

**Environmental risk factors for asthma in 13-14 year old  
African children**

Thesis presented for the degree of  
**Masters of Philosophy – Paediatric Pulmonology**

By

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## **DECLARATION**

I, Adaeze Ayuk, present this thesis in fulfilment of the requirements for the degree of Masters of Philosophy, Paediatric Pulmonology, in the Department of Paediatrics and Child Health, Faculty of Health Sciences, University of Cape Town. The contents of this thesis are entirely the work of the candidate.

This work is original unless otherwise acknowledged and is based on independent work performed by the candidate from data gathered in ISAAC III African centres. The candidate was assisted in the analysis by Jordache Ramjith from the University of Cape town (UCT) and Dr Bill Volmer from the American Thoracic Society/PATSMECOR. The manuscript was written and edited by the candidate with input and comments from the co-authors including the supervisors and collated to form the final manuscript.

No part of this work, either part or whole, has been presented to any other College for a Fellowship nor submitted for another degree to any other university, nor has it been submitted elsewhere by myself or by any other person for publication. This work has not been reported or published prior to registration for the degree of Masters of Philosophy, Paediatric Pulmonology.

Signature and date:

Signed by candidate
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February 2018



## **ABSTRACT**

**BACKGROUND:** Asthma prevalence in African children is high and increasing, with more severe disease than that in high income countries. Specific factors driving the rising prevalence or disease severity are poorly understood. The aim of this study was to investigate environmental factors associated with asthma and severity in African children using data obtained from ISAAC III.

**METHODS:** A population based cross-sectional study of children aged 13 to 14 years, from 10 African centres who participated in International Study of Asthma and Allergies in Childhood, (ISAAC) III from randomly selected schools. The prevalence of asthma or severe asthma was calculated for each centre from the ISAAC questionnaire. Environmental exposures assessed for their association with asthma or severe disease, were physical exercise 3 or more times in a week, television watching 5 or more hours in a day, biomass and ETS exposure, consumption of paracetamol at least once a month, large family sizes and having pets in the home from the ISAAC environmental questionnaire. Univariable and multivariable analyses were done adjusting for centre variations. Odds ratio and 95% confidence intervals (CI) were calculated.

**RESULTS:** Amongst 28490 adolescents from 232 schools in 10 African centres (4 middle income and 6 low income), the prevalence of asthma was 12.8% (95% CI 12.4-13.2). Prevalence of severe disease was 8.7% (95% CI 8.4-9.0). The significant environmental associations, for current asthma were maternal smoking (OR= 1.41; 95% CI: 1.23 - 1.64), exposure to open fire heating (OR=1.28; 95% CI: 1.08 - 1.51), electric heating (OR=1.13; 95% CI: 1.01 - 1.28), engaging in strenuous exercise (OR= 1.29; 95% CI: 1.11 - 1.50), monthly use of paracetamol (OR 1.23; 95% CI 1.13 - 1.33), or having an elder sibling (OR=0.87; 95% CI 0.77 - 0.98); for severe asthma: maternal smoking (OR=1.61; 95% CI: 1.38 - 1.89), cat at home (OR=1.14; 95% CI: 1.04 - 1.25), engaging in frequent physical exercise (OR=1.42; 95% CI: 1.23 - 1.64) or monthly consumption of paracetamol (OR=1.20; 95% CI: 1.07 - 1.34).

**CONCLUSION:** The study demonstrated several strong, consistent environmental associations with asthma and with severe disease in African children. Strategies to reduce harmful environmental exposures must be strengthened to reduce the burden of childhood asthma in Africa.

## **ACKNOWLEDGEMENTS**

I would like to acknowledge all the co-authors for their contributions as well as the faculty at Methods in Epidemiologic, Clinical and Operations Research (MECOR Africa and Global which are programmes of the American Thoracic Society, ATS), for providing critical review of the manuscript and particularly Bill Volmer, for all their support, comments and encouragements.

I wish to acknowledge the ISAAC III steering committee (and ISAAC III study group\*) from which the original data were obtained for analyses.

I would especially like to acknowledge Rodney Erhlich, Landon Myer, Jordache Ramjith and Heather Zar for their supervision and support at different stages of this work.

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## ABBREVIATIONS

**ISAAC** - International Study of Asthma and Allergies in Childhood

**WQ** - Written questionnaire

**VQ** – Video questionnaire

**EQ** – Environmental questionnaire

**ETS** – Environmental tobacco smoke

## **ENVIRONMENTAL RISK FACTORS FOR ASTHMA IN 13 TO 14 YEAR OLD AFRICAN CHILDREN**

Protocol version 3, May 2012- Protocol amendment and re-endorsement October 2017

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## **Chapter 1**

### **1. Introduction**

#### **1.1 Context:**

Asthma is the commonest chronic disease in children with marked geographic variation in prevalence.<sup>1,2</sup> Although asthma was considered to be less common in African children compared with those in high income countries, recent data suggests that the African prevalence is as high as the global average and increasing.<sup>3-5</sup> Gene-environmental interactions may account for much of the international variation in prevalence rates for asthma.<sup>6</sup> Several environmental factors have been associated with a rise in asthma prevalence. In children, some of these include urban migration, indoor biomass exposure, passive smoke exposure, obesity, vitamin D deficiency and adoption of a more western lifestyle.<sup>7</sup> In contrast, a rural environment, daycare attendance, and large family size have been associated with a reduced risk for current or severe asthma.<sup>7</sup> There may be interactions between these factors and a further overlap possibly accounted for by gene-environmental interactions.<sup>8</sup>

The International Study of Asthma and Allergies in Childhood (ISAAC), is a multi-country cross-sectional survey of the prevalence of asthma, allergic rhino-conjunctivitis and atopic eczema in two age groups of school children: 6 to 7 years and 13 to 14 years.<sup>9</sup> ISAAC uses standardized questionnaires of reported symptoms to diagnose asthma and to assess severity of disease.

#### **Aim:**

The purpose of this study was to investigate the association of environmental factors with asthma prevalence and severity in African children using data obtained from ISAAC III African sites in 13 to 14 year old children.

**Objectives:**

- To compare the prevalence of current and severe asthma in adolescent participants in ISAAC III in African centres.
- To compare the prevalence of environmental factors associated with (i) current asthma or (ii) severe asthma in these centres.
- To investigate the association of environmental factors with (i) current or (ii) severe asthma in African adolescents.

**Relevance**

This work will give insight to what environmental exposures are important in asthma pathogenesis and severity in African children, so informing interventions in this context. This work will also form a basis for future research to reduce the burden of childhood asthma in Africa and to ensure availability of appropriate therapy for management.

Findings from this study can contribute to informing health policies in Africa, such as regulations relating to environmental factors and access to inhaled therapy in African countries.

**1.2 Ethical considerations**

Permission was obtained from both the ISAAC central coordinating centre and UCT research ethics committee (HREC/REF: 209/2012), for analysis of this data. Renewal of ethical clearance was received October 2017. Ethical approval for collection of the data was already obtained from each participant in each centre.

### **1.3 Author guidelines of Pediatric Pulmonology journal**

#### **Main Document**

All manuscript types must include a title page, abstract, text and references in the Main Document. Standard, double-spaced manuscript format, in 12 point font is requested. Number all pages consecutively.

**Title page:** The title should be brief (no more than 100 characters in length including spaces) and useful for indexing. All authors' names with highest academic degree, affiliation of each, but no position or rank, should be listed. For cooperative studies, the institution where research was primarily done should be indicated. In a separate paragraph, specify grants, other financial support received, and the granting institutions (grant number(s) and contact name(s) should be indicated on the title page). If support from manufacturers of products used is listed, assurances about the absence of bias by the sponsor and principal author must be given. Identify meetings, if any, at which the paper was presented. The name, complete mailing address, telephone number, fax number, and e-mail address of the person to whom correspondence and reprint requests are to be sent must be included. Keywords should also be noted on the title page. For usage as a running head, provide an abbreviated title (maximum 50 characters) on the bottom of the title page.

**Summary/Abstract:** In accordance with the structure of the article, with or without separate headings, outline the objectives, working hypothesis, study design, patient-subject selection, methodology, results (including numerical findings) and conclusions. The Summary should not exceed the word counts outlined above. If abbreviations are used several times, spell out the words followed by the abbreviations in parentheses.

**Acknowledgements:** Technical assistance, advice, referral of patients, etc. may be briefly acknowledged at the end of the text under "Acknowledgements."

**Informed Consent:** Informed consent statements, if applicable, should be included in the Methods section.

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In the references, list the first ten authors of the cited paper. If there are more than ten authors, list the first 10 authors followed by 'et al'. Journals' names should be shown by their abbreviated title in Index Medicus. Manuscripts in preparation or submitted for publication are not acceptable references. If a manuscript "in press" is used as a reference, a copy of it must be provided with your submission. For a book reference only include the page numbers that have direct bearing on the work described.

**Keywords:** On the title page, supply a minimum of 3 to 5 keywords, exclusive of words in the title of the manuscript. A guide to medical subject heading terms used by PubMed is available at <http://www.nlm.nih.gov/mesh/MBrowser.html>

**Abbreviations:** Define abbreviations when they first occur in the manuscript and from there on use only the abbreviation. Whenever standardized abbreviations are available use those. Use standard symbols with subscripts and superscripts in their proper place.

**Formatting Specific to Original Research Articles:** Divide article into: Title Page, Summary/Abstract, Introduction, Materials and Methods, Results, Discussion, and References, starting each section on a new page. All methodology and description of experimental subjects should be under Materials and Methods; results should not be included in the Introduction. Please ensure the following appears in the appropriate section of your manuscript:

- a concise introductory statement outlining the specific aims of the study and providing a discussion of how each aim was fulfilled;
- a succinct description of the working hypothesis;
- a detailed explanation of assumptions and choices made regarding study design and methodology;
- a description of the reasons for choosing the type and number of experimental subjects (patients, animals, controls) and individual measurements; if applicable, information about how and why the numbers may differ from an ideal design (e.g., the number required for achieving 90% confidence in eliminating Type II error);
- specifics about statistical principles, techniques and calculations employed and, if applicable, methods for rejecting the null hypothesis;
- a concise comparison of the results with those of conflicting or confirmatory studies in the literature;
- a brief summary of the limitations of the scientific methods and results; and
- a brief discussion of the implications of the findings for the field and for future studies.

Tables



Tables should not be included in the Main Document but submitted as a separate DOC or RTF file. Number tables with Arabic numbers consecutively and in order of appearance. Type each table double-spaced on a separate page, captions typed above the tabular material. Symbols for units should be used only in column headings. Do not use internal horizontal or vertical lines; place horizontal lines between table caption and column heading, under column headings, and at the bottom of the table (above the footnotes if any). Use footnote letters (a, b, c, etc.) in consistent order in each table. All tables should be referred to in the text. Do not submit tables as photographs and do not separate legends from tables.

## REFERENCES

1. ISAAC Steering Committee. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). *Eur Respir J* 1998; 12: 315- 335.
2. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, et al. (2006) Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006; 368: 733–743.
3. Adeloje D, Yee Chan K, Rudan I, Campbell H. An estimate of asthma prevalence in Africa: a systematic analysis. *Croat Med J.* 2013; 54(6): 519–531. doi: 10.3325/cmj.2013.54.519 PMID: PMC3893990
4. Ait-Khaled N, Odhiambo J, Pearce N, Adjoh KS, Maesano IA, Benhabyles B et al. Prevalence of symptoms of asthma, rhinitis and eczema in 13- to 14-year-old children in Africa: the International Study of Asthma and Allergies in Childhood Phase III. *Allergy.* 2007;62:247-584:
5. Zar HJ, Ehrlich RI, Workman L, Weinberg EG. The changing prevalence of asthma, allergic rhinitis and atopic eczema in African adolescents from 1995 to 2002. *Pediatr Allergy Immunol.* 2007; 18:560-5
6. McLeish S, Turner SW. Gene–environment interactions in asthma *Arch Dis Child.* 2007; 92(11): 1032–1035. doi: 10.1136/adc.2006.112185.PMCID: PMC2083615
7. Cole Johnson C, Ownby DR, Zoratti EM, Alford SH, Williams LK, Joseph CLM. Environmental Epidemiology of Pediatric Asthma and Allergy. *Epidemiol Rev* 2002; 24: 154-175.
8. Martinez FD. Genes, environments, development and asthma: a reappraisal. *ERJ* 2007 29: 179-184; DOI: 10.1183/09031936.00087906
9. Ellwood P, Asher MI, Beasley R. The international study of asthma and allergies in childhood (ISAAC): phase three rationale and methods. *Int J Tuberc Lung Dis* 2005; 9:10–16.

## **CHAPTER 2**

### **PUBLICATION READY MANUSCRIPT**

Environmental risk factors for asthma in 13-14 year old African children

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The candidate undertook the data analysis and interpretation of data with biostatistical assistance from Jordache Ramjith and William Vollmer (Centre for Health Research, Kaiser Permanente, Portland, Oregon USA).

**ENVIRONMENTAL RISK FACTORS FOR ASTHMA IN 13-14 YEAR OLD AFRICAN CHILDREN**

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**KEY WORDS:** Africa, asthma, environment, risk, severe, adolescents, ISAAC

**RUNNING HEAD:** Environmental risk factors for current or severe asthma in Africa

## ABSTRACT

**BACKGROUND:** Asthma prevalence in African children is high and increasing, with more severe disease than that in high income countries. Specific factors driving the rising prevalence or disease severity are poorly understood. The aim of this study was to investigate environmental factors associated with asthma and severity in African children using data obtained from International Study of Asthma and Allergies in Childhood, (ISAAC) III.

**METHODS:** A population based cross-sectional study of children aged 13-14 years from 10 African centres who participated in ISAAC III from randomly selected schools. The prevalence of asthma or severe asthma was calculated for each centre. Self-reported environmental exposures included engaging in physical exercise, television watching, biomass and ETS exposure, consumption of paracetamol, large family sizes and having pets in the home. Univariable and multivariable analyses were done adjusting for centre variations. Odds ratio and respective 95% confidence intervals (CI) were calculated.

**RESULTS:** Amongst 28490 adolescents from 232 schools in 10 African centres (4 middle income and 6 low income), the prevalence of asthma was 12.8% (CI 12.4-13.2), while prevalence of severe disease was 8.7% (CI 8.4-9.0). Factors most strongly associated with asthma were maternal smoking (OR= 1.41; 95% CI: 1.23 - 1.64), exposure to open fire heating (OR=1.28; 95% CI: 1.08 - 1.51) and electric heating (OR=1.13; 95% CI: 1.01 - 1.28), engaging in strenuous exercise (OR= 1.29; 95% CI: 1.11 - 1.50 and monthly use of paracetamol (OR 1.23; 95% CI 1.13 - 1.33, while having an elder sibling was protective for asthma (OR=0.87; 95% CI 0.77 – 0.98). Factors strongly associated with severe asthma were maternal smoking (OR=1.61; 95% CI: 1.38 - 1.89), having a cat pet at home (OR=1.14; 95% CI: 1.04 - 1.25), engaging in  $\geq 3$  weekly physical exercise (OR=1.42; 95% CI: 1.23 - 1.64) and monthly consumption of paracetamol (OR=1.20; 95% CI: 1.07 - 1.34).

**CONCLUSION:** There was a high prevalence of severe asthma in African children. Several environmental exposures were associated with asthma or with severe disease. Strategies to reduce harmful environmental exposures must be strengthened to reduce the burden of childhood asthma in Africa.

### Word count:

Abstract = 340 Text = 2224 Tables = 5 Figures = 1 Supplementary tables = 4

References = 40

Key words: Asthma, adolescents, risk factors, environmental, ISAAC III

## ***Introduction***

Asthma is the commonest chronic disease in children with marked geographic variation in prevalence<sup>1, 2</sup>. Asthma was considered to be less common in African children compared with those in high income countries, however recent data from African studies suggests that the prevalence is as high as the global average and increasing<sup>1-5</sup>. Furthermore, a high proportion of African children with asthma have severe disease<sup>6</sup>. Several environmental factors have been associated with the rise in asthma prevalence, but these have not been well studied in African children. Further, comparison of findings across African countries is complicated by lack of consistency in methods to define and assess asthma prevalence and severity and to measure environmental exposures.

The International Study of Asthma and Allergies in Childhood (ISAAC) study is a multi-country cross-sectional survey of the prevalence of asthma, allergic rhino-conjunctivitis and atopic eczema in two age groups of school children: 6 to 7 years and 13 to 14 years<sup>7</sup>. ISAAC used standardized written questionnaires of reported symptoms. The ISAAC study phases allow standardized comparisons of the prevalence of these disorders in different countries. An environmental questionnaire was included in the latest phase of ISAAC (ISAAC III), enabling investigation of environmental factors associated with prevalence or severity of disease. The use of the written questionnaire (WQ) was compulsory for every centre participating in ISAAC III, while the use of the environmental questionnaire (EQ) was optional<sup>7</sup>. Although 10 African sites in Africa participated in ISAAC III, the results from the environmental influences on asthma in African respondents have not yet been published.

Several potentially harmful environmental exposures associated with asthma or severe disease are ubiquitous in Africa. Studies suggest that urbanizing populations may be especially susceptible to development of asthma, possibly through changes in diet and lifestyle and

exposure to environmental pollutants. Key prevalent environmental factors in Africa include exposure to diverse types of biomass for cooking or heating the home, exposure to tobacco smoke, large family sizes, pets in the home, frequent lower respiratory tract infection and life style changes that include transition to more sedentary living<sup>3</sup>.

Prior South African studies in children<sup>8</sup> have reported an association between current asthma and parental environmental tobacco exposure in school children although this was not found in a Kenyan study<sup>9</sup>. Another Kenyan study reported that cooking with kerosene increased the risk of exercise induced bronchospasm (EIB) while the use of open fire for heating did not lead to adverse respiratory effects<sup>10</sup>. These studies have limited generalizability as they were conducted in single centres, using varied methods.

The aim of this study was to investigate environmental factors associated with asthma prevalence or severity in 13 to 14 year old African adolescents participating in ISAAC III.

### ***Materials and Methods***

This was a cross-sectional study of African adolescents aged 13 to 14 years who participated in ISAAC III in African centres. Participants completed both core written questionnaire and environmental questionnaires of ISAAC III. The African data was obtained, with permission, from the ISAAC data centre. The study was approved by the Faculty of Health Sciences University of Cape town research ethics committee. Each participating centre also obtained ethics approval for the initial data collection at their sites.

*Data Collection and Quality Control:* The core and environmental questionnaires were completed according to standardized ISAAC III methodology<sup>7</sup>. Centres that administered the questionnaires in languages other than English (Afrikaans, Xhosa, Arhmaic, French, Arabic) underwent a back- translation process as per ISAAC protocol<sup>7</sup>. Further sub-categorization for purposes of comparison by language (cultural) divide into Anglophone and Francophone countries was also done, this may impact on their environmental influences. Double data entry was done at individual sites to minimize data entry errors and each centre was responsible for initial data cleaning. Cleaned data that was transferred to the central ISAAC data centre in New Zealand was utilized with careful quality control of data for analysis. This was further cleaned by the researcher.

The self- administered written questionnaire (WQ) used for the study included questions on respiratory symptoms, while the environmental questionnaires (EQ) consisted of questions covering exposures to biomass fuels, tobacco smoke and pets, physical activity, number of older and younger siblings and socioeconomic factors.

***Current asthma*** was defined according to the ISAAC definition, as wheezing or whistling in the chest in the past 12 months. ***Severe asthma*** was defined according to ISAAC as any of the

following in the past 12 months: more than 3 attacks of wheezing, sleep disturbed by wheezing on average 1 or more nights per week, or at least one episode where wheezing limited speech to only one or two words at a time between breaths. These were the primary outcome variables for the study and were analyzed independently of each other.

The following variables were analysed from the Environmental questionnaire(EQ): exposure to cooking and biomass fuels: electric cooking, gas cooking, open fire cooking, electric heating, gas heating, open fire heating (yes or no to each of electricity, gas, and open fires, with possibility of answering yes to more than one type); second-hand smoke exposure- Environmental Tobacco Smoke (ETS), which we analysed with separate analyses for mother, father and any persons smoking at home,<sup>11</sup> (recoded as ETS in  $\geq 3$  smokers as we noted that any additional smoker in the house may include the adolescent participant). This was captured as ETS in  $\geq 3$  smokers at home, to enable the analyses account additional smokers beyond the mother and father. Other variables were: having  $\geq 2$  older siblings, having  $\geq 2$  younger siblings, having pets at home (cat and dog), engaging in  $\geq 3$  weekly physical exercise, sedentary life style such as  $\geq 5$  hours of daily television watching and use of paracetamol at least once a month as compared to once or less in a year<sup>19</sup>.

#### *Data analyses*

Data were analyzed using Stata version 13 (Stata Corporation). The participants who met WQ criteria were identified from the data and were correlated with their answers to the EQ as possible risk factors for their symptoms. In the questionnaire, a “yes” answer was written as “1”, “no” as “0” while any other answers were completed “9”. All “9” were said to be indeterminate and were treated as negative answers; the frequency of such data was however less than 5% for each of the above environmental and lifestyle variables. All environmental factors were analyzed as simple binary variables.



Univariable and multivariable logistic regression analyses were used to assess the relationship between the environmental and lifestyle variables adjusted for centre with current and severe asthma. For children who indicated current asthma, a univariable logistic regression analysis was performed to assess the relationship between the environmental and lifestyle variables adjusted for centre. Similar analyses were also done for children with severe asthma. All variables with a p-value < 0.2 were then built into a multivariable logistic regression model and a backward selection procedure was used to identify significant variables. Each model included 232 clusters for school attended to adjust for the correlation between children attending the same school in the standard errors of the estimated effects of the risk factors. The key findings were compared between the Anglophone and Francophone centres. All regression outputs were summarized as odds ratios (ORs) and corresponding 95% confidence intervals (CIs). A p-value < 0.05 was considered statistically significant.

## **Results**

*Participants:* There were ~~Amongst~~ 258,267 children who were recruited among the 13 to 14-year-old and participated in ISAAC III from 10 centres in 7 African countries. Of these ~~,there were~~ 28,490 respondents from 232 schools ~~that~~ completed both the written questionnaire (WQ) and environmental questionnaire (EQ), and whose results were analyzed, fig 1. The ten centres were geographically spread across Africa- three Anglophone centres in South, East and West Africa (Cape Town, Addis Ababa, Ibadan); and seven Francophone centres in Central, West, North and East Africa (Yaoundé, Urban Cote d'Ivoire, Port-gentil, Boulmene, Casablanca, Marrakech, Khartoum). Fifty percent of overall respondents were male with a variation of sex distribution across centres. There were four middle-income centres and six low-income centres. The average response rate was 92.8% across centres, table 1.

*Asthma prevalence:* The overall prevalence of current asthma was 12.8% [95% CI 12.4-13.2], while the prevalence of severe asthma was 8.7% (95% CI 8.4-9.0); table 2. There was a 4.5-fold difference in the prevalence of current asthma between centres with the highest and lowest prevalence rates, table 2. The highest prevalence occurred in Cape Town, South Africa 20.4% (95% CI 19.3-21.5) and Urban Cote d'Ivoire, Ivory Coast 19.3% (95% CI 18.0-20.7) while the lowest prevalence was in Boulmene, Morocco 5.4% (95% CI 4.2 -6.8) and Marrakech, Morocco 4.4% (95% CI 3.5-5.5).

*Prevalence of environmental risk factors:* There was wide variability in prevalence of environmental factors across centres, table 3. Across sites, the use of gas for cooking [17,967 (63.1%)], was twice as common compared to other cooking exposures: electricity, 7,327 (25.7%) or use of open fires, 8051 (28.3%),  $p < 0.001$ . Exposure to gas as a means of home heating, was however the least common way of heating homes used by 3,333 (11.7%), table 3. There was a high prevalence of large family size reported in all African sites, where 24,378 (85.6%) of respondents had two or more older siblings and 23,811 (83.6%) had two or more younger siblings. Exposure to environmental tobacco smoke (ETS) was common: 15,371 (54.0%) children reported homes with 3 or more smokers. There were 1,959 (6.9%) who reported mothers who smoked, and 6,156 (21.6%) had a dad who smoked at home. Cat exposure occurred in 11,043 (38.8%) of homes, while dog exposure was less common in 9,596 (33.7%) homes,  $p < 0.001$ . A sedentary lifestyle as assessed by watching television 5 or more hours per day occurred in 9603 (33.7%) participants, while engaging in regular physical exercise was only reported by 5,613 (19.7%);  $p < 0.001$ . Paracetamol was reported to be consumed at least once a month by 11,654 (40.9%), table 3.

*Asthma and environmental risk factors:* Environmental factors associated with current asthma on univariable analyses were maternal smoking (OR= 1.42; 95% CI: 1.23 - 1.64;  $p < 0.001$ ),

paternal smoking (OR=1.14; 95% CI: 1.03 - 1.26, p=0.01), use of open fires (OR=1.28; 95% CI: 1.05 - 1.43; p = 0.01) or electricity (OR=1.12; 95% CI: 1.00 - 1.26; p = 0.05) for home heating, having a cat at home (OR=1.13; 95% CI 1.03-1.23; p=0.01), engaging in weekly physical exercise three or more times every week (OR= 1.31; 95% CI: 1.14 - 1.51; p < 0.001), consumption of paracetamol at least once a month (OR 1.24; 95% CI 1.15 - 1.35; p < 0.001). Respondents who had 2 or more older siblings had a reduced risk of current asthma (OR 0.88; 95% CI 0.78 - 1.00; p = 0.04), table 4.

Environmental risk factors associated with severe asthma on univariable analyses were exposure to ETS: maternal smoking (OR 1.63; 95% CI 1.39 -1.90; p<0.001), paternal smoking (OR 1.15 95% CI 1.03 -1.29; p=0.02); and other smokers at home (OR 1.17 95% CI 1.03 -1.34; p=0.02); having a cat at home (OR=1.17; 95% CI 1.07-1.29; p=0.001), engaging in physical exercise 3 or more times every week (OR 1.42; 95% CI 1.23 -1.63; p = <0.001) and ingestion of paracetamol at least once a month (OR 1.21, 95% CI 1.09 – 1.36; p=0.001).

On multivariable analysis, factors associated with current asthma were maternal smoking (OR 1.41; 95% CI 1.23 - 1.64; p < 0.001), heating the home with electricity (OR 1.13; 95% CI 1.01- 1.28; p =0.04) , open fires (OR 1.28; 95%CI 1.08-1.51; p=0.01), engaging in regular strenuous physical exercise (OR 1.29; 95% CI 1.11, 1.50; p = 0.001), consumption of paracetamol at least once a month (OR 1.23; 95% CI 1.13 -1.33; p < 0.001), while having 2 or more older siblings was protective (OR 0.87; 95% CI 0.77- 0.98; p = 0.03), table 5.

On multivariable analysis, factors associated with severe asthma were maternal smoking (OR=1.61; 95% CI: 1.38 - 1.89; p < 0.001), having a cat at home (OR=1.14; 95% CI 1.04-1.25; p=0.03), engaging in frequent physical exercise (OR=1.42; 95% CI: 1.23 - 1.64; p < 0.001) or paracetamol at least once every month (OR 1.20; 95% CI 1.07 - 1.34; p < 0.001), table 5.

*Asthma and environmental risk factors in Anglophone compared to Francophone countries*

When analyzed by language divide, asthma prevalence in the Anglophone countries was 15.1% (1723/11381), 95% CI 14.5 to 15.8), compared to 11.3% (1927/17109), 95% CI 10.8 to 11.8), in Francophone sites,  $p < 0.001$ . Severe asthma prevalence was 11.0% (1257/11381), 95% CI 10.5 to 11.6), and 7.1% (1214/17109), 95% CI 6.7 to 7.5), respectively in Anglophone vs. Francophone countries,  $p < 0.001$ .

In a multivariable analysis, the important environmental influences for asthma that were present in both areas included maternal smoking,  $\geq 3$  weekly physical exercise or monthly paracetamol use. In addition in Anglophone countries associations were found for cat in the home (OR=1.26; 95% CI 1.11 to 1.39;  $p < 0.001$ ), and a protective role for use of gas for heating (OR=0.80; 95% CI 0.67 to 0.96;  $p = 0.02$ ) while in Francophone countries, gas heating (OR=1.31; 95% CI 1.09 to 1.57;  $p = 0.003$ ) or fire heating (OR= 1.25; 95% CI 1.01 to 1.56;  $p = 0.04$ ) were significantly associated with asthma, (supplementary Tables 6 and 7).

There were similar associations with severe asthma in Anglophone and Francophone countries including maternal smoking (OR=1.38; 95% CI 1.05 to 1.83;  $p = 0.02$ ), engaging in strenuous exercise (OR=1.58; 95% CI 1.25 to 2.02;  $p = 0.002$ ) and monthly paracetamol exposure (OR=1.23; 95% CI 1.08 to 1.41;  $p = 0.003$ ); (supplementary Tables 8 and 9).

## **Discussion**

This large study of asthma in African adolescents participating in ISAAC III has shown high prevalence rates of asthma with a high proportion having severe asthma. Several environmental factors were highly prevalent and were associated with asthma or severe disease. Asthma prevalence was associated with use of open fires and electricity for heating the home, maternal smoking,  $\geq 3$  weekly physical exercise and monthly paracetamol consumption

and having an older sibling; while severe asthma was associated with exposure to maternal smoking, gas for home heating, frequent physical exercise and paracetamol consumption. There were consistent exposures associations with severe asthma in both Anglophone and Francophone countries.

Our study showed that smoke exposure was a significant risk factor for childhood asthma and for severe disease, as has been previously reported in many African countries<sup>8,12-16</sup>. These findings add to the evidence for the adverse impact of Environmental tobacco smoke (ETS), on lung health in children and adolescents. This is especially important in Africa where the prevalence of smoking is increasing and where adolescents may be at an increased risk of becoming smokers<sup>16,17,18</sup>. The association of asthma with ETS exposure even occurred in areas with a low prevalence of maternal smoking. Cigarette smoking and second-hand smoke exposure of any intensity are well documented triggers of asthma<sup>19-21</sup>. The association may be due to direct toxin effects on the bronchial epithelium and cilia, causing oxidative damage, and making the airway asthma-prone<sup>22</sup>. ETS exposure to the airways also causes the release of proinflammatory mediators and resultant increase in epithelial permeability which leads to mucosal edema and this contributes to asthma symptoms<sup>22</sup>. Furthermore, cumulative exposure to tobacco smoke culminates in a decline in lung function: approximately 18% in forced expiratory volume in 1 second (FEV1) over a ten-year period<sup>23</sup>.

Many households in low and middle-income countries burn biomass fuels in open fireplaces or in non-airtight cooking or heating stoves. This results in substantial emissions, with high levels of indoor pollution. Biomass exposure to wood for cooking or heating the home thus poses a significant risk for current asthma, due to high level of respirable particulate matter, further confirming findings from other studies<sup>24-26</sup>. Many wood smoke constituents cause both acute and chronic biologic, physiologic, and structural effects in the lungs including obstructive symptoms<sup>26</sup>. Further use of gas for heating or cooking is increasingly occurring in these areas, as

the population becomes less poor. However, concerning data suggests that exposure to volatile organic compounds (from paraffin or gas) may be associated with substantial respiratory morbidity including wheezing<sup>25,26</sup>.

In those with older siblings, a protective effect was noted, as has been reported in other studies<sup>27-31</sup>. Large family size was however not associated with severe asthma in this present study. This may be because the protective effect of frequent exposures to infection that comes from having many siblings, which influences the TH 1 pathway in the “hygiene hypothesis” may not totally account for the other inflammation pathways involved in developing severe asthma.

There was an increased risk of current asthma in children who engaged in frequent physical exercise as seen in other studies<sup>32,33</sup>. Exercise may precipitate asthma and though the exact mechanism is unknown, two theories are promulgated: the airway humidity theory, which suggests that air movement through the airway results in relative drying of the airway that serves as a trigger to a cascade of events that results in airway edema and bronchospasm. The other theory, based on airway cooling phenomenon where the moving air in the bronchial tree results in a decreased temperature of the bronchi, which triggers a hyperemic response in an effort to heat the airway. This also culminates in release of inflammatory mediators with resultant bronchial wall spasm<sup>34</sup>. However, it is also possible that exercise unmasked asthma symptoms in children with underlying or undiagnosed asthma.

There was a consistent significant association in our study between current and severe asthma with monthly paracetamol consumption as also seen in various other studies<sup>35-40</sup>.

Paracetamol when consumed, causes the total glutathione levels rise and this has been associated with marked functional bronchoconstriction.<sup>40</sup> These levels are reported to be increased in induced sputum of patients with mild and moderate asthma<sup>38</sup>, further buttressing the contribution of oxidative stress to the pathogenesis of airway inflammation.

One limitation of the study is reliance on recall and on written response to wheezing or whistling in chest in past 12 months as the measure of current asthma, especially as there is no word for wheezing in many African languages. However, this method has been widely used in ISAAC for the diagnosis of asthma. ~~As~~, this was a cross-sectional study causality cannot be inferred. Also indoor air pollution or biomass exposure was not objectively measured. The sample was not weighted for the true population sizes and the centres that did not complete the environmental questionnaire, and thus excluded from analysis, may affect generalizability of results. However, the sites studied were widely spread across geographical divisions of Africa, represent a large number of children and are thus a representative sample. Further, differences across sites and schools within sites were accounted for in the regression analysis.

In conclusion, this study highlights that asthma is common and often severe in African children and that there are specific environmental exposures associated with disease. Several exposures of public health importance were identified, highlighting the need for stronger health policies and programs to reduce exposures associated with disease. Strategies to promote cleaner fuels and reduce smoking are urgently needed in African countries to improve child health.

***Conflict of interest***

None

## **References**

1. ISAAC Steering Committee. Worldwide variations in the prevalence of asthma symptoms: The International Study of Asthma and Allergies in Childhood (ISAAC). *Eur Respir J* 1998; 12: 315- 35.
2. Mallola J, Craneb J von Mutiusc E, Odhiambo J, Keile U, Stewartf A, the ISAAC Phase Three Study Group. The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three: A global synthesis. *Allergol Immunopathol* 2013;41: 73-85.
3. Adeloye D, Yee Chan K, Rudan I, Campbell H. An estimate of asthma prevalence in Africa: a systematic analysis. *Croat Med J* 2013; 54(6): 519–531. doi: 10.3325/cmj.2013.54.519 PMCID: PMC3893990.
4. Sears MR. Trends in the Prevalence of Asthma *Chest* 2014;145: 219-25.
5. Zar HJ, Ehrlich RI, Workman L, Weinberg EG. The changing prevalence of asthma, allergic rhinitis and atopic eczema in African adolescents from 1995 to 2002. *Pediatr Allergy Immunol.* 2007; 18:560-5.
6. The Global Asthma Report 2014. Available at <http://www.globalasthmareport.org/burden/burden.php>. Last accessed February 2018.
7. Ellwood P, Asher MI, Beasley R. The international study of asthma and allergies in childhood (ISAAC): phase three rationale and methods. *Int J Tuberc Lung Dis* 2005; 9:10–16.
8. Ehrlich RI, Du Toit D, Jordaan E, Potter P, Volmink JA, Weinberg E. Risk factors for childhood asthma and wheezing- Importance of maternal and household smoking. *Am J Respir Crit Care Med* 1996; 154: 681- 8.
9. Mohamed N, Ng'ang'a L, Odhiambo J, Nyamwaya J, Menzies R. Home environment and asthma in Kenyan school children: a case-control study. *Thorax* 1995;50:74-8.



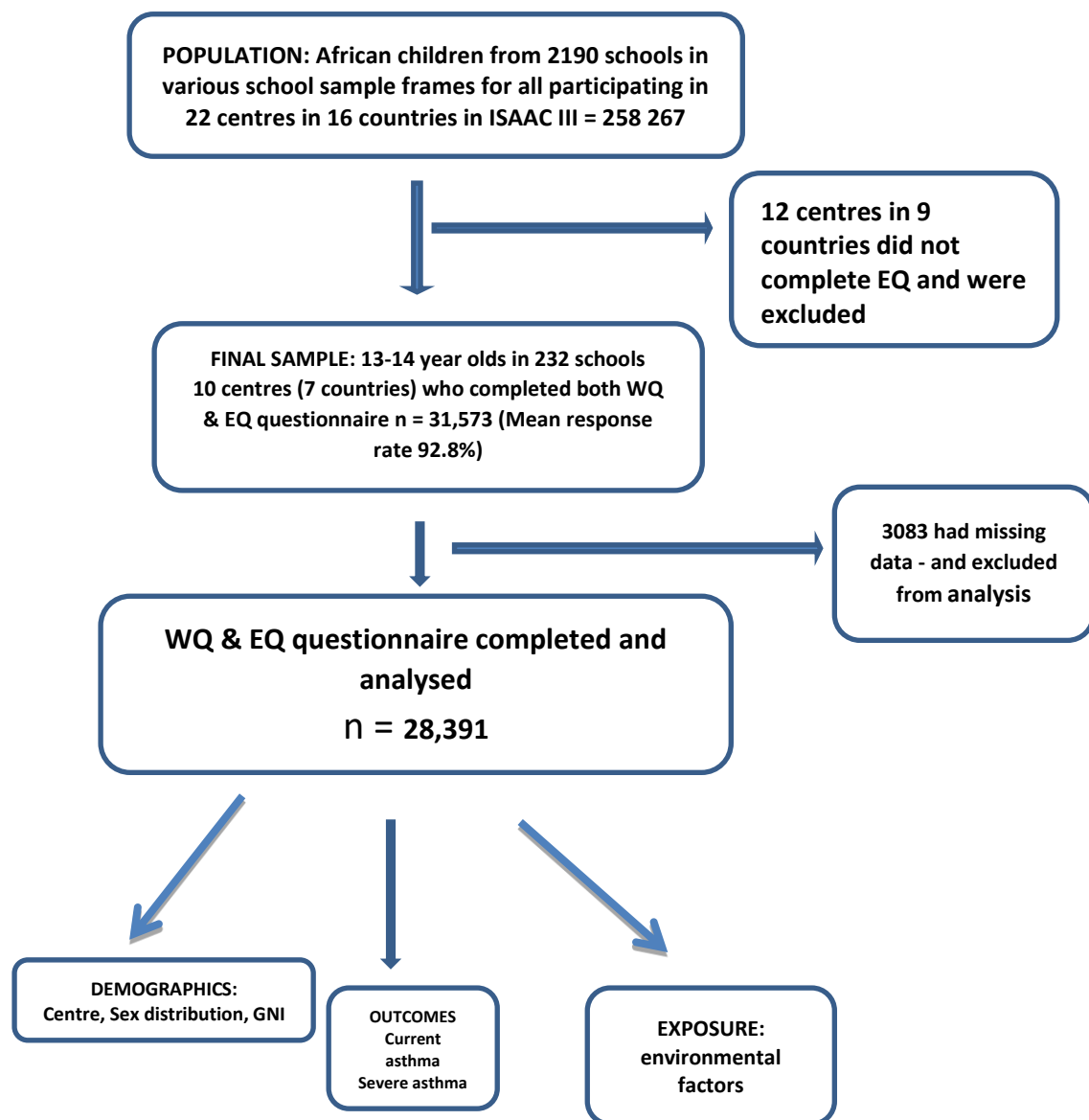
10. Ng'ang'a LW, Odhiambo JA, Mungai MW. Prevalence of exercise induced bronchospasm in Kenyan school children: an urban-rural comparison. *Thorax* 1998; 53: 919- 26.
11. Environmental questionnaire ISAAC Document 082. ISAAC Phase Three. Available at <http://isaac.auckland.ac.nz/phases/phasethree/phasethree.html> Last accessed April 2018.
12. WHO. WHO report on the global tobacco epidemic 2013. WHO; 2013 [cited October 2014].
13. Msyamboza KP, Mvula C, Kathyola D. Prevalence and correlates of tobacco smoking, use of smokeless tobacco and passive smoking in adult Malawians: National population-based NCD STEPS survey. *Science Postprint* 2013; 1(1): e00002.  
doi:10.14340/spp.2013.10A0004
14. Maluleke KR, Worku Z. Environmental Determinants of asthma among school children aged 13-14 in and around Polokwane, Limpopo province, South Africa. *Int. J. Environ. Res. Public Health* 2009; 6: 2354-74.
15. Ehrlich RI, du Toit D, Jordaan E, Potter P, Weinberg E, Volmink J, Zwarenstein M, Weinberg E. Household smoking and bronchial hyper responsiveness in asthmatic children *J Asthma* 2001;3: 239-51.
16. Butz AM, Halterman JS, Bellin M, Tsoukleris M, Donithan M, Kub J *et al.* Factors associated with second-hand smoke exposure in young inner-city children with asthma. *Journal of Asthma* 2011; 48:449-57.
17. Rudatsikira E, Abdo A, Muula AS. Prevalence and determinants of adolescent tobacco smoking in Addis Ababa, Ethiopia. *BMC Public Health* 2007; 7:176.
18. Peltzer K. Tobacco use trends among adolescents and adults in South Africa. *J Psychol Afr* 2008; 18:339-46.

19. National Institutes of Health. Expert Panel Report 3. Guidelines for the diagnosis and management of asthma. NIH Publication No. 07-4051 Bethesda, MD: National Institutes of Health; 2007.
20. Van der Vaart H, Postma DS, et al. Acute effects of cigarette smoking on inflammation in healthy intermittent smokers. *Respir Res* 2005; 6: 22.
21. Behan DF, Michael P. Eriksen MP, Lin Y. Economic effects of Environmental Tobacco Smoke in 2005 Society of Actuaries. Available at <http://erj.ersjournals.com>. Last accessed November 2017.
22. Stapleton M, Howard-Thompson A, George C, Hoover RM, Self TH. Smoking and asthma. *J Am Board Fam Med* 2011; 24:313-22.
23. Boulet L-P, Lemièrre C, Archambault F, Carrier G, Claire MD, Deschesnes F. Smoking and asthma: clinical and radiologic features, lung function, and airway inflammation. *Chest* 2006; 129: 661–8.
24. Vanker A, Barnett W, Workman L, Nduru PM, Sly PD, Gie RP *et al*. Early-life exposure to indoor air pollution or tobacco smoke and lower respiratory tract illness and wheezing in African infants: a longitudinal birth cohort study. *Lancet Planet Health* 2017; 1: e328–36.
25. Wong GWK, Brunekreef B, Ellwood P, Anderson HR, Asher MI, Crane J *et al*. Cooking fuels and prevalence of asthma: a global analysis of phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *The Lancet Respiratory Medicine* 2013; 1:386-94, DOI: [https://doi.org/10.1016/S2213-2600\(13\)70073-0](https://doi.org/10.1016/S2213-2600(13)70073-0)
26. Oguonu T, Obumneme-Anyim IN, Eze JN, Ayuk AC, Okoli CV, Ndu IK. Prevalence and determinants of airflow limitation in urban and rural children exposed to cooking fuels in South-East Nigeria. *Paediatr Int Child H* 2018. Published online 15th March 2018. <https://doi.org/10.1080/20469047.2018.1445506>.

27. Okada H, Kuhn C, Feillet H, Bach J-F. The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. *Clin Exp Immunol* 2010; 160: 1–9.
28. Cullinan P. Childhood allergies, birth order and family size. *Thorax* 2006; 61:3-5.
29. Strachan DP, Ait-Khaled N, Foliaki S, Mallol J, Odhiambo J, Pearce, N *et al.* Siblings, asthma, rhinoconjunctivitis and eczema: a worldwide perspective from the International Study of Asthma and Allergies in Childhood. *Clin Exp Allergy* 2015; 45:126-36.
30. Goldberg S, Israeli E, Schwartz S, Shochat T, Izbicki G, Toker-Maimon O, Klement E, Picard E. Asthma prevalence, family size, and birth order. *Chest* 2007;131:1747-52.
31. Steinman HA, Donson HA, Kawalski M, Toerien A, Potter PC. Bronchial hyper-responsiveness and atopy in urban, peri-urban and rural South African children. *Pediatr Allergy Immunol* 2003; 14:383-93.
32. Vlaski E, Stavric K, Seckova L, Kimovska M, Isjanovska R. Influence of physical activity and television-watching time on asthma and allergic rhinitis among young adolescents: preventive or aggravating? *Allergologia et Immunopathologia*, 2008; 36;5 247- 53.
33. Anderson SD. How does exercise cause asthma attacks? *Curr Opin Allergy Clin Immunol* 2006; 6:37-42.
34. Shaheen SO, Newson RB, Smith GD, Henderson AJ, Stratton FD, Jones RW, Strachan DP and the ALSPAC Study Team. Prenatal paracetamol exposure and risk of asthma and elevated immunoglobulin E in childhood. *Clin Exp Allergy* 2005; 35: 18–25.
35. Shaheen SO, Newson RB, Sherriff A, Henderson AJ, J E Heron JE, Burney PGJ, J Golding J and the ALSPAC Study Team. Paracetamol use in pregnancy and wheezing in early childhood. *Thorax* 2002; 57: 958–63.
36. Oshnouei S, Salarilak Sh, Khalkhali A, Karamyar M, Rahimi R, Delpishe A. Effects of Acetaminophen consumption in asthmatic children. *Iran Red Crescent Med J* 2012; 14:641–6.

37. Davey G, Berhane Y, Duncan P, Aref-Adib G, Britton J, Venn A. Use of acetaminophen and the risk of self-reported allergic symptoms and skin sensitization in Butajira, Ethiopia. *J Allergy Clin Immunol* 2005; 116: 863–8.
38. Beasley R, Clayton T, Crane J, von Mutius E, Lai CKW, Montefort S, Stewart A, for the ISAAC Phase Three Study Group. Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6–7 years: analysis from Phase Three of the ISAAC programme. *Lancet* 2008; 372: 1039–48.
39. Beier J, Beeh KM, Semmler D, Beike N. Increased concentrations of glutathione in induced sputum of patients with mild or moderate allergic asthma. *Annals of Allergy* 2004; 92: 459–63.
40. Dimova, S, Hoet, PHM, Dinsdale, D, Nemery, B. Acetaminophen decreases intracellular glutathione levels and modulates cytokine production in human alveolar macrophages and type II pneumocytes in vitro. *Int J Biochem Cell Biol.* 2005; 37:1727-37.

**FIGURES**



**Figure 1:** Flow chart for selection of adolescent participants in the environmental ISAAC III study for African centres

## TABLES

**Table 1: Characteristics of Participants in African centres in ISAAC III**

Centre	Cape Town [SOUTH AFRICA]	Ibadan [NIGERIA]	Addis Ababa [ETHIOPIA]	Yaoundé [CAMEROON]	Urban Cote d'Ivoire [COTE D'IVOIRE]	Port-Gentil [GABON]	Boulmene [MORROCCO]	Casablanca [MORROCCO]	Marrakech [MORROCCO]	Khartoum [SUDAN]
<b>Number of Participants</b>	5037	3142	3195	2983	3342	3166	1254	1777	1689	2896
<b>Language divide</b>	Anglophone	Anglophone	Anglophone	Francophone	Francophone	Francophone	Francophone	Francophone	Francophone	Francophone
<b>Gender (Male %)</b>	40	57	43	46	60	47	60	52	42	53
<b>GNI gross national income</b>	Middle	Low	Low	Low	Low	Low	Middle	Middle	Middle	Low
<b>Response rate (%)</b>	83.4	99.7	96.8	90.6	82.5	78.7	100	100	99.9	96.5

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**Table 2: Prevalence rates of asthma in adolescents in African centres in ISAAC III**

Centre	Cape Town [SOUTH AFRICA]	Ibadan [NIGERIA]	Addis Ababa [ETHIOPIA]	Yaoundé [CAMEROON]	Urban Cote d'Ivoire [COTE D'IVOIRE]	Port-Gentil [GABON]	Boulmene [MORROCCO]	Casablanca [MORROCCO]	Marrakech [MORROCCO]	Khartoum [SUDAN]
<b>Current asthma % (95%CI)</b>	<b>20.4</b> (19.3-21.5)	<b>13.0</b> (11.8-14.2)	<b>9.1</b> (8.1-10.1)	<b>5.7</b> (4.9-6.6)	<b>19.3</b> (18.0-20.7)	<b>10.2</b> (9.2-11.3)	<b>5.4</b> (4.2-6.8)	<b>16.0</b> (14.4-17.8)	<b>4.4</b> (3.5-5.5)	<b>12.5</b> (11.3-13.7)
<b>n/N*</b>	1025/5037	408/3149	290/3195	169/2983	645/3342	324/3168	68/1254	285/1777	75/1689	361/2876
<b>Severe asthma/Total (%) (95% CI)</b>	<b>12.4</b> [11.5-13.3]	<b>9.5</b> [8.5-10.6]	<b>8.2</b> [7.3-9.2]	<b>4.3</b> [3.6-5.1]	<b>12.0</b> [10.9-13.1]	<b>5.9</b> [5.1-6.8]	<b>2.7</b> [1.9-3.8]	<b>8.7</b> [7.5-10.1]	<b>2.2</b> [1.6-3.0]	<b>9.5</b> [8.5-10.6]
<b>Severe asthma/current asthma% (n/N)*†</b>	46.4 (476/1025)	39.2 (132/337)	63.8 (185/290)	47.3 (80/169)	61.9 (399/645)	44.1 (143/324)	48.5 (33/68)	54.0 (154/285)	48.0 (36/75)	58.2 (210/361)
<b>Asthma ever</b>	33.15	20.4	17.5	8.9	28.4	16.5	10.9	23.8	10.1	16.3
<b>Severe/asthma ever proportion (%)</b>	32.6	10.3	46.8	36.4	42.19.31	27.8	23.5	36.7	21.8	46.7

\*unweighted prevalence † proportion of severe asthma of those with current asthma

**Table 3: Prevalence of environmental risk factors in Africa**

<b>Environmental factors (variables)</b>	<b>All African centres combined prevalence n (%)</b>	<b>Prevalence range of centres (%)</b>
Mom smokes	1,959 (6.9)	0.5 to 27.9
Dad smokes	6,156 (21.6)	2.8 to 42.3
≥ 3 Smokers at home	15,371 (54.0)	14.8 to 100
Electric cooking	7327 (25.7)	0.5 to 88.1
Gas cooking	17967 (63.1)	10.0 to 97.6
Fire cooking	8051(28.3)	0.1 to 85.8
Electric heating	7,394 (26.0)	0.00 to 70.3
Gas heating	3,333 (11.7)	0.00 to 27.7
Fire heating	6,472 (22.7)	0.03 to 88.2
≥2 Older siblings	24,378 (85.6)	69.6 to 99.9
≥2 Younger siblings	23,811 (83.6)	67.5 to 99.9
Cat at home	11,043 (38.8)	20.0 to 75.3
Dog at home	9,596 (33.7)	14.5 to 52.9
≥3 weekly exercise	5613 (19.7)	5.9 to 33.3
≥5 television hours	9603 (33.7)	17.1 to 58.9
Monthly paracetamol	11,654 (40.9)	16.4 to 64.3



**Table 4: Environmental exposures and association with current asthma in African adolescents participating in ISAAC III**

Variables*	Univariable			Multivariable**		
	OR	95% CI	p value	OR	95% CI	p value
Mom smokes	1.42	1.23 - 1.64	<b>&lt;0.001</b>	1.41	1.23 - 1.64	<b>&lt;0.001</b>
Dad smokes	1.14	1.03 - 1.26	<b>0.01</b>			
Smokers at home	1.07	0.96 – 1.19	0.21			
Electric cooking	1.00	0.89 - 1.13	0.99			
Gas cooking	1.01	1.00 - 1.14	0.85			
Fire cooking	1.01	0.86-1.20	0.84			
Electric heating	1.12	1.00 - 1.26	<b>0.05</b>	1.13	1.01 - 1.28	<b>0.04</b>
Gas heating	0.88	0.76 – 1.02	0.09			
Fire heating	1.28	1.05 - 1.43	<b>0.01</b>	1.28	1.08 - 1.51	<b>0.01</b>
Older siblings	0.88	0.78 – 1.00	<b>0.04</b>	0.87	0.77 – 0.98	<b>0.03</b>
Younger siblings	0.94	0.85 -1.04	0.23			
Cat at home	1.13	1.03 - 1.23	<b>0.01</b>			
Dog at home	1.06	0.97 – 1.16	0.20			
≥3 exercise weekly	1.31	1.14 - 1.51	<b>&lt;0.001</b>	1.29	1.11 - 1.50	<b>0.001</b>
≥5 hour daily television watching	1.06	0.97 – 1.16	0.21			
≥1 Monthly paracetamol	1.24	1.15 - 1.35	<b>&lt;0.001</b>	1.23	1.13 - 1.33	<b>&lt;0.001</b>

\*All variables individually adjusted for inter- centre and cluster variability. \*\*Backward elimination

**Table 5: Environmental exposures and association with severe asthma in African adolescents participating in ISAAC III**

Variables*	Univariable			Multivariable		
	OR	95% CI	p value	OR	95% CI	p value
Mom smokes	1.63	1.39 – 1.90	<b>&lt;0.001</b>	1.61	1.38 – 1.89	<b>&lt;0.001</b>
Dad smokes	1.15	1.03 - 1.29	<b>0.02</b>			
Smokers at home	1.17	1.03 - 1.34	<b>0.02</b>			
Electric cooking	1.03	0.82 - 1.28	0.81			
Gas cooking	1.07	0.93 - 1.23	0.33			
Fire cooking	1.07	0.91 - 1.26	0.43			
Electric heating	1.00	0.87 - 1.14	0.99			
Gas heating	1.02	0.89 - 1.17	0.77			
Fire heating	1.15	0.94 -1.40	0.17			
Older siblings	0.95	0.83- 1.09	0.46			
Younger siblings	1.07	0.94 – 1.20	0.31			
Cat at home	1.17	1.07 – 1.29	<b>0.001</b>	1.14	1.04 - 1.25	<b>0.03</b>
Dog at home	1.11	1.00 - 1.24	0.06			
≥3 weekly exercise	1.42	1.23 - 1.63	<b>&lt;0.001</b>	1.42	1.23 - 1.64	<b>&lt;0.001</b>
≥5 hour daily television watching	1.12	0.99 - 1.24	0.07			
≥1 Monthly paracetamol	1.21	1.09 - 1.36	<b>0.001</b>	1.20	1.07 - 1.34	<b>&lt;0.001</b>

\*All variables adjusted for inter- centre and cluster variability and \*\*Backward elimination

**\*\*Supplementary tables: Environmental exposures and association with language (cultural) divide**

**Table 6: Environmental exposures and association with current asthma in Anglophone African adolescents participating in ISAAC III**

Variables*	Univariable			Multivariable**		
	OR	95% CI	p value	OR	95% CI	p value
Mom smokes	1.40	1.18 - 1.66	<b>&lt;0.001</b>	1.32	1.13 - 1.55	<b>&lt;0.001</b>
Dad smokes	1.20	1.04 - 1.39	<b>0.01</b>			
Smokers at home	1.10	0.92 - 1.31	0.30			
Electric cooking	1.05	0.91 - 1.21	0.52			
Gas cooking	0.98	0.86 - 1.13	0.82			
Fire cooking	1.09	0.83 - 1.42	0.52			
Electric heating	1.23	1.04 - 1.48	<b>0.02</b>			
Gas heating	0.76	0.63 - 0.92	<b>0.004</b>	0.80	0.67 - 0.96	<b>0.02</b>
Fire heating	1.30	1.02 - 1.66	<b>0.03</b>			
Older siblings	0.91	0.76 - 1.12	0.36			
Younger siblings	0.94	0.80 - 1.09	0.39			
Cat at home	1.28	1.14 - 1.44	<b>&lt;0.001</b>	1.26	1.11 - 1.39	<b>&lt;0.001</b>
Dog at home	1.03	0.92 - 1.15	0.59			
≥3 exercise weekly	1.18	1.01 - 1.39	<b>0.04</b>	1.29	1.11 - 1.50	<b>0.001</b>
≥5 hour daily television watching	1.03	0.90 - 1.19	0.64			
≥1 Monthly paracetamol	1.21	1.06 - 1.38	<b>0.01</b>	1.23	1.13 - 1.33	<b>&lt;0.001</b>

\*All variables individually adjusted for inter- centre and cluster variability. \*\*Backward elimination

**Table 7: Environmental exposures and association with current asthma in Francophone African adolescents participating in ISAAC III**

Variables*	Univariable			Multivariable		
	OR	95% CI	p value	OR	95% CI	p value
Mom smokes	1.52	1.23 – 1.88	<b>&lt;0.001</b>	1.47	1.19 – 1.83	<b>&lt;0.001</b>
Dad smokes	1.09	0.95 - 1.24	0.22			
Smokers at home	1.06	0.92 - 1.21	0.43			
Electric cooking	0.90	0.71 - 1.15	0.41			
Gas cooking	1.05	0.85 - 1.29	0.66			
Fire cooking	0.96	0.78 - 1.18	0.72			
Electric heating	1.02	0.87 - 1.14	0.99			
Gas heating	1.18	1.00 - 1.40	<b>0.05</b>	1.31	1.09 - 1.57	<b>0.003</b>
Fire heating	1.18	0.96 -1.44	0.12	1.25	1.01 - 1.56	<b>0.04</b>
Older siblings	0.95	0.83- 1.09	0.46			
Younger siblings	0.95	0.83 – 1.08	0.40			
Cat at home	1.01	0.90 – 1.14	0.83			
Dog at home	1.09	0.95 - 1.26	0.22			
≥3 weekly exercise	1.46	1.16 - 1.83	<b>0.001</b>	1.45	1.15 - 1.82	<b>0.002</b>
≥5 hour television watching daily	1.08	0.95 - 1.21	0.22			
≥1 Monthly paracetamol	1.27	1.15 - 1.41	<b>&lt;0.001</b>	1.27	1.19 - 1.83	<b>&lt;0.001</b>

\*All variables adjusted for inter- centre and cluster variability and \*\*Backward elimination

**Table 8: Environmental exposures and association with severe asthma in Anglophone African adolescents participating in ISAAC III**

Variables*	Univariable			Multivariable**		
	OR	95% CI	p value	OR	95% CI	p value
Mom smokes	1.68	1.39 – 2.02	<b>&lt;0.001</b>	1.38	1.05 – 1.83	<b>0.02</b>
Dad smokes	1.23	1.05 - 1.43	<b>0.01</b>			
Smokers at home	1.45	1.16 – 1.81	0.001			
Electric cooking	1.06	0.89 - 1.26	0.51			
Gas cooking	1.02	0.88 - 1.17	0.81			
Fire cooking	1.12	0.87 -1.44	0.36			
Electric heating	1.06	0.87 - 1.30	0.55			
Gas heating	0.97	0.82 – 1.16	0.77			
Fire heating	1.05	0.78 - 1.40	0.76			
Older siblings	1.02	0.85 – 1.22	0.87			
Younger siblings	1.15	0.97 -1.37	0.10			
Cat at home	1.27	1.13 - 1.43	<b>&lt;0.001</b>			
Dog at home	1.08	0.96 – 1.23	0.22			
≥3 exercise weekly	1.27	1.08 - 1.50	<b>0.003</b>	1.58	1.25 – 2.02	<b>&lt;0.001</b>
≥5 hour daily television watching	1.13	0.97 – 1.31	0.64			
≥1 Monthly paracetamol	1.17	1.00 - 1.41	0.07	1.23	1.08 - 1.41	<b>0.003</b>

\*All variables individually adjusted for inter- centre and cluster variability. \*\*Backward elimination

**Table 9: Environmental exposures and association with severe asthma in Francophone African adolescents participating in ISAAC III**

Variables*	Univariable			Multivariable		
	OR	95% CI	p value	OR	95% CI	p value
Mom smokes	1.46	1.10 – 1.92	<b>0.01</b>	1.38	1.05 – 1.83	<b>0.02</b>
Dad smokes	1.09	0.92 - 1.29	0.34			
Smokers at home	1.04	0.89 - 1.21	0.65			
Electric cooking	1.00	0.75 - 1.34	0.99			
Gas cooking	1.16	0.87 - 1.56	0.31			
Fire cooking	1.02	0.82 - 1.27	0.86			
Electric heating	0.93	0.78 - 1.11	0.43			
Gas heating	1.14	0.93 - 1.40	0.22			
Fire heating	1.24	0.94 -1.62	0.12			
Older siblings	0.90	0.74- 1.10	0.29			
Younger siblings	0.99	0.83 – 1.18	0.919			
Cat at home	1.01	0.95 – 1.24	0.24			
Dog at home	1.15	0.95 - 1.41	0.12			
≥3 weekly exercise	1.61	1.27 – 2.04	<b>0.001</b>	1.59	1.25 – 2.02	<b>&lt;0.001</b>
≥5 hour television watching daily	1.09	0.93 - 1.27	0.29			
≥1 Monthly paracetamol	1.25	1.09 - 1.43	<b>0.001</b>	1.23	1.08 - 1.41	<b>0.003</b>

\*All variables adjusted for inter- centre and cluster variability and \*\*Backward elimination

\*All variables adjusted for inter- centre and cluster variability and \*\*Backward elimination

## **CHAPTER 3**

## **APPENDICES**

### **Appendix 1**

#### **Approval of protocol**

Questionnaire/data capture instrument(s) • Consent forms and related participant information sheets • Technical appendices and relevant additional tables not included in the main manuscript. These should be accompanied by a brief narrative. • Ethics approval letters (except for a full systematic review) and other relevant permissions • Instructions to authors if format I or II is submitted

## APPENDICES

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