The Role of Fractional Exhaled Nitric Oxide Measurements in Identifying Subjects with Asthma Symptoms in Western Kenya

by

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Thesis submitted in partial fulfillment of
the requirements for the degree of
Master of Science in the Duke Global Health Institute
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ABSTRACT

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Abstract

Background: Fractional exhaled nitric oxide (FeNO) is a novel biomarker that is utilized as a tool to assist with the diagnosis and management of asthma in developed countries. Little data exists from sub-Saharan Africa to understand the role for exhaled nitric oxide in subjects suspected of having asthma. In this study, we aim to elucidate if a relationship exists between elevated FeNO levels and symptoms of asthma.

Methods: Using a cluster randomized stratified sampling strategy, 154 subjects age 12 and above in Uasin Gishu County, Kenya were enrolled. Questionnaires including International Study of Asthma and Allergies in Childhood (ISAAC) written and video questionnaires and the St George's Respiratory Questionnaire for COPD were completed. Subjects were tested for FeNO, pre-and post-bronchodilator spirometry, and exhaled carbon monoxide. Odds ratios for the presence of asthma symptoms based on FeNO levels above or below a cutoff point of 71 ppb were generated.

Results: Overall, 5.8% of subjects were identified with asthma symptoms by video questionnaires, and 17.5% by written questionnaires. Median FeNO levels were significantly higher in subjects with wheezing compared to those without. The odds ratio for wheezing in individuals with FeNO levels greater than 71 ppb compared to less than 71 ppb was 7.8 (video questionnaire) and 11.3 (written questionnaire).

Conclusions: A statistically significant relationship exists between elevated levels of FeNO and symptoms of asthma in this western Kenyan population. Further work is needed to explore this link for clinical and research purposes.

Contents

List of Tables

List of Figures

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1. Introduction

Chronic respiratory diseases make up the 3rd largest cause of noncommunicable disease mortality worldwide.[1] Of these, a significant proportion are due to asthma, a disease characterized by chronic inflammation with variable symptoms and airflow obstruction. People suffering from asthma often experience paroxysms of cough, chest tightness, wheezing, and difficulty breathing. The disease affects people of all ages, from young children to the elderly. In severe cases, exacerbations of asthma can be life threatening.[2]

Given its high prevalence and substantial associated morbidity and mortality, asthma has been the target of recent research efforts to better understand its epidemiology, biology, and determinants. Global initiatives, including the International Study of Asthma and Allergies in Childhood (ISAAC),[3] the Global Initiative for Asthma (GINA),[2] and Global Asthma Network (GAN)[4] have made large strides in our understanding of the rising prevalence of asthma worldwide. However, even with these large multinational collaborative efforts, research in asthma is limited in part due to difficulties obtaining accurate diagnoses. The diverse biology of the disease makes this more complex.

In recent years, research priorities have shifted to the identification and development of biomarker assays as adjunct tools for the diagnosis and management of chronic diseases. One promising new biomarker that has gained international attention

in the field of asthma research is exhaled nitric oxide. This odorless, colorless gas is found in the exhaled breath of all people, with higher levels identified in the airways of individuals with eosinophilic mucosal inflammation, such as is frequently seen in asthma.[5] Given advances in biotechnology, point of care testing for fractional exhaled nitric oxide (FeNO) is now possible. Through quantifying the concentration of this gas in exhaled breath, this noninvasive test provides insights into underlying airway biology. Recent guidelines from leading international respiratory societies have advocated for the inclusion of exhaled nitric oxide testing in diagnosis and management algorithms for patients with asthma.[5] However, the heterogeneous biology of the disease has led some to caution its use, pointing to subgroups of asthma with non-eosinophilic inflammation less accurately classified by FeNO measurements.[6,7]

Given that little has been done in sub-Saharan Africa to understand the underlying biology of clinically diagnosed asthmatic patients, in this study we aimed to investigate the relationship between exhaled nitric oxide levels and the presence of asthma symptoms in a sub-Saharan African population. We used the presence of wheezing in the past 12 months as a surrogate for asthma diagnosis, following the methods of the largest international asthma studies.[3] We hypothesize that a statistically significant relationship exists between exhaled nitric oxide values and asthma symptoms, with higher values of FeNO correlating with the presence of wheezing in the past 12 months.

2. Methods

2.1 Setting

This study took place in Uasin Gishu County, Kenya. Located in western Kenya, Uasin Gishu is home to the city of Eldoret, the 5th largest metropolitan area in Kenya, and Moi University. Comprised of urban, periurban, and rural areas and with an estimated population of 900,000 individuals in 2009, this setting affords a unique opportunity to investigate airway disease across geographical and socioeconomic gradients.[8] The county is comprised of 47 unique administrative locations which form the basis of our sampling procedures (Appendix A).[8]

2.2 Sample Size Calculation

We estimated that the overall prevalence of asthma in subjects in our study would be seven percent, in keeping with data from ISAAC.[3] Using a FeNO cutoff point as a tool to aid in the diagnosis of asthma, we estimated that the prevalence of asthma symptoms in subjects with a FeNO level less than 71 ppb would be five percent, and the prevalence of asthma symptoms in subjects with a FeNO level greater than 71 ppb would be 30%.[9] This cutoff point was selected based on data which demonstrated greater than 80% positive predictive value for asthma diagnosis above this value.[9] We used a ratio of sample sizes of seven percent between the two groups, and set an alpha of 0.05 and power of 80% to detect a difference between the two groups. This yielded a

sample size of 144 individuals, with 134 in the low FeNO group, and 10 in the high FeNO group.

2.3 Participants

Participants were identified for eligibility screening using a standardized cluster randomized stratified sampling protocol. Subjects age 12 and above were eligible for participation in the study if they resided in Uasin Gishu County at the time of enrollment. Exclusion criteria included contraindications to spirometry or bronchodilator administration, inability to perform breathing maneuvers, eye, abdominal, or thoracic surgery within the 6 weeks preceding enrollment, myocardial infarction within the previous 6 weeks, self-reported pregnant status, history of tachyarrhythmias, or clinical and/or radiographic diagnosis of a respiratory infection in the past four weeks. Exclusion criteria were modified from the National Health and Nutrition Examination Survey (NHANES) spirometry procedures manual.[10]

A subset of nine of the 147 administrative subunits encompassing and surrounding Eldoret were selected for recruitment based on proximity to the city center. Using ArcGIS software (version 10.5, Esri, Redlands, CA), a random GPS point was dropped within each of the nine administrative locations, and served as the initial point of contact in determining our population for recruitment.

Once GPS points within each location were identified, members of the study team used portable GPS units to get as close to the original GPS point within the individual location as physically and safely possible. Once at the GPS coordinates provided, 360-degree assessment was conducted to find the closest dwelling to the starting point. This served as the first dwelling approached for enrollment. All members of the dwelling were eligible for enrollment provided they fulfilled all inclusion/exclusion criteria and agreed to participate.

Following enrollment completion at the first dwelling, the next dwelling was identified by members of the study team standing at the main entrance to the dwelling and flipping a coin to determine in which direction to proceed, left or right. Next, a die was rolled to determine how many dwellings to skip prior to attempting enrollment. This process was repeated until the goal of 7 dwellings per GPS point was accomplished.[11]

2.4 Procedures

Subjects identified by the sampling procedures above and meeting eligibility criteria were approached for participation in the study by key personnel. The study, including risks and benefits, were discussed in detail with participants and written informed consent was performed in English (official language), Kiswahili (national language), or Kalenjin (local language) according to the preferences of the subject.

Following informed consent, subjects completed questionnaires facilitated by key personnel. FeNO testing was performed, followed by exhaled carbon monoxide testing (eCO) and pre-bronchodilator spirometry following successful safety screening. Those subjects identified to have abnormalities in their spirometry or multiple positive respiratory symptom questions also completed post-bronchodilator spirometry in accordance with American Thoracic Society guidelines for spirometry.[12] All data was captured electronically using tablet computers and Qualtrics survey software (Version 2017, Qualtrics, Provo, UT). Digital copies of spirograms and FeNO testing results were archived on secure servers. Upon completion of data collection, subjects were given written copies of their test results. Those subjects identified as having abnormalities in their FeNO, eCO, or spirometry testing, or with significant respiratory symptom burdens on questionnaires, were referred to subspecialty care with a pulmonary medicine provider. All subjects completing the protocol were compensated either with a 100 KES mobile phone credit voucher (approximate value $1 USD) or cookies according to their preference. All study procedures were approved by the ethical review boards at Duke University (Pro00070184), Moi University (IREC/2016/07), and the Kenyan National Commission for Science, Technology, and Innovation (NACOSTI/P/16/25171/13266).

2.5 Measures

2.5.1 ISAAC Questionnaire

For this study, the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was adopted to serve as both a diagnostic instrument and a severity-scoring tool for asthma. Developed and validated as part of an international collaborative effort to better understand childhood atopic diseases, since its publication it currently serves as the gold standard for epidemiological assessments of atopic disease. The original videos and questionnaires were obtained by the ISAAC steering committee and reproduced with permission, with videos being displayed on tablets and answers recorded on Qualtrics data collection forms electronically (Appendix B).[3]

2.5.2 St George's Respiratory Questionnaire for COPD (SGRQ-C)

The St George's Respiratory Questionnaire for COPD (SGRQ-C) was selected to provide a general assessment of respiratory symptom burden for individual subjects. Modified from the full St George's Respiratory Questionnaire, this validated survey focuses on symptoms most commonly identified by patients with obstructive lung diseases, and in doing so provides high quality data in a much shorter period than the full version. This form was reproduced from the original to be displayed on electronic data capture devices with the permission of the owning institution (Appendix B).[13,14]

2.5.3 Spirometry

Spirometry maneuvers were performed both pre- and post-bronchodilator administration, in accordance with the most recent American Thoracic Society performance guidelines. A CareFusion MicroLoop spirometer (Becton, Dickinson and Company, Franklin Lakes, NJ) was used for the measurements, and was calibrated daily with a 3-liter calibration syringe according to manufacturer recommendations. Bronchodilation was achieved with the administration of 400 micrograms of salbutamol delivered via metered dose inhaler using single use spacers with one-way valves. Spirometry was performed using single use disposable particle filters capable of removing bacteria, viruses, and mycobacterial pathogens.[12]

2.5.4 Fractional Exhaled Nitric Oxide

Fractional exhaled nitric oxide measurements were performed using an Circassia Niox Vero machine (Circassia, Oxford, UK) in accordance with manufacturer recommendations. Single use disposables with integrated air filters were obtained from the manufacturer for use in the study for subject protection. Single measurements were obtained and recorded, with data being stored on both the Niox Vero device and recorded electronically.

2.5.5 Exhaled Carbon Monoxide

Exhaled carbon monoxide measurements were obtained using a CareFusion MicroCO monitor (Becton, Dickinson and Company, Franklin Lakes, NJ). Single use disposable mouthpieces in combination with disinfection-compatible one-way valves were used. One-way valves were disinfected according to hospital standards following each use by trained hospital equipment sterilization nurses.

2.6 Analysis

All data were captured electronically using tablet computers and Qualtrics offline software. Data was entered a single time, and then a subset of 20% of entries were checked for internal consistency and accuracy, including verifying measurements from equipment records. GPS locations were automatically stored using the tablet computer's internal GPS and the Qualtrics software.

Survey data were analyzed using Chi squared and Fisher's exact tests for categorical data and Wilcoxon rank sum for continuous data. Comparisons of FeNO and eCO values based upon survey responses were conducted using Wilcoxon rank sum tests. Odds ratios for asthma, identified by the presence of wheezing in the past 12 months by either ISAAC video questionnaire or ISAAC written survey, and 95% confidence intervals were calculated using logistic regression modelling. Missing data

were assumed to occur randomly, and were excluded from the final analyses. All analyses were performed using Stata (version 14, StataCorp, College Station, TX).

3. Results

3.1 Baseline Demographics

Baseline demographics are outlined in Table 1. In total, 160 individuals were screened, and 154 met eligibility criteria and completed the study (Figure 1). Of these, 33% were male and 67% were female. Participants ranged from age 12 to 91, with most participants falling in the 19-49 age range. Median BMI was within the normal range, with the IQR for women extending into the overweight range. Eighty-two percent of subjects reported prior HIV testing, with only two subjects self-reporting HIV infection,

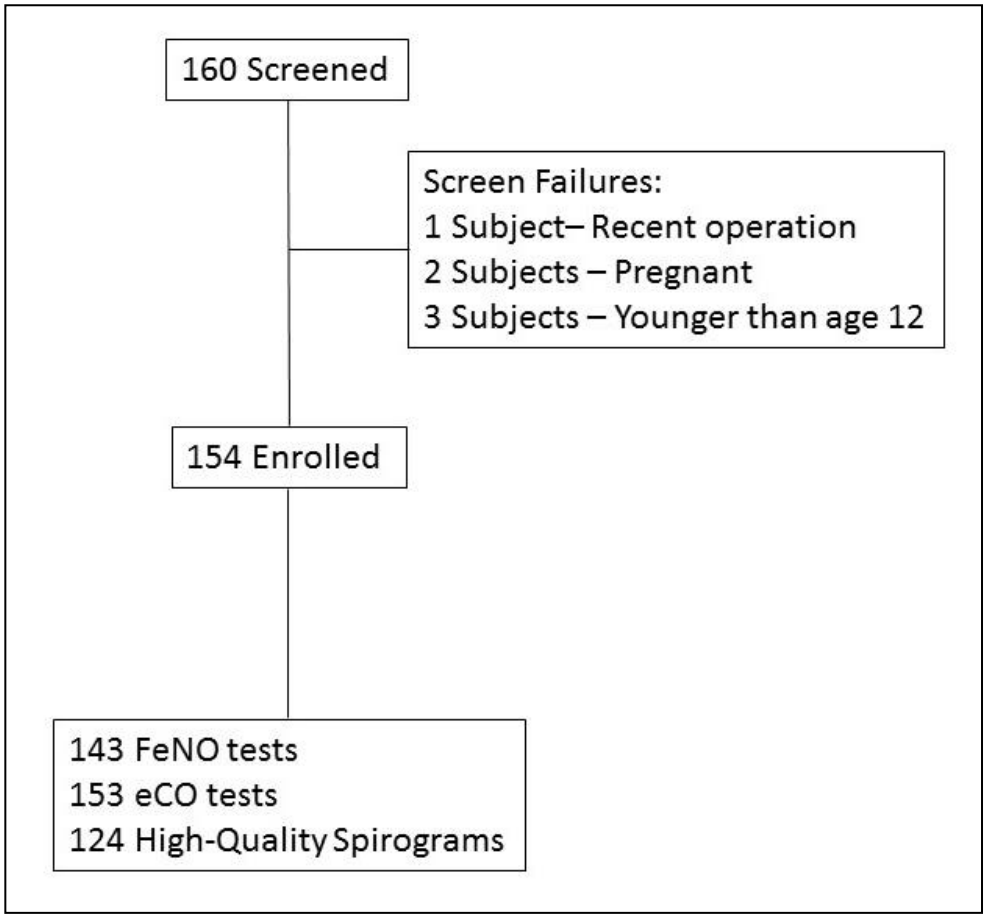

Figure 1: Consort Diagram for Participant Enrollment.

significantly less than the publically reported 7% prevalence in Kenya. One subject reported a history of prior tuberculosis. Interquartile ranges for blood pressure, heart rate, and pulse oximetry were all normal when analyzed as a composite and separately by gender. Unemployment was reported to be 76%, with median wages averaging 300 KES per day, or approximately $3 USD per day. Ninety-four percent of subjects reported using biomass as a household fuel, with 86% using biomass for at least 50% of household fuel needs.

Table 1: Baseline Demographics

	Total	**Male**	**Female**
Total Participants	154	51 (33%)	103 (67%)
Age (Range, yrs)	12-91	12-79	12-91
12 – 18	21 (14%)	11	10
19 – 34	67 (44%)	19	48
35 - 49	34 (22%)	8	26
50 - 65	22 (14%)	7	15
>65	10 (6%)	6	4
Height, cm (median, IQR)	168 (162 – 174)	174 (168 - 179)	165 (161 – 171)
Weight, kg (median, IQR)	62.5 (55 – 74)	61 (55 – 70)	64 (55 – 75)
BMI (median, IQR)	22 (18 – 23)	20 (18 – 23)	24 (20 – 27)
H/O TB Diagnosis	1		
H/O HIV Testing	126 (82%)	38 (75%)	88 (85%)
Positive HIV Test	2 (1%)	0 (0%)	2 (2%)
SBP, mmHg (median, IQR)	124 (115 – 133)	128 (115 – 134)	123 (114 – 131)
DBP, mmHg (median, IQR)	80 (73 – 86)	82 (74 – 87)	78 (71 – 85)
Heart rate, bpm (median, IQR)	75 (67 – 84)	68 (65 – 76)	77 (70 – 87)
SpO2	96 (94 – 97)	96 (94 – 97)	96 (94 – 97)

Employed	36 (24%)	17 (34%)	19 (18%)
Daily wage (median, IQR)*	300 (50 – 400)	300 (50 – 500)	200 (25 – 335)
Biomass Fuel Use	145 (94%)	48 (94%)	97 (94%)
>50% Biomass Use	133 (86%)	44 (86%)	89 (86%)
Baseline demographics for enrolled subjects, displayed as a whole and by gender. *total of 115 respondents, emphasizing informal labor sector not considered traditional employment			

3.2 Results of Respiratory Questionnaires

Results of the ISAAC video survey, written survey, and SGRQ-C survey are listed in Table 2. Our main diagnostic question of interest, the presence of wheezing within the past twelve months based on the ISAAC video questionnaire, was 5.8% overall, with no statistically significant difference between males and females. The same question provided in written form, however, yielded a positive response 17.5% of times, again with no statistically significant difference between males and females (15.7% and 18.4% respectively). Nighttime cough was the most commonly reported asthma symptom based on the video questionnaire, with 10% of respondents answering affirmatively. SGRQ-C total scores, adjusted for comparison to the original SGRQ scale and normal values according to the SGRQ group's recommendations, were 8.3 overall, with a median score of 6.2 for males and 9.3 for females ($p > 0.05$ for gender difference analysis). The reference mean value for the SGRQ total score in healthy subjects with no history of respiratory disease is 6 (95% CI 5 to 7).

Table 2: Survey Results (symptoms present within past 12 mos)

	Total	Male	Female
ISAAC Questionnaire Wheeze	27 (17.5%)	8 (15.7%)*	19 (18.4%)*
ISAAC Video			
Wheeze	9 (5.8%)	3 (5.9%)*	6 (5.8%)*
Exercise Wheeze	10 (6.5%)	3 (5.9%)	7 (6.8%)
Night Wheeze	6 (3.9%)	1 (2.0%)	5 (4.8%)
Night Cough	16 (10.4%)	4 (7.8%)	12 (11.6%)
Severe Wheeze	4 (2.6%)	1 (2%)	3 (3%)
SGRQ-C Total Score (Median, IQR)	5.8 (1.8 – 18.0)	3.5 (1.8 – 9.2)*	6.9 (1.8 – 18.0)*
SGRQ-C Total Score Adjusted (Median, IQR)	8.3 (4.7 – 19.3)	6.2 (4.7 – 11.3)*	9.3 (4.7 – 24.7)*

Results of key questions from ISAAC video, ISAAC written, and SGRQ-C surveys. Total numbers of respondents answering that symptoms were present in the past twelve months for each of the ISAAC symptoms listed. SGRQ-C Total scores were computed, along with adjustments for comparison with SGRQ original survey normal results.
* $p > 0.05$ for between gender analysis

3.3 Results of Breathing Tests

Results of breathing tests, including FeNO, eCO, and spirometry pre- and post-bronchodilator are listed in Table 3. One hundred twenty-four individuals (81%) were able to generate high quality, reproducible spirograms suitable for analysis. One hundred fifty-three subjects completed eCO maneuvers, and 143 completed FeNO

measurements. Median values of FeNO were 18 ppb (IQR 9 – 33), with a median of 21.5 for males and 16.0 ppb for females. Statistically significant differences were found in FeNO values in subjects reporting wheezing in the past twelve months, with wheezing subjects having higher values than those who denied wheezing (53.0 vs 17.5 ppb for video responses, p = 0.003). Median eCO values were the same for men and women (5 ppm, IQR 3 to 8), and were not statistically different based on the presence or absence of wheezing in the past twelve months.

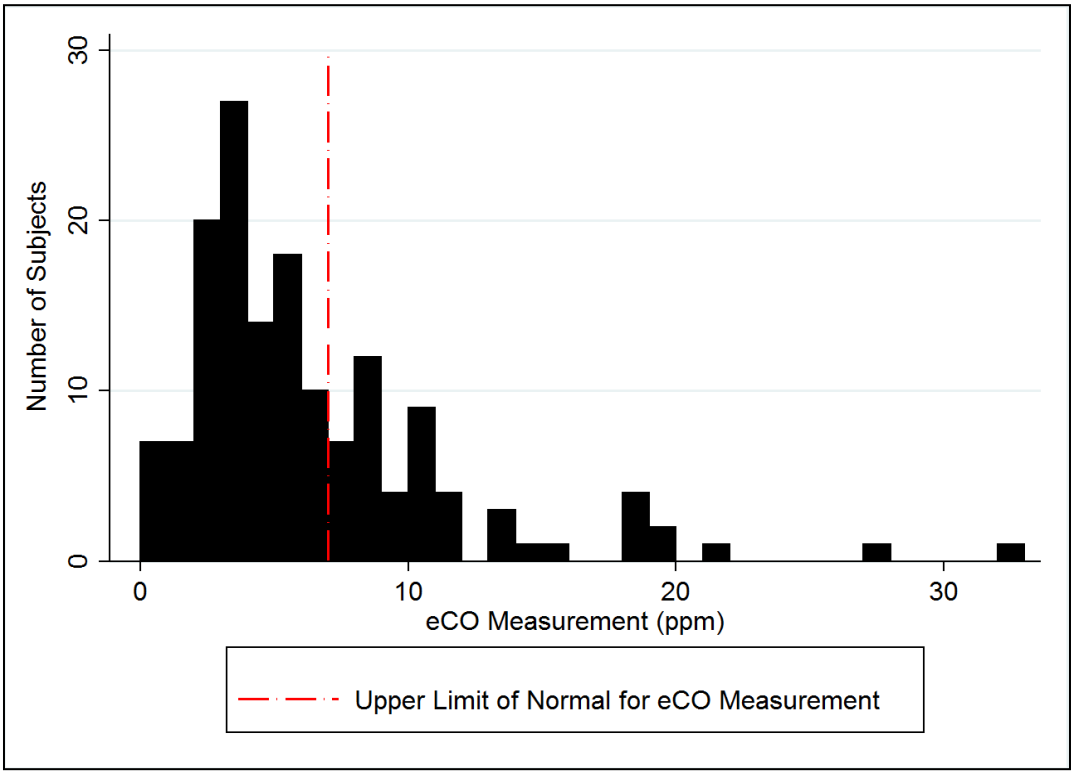

Figure 2: Exhaled carbon monoxide measurements for all participants. The median value observed was 5 ppm, falling below the upper limit of normal of 7 ppm (red line). However, significant right skew exists in our population, potentially indicating variable exposure levels to biomass fuels.

Table 3: Pulmonary Function Test Results

	Median (IQR)	Male	Female	Wheeze video (n=9)	Wheeze Written (n=27)
eCO (ppm)	5 (3 – 8)	5 (2 - 8) ‡	5 (3 – 8) ‡	3 (3-5)⁺	5 (3-9)⁺
FeNO (ppb)	18 (9 – 33)	21.5 (13.5 – 31) ‡	16 (8 – 33)‡	53 (32 – 103)*	45 (20.5 – 95)*
Spirograms meeting quality criteria	124 (81%)	42 (82%)	82 (80%)	7 (78%)	17 (63%)
Obstructed	10 (8%)	3 (7%)	7 (9%)	2	4
Irreversible Obstruction	7 (6%)	2 (5%)	5 (6%)		
Reversible Obstruction	3 (2%)	1 (2%)	2 (2%)		

Results of pulmonary function tests. Median values are reported with interquartile ranges for eCO and FeNO measurements. Separate analyses based on the presence of wheezing in the past twelve months from the ISAAC video questionnaire and ISAAC written questionnaire are listed for eCO and FeNO measurements, as well as spirometry results. Spirograms meeting ATS definitions for quality were then analyzed and interpreted according to GOLD criteria. Comparison of FeNO and eCO measurements by presence or absence of wheezing was performed using Wilcoxon rank sum test.

* $p < 0.01$

⁺ $p > 0.05$

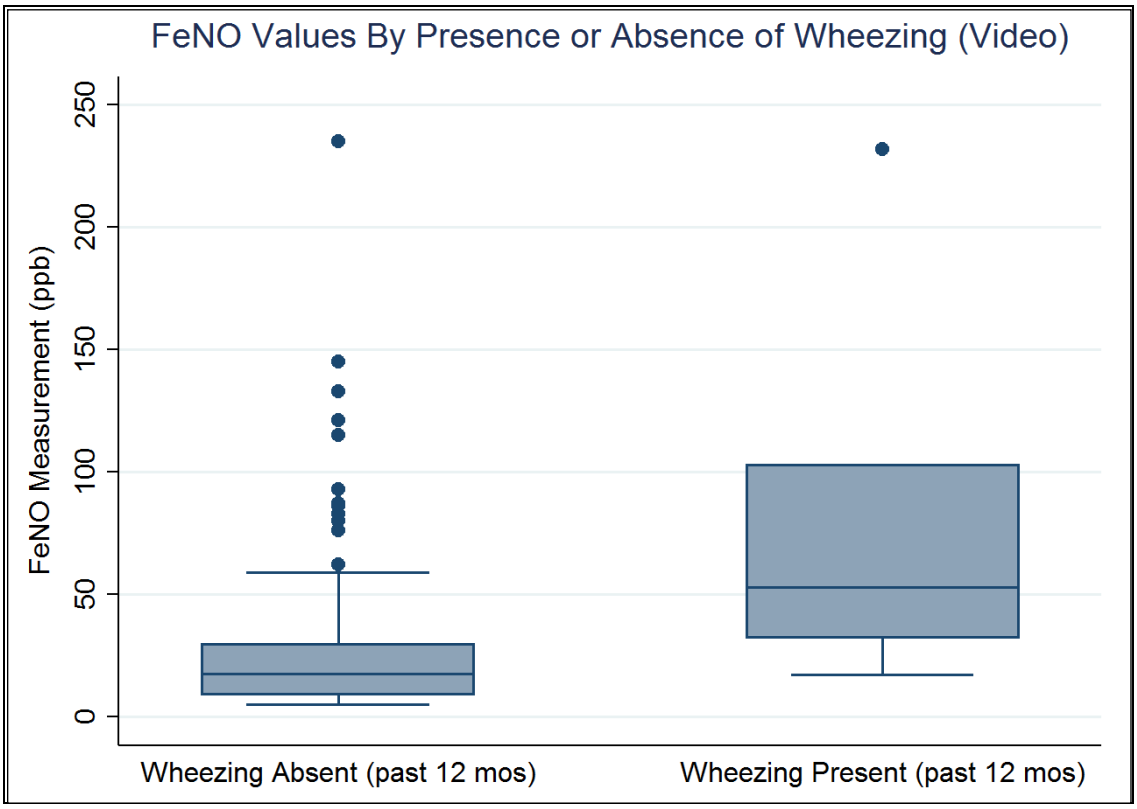

Figure 3: FeNO measurement by presence or absence of wheezing in the past 12 months based on ISAAC video questionnaire responses. Subjects reporting wheezing had a statistically significantly higher median FeNO measurement than those who denied wheezing over the same time period.

3.4 Results of FeNO versus Asthma Symptoms Analysis

Results of analyses comparing survey responses to FeNO levels are listed in Table 4. Of the nine subjects acknowledging wheezing in the past 12 months on the ISAAC video questionnaire, four had a FeNO cutoff of less than 71 ppb, corresponding to a prevalence of 3% of the low FeNO population (n=128). Three were found to have FeNO values above this cut point, corresponding to a prevalence of 20% among the high

FeNO population (n=15). Two were unable to complete FeNO maneuvers. Using the written survey responses to wheezing in the past 12 months, of the 27 subjects identified, 15 had FeNO values below 71 ppb (12%) versus 9 with FeNO values above 71 (60%). This pattern of higher prevalence of wheezing at higher FeNO values held true when analyzed as a single dataset or when stratified by gender. Odds ratios for the presence or absence of wheezing in the past twelve months based on FeNO levels above or below our threshold of 71 ppb were 11.3 for wheezing identified by ISAAC written questionnaires (95% CI 3.5 to 36.2, $p < 0.001$) and 7.8 for video questionnaires (95% CI 1.5 to 38.8, $p = 0.013$).

SGRQ-C adjusted total scores were also compared for FeNO high and low categories. Median SGRQ-C adjusted scores were 7.3 overall, with median values of 6.3 in the FeNO less than 71 ppb category, compared to 18.5 in the FeNO greater than 71 ppb category, corresponding to a higher respiratory symptom burden in subjects with higher FeNO levels ($p = 0.047$). This difference was more notable amongst women than amongst men.

Table 4: Survey Results by FeNO Category

	FeNO ≤ 71 ppb			**FeNO > 71 ppb**			**Odds Ratio**	**p value**
	Total (n=128)	**Male (n=42)**	**Female (n=86)**	**Total (n=15)**	**Male (n=6)**	**Female (n=9)**	**Total (95% CI)**	**Total**
ISAAC Survey Wheeze	**15 (12%)**	3 (7%)	12 (14%)	**9 (60%)**	4 (67%)	5 (56%)	**11.3 (3.5 – 36.2)**	<0.01
ISAAC Video wheeze	**4 (3%)**	1 (2%)	3 (3%)	**3 (20%)**	1 (17%)	2 (22%)	**7.8 (1.5 – 38.8)**	0.01
SGRQ Total Adjusted	**7.3 (4.7 – 17.7)***	6.3 (4.7 – 10.5)	7.6 (4.7 – 22.2)	**18.5 (5.4 – 39.7)***	6.5 (4.7 – 19.0)+	26.8 (15.4 – 41.1)+		

The results of ISAAC video, written, and SGRQ-C adjusted surveys by FeNO level and gender. There are significantly higher odds of wheezing, by both video and written questionnaires, in subjects with elevated FeNO levels above the cut point of 71ppb. Odds ratios for having wheeze present in the past 12 months based on ISAAC video or ISAAC written questionnaire were calculated using logistic regression modelling.

*$p < 0.05$

+$p > 0.05$

4. Discussion

In this study, multiple findings help improve our understanding of asthma in western Kenya. First, the unadjusted prevalence of wheezing within the past twelve months based on the ISAAC video and written questionnaires were 5.8% and 17.5%, respectively, with no gender differences in symptom reporting. This large difference in the prevalence estimates is consistent with the prior ISAAC studies, and may be related to the severity of asthma symptoms depicted in the video questionnaire.[3]

Overall SGRQ-C total scores were elevated, with adjusted median scores above the normal range based on studies of normal, healthy volunteers. This may reflect that we captured a significant number of individuals with true respiratory disease. There was again no differences between men and women noted in their scores.

Median eCO values fell within the normal range (5 ppm), with interquartile ranges just reaching above the 7ppm upper limit of normal (3 to 8 ppm).[15] Our initial suspicion was that eCO levels would correlate with biomass burning or vehicle emissions given that the prevalence of smoking in Uasin Gishu is low.[16] This makes it notable that men and women did not have differences in their exhaled carbon monoxide levels, which we would expect given that in this traditional society with heavy biomass fuel use, women have higher exposure levels to biomass fumes. There was also no difference between the eCO results of subjects who reported wheezing and those who

did not. These results taken together call into question the use of eCO as a measure of biomass fuel exposure in this population.

Analysis of FeNO results provided interesting insights. First, the median FeNO for all subjects fell within the normal range. However, when stratified by responses to the ISAAC questionnaires, a statistically significant relationship was identified between the presence of asthma symptoms and elevated FeNO levels, with median FeNO levels rising to 53 ppb for positive responses to the video questionnaire and 45 ppb for the written questionnaire, both well above the normal range. This relationship was further tested when a FeNO cutoff of 71 ppb was used to stratify subjects into two categories. When the proportion of subjects in each FeNO stratum who reported wheezing within the past twelve months were compared, a statistically significant odds ratio of 11.3 (written) and 7.8 (video) was found favoring more wheezing in the high FeNO stratum.

4.1 Implications for policy and practice

This study has multiple implications for the practice of pulmonary medicine in sub-Saharan Africa. First, the confirmation that a significant proportion of people with asthma symptoms have a high FeNO phenotype is an important one. Countries like Kenya, where tuberculosis and HIV have a high prevalence in the general population and diagnostic testing options are limited, have erred on the side of aggressive screening and treatment for TB symptoms, even in the absence of confirmation of a TB diagnosis.[17]

The use of point of care FeNO testing as an adjunct to basic radiology, sputum analysis, and spirometry could greatly help guide treatment options toward more appropriate therapies for those suffering from asthma, and is even mentioned in the most recent Kenyan asthma guidelines.[18]

A second policy implication from this study is that FeNO has the potential to be a tool to assist with asthma management in the outpatient setting. Because many asthma symptom sufferers have a high FeNO phenotype in Kenya, FeNO testing could be used to select those uncontrolled severe asthma patients who may best respond to further increases in steroid medications. Stratification by FeNO would allow a precision medicine approach to appropriately target high-risk asthmatics with high likelihood of response to corticosteroids, reducing exposure to corticosteroids similar to what has been demonstrated in higher resource settings.

4.2 Implications for further research

Based on these results, further research is warranted in this area. A first step should be the further characterization and phenotyping of those individuals with asthma symptoms to confirm a true clinical asthma diagnosis. The same should be done for all of those individuals found to have an elevated FeNO, to better understand confounding diagnoses and clinical presentations in our sub-Saharan African population.

A second topic that requires further study is the role of eCO measurement as a surrogate for biomass exposure in a high biomass fuel population. In our population, 86% of individuals reported significant biomass use totaling greater than 50% of their household energy supply, however the median eCO measurement in this study was in the normal range.[15,16]

Finally, given the linkage between asthma symptoms and elevated FeNO in our population, further research should be focused on the clinical role of FeNO in the treatment of subjects with chronic respiratory complaints. This should include evaluating outcomes in patients with asthma treated according to FeNO guidelines from major international respiratory societies, to see how these guidelines perform in a low resource setting with a high tuberculosis incidence rate.[5]

4.3 Study strengths and limitations

There are multiple strengths to this study. The first is the rigorous sampling methodology that was used to generate a probability sample in an otherwise difficult research environment. Combining GIS mapping with a standardized sampling methodology allowed for probability sampling of individuals across a rural to urban spectrum, capturing diverse exposure patterns that add to the strength and generalizability of this study.

Another strength to the study is the use of FDA approved, innovative biomarkers in novel ways according to internationally approved methods and guidelines. Bringing point of care FeNO testing to field sites in sub-Saharan Africa to phenotype individuals with chronic respiratory complaints demonstrates both feasibility and utility for this technology in this setting.

Despite the multiple strengths of this study, there are limitations as well. First, while great effort was taken to generate a probability sample in a location where no sampling frame exists, our single visit strategy during business hours was pragmatic, but may have led to underrepresentation of males, who may have been working, as well as children who may have been at school. We see this demonstrated in the gender distribution of participants as well as the smaller number of individuals in the 12-18 year age range.

A second limitation to this study was the use of surveys that were validated outside of sub-Saharan Africa. In order to better communicate with individuals in the field, we performed translations with confirmatory back-translations of standardized surveys into local languages, and implemented them using native speakers of these languages who carried nursing degrees and licensures. However, there is the possibility that some concepts may not have translated accurately, and caution must be implemented in the interpretation and generalizability of these results outside our studied population.

5. Conclusion

In this study, we identified a linkage between asthma symptoms and elevated levels of exhaled nitric oxide in a probability sample of mixed aged individuals in western Kenya. This study highlights the high burden of respiratory symptoms in the area and the potential utility of noninvasive point-of-care testing in the diagnosis and management of these individuals, while suggesting possible mechanisms for these symptoms. Further study is needed to clarify the exact diagnoses of these subjects with asthma symptoms and to better examine optimal cutoffs for FeNO in this population for research and clinical purposes.

Appendix A

SCREENING SURVEY

Q1 Study ID

Q2 Are you age 12 or over?

- ❍ Yes (1)
- ❍ No (2)

Q3 Have you had an operation on your eyes, abdomen, or chest within the past 6 weeks?

- ❍ Yes (1)
- ❍ No (2)

Q4 Have you had a heart attack within the past 6 weeks?

- ❍ Yes (1)
- ❍ No (2)

Q5 Are you currently pregnant?

- ❍ Yes (1)
- ❍ No (2)

Q6 Have you ever been diagnosed with a fast, abnormal heart rhythm (uncontrolled atrial fibrillation, atrial flutter, SVT, ventricular tachycardia, ventricular fibrillation)?

- ❍ Yes (1)
- ❍ No (2)

Q7 Have you had a chest infection in the past 4 weeks?

- ❍ Yes (1)
- ❍ No (2)

Appendix B

DATA COLLECTION INSTRUMENT

Q2 Study ID:

Q3 Household ID:

Q4 What is your surname?

Q5 What is your first name?

Q188 What is your middle name?

Q6 What is your date of birth?

Q7 What is your age

Q8 What is your gender?

- ❍ Male (1)
- ❍ Female (2)

Q9 What county are you from?

Q187 What village do you currently stay in?

Q10 What is your tribe?

Q11 Phone number #1

Q170 Phone number #2

Q171 Phone number #3

Q12 Email

Q13 Is it OK to contact you for possible future studies?

- ❍ Yes (1)
- ❍ No (2)

Q174 GPS location of household (latitude)

Q175 GPS location of household (longitude)

Q14 Are you currently a student?

- ❍ Yes (1)
- ❍ No (2)

Q15 What was the last level of schooling you completed?

- ❍ None (1)
- ❍ Primary School (2)
- ❍ Secondary School (3)
- ❍ Diploma Level School (4)
- ❍ Degree Level School (5)
- ❍ Masters or Doctoral Level School (6)

Q16 Are you currently employed?

- ❍ Yes (1)
- ❍ No (2)

Q17 What is your occupation?

Q18 In an average day, how much do you make in your occupation? (in KSH)

Q19 What is your tobacco smoking history?

- ❍ Current smoker (1)
- ❍ Former smoker (2)
- ❍ Never smoker (3)

Q20 How old were you when you first began to smoke

Q21 How many sticks do/did you smoke on an average day

Q22 How old were you when you stopped smoking?

Q23 How many years did you/have you smoked?

Q24 Do you/have you smoked anything other than tobacco?

- ❍ Yes (1)
- ❍ No (2)

Q25 What do you/did you smoke?

Q26 Do you drink alcohol?

- ❍ Yes (1)
- ❍ No (2)

Q27 What types of alcohol do you drink?

- ❑ Beer (1)
- ❑ Locally made alcohol (2)
- ❑ Liquor (3)

Q28 How many times per week do you drink?

- ❍ 0-2 (1)
- ❍ 3-5 (2)
- ❍ 6-7 (3)

Q29 How many drinks do you have when you drink?

- ❍ 0-2 (1)
- ❍ 3-5 (2)
- ❍ >5 (3)

Q30 Are you the head of your household?

- ❍ Yes (1)
- ❍ No (2)

Q31 How many people live in your home?

Q32 Do you have access to electricity?

- ❍ Yes (1)
- ❍ No (2)

Q33 Do you have access to running water?

- ❍ Yes (1)
- ❍ No (2)

Q34 What type of toilet do you use?

- ❍ Community Toilet (1)
- ❍ Outdoor Latrine (2)
- ❍ Outdoor Toilet (3)
- ❍ Indoor Toilet (4)
- ❍ Other (5) _____

Q35 Do you cook for your household?

- ❍ Yes (1)
- ❍ No (2)

Q36 Are you the primary cook for your household?

- ❍ Yes (1)
- ❍ No (2)

Q37 What type of fuels are used in your household for cooking?

- ❑ Firewood (1)
- ❑ Charcoal (2)
- ❑ Gas (3)
- ❑ Kerosene (4)
- ❑ Electricity (5)
- ❑ Dung (6)
- ❑ Other Biomass (twigs, crop residues, leaves) (8)
- ❑ Other (7) _____

Q38 How many hours per week do you spend obtaining fuel for cooking?

Q39 How much do you spend per month obtaining fuel for cooking?

Q40 How often do you use firewood, charcoal, dung, or other biomass for cooking?

- ❍ 1-2 days per week (1)
- ❍ 3-4 days per week (2)
- ❍ 5-6 days per week (3)
- ❍ every day (4)

Q41 What type of stove do you use in your household?

- ❑ Jiko (1)
- ❑ 3 Stone Stove (2)
- ❑ Gas (3)
- ❑ Electric (4)
- ❑ Other (5) _____

Q42 What percentage of the time do you use each stove?

_____ Jiko (1)
_____ 3 stone (2)
_____ Gas (3)
_____ Electric (4)
_____ Other (5)

Q43 Does your cooking room have ventilation? (a hole in the wall or roof for smoke to escape, or a chimney)

- ❍ Yes (1)
- ❍ No (2)

Q44 How many hours per day do you or your family member spend cooking?

Q45 How many hours per day do you breathe the smoke from the cooking fire?

Q46 What type of fuel do you use for lights?

- ❑ Electricity (1)
- ❑ Kerosene (lamp) (2)
- ❑ Candles (3)
- ❑ Other (4) _____

Q47 How do you dispose of your garbage?

- ❍ Burned (1)
- ❍ Collected (2)
- ❍ Littered (3)
- ❍ Other (4) _____

Q48 Have you ever been tested for HIV?

- ❍ Yes (1)
- ❍ No (2)

Q49 What year were you tested for HIV?

Q50 What was the result of your HIV test?

- ❍ Positive (1)
- ❍ Negative (2)

Q51 Do you currently take medication for HIV?

- ❍ Yes (1)
- ❍ No (2)

Q189 What is your AMPATH number?

Q52 Have you ever been diagnosed with tuberculosis (TB)?

- ❍ Yes (1)
- ❍ No (2)

Q53 What year were you diagnosed with tuberculosis (TB)?

Q54 Were you ever treated for tuberculosis (TB)?

- ❍ Yes (1)
- ❍ No (2)

Q55 What year were you treated for tuberculosis?

Q56 What part of your body was affected by tuberculosis?

- ❑ Lungs (1)
- ❑ Brain (2)
- ❑ Spine (3)
- ❑ Abdomen (4)
- ❑ Heart (5)
- ❑ Other (6) _____

Q57 Have you ever been hospitalized for any medical problem?

- ❍ Yes (1)
- ❍ No (2)

Q58 What was the medical problem?

Q59 What year were you hospitalized for the medical problem?

Q60 Have you ever been diagnosed with any heart problem?

- ❍ Yes (1)
- ❍ No (2)

Q61 What heart problem do you have?

Q62 What year were you diagnosed with a heart problem?

Q63 Do you have any medical problems other than those listed above?

- Yes (1)
- No (2)

Q64 What additional medical problems do you have?

Q65 Have you ever had surgery before?

- Yes (1)
- No (2)

Q66 What surgery have you had?

Q67 What year did you have surgery?

Q68 Do you have any allergies (medication, animals, foods, etc)?

- Yes (1)
- No (2)

Q69 What are you allergic to?

Q70 Do you take any medications?

- Yes (1)
- No (2)

Q71 What medications do you take?

Click to write Choice 1 (1)
Click to write Choice 2 (2)
Click to write Choice 3 (3)
Click to write Form field 4 (4)
Click to write Form field 5 (5)
Click to write Form field 6 (6)

Q161 Data Collection:

Q210 Height (cm)

Q211 Weight (kg)

Q212 Systolic Blood Pressure

Q213 Diastolic Blood Pressure

Q214 Heart Rate (bpm)

Q215 Pulse Ox (%)

Q216 How many hours has it been since you last ate?

Q217 FeNO measurement

Q218 eCO measurement

Q162 Spirometry:

Q163 Does the patient have ANY exclusion criteria for spirometry safety? (Exclusions: current painful ear infection; Eye/Chest/Abdominal surgery in the past 3 months; history of aneurysm/collapsed lung/retinal detachment; history of coughing up blood in last

month; history of stroke or heart attack in the last 3 months; elevated blood pressure for age (>132/92 age 12-16 or >180/110 age 17 and over).

- ❍ Yes (1)
- ❍ No (2)

Q165 ****STOP HERE**** DO NOT PROCEED WITH SPIROMETRY OR BRONCHODILATOR TESTING

Q159 Predicted Values from GLI 2012 for African American Prediction Equations:

Q219 Predicted FVC (L)

Q220 Predicted FEV1 (L)

Q221 Predicted FEV1 / FVC Ratio (%)

Q222 Predicted Peak Flow

Q183 Predicted FEF25-75%

Q160 Measured Values Before Salbutamol

Q223 Measured FVC (L), before salbutamol

Q224 Measured FEV1 (L), before salbutamol

Q225 Measured FEV1 / FVC Ratio (%), before salbutamol

Q226 Measured Peak Flow, before salbutamol

Q184 Measured FEF25-75%

Q178 Does the spirometry meet ATS quality criteria?

- ❍ Yes (1)
- ❍ No (2)

Q169 Does the subject have ANY evidence of lung disease on pre-bronchodilator spirometry?

- ❍ Yes (1)
- ❍ No (2)

Q167 Does the subject have ANY exclusion criteria for post-bronchodilator spirometry? (Exclusion criteria: pregnant or might be pregnant, breastfeeding, history of congenital heart disease, diagnosed VT/VF/Afib/AFlutter/arrhythmia, elevated blood pressure for age (>132/92 age 12-16 or >180/110 age 17 and over), elevated pulse for age (>102 age 12-15 or >100 age 16 and over), >2 dropped beats or irregularly irregular pulse on palpation of pulse over 30 seconds, an implanted automatic defibrillator, any exclusion medications)

- ❍ Yes (1)
- ❍ No (2)

Q166 ****STOP HERE**** DO NOT DO BRONCHODILATOR TESTING

Q172 Administer 4 puffs of salbutamol per protocol and continue.

ISAAC WRITTEN QUESTIONNAIRE

Q142 1 - Have you ever had wheezing or whistling in the chest at any time in the past?

- ❍ Yes (1)
- ❍ No (2)

Q143 If you have answered "No" please skip to Question 6

Q144 2 - Have you had wheezing or whistling in the chest in the last 12 months?

- ❍ Yes (1)
- ❍ No (2)

Q145 If you have answered "No" please skip to Question 6

Q146 3 - How many attacks of wheezing have you had in the past 12 months?

- None (1)
- 1-3 (2)
- 4-12 (3)
- More than 12 (4)

Q147 4 - In the past 12 months, how often, on average, has your sleep been disturbed due to wheezing?

- Never woken with wheezing (1)
- Less than one night per week (2)
- One or more nights per week (3)

Q148 5 - In the past 12 months, has wheezing ever been severe enough to limit your speech to only one or two words at a time between breaths?

- Yes (1)
- No (2)

Q149 6 - Have you ever had asthma

- Yes (1)
- No (2)

Q150 7 - In the past 12 months, has your chest sounded wheezy during or after exercise?

- Yes (1)
- No (2)

Q151 8 - In the past 12 months, have you had a dry cough at night, apart form a cough associated with a cold or chest infection?

- Yes (1)
- No (2)

Q152 All questions are about problems which occur when you DO NOT have a cold or the flu.

Q153 1 - Have you ever had a problem with sneezing, or a runny, or blocked nose when you DID NOT have a cold or the flu?

- ❍ Yes (1)
- ❍ No (2)

Q154 If you have answered "No" please skip to question 6

Q155 2 - In the past 12 months, have you had a problem with sneezing, or a runny, or blocked nose when you DID NOT have a cold or the flu?

- ❍ Yes (1)
- ❍ No (2)

Q156 If you have answered "No" please skip to question 6

Q157 3 - In the past 12 months, has this nose problem been accompanies by itchy-watery eyes?

- ❍ Yes (1)
- ❍ No (2)

Q158 4 - In which of the past 12 months did this nose problem occur? (Please tick any which apply)

- ❑ January (1)
- ❑ February (2)
- ❑ March (3)
- ❑ April (4)
- ❑ May (5)
- ❑ June (6)
- ❑ July (7)
- ❑ August (8)
- ❑ September (9)
- ❑ October (10)
- ❑ November (11)
- ❑ December (12)

Q159 5 - In the past 12 months, how much did this nose problem interfere with your daily activities?

- ❍ Not at all (1)
- ❍ A little (2)
- ❍ A moderate amount (3)
- ❍ A lot (4)

Q160 6 - Have you ever had hayfever?

- ❍ Yes (1)
- ❍ No (2)

Q161 1 - Have you ever had an itchy rash which was coming and going for at least 6 months?

- ❍ Yes (1)
- ❍ No (2)

Q162 If you have answered "No" please skip to question 6

Q163 2 - Have you had this itchy rash at any time in the past 12 months?

- ❍ Yes (1)
- ❍ No (2)

Q164 If you have answered "No" please skip to question 6

Q165 3 - Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?

- ❍ Yes (1)
- ❍ No (2)

Q166 4 - Has this rash cleared completely at any time during the past 12 months?

- ❍ Yes (1)
- ❍ No (2)

Q167 5 - In the past 12 months, how often, on average, have you been kept awake at night by this itchy rash?

- ❍ Never in the past 12 months (1)
- ❍ Less than one night per week (2)
- ❍ One or more nights per week (3)

Q168 6 - Have you ever had eczema?

- ❍ Yes (1)
- ❍ No (2)

ISAAC VIDEO QUESTIONNAIRE

Q169 The first scene is of a young person at rest. Has your breathing ever been like this, at any time in your life?

- ❍ Yes (1)
- ❍ No (2)

Q170 Has this happened in the past year?

- ❍ Yes (1)
- ❍ No (2)

Q171 Has this happened one or more times per month?

- ❍ Yes (1)
- ❍ No (2)

Q172 The second scene is of two young people exercising. One is in a dark shirt and the other is in a white shirt. Has your breathing been like the boy's in the dark shirt during or following exercise at any time in your life?

- ❍ Yes (1)
- ❍ No (2)

Q173 Has this happened in the last year?

- ❍ Yes (1)
- ❍ No (2)

Q174 Has this happened one or more times a month?

- ❍ Yes (1)
- ❍ No (2)

Q175 The third scene is of a young person waking at night. Have you been woken at night like this at any time in your life?

- ❍ Yes (1)
- ❍ No (2)

Q176 Has this happened in the past year?

- ❍ Yes (1)
- ❍ No (2)

Q177 Has this happened one or more times a month?

- ❍ Yes (1)
- ❍ No (2)

Q178 The fourth scene is also of a young person waking at night. Have you been woken at night like this at any time in your life?

- ❍ Yes (1)
- ❍ No (2)

Q179 Has this happened in the past year?

- ❍ Yes (1)
- ❍ No (2)

Q180 Has this happened one or more times a month?

- ❍ Yes (1)
- ❍ No (2)

Q181 The final scene is of another person at rest. Has your breathing been like this at any time in your life?

- ❍ Yes (1)
- ❍ No (2)

Q182 Has this happened the past year?

- ❍ Yes (1)
- ❍ No (2)

Q183 Has this happened one or more times a month?

- ❍ Yes (1)
- ❍ No (2)

SGRQ-C QUESTIONNAIRE

Q184 This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are. Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Q185 Before completing the rest of the questionnaire, please select one box to show how you describe your current health:

- ❍ Very good (1)
- ❍ Good (2)
- ❍ Fair (3)
- ❍ Poor (4)
- ❍ Very Poor (5)

Q186 Questions about how much chest trouble you have. Please select ONE box for each question:

Q187 I cough:

- ❍ most days a week (1)
- ❍ several days a week (2)
- ❍ only with chest infections (3)
- ❍ not at all (4)

Q188 I bring up phlegm (sputum):

- ❍ most days a week (1)
- ❍ several days a week (2)
- ❍ only with chest infections (3)
- ❍ not at all (4)

Q189 I have shortness of breath:

- ❍ most days a week (1)
- ❍ several days a week (2)
- ❍ not at all (3)

Q190 I have attacks of wheezing:

- ❍ most days a week (1)
- ❍ several days a week (2)
- ❍ a few days a month (3)
- ❍ only with chest infections (4)
- ❍ not at all (5)

Q191 How many attacks of chest trouble did you have during the last year?

- ❍ 3 or more attacks (1)
- ❍ 1 or 2 attacks (2)
- ❍ none (3)

Q192 How often do you have good days (with little chest trouble)?

- ❍ no good days (1)
- ❍ a few good days (2)
- ❍ most days are good (3)
- ❍ every day is good (4)

Q193 If you have a wheeze, is it worse in the morning?

- ❍ No (1)
- ❍ Yes (2)

Q194 How would you describe your chest condition?

- ❍ Causes me a lot of problems or is the most important problem that I have (1)
- ❍ Causes me a few problems (2)
- ❍ Causes no problem (3)

Q195 Questions about what activities usually make you feel breathless. For each statement please select the box that applies to you these days:

	True (1)	False (2)
Getting washed or dressed (1)	❍	❍
Walking around the home (2)	❍	❍
Walking outside on the level (3)	❍	❍
Walking up a flight of stairs (4)	❍	❍
Walking up hills (5)	❍	❍

Q196 Some more questions about your cough and breathlessness. For each statement please select the box that applies to you these days:

	True (1)	False (2)
My cough hurts (1)	❍	❍
My cough makes me tired (2)	❍	❍
I am breathless when I talk (3)	❍	❍
I am breathless when I bend over (4)	❍	❍
My cough or breathing disturbs my sleep (5)	❍	❍
I get exhausted easily (6)	❍	❍

Q197 Questions about other effects that your chest trouble may have on you. For each statement please select the box that applies to you these days:

	True (1)	False (2)
My cough or breathing is embarrassing in public (1)	❍	❍
My chest trouble is a nuisance to my family, friends or neighbors (2)	❍	❍
I get afraid or panic when I cannot get my breath (3)	❍	❍
I feel that I am not in control of my chest problem (4)	❍	❍
I have become frail or an invalid because of my chest (5)	❍	❍
Exercise is not safe for me (6)	❍	❍
Everything seems too much of an effort (7)	❍	❍

Q198 These are questions about how your activities might be affected by your breathing. For each statement please select the box that applies to you because of your breathing:

	True (1)	False (2)
I take a long time to get washed or dressed (1)	❍	❍
I cannot take a bath or shower, or I take a long time (2)	❍	❍
I walk slower than other people, or I stop for rests (3)	❍	❍
Jobs such as housework take a long time, or I have to stop for rests (4)	❍	❍
If I walk up one flight of stairs, I have to go slowly or stop (5)	❍	❍
If I hurry or walk fast, I have to stop or slow down (6)	❍	❍
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf (7)	❍	❍
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim (8)	❍	❍

Q199 We would like to know how your chest trouble usually affects your daily life. For each statement please select the box that applies to you because of your breathing:

	True (1)	False (2)
I cannot play sports or games (1)	❍	❍
I cannot go out for entertainment or recreation (2)	❍	❍
I cannot go out of the house to do the shopping (3)	❍	❍
I cannot do housework (4)	❍	❍
I cannot move far from my bed or chair (5)	❍	❍

Q200 How does your chest trouble affect you?

- ❍ It does not stop me doing anything I would like to do (1)
- ❍ It stops me doing one or two things I would like to do (2)
- ❍ It stops me doing most of the things I would like to do (3)
- ❍ It stop me doing everything I would like to do (4)

Q201 Over the last 3 months how often, on average, did you have the following symptoms:

Q202 Runny Nose:

- ❍ Never (1)
- ❍ 1-4 times per month (2)
- ❍ 2-6 times per week (3)
- ❍ Daily (4)

Q203 Post nasal drip:

- ❍ Never (1)
- ❍ 1-4 times per month (2)
- ❍ 2-6 times per week (3)
- ❍ Daily (4)

Q204 Need to blow your nose:

- ❍ Never (1)
- ❍ 1-4 times per month (2)
- ❍ 2-6 times per week (3)
- ❍ Daily (4)

Q205 Facial pain/pressure:

- ❍ Never (1)
- ❍ 1-4 times per month (2)
- ❍ 2-6 times per week (3)
- ❍ Daily (4)

Q206 Nasal Obstruction

- ❍ Never (1)
- ❍ 1-4 times per month (2)
- ❍ 2-6 times per week (3)
- ❍ Daily (4)

Q228 Measured FVC (L), after salbutamol

Q176 FVC percent change

Q229 Measured FEV1 (L), after salbutamol

Q177 FEV1 percent change

Q230 Measured FEV1/FVC Ratio (%), after salbutamol

Q231 Measured Peak Flow, after salbutamol

Q185 Measured FEF25-75%, after salbutamol

Q179 Does the post-bronchodilator spirometry meet ATS criteria?

- ❍ Yes (1)
- ❍ No (2)

Q180 Results of Spirometry Testing:

- ❑ Normal (1)
- ❑ Reversible Obstruction (2)
- ❑ Fixed Obstruction (3)
- ❑ Restriction (4)

Q186 Was this subject referred to clinic?

- ❍ No (1)
- ❍ Yes - Chest Clinic (2)
- ❍ Yes - Dispensary (3)
- ❍ Yes - Casualty (4)

Q173 ***Please provide subject with copy of ACQ to complete***

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