about the child's medical history and diet. We will also ask you about any allergies you may know of and some questions about allergies in your family. If there is anything from what you tell us that makes us think that your child might have had a reaction to food in the past, we will ask you to come to Red Cross Children's Hospital where your child will have a Skin Prick Test, some blood tests and an Oral Food Challenge done. We will explain these to you should it be necessary. If there is no concern from what you tell us about food allergies, we will do a Skin Prick Test here in the Clinic. If the skin prick test shows no reaction, your child will have no further test performed.

3. We will examine your child to see if we can find any evidence of eczema, hay fever or asthma.

4. You will be seen by a nurse who will do skin prick tests for 7 common foods to look for signs of possible allergies (egg, milk, peanut, tree nuts, wheat, soya and fish). For the Skin Prick test we will put small drops of special mixtures containing food proteins on to the child's arm or back and gently scratch the skin with a sharp lancet and wait for 15 minutes to see if there is a reaction on the skin. Skin prick tests are not very painful – they feel a bit like a mosquito bite. The arm may become itchy, and if this happens we will give your child a cream to put on or a medicine to drink (both antihistamines). Very rarely do children get more serious reactions like a wheeze or a more serious allergic reaction. Even though these reactions are extremely rare (about one in a 1000 children will have a more severe reaction) we are experienced to recognise any problems and will have emergency medicine with us to give immediately should your child have any signs of a more serious reaction. After the Skin Prick test is done you will need to wait for 15 minutes to see what the result is. If there is any reaction it may indicate that your child is sensitive or maybe even allergic to that particular food. We will then arrange for your child to have further tests (an oral food challenge and blood and stool tests) done at Red Cross Children's Hospital.

5. If your child has a history or a skin prick test result that makes it likely that he/she has a food allergy, we will also do some blood tests and request samples of stool, urine and hair and a sample of breast milk from the child's mother, should she still be breastfeeding. Some of these tests are part of the routine care of a child with a possible food allergy. Other tests are for the purposes of our research study and will help us to look for risk factors that might cause food allergies.

   Part of our research study includes genetic analysis of the blood of some of our participants. This analysis will only be of factors related to allergic diseases and not of any other illnesses that can be investigated through genetic testing. Some of the bloods will be stored for future testing but once again only for research related to allergy diseases.

   The test samples and the information they contain will stay the property of the University of Cape Town and will not be sold for profit and will only be used for research that has been approved by the Human Research Ethics Committee of the University of Cape Town.

6. If there are any positive results for allergy tests your child may be asked to come to a hospital another day for a "food challenge." A food challenge involves coming in to hospital for the morning, and your child will be given very small amounts of the food to which they had a positive allergy test. This will be given under medical supervision to check for a reaction. We will then give bigger and bigger amounts of the food as long as there is no reaction. We will explain this in detail to you if your child needs a food challenge.

7. If we find that your child has a food allergy, we will arrange for you to see a dietician to give advice on avoiding the food; and we will give you a treatment plan and medications for an accidental allergic reaction. We will also arrange for you to be seen in the allergy clinic or the local hospital along with the history, results of your investigations and the challenge test.

How much time will you have to spend on the study?
We are hoping to perform all of the tests (questions and skin tests) on the same day over about ½ hour. If your child has taken antihistamine medicines in the previous few days we will need to arrange the skin tests for another day.

If your child needs a food challenge, this will be arranged for another day and will involve a half day visit to the hospital. If your child has a reaction during the food challenge they will need to stay a few hours longer so that we can watch them carefully. Very rarely children may need to be observed in hospital overnight if they have had a more severe reaction.

What about expenses and payment for the study?
You will not be paid for taking part in the study, but if you need to make any trips to the hospital for the study, we will pay travel expenses of R150 per day (or actual expenses should they be more than this).

What are the possible benefits of taking part?
The information from this study may help to improve our understanding of food allergies in South African children. It will be helpful to know if your child has food allergies so that we can try and avoid reactions to certain foods and refer you for follow up. It will also be helpful to know if your child is *not* allergic to foods as you can then use the food in the child's diet without worrying about it. Tests we will perform might show worm infection or exposure to toxins (e.g. pesticides). If we find these problems we will refer your child for treatment.

What are the possible disadvantages of taking part?
There is a very small risk of a reaction to skin tests but these will be performed in a safe environment by trained individuals. For those having blood tests there is a chance of temporary bruising and pain where the blood was taken. We will put a special local pain-numbing cream on the skin to numb where the needle goes in.

If your child needs a food challenge, there is a risk of an allergic reaction. If there is an allergic reaction, it is usually mild, such as a rash. In a small proportion of children having a food challenge (about one in ten) there may be a more severe reaction such as breathing difficulties, which we will treat immediately. We will give the foods starting in very small amounts, and the child will be closely watched between each dose to make sure we recognise any reactions early on. Your child will be in the hospital setting where all emergency treatment is available, so it is much safer than giving the food at home.

What if there is a problem?
You may at any stage decide to withdraw from the study. This will not affect any treatment your child is receiving. If you have any concerns about any aspects of the study, please speak to the researcher who will try and help you.
Should anything go wrong with your child during the study, you will be covered by the no-fault insurance offered by the University of Cape Town.

Confidentiality
Any information on your child will be kept strictly private, and if the information is published, we will not use any names. Thus you and your child will never be able to be identified by anyone except study staff. If your child has food allergy we will, however, refer you by name to the local health service for follow up.

Who has reviewed the study?
This study has been reviewed and approved by the University of Cape Town's research ethics committee.

Further information and contact details
If you need any further information at any stage, you can contact:
Dr Mike Levin: 021 6585111
Dr Claudia Gray: 021 6585111
Dr Maresa Botha: 0216585779
UCT Research Ethics Committee: Tel 021 406 6338 Fax 021 406 6411

Consent Form for Participation in the SAFFA Study

Crèche/(CDCs) name		PID	OOOO/XX
Child's Name		Child's Date of birth	
Mother's name		Name of guardian (if not mother)	
Physical Address		Telephone numbers	1. 2. 3.

This consent includes the following study procedures:	
Asking some health-related questions	YES/NO
Examining the child	YES/NO
Skin prick tests	YES/NO
Blood, urine, hair and stool tests if needed	YES/NO
Dust samples from the home if needed.	YES/NO
Oral Food challenge if needed	YES/NO
Blood to be stored for later genetic analysis related to allergy research and for the SOS-ALL collaboration **(see separate Parent Information Sheet)**	YES/NO
Using the health information gathered from the study in a confidential manner	YES/NO
Breast milk sample from the mother of the child. (Consent only to be signed by mother herself)	YES/NO
I understand that my participation is voluntary. If I refuse to permit my child to participate, or choose to withdraw my child at any anytime, I understand there will be no prejudice against me or my child by the doctors or hospital	
I have been given a copy of this form	
I (name of parent or legal guardian)_____ have been fully informed about the above study with its risks and benefits, and give permission for my child _____to participate in this study.	

Signature		Date	

For illiterate parents only:

Signature substitute (cross or finger print)……

Witness (name)……...

(Sign)……Date……..

I (study personnel name)……
have fully explained the nature and purpose of the above described study with its risks and benefits. I have answered all the questions to the best of my ability. I will inform the participant of any changes in the procedures or the risks and benefits should they change during the course of the study. I have given a copy of the consent form to the parents/guardian.

(Sign)……..Date……

APPENDIX 5: PARTICIPANT QUESTIONNAIRE

Participant details

Q1	Crèche/(CDCs) name		
Q2	Enrolment date	DD/MM/YYYY	
Q3	Study site	1 = Urban	2= Rural
Q4	Date of birth	DD/MM/YYYY	
Q5	Age at enrolment	00 months	
Q6	Sex	1= Male	2=Female
Q7	Weight	00.0 kg	
Q8	Height/Length	000 cm	

Q9 Immunisations

			Yes	No				Yes	No
Birth	**9.1**	BCG			14 weeks	**9.10**	RV(2)		
	9.2	OPV (0)				**9.11**	DTaPIPV/HiB(3)		
6 weeks	**9.3**	OPV (1)				**9.12**	HepB(3)		
	9.4	RV (1)				**9.13**	PCV7 or 13 (2)		
	9.5	DTaPIPV/HiB (1)			9 months	**9.14**	Measles vaccine		
	9.6	HepB (1)				**9.15**	PCV 7 or 13 (3)		
	9.7	PCV7 or 13(1)			18 months	**9.16**	DTaPIPV/HiB (4)		
10 weeks	**9.8**	DTaPIPV/HiB (2)				**9.17**	Measles Vaccine		
	9.9	HepB (2)							

Q10 Vaccination Status

1 = Complete		2 = Incomplete	

Q11 Paracetamol Exposure

Q11.1	Did your child have paracetemol or medicines containing paracetamol in the first year of life? (Panado, Calpol, Paramed)		0 = No	1 = Yes
Q11.2	If Yes, How old was your child when they first had paracetamol?		Months	999 = Don't know
Q11.3	If Yes, How often did your child have paracetamol on the first year of life?	1 = 1-10 days	2 = 10-20 days	3 = More than 20 days

Q12 Childhood infections

Has your child had any of the following childhood infections?									
		0 = No	1 = Yes	999 = don' t know			0 = No	1 = Yes	999 = don't know
12.1	Measles				12.5	Glandular Fever			
12.2	Mumps				12.6	Tuberculosis			
12.3	Rubella				12.7	Hepatitis			

12.4	Chickenpox				12.8	Other (please specify)			

Q13 Antibiotic and anti-helminthic exposure

13.1	Did your child have any antibiotics in the first year of life?	0 = no	1 = Yes	999 = Don't know	
13.2	If Yes, how old were they with the first course??	Months		999=Don't know	
13.3	How many courses did your child have in the first year of life?	1 = None	2 = 1 to 2 Courses	3 = 3 to 5 courses	4 = > 5 courses
13.4	Did your child have any antibiotics in the last 2 months?	0 = No	1 = Yes	999 = Don't know	

13.5	Has your child ever had medicines for worms?	0= No	1 = Yes	999=Don't Know
13.6	If Yes, at what age were they dewormed?	months		999=Don't know
13.7	If Yes, at what age did they last take anti worm medicines?	months		999=Don't know
13.8	Has your child had regular (yearly) medicine for worms?	0 = No	1 = Yes	999 = Don't know

Q14 Probiotic Exposure and *Amasi* Exposure (CHILD)

14.1	Did this **child** have probiotics in food or supplements in the first year of life?	0 = No	1 = Yes	999 = Don't know
14.2	**If Yes**, how old was this child when they first had probiotics?			Months
14.3	**If Yes**, How often did this child have probiotics in the first year of life?	1 = 1-10 days	2 = 10-20 days	3 = >20 days
14.4	**If Yes**, which probiotic product were they given?			

14.3	Has your **child** ever have **amasi**?	0 = No	1 = Yes	999 = Don't know
14.4	**If Yes**, how old was this child when they first had **amasi**?			Months
14.5	**If Yes**, how often does your child take amasi?	1 =	2 =	3 =

		Less than once a month	1-4 times per month	more than 4 times per month

Probiotic and *Amasi* exposure (MOTHER)

14.6	Did this child's mother have probiotics during pregnancy?	0 = No	1 = Yes	999 =Don't know
14.7	If Yes, How often did she use probiotics?	1 = 1-10 days	2 = 10-20 days	3 = >20 days
14.8	Which yes, which products did she use?			
14.9	Did this child's mother regularly have amasi during pregnancy? (more than once a month)	0 = No	1 =Yes	999 = Don't know

Q15 Delivery mode

Q15	How was this child born?	1 = Normal vaginal delivery	2 = Caesarean section	999 = Don't Know

Q16 Sunlight Exposure

How much time does your child spend outdoors on an average day? *(Add crèche daily average X5, to weekend total hours and divide by 7. Report to nearest 0.1)*	
Q16.1 Winter	**Q16.2 Summer**
00.0 hours	00.0 hours
999 = Don't Know	**999 =** Don't Know

Q17 Peanut exposure in pregnancy

17.1	Did this child's mother eat peanuts regularly (every week) during pregnancy?	0 = No	1 = Yes	999 = Don't know
17.2	Did this child's mother completely avoid peanuts during pregnancy?	0 = No	1 = Yes	999 = Don't know

Q18 Breastfeeding information

Q18.1	Was this child ever breastfed?	0 = No	1 = Yes	999 = Don't know
Q18.2	If Yes, up to what age was this child exclusively breastfed (i.e. no milk or other fluids via bottle nor given any solids)		Months	999 = Don't know
Q18.3			Months	999 = Don't know

	At what age did you completely stop breastfeeding this child?			Still breastfeeding
Q18.4	At what age did you first introduce any other milk (other than breast milk)		Months	999 = Don't know

Q19 Weaning foods

Q19.1	When did you first introduce solids into your child's diet?		Months	999=Don't know
Q19.2	Which three types of foods did you introduce first**?** *(see coding chart for food categories)*			

Q20 Exposure to Unpasteurised milk

Q20	Has this child ever had non-pasteurised (Fresh farm) milk?	0 = No	1 = Yes	999 = Don't know

Q21 Food exposure

Foods Eaten		**Ever Eaten**			**Age first eaten**				**Still eating regularly** *(once a month or more)*		
21.1	**Peanut** e.g. peanut butter, peanut oil, peanuts in cookies or chocolates	**21.1.1**	0 = No	1 = Yes	**21.1.2**		months	999 = don't know	**21.1.3**	0 = No	1 = Yes **If yes please continue with 21.1.4**

If yes to 21.1.4

Please try an remember how many times your child ate the following peanut containing foods in the last day and *week*

Type of peanuts consumed	**Number of times per day**	**Number of times per week**	**Usual amount**			**Total amount in grams**
Peanut butter on bread				Thin slices	**21.1.4**	
				Thick slices	**21.1.5**	
Peanut butter in porridge				Teaspoons	**21.1.6**	
Raw/boiled peanuts				Handfuls	**21.1.7**	
Roasted peanuts				Handfuls	**21.1.8**	
Peanuts in chocolate or biscuits					**21.1.9**	
Total amount of peanut consumed in the last week					**21.1.10**	

21.2	**Other nuts** e.g. Cashew, hazelnut, brazil nut, almonds, walnuts, pistachio, macadamia in chocolate and cookies or cakes and breads	**21.2.1**	0 = No	1 = Yes	**21.2.2**		months	999 = don't know	**21.2.3**	0 = No	1 = Yes

21.3	**Cow's milk products** e.g. fresh milk, cheese, yoghurt, cream	**21.3.1**	0 = No	1 = Yes	**21.3.2**		month s	999 = don't know	**21.3.3**	0 = No	1 = Yes
21.4	**Cow's milk formula** e.g. Nan, Lactogen, Novolac, S26, Infacare, Pelargon	**21.4.1**	0 = No	1 = Yes	**21.4.2**		Month s	999 = don't know	**21.4.3**	0 = No	1 = Yes
21.5	**Soya products** e.g. soya mince, soya sauce, tofu, baby foods, soya in bread	**21.5.1**	0 = No	1 = Yes	**21.5.2**		Month s	999 = don't know	**21.5.3**	0 = No	1 = Yes
21.6	**Soya milk products** e.g. Infasoy, Isomil, Infacare	**21.6.1**	0 = No	1 = Yes	**21.6.2**		Month s	999 = don't know	**21.6.3**	0 = No	1 = Yes
21.7	**Hen's egg** e.g. boiled, scrambles eggs, omelettes	**21.7.1**	0 = No	1 = Yes	**21.7.2**		Month s	999 = don't know	**21.7.3**	0 = No	1 = Yes
21.8	**Wheat** e.g. cereal (Wheetabix, All Bran, Tasty Wheat), bread or pasta, cakes, rusks, couscous, semolina	**21.8.1**	0 = No	1 = Yes	**21.8.2**		Month s	999 = don't know	**21.8.3**	0 = No	1 = Yes
21.9	**Fish (excluding shellfish)** Hake, snoek, sardines,pilchards, tuna, kingklip, salmon etc and fish products: Fish paste(Redro), Worcester sauce, fish sauce	**21.9.1**	0 = No	1 = Yes	**21.9.2**		month s	999 = don't know	**21.9.3**	0 = No	1 = Yes

Q22 Food Reactions

22.1 PEANUTS				
22.1.1	Has your child ever had any of these reactions below to peanuts or food containing peanuts		0 = No	1 = Yes
22.1.2	If yes, which of the following reactions has this child had? (you can circle more than one)			
	1= none	**6**= tight throat	**11**=shock/low blood pressure	
	2= itchy Rash	**7**= wheeze	**12**= collapse/loss of consciousness	
	3=swelling(face/lips/eyes)	**8**= vomiting	**13** = worsening of eczema	
	4= flushing	**9**= diarrhoea		
	5= itchy mouth/throat	**10**= blue lips		
22.1.3	If Yes, how old was this child when he/she had the first reaction?			Months

22.1.4	If yes, how long after the eating the food did the reaction occur?	1 = < 1 hour	2 = 1-24 hours	3 = >24 hours
22.1.5	If yes, was this reaction confirmed by a doctor?	0 = No	1 = Yes	

22.2 OTHER NUTS				
22.2.1	Has your child ever had any of these reactions below to other nuts or food containing nuts other than peanuts		0 = No	1 = Yes
22.2.2	If yes, which of the following reactions has this child had? (you can circle more than one)			
	1 = none	**6** = tight throat	**11** =shock/low blood pressure	
	2 = itchy Rash	**7** = wheeze	**12** = collapse/loss of consciousness	
	3 =swelling(face/lips/eyes)	**8** = vomiting	**13** = worsening of eczema	
	4 = flushing	**9** = diarrhoea		
	5 = itchy mouth/throat	**10** = blue lips		
22.2.3	If Yes, how old was this child when he/she had the first reaction?			Months
22.2.4	If yes, how long after the eating the food did the reaction occur?	1 = < 1 hour	2 = 1-24 hours	3 = >24 hours
22.2.5	If yes, was this reaction confirmed by a doctor?	0 = No	1 = Yes	

22.3 COW'S MILK				
22.3.1	Has your child ever had any of these reactions below to cow's milk or food containing cow's milk		0 = No	1 = Yes
22.3.2	If yes, which of the following reactions has this child had? (you can circle more than one)			
	1 = none	**6** = tight throat	**11** = shock/low blood pressure	
	2 = itchy Rash	**7** = wheeze	**12** = collapse/loss of consciousness	
	3 =swelling(face/lips/eyes)	**8** = vomiting	**13** = worsening of eczema	
	4 = flushing	**9** = diarrhoea		
	5 = itchy mouth/throat	10 = blue lips		
22.3.3	If Yes, how old was this child when he/she had the first reaction?			Months
22.3.4	If yes, how long after the eating the food did the reaction occur?	1 = < 1 hour	2 = 1-24 hours	3 = >24 hours
22.3.5	If yes, was this reaction confirmed by a doctor?	0 = No	1 = Yes	

22.4 SOYA				
22.4.1	Has your child ever had any of these reactions below to soya or food containing soya		0 = No	1 = Yes
22.4.2	If yes, which of the following reactions has this child had? (you can circle more than one)			
	1 = none	6= tight throat	11=shock/low blood pressure	
	2 = itchy Rash	7= wheeze	12= collapse/loss of consciousness	

	3 =swelling(face/lips/eyes)	8= vomiting	13 = worsening of eczema
	4 = flushing	9= diarrhoea	
	5 = itchy mouth/throat	10= blue lips	
22.4.3	If Yes, how old was this child when he/she had the first reaction?		Months
22.4.4	If yes, how long after the eating the food did the reaction occur?	1 = < 1 hour	2 = 1-24 hours / 3 = >24 hours
22.4.5	If yes, was this reaction confirmed by a doctor?	0 = No	1 = Yes

22.5 HEN'S EGG			
22.5.1	Has your child ever had any of these reactions below to hen's egg or food containing egg	0 = No	1 = Yes
22.5.2	If yes, which of the following reactions has this child had? (you can circle more than one)		
	1 = none	6 = tight throat	11 =shock/low blood pressure
	2 = itchy Rash	7 = wheeze	12 = collapse/loss of consciousness
	3 =swelling(face/lips/eyes)	8 = vomiting	13 = worsening of eczema
	4 = flushing	9 = diarrhoea	
	5 = itchy mouth/throat	10= blue lips	
22.5.3	If Yes, how old was this child when he/she had the first reaction?		months
22.5.4	If yes, how long after the eating the food did the reaction occur?	1= < 1 hour	2= 1-24 hours / 3= >24 hours
22.5.5	If yes, was this reaction confirmed by a doctor?	0 = No	1 = Yes

22.6 WHEAT			
22.6.1	Has your child ever had any of these reactions below to wheat or food containing wheat	0 = No	1 = Yes
22.6.2	If yes, which of the following reactions has this child had? (you can circle more than one)		
	1= none	6= tight throat	11=shock/low blood pressure
	2= itchy Rash	7= wheeze	12= collapse/loss of consciousness
	3=swelling(face/lips/eyes)	8= vomiting	13 = worsening of eczema
	4= flushing	9= diarrhoea	
	5= itchy mouth/throat	10= blue lips	
22.6.3	If Yes, how old was this child when he/she had the first reaction?		Months
22.6.4	If yes, how long after the eating the food did the reaction occur?	1= < 1 hour	2= 1-24 hours / 3= >24 hours
22.6.5	If yes, was this reaction confirmed by a doctor?	0 = No	1 = Yes

22.7 FISH (excluding shellfish)			
22.7.1	Has your child ever had any of these reactions below to fish or food containing fish	0 = No	1 = Yes
22.7.2	If yes, which of the following reactions has this child had? (you can circle more than one)		

	1 = none	6 = tight throat	11 =shock/low blood pressure		
	2 = itchy Rash	7 = wheeze	12 = collapse/loss of consciousness		
	3 =swelling(face/lips/eyes)	8 = vomiting	13 = worsening of eczema		
	4 = flushing	9 = diarrhoea			
	5 = itchy mouth/throat	10 = blue lips			
22.7.3	If Yes, how old was this child when he/she had the first reaction?			Months	
22.7.4	If yes, how long after the eating the food did the reaction occur?		1= < 1 hour	2= 1-24 hours	3= >24 hours
22.7.5	If yes, was this reaction confirmed by a doctor?		0 = No	1 = Yes	

Q23 Asthma

Q23.1	Has your child ever symptoms of asthma without having a cold or chest infection? (e.g. wheeze, persistent cough at night or when exercising, shortness of breath)	0 = No	1 = Yes	
Q23.2	If Yes, how old was he/she?		Months	
Q23.3	If yes, who diagnosed the asthma?	**1** = Self	**2** = Nurse	**3** = Doctor

Q24 Hay fever

Q24.1	Has your child ever had symptoms of hay fever (e.g. itchy runny eyes, itchy runny nose, blocked nose, frequent sneezing) without having a "cold" or upper respiratory tract infection?	0 = No	1 = Yes	
Q24.2	If Yes, how old was he/she?		Months	
Q24.2	If yes, who diagnosed the hay fever?	1 = Self	2 = Nurse	3 = Doctor

Q25 Eczema

Q25.1	Has your child ever had symptoms of eczema (e.g. an itchy rash especially in the folds of the elbows, behinds the knees, in front of the ankles, under the buttocks or around the neck, ears or eyes?)	**0 = No**	**1 = Yes**	
Q25.2	If yes, how old was your child then?		Months	
Q25.3	If yes, who diagnosed the eczema?	**1** = Self	**2** = Nurse	**3** = Doctor

Q26 Medication use

Q26.1	Is your child on any of the following medication? (see NAEP Chart)							
26.1.1	INHALERS	Relievers (blue) e.g. Asthavent	0 = No	1 = Yes	**25.1.5**	Nasal corticosteroid spray e.g. Beclate	0 = No	1 = Yes
26.1.2		Controllers (brown/cream) e.g. Budeflam	0 = No	1 = Yes	**25.1.6**	Antihistamines **(If yes, please complete Q26.4 below)**	0 = No	1 = Yes
26.1.3		Other (please specify below)	0 = No	1 = Yes	**25.1.7**	Steroid creams	0 = No	1 = Yes
26.1.4		Home nebuliser	0 = No	1 = Yes	**25.1.8**	Adrenalin auto injector or pen e.g. Epipen	0 = No	1 = Yes
Q26.2	If your child is on any other oral medication (pills or syrups) for asthma, please **specify each one**. (e.g. oral steroids or leukotriene receptor antagonists)				Free text			
Q26.3	If your child is on antihistamines, **please specify** which type/brand?				Free text			
Q26.4	If your child is on antihistamines, how many days since they were last taken?				**1 =** <2 days	**2 =** 2-5 days	**3 =** >5 days	
Q27.5	If your child is on any other medication for other illnesses, please specify each one.				Free text			

Q27 Family history of allergic disease

Does anyone in your Family have allergic diseases? Please circle. (you can choose more than one option)						
	Family member	None	Asthma	Hay fever	Eczema	Food allergy
Q27.1	Mother	1 = none	2 = asthma	3 = hay fever	4 = eczema	5 = food allergy
Q27.2	Father	1 = none	2 = asthma	3 = hay fever	4 = eczema	5 = food allergy
Q27.3	Full Sibling 1	1 = none	2 = asthma	3 = hay fever	4 = eczema	5 = food allergy
Q26.4	Full Sibling 2	1 = none	2 = asthma	3 = hay fever	4 = eczema	5 = food allergy
Q27.5	Full Sibling 3	1 = none	2 = asthma	3 = hay fever	4 = eczema	5 = food allergy
Q27.6	Full Sibling 4	1 = none	2 = asthma	3 = hay fever	4 = eczema	5 = food allergy

Q28 Child's Medical history

Q28.1	Does your child have any other significant medical problems? (e.g. heart or lung problems, kidney or liver disease, epilepsy, diabetes)	0 = No	1 = Yes
Q28.2	If yes, please specify		

Q29 Home Language and Migration

Q29.1	What language do you mainly speak at home? (Please choose only one)			
	1 = IsiXhosa	**2** = English	**3** = Afrikaans	
	4 = IsiZulu	**5** = Sesotho	**6** = Setswana	
	7 = SiSwati	**8** = IsiNdebele	**9**=Xitsonga	
	10 = Sepedi	**11**=Tshivenda	**12** = Other	
Q29.1.2	If Xhosa speaking, was this child born in the rural Eastern Cape??		0 = No	1 = Yes

29.2.1	If No, where was this child born?	Province			
		1 = Western Cape 2 = Eastern Cape 3 = Northern Cape 4 = Free state 5 = Gauteng		6 = Kwazulu Natal 7 = Mpumalanga 8 = Limpopo 9 = North West Province 10 = Other	
		Town (specify)		Free text	
29.2.2	When did this child move to Cape Town?		Year		Month

Q29.3	Was this child's **MOTHER** born in the rural Eastern Cape??			0 = No	1 = Yes
29.3.1	**If No,** where was she born?	Province (please circle)			
		1 = Western Cape 2 = Eastern Cape 3 = Northern Cape 4 = Free state 5 = Gauteng		6 = Kwazulu Natal 7 = Mpumalanga 8 = Limpopo 9 = North West Province 10 = Other	
		Town (specify)		Free text	
29.3.2	**If no** when did **SHE** move to Cape Town?		Year		Month
29.3.3	Was this child's **FATHER** born in the rural Eastern Cape?			0 = No	1 = Yes
	If No, where was he born?	Province			
		1 = Western Cape 2 = Eastern Cape 3 = Northern Cape 4 = Free state 5 = Gauteng		6 = Kwazulu Natal 7 = Mpumalanga 8 = Limpopo 9 = North West Province 10 = Other	
		Town(specify)			
29.3.4	**If no** when did **HE** move to Cape Town?		Year		Month

Q30 Ethnicity

Q30	What is your child's ethnic origin? (circle as appropriate)	**1** = White/Caucasian	**2** = Coloured / Mixed race
		3 = Black African	**4** = Asian/Indian
		5 = Other (Specify)	

Q30 Household information

Q31.1	How many people live together in your house?	
Q31.2	How many children (12 years or less) that are OLDER than this child live in the same household?	
Q31.3	How many children that are YOUNGER than this child live in the same household?	

Q32 Parental Education level

1 = None	**11** = Grade 9 / Std 7
2 = Grade R / preschool	**12** = Grade 10 / Std 8
3 = Grade 1 / SubA	**13** = Grade 11 / Std 9
4 = Grade 2 / Sub B	**14** = Grade 12 / Matric
5 = Grade 3 / Std 1	**15** = Grade 9,10,11 (Std 7,8,9) & diploma
6 = Grade 4 / Std 2	**16** = Grade 12 (Std 10) & Certificate or Diploma
7 = Grade 5 / Std 3	**17** = Grade 12 (Std 10) & Degree
8 = Grade 6 / Std 4	**18** = Grade 12 (Std 10) & Degree plus Diploma or further degree
9 = Grade 7 / Std 5	**19** = Grade 12 (Std 10) & PhD
10 = Grade 8 / Std 6	Other (**Specify) :** Free text

Q33 Household income

Q33.1	What job does this child's mother/female guardian do?		999=Don't Know
Q33.2	What job does this child's Father/male guardian do?		999= Don't Know
Q33.3	How much money or income does your household receive every month after tax? (Incl. money from work, pensions, informal business etc.)	R	999 = Don't know

Q34 Contact with pets and animals

Q34.1	Do you own a cat or have a cat in your home?		0 = No	1 = Yes
Q34.2	Do you own a dog or have a dog in your home?		0 = No	1 = Yes
Q34.3	Does your child have regular (at least once a week) contact with Farm animals (e.g. cattle, pigs, goats, sheep or poultry)?	0 = No	1 = Yes	999 = Don't know
Q34.4	Has this child's mother had regular (at least once a week) contact with Farm animals (e.g. cattle, pigs, goats, sheep or poultry) while being pregnant with this child?	0 = No	1 = Yes	999 = Don't know

Q35 Fuel exposure

Q35.1	At your house, what fuel is used for cooking?	
	1 = Electricity/Gas	4 = Open fires outside the house
	2 = Paraffin Stove	5 = Other (specify)
	3 = Open fires in the house	

Q35.2	At your house, what fuel is used for heating?	
	1 = Electricity	4 = Wood/coal
	2 =Gas	5 = Other (specify)
	3 =Kerosene/Paraffin	

Q36 Cigarette smoke exposure

Q36.1	Does this child's mother (or female guardian) currently smoke cigarettes?	0 = No	1 = Yes	999 = Don't know
36.1.1	If **YES**, about how many cigarettes does the child's mother (or female guardian) smoke each day?	number of cigarettes:		
Q36.2	Does this child's Father (or male guardian) currently smoke cigarettes?	0 = No	1 = Yes	999= Don't know
36.2.1	If **YES**, about how many cigarettes does the child's Father (or male guardian) smoke each day?	number of cigarettes:		
Q36.3	How many people living in the house currently smoke cigarettes, including parents?	No of people:		
Q36.4	Did this child's mother smoke cigarettes while being pregnant with this child?	0 = No	1 = Yes	999 = Don't know

Q37	**How often does your child eat Fast foods?**				
	1= <1 a month	2= 1-3 a month	3= 1-2 x a week	4= 3-4 x a week	5= >5 x a week
Q38	**How often does your child drink soft drinks and fruit juices?** *(except pure orange juice)*				
	1= <1 a month	2= 1-3 a month	3= 1-2 x a week	4= 3-4 x a week	5= >5 x a week
Q39	**How many pieces of fruit and vegetables has your child eaten in the last 48 hours?**				
	1= <1	2= 2-3	3= 4-5	4= 6+	
Q40	**How often does your child have fried or microwaved sources of meat?**				
	1= <1 a month	2= 1-3 a month	3= 1-2 x a week	4= 3-4 x a week	5= >5 x a week

APPENDIX 6: NON-PARTICIPANT QUESTIONNAIRE

We would be very grateful if you could take the time to complete a short survey which will help us to improve the quality of our study findings.
These questions will be about your child's diet, history of allergies and also some questions regarding your family's history of allergy and where you and your child were born.

This information will be anonymous and we will not keep any record of you or your child's name. It will therefore not be possible to identify you or your child from the information you give us.
The SAFFA study was approved by the Human Research Ethics Committee of the University of Cape Town.

Consent for my anonymous information to be used in the SAFFA study.

I (name of parent or legal guardian)

……..

have been fully informed about the above study with its risks and benefits, and hereby consent for the information I share in this non-participant questionnaire to be used in the study.
This consent includes the following study procedures:

- Asking some health-related questions about my child and my family
- Using the health information gathered from the study in a confidential manner

Signature: …….

For illiterate parents only:
Signature substitute (cross or finger print)…….

Witness (name)……...

(Sign)……Date……..

I (study personnel name)……,
have fully explained the nature and purpose of the above described study with its risks and benefits. I have answered all the questions to the best of my ability. I will inform the participant of any changes in the procedures or the risks and benefits should they change during the course of the study. I have given a copy of the consent form to the parents/guardian.

Non-Participant's details

Q1	NPID number	00000	
Q2	Questionnaire date	DD/MM/YYYY	
Q3	Study site	1 = Urban	2= Rural
Q4	Date of birth	DD/MM/YYYY	
Q5	Age at survey	XX months	
Q6	Sex	1= Male	2=Female
Q7	You have chosen not to take part in our SAFFA study. Could you please tell us what your reasons are?		
	1 = I don't have enough time		
	2 = I am not concerned about food allergies in my child		
	3 = I do not wish my child to undergo a skin prick test		
	4 = I do not wish my child to undergo any blood tests		
	5 = I am not the parent or guardian and the parent is not available		
	6 = Other reasons (please specify):		

Q21 Food exposure

Foods Eaten		Ever Eaten			Age first eaten				Still eating regularly (once a week or more)		
21.1	**Peanut** e.g. peanut butter, peanut oil, peanuts in cookies or chocolates	**21.1.1**	1 = Yes	0 = No	**21.1.2**	XX	months	999 = don't know	**21.1.3**	1 = Yes	0 = No
21.2	**Other nuts** e.g. Cashew, hazelnut, brazil nut, almonds, walnuts, pistachio, macadamia in chocolate and cookies or cakes and breads	**21.2.1**	1 = yes	0 = no	**21.2.2**	XX	months	999 = don't know	**21.2.3**	1 = Yes	0 = No
21.3	**Cow's milk products** e.g. fresh milk, cheese, yoghurt, cream	**21.3.1**	1 = yes	0 = no	**21.3.2**	XX	months	999 = don't know	**21.3.3**	1 = Yes	0 = No
21.4	**Cow's milk formula** e.g. Nan, Lactogen, Novolac, S26, Infacare, Pelargon	**21.4.1**	1 = yes	0 = no	**21.4.2**	XX	Months	999 = don't know	**21.4.3**	1 = Yes	0 = No
21.5	**Soya products** e.g. soya mince, soya sauce, tofu	**21.5.1**	1 = yes	0 = no	**21.5.2**	XX	Months	999 = don't know	**21.5.3**	1 = Yes	0 = No
21.6	**Soya milk products** e.g. Infasoy, Isomil, Infacare	**21.6.1**	1 = yes	0 = no	**21.6.2**	XX	Months	999 = don't know	**21.6.3**	1 = Yes	0 = No
21.7	**Hen's egg** e.g. boiled, scrambles eggs, omelettes, quiches(souttert), cakes, cookies, rusks	**21.7.1**	1 = yes	0 = no	**21.7.2**	XX	Months	999 = don't know	**21.7.3**	1 = Yes	0 = No
21.8	**Wheat** e.g. cereal (Wheetabix, All Bran, Tasty Wheat), bread or pasta, cakes, rusks, couscous, semolina	**21.8.1**	1 = yes	0 = no	**21.8.2**	XX	Months	999 = don't know	**21.8.3**	1 = Yes	0 = No
21.9	**Fish (excluding shellfish)** Hake, snoek, sardines, tuna, kingklip, salmon etc and fish products: Fish paste(Redro), Worcester sauce, fish sauce	**21.9.1**	1 = yes	02 = no	**21.9.2**	XX	months	999 = don't know	**21.9.3**	1 = Yes	0 = No

Q22 Food Reactions

22.1 PEANUTS					
22.1.1	Has your child ever had any of these reactions below to peanuts or food containing peanuts			**1** = yes	**0** = no
22.1.2	If yes, which of the following reactions has this child had? (you can circle more than one)				
	1= none	**6**= tight throat	**11**=shock/low blood pressure		
	2= itchy Rash	**7**= wheeze	**12**= collapse/loss of consciousness		
	3=swelling(face/lips/eyes)	**8**= vomiting	**13** = worsening of eczema		
	4= flushing	**9**= diarrhoea			
	5= itchy mouth/throat	**10**= blue lips			
22.1.3	If Yes, how old was this child when he/she had the first reaction?		XX	months	
22.1.4	If yes, how long after the eating the food did the reaction occur?		**1** = < 1 hour	**2** = 1-24 hours	**3** = >24 hours
22.1.5	If yes, was this reaction confirmed by a doctor?		**1** = yes	**0** = no	

22.2 OTHER NUTS					
22.2.1	Has your child ever had any of these reactions below to other nuts or food containing nuts other than peanuts			**1** = yes	**0** = no
22.2.2	If yes, which of the following reactions has this child had? (you can circle more than one)				
	1 = none	**6** = tight throat	**11** =shock/low blood pressure		
	2 = itchy Rash	**7** = wheeze	**12** = collapse/loss of consciousness		
	3 =swelling(face/lips/eyes)	**8** = vomiting	**13** = worsening of eczema		
	4 = flushing	**9** = diarrhoea			
	5 = itchy mouth/throat	**10** = blue lips			
22.2.3	If Yes, how old was this child when he/she had the first reaction?		XX	months	
22.2.4	If yes, how long after the eating the food did the reaction occur?		**1** = < 1 hour	**2** = 1-24 hours	**3** = >24 hours
22.2.5	If yes, was this reaction confirmed by a doctor?		**1** = Yes	**0** = No	

22.3 COW'S MILK					
22.3.1	Has your child ever had any of these reactions below to cow's milk or food containing cow's milk			**1** = Yes	**0** = No
22.3.2	If yes, which of the following reactions has this child had? (you can circle more than one)				
	1 = none	**6** = tight throat	**11** = shock/low blood pressure		
	2 = itchy Rash	**7** = wheeze	**12** = collapse/loss of consciousness		
	3 =swelling(face/lips/eyes)	**8** = vomiting	**13** = worsening of eczema		
	4 = flushing	**9** = diarrhoea			
	5 = itchy mouth/throat	10 = blue lips			
22.3.3	If Yes, how old was this child when he/she had the first reaction?		XX	months	
22.3.4	If yes, how long after the eating the food did the reaction occur?		**1** = < 1 hour	**2** = 1-24 hours	**3** = >24 hours

22.3.5	If yes, was this reaction confirmed by a doctor?	**1** = Yes	**0** = No

22.4 SOYA				
22.4.1	Has your child ever had any of these reactions below to soya or food containing soya		**1** = Yes	**0** = No
22.4.2	If yes, which of the following reactions has this child had? (you can circle more than one)			
	1 = none	6= tight throat	11=shock/low blood pressure	
	2 = itchy Rash	7= wheeze	12= collapse/loss of consciousness	
	3 =swelling(face/lips/eyes)	8= vomiting	13 = worsening of eczema	
	4 = flushing	9= diarrhoea		
	5 = itchy mouth/throat	10= blue lips		
22.4.3	If Yes, how old was this child when he/she had the first reaction?		XX	months
22.4.4	If yes, how long after the eating the food did the reaction occur?		**1** = < 1 hour	**2** = 1-24 hours	**3** = >24 hours
22.4.5	If yes, was this reaction confirmed by a doctor?		**1** = Yes	**0** = No

22.5 HEN'S EGG				
22.5.1	Has your child ever had any of these reactions below to hen's egg or food containing egg		**1** = Yes	**0** = No
22.5.2	If yes, which of the following reactions has this child had? (you can circle more than one)			
	1 = none	6 = tight throat	11 =shock/low blood pressure	
	2 = itchy Rash	7 = wheeze	12 = collapse/loss of consciousness	
	3 =swelling(face/lips/eyes)	8 = vomiting	13 = worsening of eczema	
	4 = flushing	9 = diarrhoea		
	5 = itchy mouth/throat	10= blue lips		
22.5.3	If Yes, how old was this child when he/she had the first reaction?		XX	months
22.5.4	If yes, how long after the eating the food did the reaction occur?		1= < 1 hour	**2=** 1-24 hours	**3=** >24 hours
22.5.5	If yes, was this reaction confirmed by a doctor?		1 = Yes	**0** = No

22.6 WHEAT				
22.6.1	Has your child ever had any of these reactions below to wheat or food containing wheat		**1** = Yes	**0** = No
22.6.2	If yes, which of the following reactions has this child had? (you can circle more than one)			
	1= none	6= tight throat	11=shock/low blood pressure	
	2= itchy Rash	7= wheeze	12= collapse/loss of consciousness	
	3=swelling(face/lips/eyes)	8= vomiting	13 = worsening of eczema	
	4= flushing	9= diarrhoea		
	5= itchy mouth/throat	10= blue lips		
22.6.3	If Yes, how old was this child when he/she had the first reaction?		XX	months

22.6.4	If yes, how long after the eating the food did the reaction occur?	**1=** < 1 hour	**2=** 1-24 hours	**3=** >24 hours
22.6.5	If yes, was this reaction confirmed by a doctor?	**1** = Yes		**0** = No

22.7 FISH (excluding shellfish)				
22.7.1	Has your child ever had any of these reactions below to fish or food containing fish		**1** = Yes	**0** = No
22.7.2	If yes, which of the following reactions has this child had? (you can circle more than one)			
	1 = none	6 = tight throat	11 =shock/low blood pressure	
	2 = itchy Rash	7 = wheeze	12 = collapse/loss of consciousness	
	3 =swelling(face/lips/eyes)	8 = vomiting	13 = worsening of eczema	
	4 = flushing	9 = diarrhoea		
	5 = itchy mouth/throat	10 = blue lips		
22.7.3	If Yes, how old was this child when he/she had the first reaction?		XX	Months
22.7.4	If yes, how long after the eating the food did the reaction occur?	**1=** < 1 hour	**2=** 1-24 hours	**3=** >24 hours
22.7.5	If yes, was this reaction confirmed by a doctor?	1 = Yes		**0** = No

HISTORY OF ALLERGIC ILLNESSES

Q23 Asthma

Q23.1	Has your child ever had symptoms of asthma? (e.g. wheeze, persistent cough at night or when exercising, shortness of breath)	**1** = Yes		**0** = No
Q23.2	If Yes, how old was he/she?	XX		Months
Q23.3	If yes, who diagnosed the asthma?	**1** = Self	**2** = Nurse	**3** = Doctor

Q24 Hay fever

Q24.1	Has your child ever had symptoms of hay fever (e.g. itchy runny eyes, itchy runny nose, blocked nose, frequent sneezing) without having a "cold" or upper respiratory tract infection?	**1** = Yes		**0** = No
Q24.2	If Yes, how old was he/she?	XX		Months
Q24.2	If yes, who diagnosed the hay fever?	**1** = Self	**2** = Nurse	**3** = Doctor

Q25 Eczema

Q25.1	Has your child ever had symptoms of eczema (e.g. an itchy rash especially in the folds of the elbows, behinds the knees, in front of the ankles, under the buttocks or around the neck, ears or eyes?	**1** = Yes	**0** = No

Q25.2	If yes, how old was your child then?	XX		Months
Q25.3	If yes, who diagnosed the eczema?	**1** = Self	**2** = Nurse	**3** = Doctor

Q27 Family history of allergic disease

Does anyone in your Family have allergic diseases? Please circle. (you can choose more than one option)						
	Family member	None	Asthma	Hay fever	Eczema	Food allergy
Q27.1	Mother	1 = none	2 = asthma	3 = hay fever	4 = eczema	5 = food allergy
Q27.2	Father	1 = none	2 = asthma	3 = hay fever	4 = eczema	5 = food allergy
Q27.3	Full Sibling 1	1 = none	2 = asthma	3 = hay fever	4 = eczema	5 = food allergy
Q26.4	Full Sibling 2	1 = none	2 = asthma	3 = hay fever	4 = eczema	5 = food allergy
Q27.5	Full Sibling 3	1 = none	2 = asthma	3 = hay fever	4 = eczema	5 = food allergy
Q27.6	Full Sibling 4	1 = none	2 = asthma	3 = hay fever	4 = eczema	5 = food allergy

Q28 Child's Medical history

Q28.1	Does your child have any other significant medical problems? (e.g. heart or lung problems, kidney or liver disease, epilepsy, diabetes)		**1** = Yes	**0** = No
Q28.2	If yes, please specify			

Q29 Home Language and Migration

Q29.1	**What language do you mainly speak at home? (Please choose only one)**		
	1 = IsiXhosa	2 = English	3 = Afrikaans
	4 = IsiZulu	5 = Sesotho	6 = Setswana
	7 = SiSwati	8 = IsiNdebele	9=Xitsonga
	10 = Sepedi	11=Tshivenda	12 = Other
Q29.1.2	**If Xhosa speaking, was this child born in Cape Town?**	**1 = Yes**	**0 =** No
	If No, please complete **Q 29.2** **If Yes,** please skip to **Q29.3**		

29.2.1	**Where was this child born?**	**Province**			
		1 = Western Cape 2 = Eastern Cape 3 = Northern Cape 4 = Free state 5 = Gauteng		6 = Kwazulu Natal 7 = Mpumalanga 8 = Limpopo 9 = North West Province 10 = Other	
		Town (specify)		Free text	
29.2.2	**When did this child move to Cape Town?**	XXXX	**Year**	XX	**Month**

Q29.3	**Was this child's mother born in Cape Town?**			**1** = Yes	**0** = No
29.3.1	**If No, where was he/she born?**	**Province (please circle)**			
		1 = Western Cape 2 = Eastern Cape 3 = Northern Cape 4 = Free state 5 = Gauteng		6 = Kwazulu Natal 7 = Mpumalanga 8 = Limpopo 9 = North West Province 10 = Other	
		Town (specify)	Free text		
29.3.2	**If no when did she move to Cape Town?**	XXXX	**Year**	XX	**Month**
			Year		

Q30 Ethnicity

Q30	What is your child's ethnic origin? (circle as appropriate)	**1** = White/Caucasian	**2** = Coloured / Mixed race
		3 = Black African	**4** = Asian/Indian
		5 = Other (Specify)	

Q32 Parental Education level

What is the highest level of education obtained by any parent of this child?	
1 = None	**11** = Grade 9 / Std 7
2 = Grade R / preschool	**12** = Grade 10 / Std 8
3 = Grade 1 / SubA	**13** = Grade 11 / Std 9
4 = Grade 2 / Sub B	**14** = Grade 12 / Matric
5 = Grade 3 / Std 1	**15** = Grade 9,10,11 (Std 7,8,9) & diploma
6 = Grade 4 / Std 2	**16** = Grade 12 (Std 10) & Certificate or Diploma
7 = Grade 5 / Std 3	**17** = Grade 12 (Std 10) & Degree
8 = Grade 6 / Std 4	**18** = Grade 12 (Std 10) & Degree plus Diploma or further degree
9 = Grade 7 / Std 5	**19** = Grade 12 (Std 10) & PhD
10 = Grade 8 / Std 6	Other (**Specify) :** Free text

APPENDIX 7: GENERAL PROTOCOL FOR OPEN ORAL FOOD CHALLENGE

Note: Exact doses of individual foods to be challenged will be held in a separate study folder

Q 1	Participant ID		**Q4**	Today's Date	
Q 2	Date of Birth		**Q5**	Today's Weight	
Q 3	Sex (please circle)	1 = Male 2 = Female	**Q6**	Food challenge being performed	

Step 1: Pre-challenge assessment	**Tick when complete**
1. Ensure that oxygen and suction are in working order	
2. Ensure that the drug box is complete and accessible	
3. Calculate the emergency drug doses for the participants weight of today	

Drug	**Recommended dos**	**Calculated dose for participant weight: ___kg**
Adrenaline 1:1000	0.01mL/kg IM	
Adrenaline neb 1:1000	0.2-0.4mL/kg adrenaline (max 5 mL) mixed with equal amounts of normal saline	
Hydrocortisone	4mg/kg IV (max 100 mg)	
Nebulised salbutamol	2.5-5 mg	
Promethazine (Phenergan)	1mg/kg IV	
Salbutamol via MDI	6-10 puffs	
Cetirizine	2.5mg/5mg	

4. Assess if this is a high risk child (and gain IV access if needed)
- Any symptoms of asthma within the last 4 years.
- Any previous severe allergic reactions i.e. cardio-respiratory symptoms regardless of the allergen
- Any child who has received adrenaline for an allergic reaction in the past.

5. Ensure that the child has not had an acute exacerbation of asthma, rhinitis or eczema in the last 2 weeks.
(If he/she has, discuss with consultant and decide whether challenge should be postponed)

6. Ensure that the child has not taken any medications that need to be stopped prior to the food challenge. *(see note below)*

Medication	**Duration to be stopped prior to the challenge**
• **Long acting antihistamines**, i.e.Cetirizine, Loratadine, Aterax • **Oral steroids**	5 days
• **Long acting β agonists**, i.e. Serevent or Formoterol (green inhalers), Seretide(purple inhaler) or Symbicord (red inhaler) • **Short acting antihistamines**, i.e.Piriton, Vallergan, Phenergan	48 hours
• **Leukotrine receptor antagonists**, i.e. Montelukast or Singulair	24 hours

7. Ensure that the child has not eaten (apart from sips of water) for 2 hours prior to the start of the challenge

8. Ensure that the child is fit for challenge on brief physical examination

Note:

- Regular preventative (steroid) inhalers, brown or orange in colour, such as Becotide should not be stopped prior to a challenge.
- Reliever inhalers may also be given, however, any child who is using their blue inhaler more frequently than normal in the two weeks prior to the challenge should discuss this with the study team before a decision is made whether or not to challenge them.
- Combined preventative and long acting relievers, i.e. Seretide and Symbicord inhalers should be stopped and the preventative part of the inhaler should be commenced instead for 72 hours prior to the challenge

Step 2: Preparation for oral food challenge	**Tick when complete**
The study nurse/doctor (and dietician if necessary) will organise both the challenge foods and any carrier foods on the day of admission. The foods should be labelled and dated and should be checked by 2 staff members prior to administration.	
The challenge food can be disguised in a food which the child eats regularly and is known to tolerate well.	
Follow the challenge protocol step by step as shown in Step 3 below	
The challenge should be discontinued at any stage when a reaction occurs, and action taken where necessary.	
At each stage, a full assessment set of observations should be performed 15-20 minutes after the dose has been given, or immediately when there are signs of a reaction.	
If there has been no reaction then observe for 2 hours with half-hourly observations	
If there has been a reaction, stop the challenge and refer to Step 4	

Criteria for a positive challenge
One or more of the following within 2 hours of the last dose within the food challenge • three or more concurrent non-contact hives (urticarial lesion) lasting for more than 5 min • Perioral or peri-orbital angioedema • Vomiting (excluding immediate post-ingestion gag/ vomits) • Circulatory compromise • Respiratory compromise (Wheezing, Inability to speak, Stridor, Dysphonia, Aphonia or signs of respiratory "distress")
Additional signs noted (but not positive challenge)
• Transient urticaria (less than three hives lasting less than 5min) • Erythematous rashes • Diarrhoea • Abdominal pain (such as abnormal stillness or doubling over) that persists for ≥ 3 minutes • Persistent rubbing of nose or eyes that lasts for ≥ 3 minutes • Persistent rhinorrhoea that lasts for ≥ 3 minutes • Persistent scratching that lasts for ≥ 3 minutes

Step 3: Oral Food Challenge						
Time	Dose number	Time into challenge (minutes)	Test Dose	Time interval	Reaction If YES stop challenge and go to step 4	Observations
	Baseline (pre-dose) observations					Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	1	0		15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	2	15		15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	3	30		15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	4	45		15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	5	60		15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____

	6	75		15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
	7	90		15	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		120	Observations only	30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		150		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		180		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____
		210		30	YES/NO	Pulse _____ Resp Rate_____ BP _____ SaO2 _____

Step 4. Positive Reactions: Record any reactions in the table below, then follow the steps for management		
Time	Symptoms	Treatment Given
Post challenge check		
OUTOME OF OFC and follow-up arrangement:		

Mild, non-cardiorespiratory reactions (e.g. rash/angioedema)

- The child should receive chlorpheniramine and be closely observed.
- If the child is asthmatic, also give 10 puffs of their salbutamol inhaler via a spacer device and a dose of prednisone to prevent a late phase reaction. The patient should be observed for at least 3 hours post challenge.

Reaction involving wheeze

- Give 15 litres of oxygen via a face mask with a reservoir bag.
- Give a salbutamol nebulizer.If **ANY** respiratory distress occurs give IM adrenaline.
- Following administration of the adrenaline give a dose of chlorpheniramine and give hydrocortisone/prednisone to prevent late phase reaction.
- If there is no response in 5 minutes, give a second dose of IM adrenaline and another salbutamol nebulizer and contact paediatric ICU for advice.
- The patient should be observed for at least 6 hours post-reaction and admitted overnight if deemed necessary.

Reaction involving stridor

- Give 15 litres of oxygen via a face mask with a reservoir bag.
- Give an adrenaline nebulizer.
- If **ANY** respiratory distress occurs give IM adrenaline.
- Following administration of the adrenaline give a dose of cetirizine or Phenergan and give hydrocortisone/prednisone to prevent late phase reaction.
- If there is no response in 5 minutes, give a second dose of IM adrenaline and contact paediatric ICU.
- The patient should be observed for at least 6 hours post-reaction and admitted overnight if deemed necessary.

Reaction involving hypotension or collapse

- Give IM adrenaline**.**
- Gain IV access and give 20ml/kg bolus of fluid, 0.9% NaCl.
- Give Phenergan IV, and IV hydrocortisone to prevent late phase reaction
- If no response in 5 minutes, repeat IM adrenaline and fast bleep an anaesthetist if they are not already present.

The patient should be observed for at least 6 hours post-reaction and admitted overnight if deemed necessary.

ORAL FOOD CHALLENGE: PARENT INFORMATION AND CONSENT

Dear Parent

The results of the allergy tests in your child suggest that he/she may have a food allergy. However, we are not sure of this so we need to find out for sure by doing a food challenge.

What is a Food Challenge?
In a food challenge we bring the child in to hospital for the day and give them small amounts of the food to which they had a positive allergy test, to see if there is any reaction. This is done in a very controlled way and the doctors and nurses will be there with you and your child to watch them closely. That way we can notice reactions early and treat them if needed.

If the child has no reactions to a very tiny amount of the food, then we will give them a little more, step by step, until we reach the top dose. The top dose will be similar to a normal "portion" of the food, for example about 1 tablespoon of peanut butter or one cupful of milk. In between each dose we will gently examine the child to look for any reactions, and also measure the temperature, pulse rate, heart rate, and blood pressure and oxygen levels.

If there are any reactions along the way, we will stop the food challenge and treat the child if necessary.

We will then give you the correct advice on the food in the child's diet according to the results of the challenge.

The doctor will also phone you at home after 2 days to make sure everything is alright and to ask if the child's eczema has got any worse.

How long will the challenge take?
You and your child will need to be in hospital for at least a whole morning. Giving the doses of food takes up to 2 hours because we leave a 20 minute gap between each dose.

After the challenge, we will keep an eye on the child for at least 2 hours if there has been no reaction. This is to be safe that the child remains well and that there are no "late reactions."

If there has been a reaction, we will keep an eye on your child for at least 4 hours until we are happy that all is well. Sometimes, if children have had a bad reaction, we may decide it is better to keep them in hospital overnight. However, this is very rare.

Will it hurt my child?
The actual food challenge is not painful in any way. Some children may be a bit frightened of having their temperature and pulse etc taken but it is not sore.
In a few children who are at higher risk of a reaction, especially those with asthma, we may consider putting a drip up before the challenge. We will only do this if absolutely necessary.

If children have a reaction during the challenge, the doctors and nurses will be right there to treat the child as quickly as possible. Most reactions are mild, such as rashes, and the child may need to take some antihistamine syrup. A few children will have more severe reactions, and these children may need an injection or even a drip. It is possible for a child to have a life threatening allergic reaction however this is extremely rare and has never happened in our clinic. We do not expect this because we start off with such small doses of food and watch the children so carefully so that the test is as safe as possible. Should a serious reaction happen we have all the emergency equipment immediately available in the room and there will always be a trained nurse and doctor present during the food challenge test..

What do you need to do?

1. Your child will need to be off some of their regular medications for up to a week before the challenge. Your doctor will give you details of these below:

   Medication…….When to stop……

   Medication…….When to stop……

   Medication…….When to stop……

2. If your child has been unwell in the 2 weeks before the challenge, please let the study doctor know a few days before the challenge so that we can decide whether we need to postpone the challenge. The doctor or nurse will also phone you 2 days before the challenge to make sure all is well.

3. We will ask you to come to the paediatric allergy clinic at 8.30 on the morning of the challenge. We will then ask a few questions to make sure all is well, have a quick look at the child and take their observations such as temperature and pulse. We will aim to start the actual challenge by 9 am.

4. On the morning of the challenge, your child can have their regular milk and/or a light breakfast between 6 and 7 am. After that they should not eat or drink anything (except a few sips of water) before the challenge.

5. We may ask you to bring along some of the child's favourite food or regular milk so that we can mix the test food into it for the child to eat.

6. Please dress the child in comfortable clothes that are easy to lift up for examining the child.

7. Bring along any favourite toys/dummies/blankets. It is a long morning for the children and we would like to make it as nice as possible for them!

8. We will give you travel money once you are in hospital for the challenge.

Thank you

If you have any questions or concerns at any stage about the food challenge, please contact: Dr Maresa Botha on 0216585779