ORIGINAL ARTICLE

Impact of Operational Definitions on the Predictors and Prevalence of Asthma Estimates: Experience from a University Students' Survey and Implications for Interpretation of Disease Burden

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ABSTRACT

BACKGROUND: Inconsistent operational definitions during asthma surveillance can lead to inaccurate estimation of disease burden and formulation of health policy. This study aimed to evaluate the impact of different definitions on the prevalence estimates and predictors of asthma among university students in Ilorin, Nigeria. The secondary aim was to compare level of agreement of the different definitions.

METHODS: This cross-sectional study was carried out from June to August 2015. The European Community Respiratory Health Survey (ECRHS) questionnaire was self-administered by 1485 students. Asthma diagnosis was based on five definitions used in previous studies in the country. These were ECRHS, International Study of Asthma, Allergies in Childhood (ISAAC), Probable, Modified ECRHS and Modified Probable asthma definitions.

RESULTS: The prevalence rates varied from 10.4 to 24.1% depending on the definition. Prevalence obtained by using ECRHS definition significantly differed from estimates by other definitions (Z score ≥ 1.96 p<0.0001) except modified probable asthma. Identified predictors of asthma varied from five to six depending on the definition, and their strength also differed by definition. Regardless of the definition, reported nasal allergy, skin allergy, family history of nasal allergy, asthma and parental smoking were the predictors of asthma. The Kappa statistics demonstrated a fair to almost perfect association between the ECRHS and other asthma definitions (Kappa = 0.334-0.841, p < 0.001).

CONCLUSION: The prevalence rates and predictors of asthma are affected by operational definitions. Researchers need to adopt a uniform definition for accurate estimation of disease burden, international comparison of result and formulation of prevention policy.

KEYWORDS: Asthma definitions, Prevalence, Surveillance, Disease Burden, Health Policy

INTRODUCTION

Asthma is one of the world's most common long-term medical conditions. The disease causes an estimated 250,000 deaths annually, and around 15 million disability-adjusted life years (DALYs) are lost annually through this disease (1-2). The burden of asthma in most regions of the world including developing countries have increased remarkably in recent years due to urbanization, industrialization, western lifestyle and increased awareness of the disease (2,4). Previous epidemiological studies in different Nigerian populations have reported the prevalence range of 3% to 18.2% using different case definitions (5-13). These wide variations are attributed to study population, epidemiologic instrument and the lack of uniformity in the asthma definition. In clinical practice, evaluation of asthma applies a combination of history, physical examination and lung function test while less rigorous definitions mostly based on questionnaire history of symptoms and lung function are usually used for population-based studies (14-18). The operational definitions of asthma in recent epidemiological studies are inconsistent worldwide (19). The National Health and Nutrition Examination Survey (NHANES) has adopted uniform asthma definition for all ages in the USA (18). The European Community Respiratory Health Survey (ECRHS) and International study of asthma and allergies in childhood (ISAAC) (14-16) used a uniform definition to assess and compare the variation in the prevalence of asthma and risk factors. Unfortunately, there is no agreed consensus on epidemiological definition of asthma in adults in our setting; despite using similar survey instrument, the asthma definitions used in studies beyond childhood are inconsistent (5,7,11,20). There are several advantages in studying asthma epidemiology using the same definitions; these include easy comparison with other studies; accurate estimation of the disease burden and formulation of appropriate prevention policies. Therefore, achieving precise estimates of the prevalence of asthma and risk factors are essential. We hypothesized that asthma definitions does not affect the prevalence estimates and burden in our study population. The study aimed to evaluate the impact of using different operational definitions on the predictors and prevalence of asthma estimates among University students in the middle belt, Nigeria. The secondary aim was to compare the level of agreement of these asthma definitions.

METHODS

Study design and setting: This was a cross-sectional study carried out in three universities located in Ilorin, Middle Belt Nigeria. The first institution is a federal university with a student population of 34000. The second institution is a private institution established by a religious organization with a student population of 4000, and the third one is established by the state government with a total population of 4820. All the three universities are located within Ilorin, the state capital. The majority of the students reside within the community.

Sample size: We determined the minimum sample size using the Raosoft online sample calculator (21). The response distribution was 18.2% obtained from a previous study (11). The standard deviation is set at 1.96 for 95% confidence interval. The margin of error was ± 2%. The recommended sample size was 1384. The design effect =1.0 because of the homogeneity of the students in participating institutions. Taking into account the expected response rate based on the pilot study, which was 85%, and the minimum sample was increased to 1591, a total of 1600 copies of the survey questionnaire were sent out.

Sampling technique: A multistage sampling technique with proportional allocation was used to select participating students. The total student population and the list of registered students in each department and their year of study were obtained from their respective academic offices. The faculty of study was the first sample frame containing the list of the faculties. In the second stage, a list of departments was the second sampling frame while the registered students formed the third sample frame. The trained interviewers selected students by simple random sampling from the list of registered students till

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the desired proportionate sample size was obtained.

Participants' recruitment: The student's societies were contacted two weeks prior to the data collection to solicit for their support. On the day of administering the questionnaire, the students were informed by trained interviewers before or after their lecture. Consented students' were recruited into the study. The students who declined to participate were excluded from the study.

Survey instruments: A self-administered respiratory questionnaire from the European Community Respiratory Health Survey (ECRHS) (14-16) was adapted to the study. The adaptation was to reflect only the academic profile namely; the program and year of study of the students and not their clinical information. We obtained socio-demographic information, asthma symptoms, self-reported asthma attacks, asthma diagnosis, and self-reported use of asthma medication. In addition, information on family history of asthma, and allergic conditions, and cigarette smoking (active and parental) were collected. Trained research assistants were available, if needed, to provide additional clarification during the administration period to ensure the collection of valid and reliable data. To ensure the validity of data, the assistants had classroom lecture and audiovisual training prior to the administration of the questionnaire. Furthermore, they were given different audio recordings of wheezing to verify reported wheezing and remove the variability in intercultural responses to the descriptive terms used for wheezing.

Operational definitions: We performed a literature search of Pubmed and Google Scholar. The search targeted papers with the terms "asthma", "prevalence" and "Nigeria". Five definitions used in previous asthma prevalence studies in the country were identified. Asthma diagnosis in this study was based on these definitions(Table 1). These different definitions were the European Community Respiratory Health Survey (ECRHS), Modified ECRHS, Probable, Modified Probable, International Study of Asthma and Allergies in Childhood (ISAAC) asthma definitions. Smoking was defined as smoking at least 100 sticks of cigarettes in a lifetime or at least one cigarette per day or one cigar a week for one year. Current smoker was defined as someone smoking as of one month ago (14-16). Parental smoking was defined as having father or mother or guardian who smoke regularly at home.

Tab1e 1: Operational definitions of asthma prevalence studies.

Previous Prevalence Studies	Asthma definitions
ECRHS [13-15]	Possible asthma -woken up by an attack of breathlessness or previous asthma attack or currently taking asthma medication within the preceding 12 months
ISAAC[9,12,17,20]	Presence of symptoms of recurrent "wheezing or whistling"in the last 12 months preceding the study
Modified ECRHS[11]	Presence of symptoms of "wheezing or whistling", "attack of shortness of breath", "diagnosed attack of asthma" in the last 12 months or "currently taking medicines for asthma
Probable asthma[6]	Probable asthma -Presence three or more symptoms or who had a diagnosis of asthma
Modified Probable asthma[5,7]	Presence of two or more recurrent asthma symptoms (current asthma) or physician-diagnosed asthma

Data analysis: The data were analyzed using Statistical Package for Social Sciences (SPSS)/IBM version 21. Missing values were excluded from all the analyses. Descriptive and frequency statistics were generated to examine demographic and other clinical variables. Chi-square X^2 was used to determine the level of significance between two or more variables. The prevalence was estimated using the five different asthma definitions. Using the ECRHS definition as the reference standard to identify subject with asthma, we determined whether significant difference existed between the estimates by ECRHS and other definitions by 2 proportion z

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test. The null hypothesis (H0) was rejected if Z score ≥ 1.96 or if Z ≤ −1.96. Thereafter, we also calculated the agreement between ECRHS definition and 4 other definitions using the kappa estimate. Kappa indexes between 0.81 to 1.00 indicates a very good agreement, 0.61 to 0.80 represents substantial agreement, 0.41 to 0.60 means moderate agreement, 0.21 to 0.40 is interpreted as fair agreement and a value of less than 0.20 reflects a weak agreement between the definitions. Logistic regression analysis was performed to obtain the adjusted odds ratios (OR) and 95% confidence interval (95% CI) to predict the risk of asthma. A *p* value less than 0.05 was considered as statistically significant. The bar chart was generated for illustrating the sex distribution of the five asthma definitions.

Ethical approval: The study was conducted after receiving research approval from the Ethics and Research Committee of the Kwara State Ministry of Health Ilorin, Nigeria.

RESULTS

General characteristics of the students: Out of the 1600 copies of the questionnaire that were distributed in the institutions, 1485 were fully completed and returned giving a response rate of 93.0% and constituting 3.5% of the overall student population of 42820. There was no difference in mean age and gender of those excluded and the participants included the study. The only difference was in the year of study.

The mean age of the participating students was 20.9 ±3.1years. Seven hundred and eighty three were males (52.7%) and 603 (40.6%) were in their first year of study. A total of 386 (26.0%) respondents reported a family history of allergic conditions, 51 (3.4%) currently smoked tobacco at the time of the survey while 40(2.7%) reported parental smoking (Table 2).

Table 2: Characteristics of the participating students.

Characteristics	n (%)
Mean age (Mean ± STD)	20.9±3.1 years
Sex	
Male	783(52.7)
Female	702(47.3)
Marital status	
Single	1440(97.0)
Married/Divorced	45(3.0)
Year of study	
1-2	1040(71.0)
3- ≥4	445(29.0)
Family history of allergy	
Yes	386(26.0)
No	1099(74.0)
Types of family allergy*	
Asthma	148(10)
Nasal Allergy	245(16.5)
Tobacco smoking	
Current smokers	51(3.4)
History of Parental smoking	40(2.7)
Total number of participants	1485

*Multiple responses

Prevalence of respiratory symptoms and use of asthma medications: The prevalence of nocturnal cough was 21.4% (95% CI: 19.3-23.7%); it was the most common asthma

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symptom followed by nocturnal shortness of breath was 13.5% (95% CI: 11.6-15.4%) and chest tightness was 12.8% (95% CI: 11.1-14.5%). Also, 9.5% (95% CI: 7.9-11.1%) had diagnosed current asthma (an asthma attack in past 12 months and currently uses asthma medication).

Prevalence of asthma using the different definitions: The prevalence estimate varied from 10.4 to 24.1% depending on the definition. The prevalence of asthma using ECRHS, modified ECRHS and ISAAC definition were 18.7% (95% CI: 16.7-20.7%) , 24.1% (95% CI: 22.0-26.5%), 12.1% (95% CI: 10.5-13.9%) respectively. The prevalence of asthma using the definition of probable asthma and modified definition of probable asthma were respectively 10.4% (95% CI: 9.0-12.1%) and16.9% (95% CI: 15.0-18.9%). All the definition for prevalence of asthma reported more asthma occurrence in the females than in the male subjects (Figure 1). On stratified analysis of the study sites, there was no significant difference in the prevalence of asthma among the universities using any of the five definitions: ECRHS ($\chi 2$=1.54 df=2 p=0.462), modified ECRHS($\chi 2$=1.40 df=2 p=0.498), ISAAC($\chi 2$=3.19 df=2 p=0.203), probable asthma($\chi 2$=0.462 df=2 p=0.794) and modified probable asthma($\chi 2$=4.10 df=2 p=0.129).

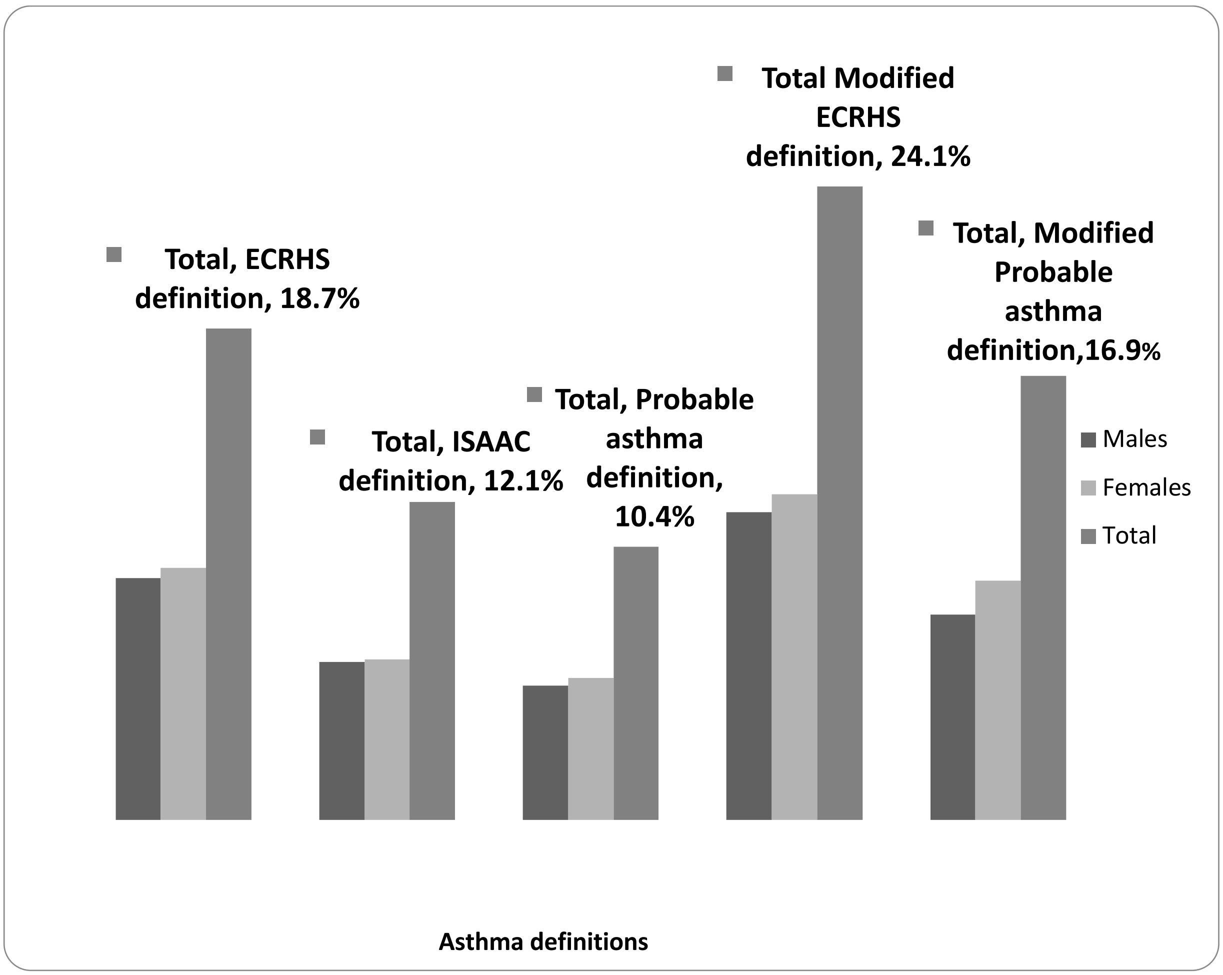

***Figure 1**: Sex distribution by different asthma definition*

Comparison of the different estimates of asthma prevalence: A two-proportion z score-test was performed to determine whether there was a significant difference between the prevalence estimates obtained. There were statistically significant differences between the

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asthma estimates by ECRHS and three other definitions: probable asthma modified ECRHS and ISAAC used in this study (Z score ≥ 1.96 p<0.0001) with the exception of modified probable asthma (Table 3).

Table 3: Comparison of the difference estimates of asthma prevalence.

ECRHS % (95% CI)	Other definitions % (95% CI)	Difference	Z score	*p* value	Interpretation
18.7% (16.7-20.7%)	ISACC 12.1% (10.5-13.9%)	0.066	5	<0.0001	Significant difference
	Probable asthma 10.4% (9.0-12.1%).	0.083	6.4	<0.0001	Significant difference
	Modified ECRHS 24.1 %(22.0-26.5%).	0.053	3	0.0003	Significant difference
	Modified probable 16.9% (15.0-18.9%).	0.018	1.3	0.1998	No Significant difference

Degree of agreement and Diagnostic Performance of definitions: The Kappa statistics demonstrated a fair to almost perfect between the definitions (Kappa = 0.334-0.841, p < 0.001), where the modified ECRHS revealed the highest concordance with the ECRHS definition (kappa = 0.841, p < 0.001) (Table 4).

Table 4: The agreement between the definition and the ECRHS definition

Operational definitions I	Operational definitions II	Kappa	P values	Agreement
ECRHS	ISACC	0.334	<0.0001	Fair
	Probable asthma	0.581	<0.0001	Moderate
	Modified ECRHS	0.841	<0.0001	Almost Perfect
	Modified probable asthma	0.639	<0.0001	Substantial

Impact of operational definitions on identified risk factor for asthma: Five risk factors for asthma were identified respectively using ECRHS, ISAAC, Probable asthma and modified ECRHS asthma case definition; these were self reported nasal allergy, skin allergy, family history of nasal allergy and asthma and parental smoking. Six risk factors for asthma were identified using the definition of probable asthma, these were female sex, self-reported nasal allergy, skin allergy, family history of nasal allergy and asthma and parental smoking. The ECRHS, modified ECRHS and modified probable asthma identified family history of asthma aOR =3.34(95 CI 2.20-5.06), 2.91(95CI 1.13-4.35) and 3.37(95CI 2.11-5.49) respectively as the strongest predictor. The ISAAC and probable asthma definition as a dependent variable, identified parental smoking aOR=3.42(95 CI 1.55-7.51) and 3.94(95 CI 1.67-9.27) respectively as the strongest predictor of asthma (Table 5).

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Table 5: Predictors of asthma using the different asthma definitions.

Predictors	ECRHS aOR(95CI)	ISAAC aOR(95CI)	Probable asthma aOR(95CI)	Modified ECRHS aOR(95CI)	Modified probable aOR(95CI)
Age	0.97(0.92-1.01)	0.98(0.93-1.04)	0.98(0.92-1.04)	0.98(0.94-1.02)	0.97(0.93-1.02)
Female Sex	1.23(0.91-1.67)	1.23(0.87-1.72)	1.27(0.87-1.86)	1.26(0.96-1.64)	1.40(1.03-1.91)
History of Nasal allergy	2.76(2.02-3.78)	2.56(1.79-3.66)	3.13(2.11-4.65)	2.71(2.04-3.60)	3.74(2.72-5.16)
History of skin allergy	2.58(1.77-3.76)	1.70(1.11-2.60)	2.62(1.70-4.06)	2.14(1.49-3.07)	1.80(1.22-2.66)
Family history of skin allergy	1.09(0.72-1.66)	0.92(0.57-1.48)	0.97(0.59-1.59)	1.14(0.77-1.69)	1.36(0.89-2.06)
Family of nasal allergy	1.99(1.37-2.89)	1.63(1.06-2.49)	2.30(1.48-3.58)	1.72(1.21-2.46)	1.62(1.01-2.37)
Family history of asthma	3.34(2.20-5.06)	1.84(1.15-2.94)	3.37(2.11-5.38)	2.91(1.13-4.35)	3.37(2.11-5.49)
Parental smoking	2.62(1.18-5.84)	3.42(1.55-7.51)	3.94(1.67-9.27)	2.48(1.18-5.43)	2.59(1.14-5.88)
Cigarette smoking	1.61(0.77-3.36)	1.66(0.78-3.54)	0.80(0.32-1.98)	1.68(0.84-3.37)	0.82(0.37-1.83)

Data presented as adjusted odd ratio with 95% Confidence Interval
Model adjusted for age, sex, history of reported nasal allergy, skin allergy, and family history of skin allergy, nasal allergy, and asthma. parental smoking and active tobacco smoking

DISCUSSION

The main findings of this study show that the prevalence estimate varied from 10.4 to 24.1% depending on the definition used. The prevalence estimate by ECRHS definition differs significantly from the three other definitions. One asthma definition identified six risk factors of asthma while the others identified five. Reported nasal allergy, skin allergy, family history of nasal allergy and asthma and parental smoking were the predictors of asthma regardless of the definition. The modified ECRHS had the highest concordance with the ECRHS definition (kappa = 0.841, $p < 0.001$). It has been reported that the prevalence estimate and disease burden are determined by adopted asthma definition (22-24). This was clearly observed in this study where there was a statistically significant difference and a wide variation in asthma prevalence estimates using the five sets of diagnostic criteria. The lowest estimate was 10.4% by ISAAC definition of asthma and the highest estimate was 24.1% by modified ECRHS. The reason for this variation was their difference sensitivity as a diagnostic tool. The prevalence of asthma using the ECRHS definition in this study was 18.7%. This is in tandem with 18.2% reported by Erhabor et al in Southwestern Nigeria. This closeness may be as result of the substantial agreement between ECRHS and modified ECRHS(kappa=0.841). However, our values was higher than 14.1- 16.4% determined in previous studies among students in Nigeria (6,7,20). All these previous studies lack uniformity in asthma definition despite having almost similar survey instruments. Currently, the available asthma definitions have their pros and cons, and there is no gold standard definition of asthma because of its heterogeneity and many phenotypes (25-27). In this regard, the lack of a widespread and accepted operational definition of asthma beyond childhood may lead to a potential problem of international comparison, under or over-diagnosis, inaccurate estimation of burden and healthcare resource planning.

This study also found that irrespective of asthma case definition, asthma was more frequent in female than in male subjects, although not statistically significant. It is due to smaller airway calibre size and higher bronchial reactivity in females (28). Apart from nasal allergy, nocturnal cough was the most common reported symptom, and this is in agreement with what was reported in previous studies (6,11).

In this study, there was a slight variation in number and strength of identified predictors of

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asthma by different asthma definitions (6 vs. 5). The independent predictors of asthma in this study are similar to what was reported in a previous study in locality ten years ago (29). Another important finding is the association of parental smoking with asthma in this study; those who reported parental smoking were three to four times likely to be associated with diagnosis of asthma. This is in agreement with other studies that observed a clear association between parental smoking and asthma or wheezing (30-32). The findings might prompt a future case-control and longitudinal study which will allow in depth exploration and analysis of impact of environmental tobacco smoking before a generalisation and causal inference can be made.

Asthma defined by ECRHS, modified ECRHS and modified probable asthma definition identified family history of asthma as the strongest predictor, aOR =3.34(95 CI 2.20-5.06), 2.91(95 CI 1.13-4.35) and 3.37(95 CI 2.11-5.49) respectively. In contrast, asthma defined by ISAAC and probable asthma definition identified parental smoking aOR=3.42(95 CI 1.55-7.51) and 3.94(95 CI 1.67-9.27) as the strongest predictor of asthma. This study also noted that estimated odd ratios were larger for the probable asthma definition than the other definitions of asthma. This is due to very high specificity of definition of probable asthma when compared to other definitions. The probable asthma requires three or more positive answers to questions on symptoms of asthma, which strengthened the associations with the risk factors and also increased the estimated specificity and positive predictive value (PPV) of the definition. The PPV is a function of true prevalence of a disease, specificity and sensitivity (33-34).

This study was able to assess the impact of the operational definitions on the prevalence of asthma estimate in a younger population that has a lesser risk of misclassification of the disease. The confounding effect of language on the reporting of symptoms was minimized in our study by using a self-administered and standardized questionnaire written in the language of instruction which was well understood by the participants. This study was a cross-sectional design. Therefore, a causal relationship cannot be established between identified predictors and asthma. Also, the data on parental smoking was self- reported with no objective measurement of exposure to smoking like measurement of nicotine level. The questionnaire estimation is controversial because it underestimates the level of exposure. Some studies have reported a good correlation between smoking evaluated by questionnaire and serum cotinine levels (35).

In conclusion, this study has shown that the prevalence and risk factors for asthma are affected by operational definitions. There is a need for epidemiologist and researchers to adopt a uniform definition with good performance for accurate determination of disease burden, international comparison and formulation of effective prevention and disease control policy.

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