PHENOTYPIC CLASSIFICATION AND RISK FACTORS ASSOCIATED WITH RECURRENT WHEEZE AMONG PRESCHOOL CHILDREN IN A TERTIARY TEACHING HOSPITAL IN ADDIS ABABA, ETHIOPIA; A CASE CONTROL STUDY By Melat Tesfaye

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PHENOTYPIC CLASSIFICATION AND RISK FACTORS ASSOCIATED WITH RECURRENT WHEEZE AMONG PRESCHOOL CHILDREN IN A TERTIARY TEACHING HOSPITAL IN ADDIS ABABA, ETHIOPIA; A CASE CONTROL STUDY

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Abstract

Background: Recurrent wheeze represents a substantial burden on pediatric respiratory health globally, and particularly in resource-limited settings like Ethiopia. Effective management necessitates a nuanced understanding of its phenotypic classification and associated risk factors. Yet, data characterizing these aspects remain scarce within developing nations, hindering the development of targeted interventions.

Objective- To identify phenotypic classification and risk factor associated with recurrent wheeze in a Tertiary Teaching Hospital in Addis Ababa, Ethiopia

Methods: Institution based unmatched case control study was done to assess the risk factor associated with recurrent wheeze among preschool children in a Tertiary Teaching Hospital in Addis Ababa, Ethiopia. Hundred forty-five children participated in the study with 48 cases and 97 controls. Bivariate analysis was performed to identify potential associated factors for the recurrent wheeze. Variables with $P<0.25$ on bivariate analysis was entered on multivariate logistic regression to identify independent risk factors associated with recurrent wheeze in preschool children. The significance of Odds Ratio (OR) was determined with 95% CI and $P<0.05$.

Results: The phenotypic characteristics of recurrent wheezing among the study population revealed that multi-trigger wheezing was present in 27 (56.3% with 95% CI: 41.5%-71.1%) of the participants. Atopic wheezing was observed in 30 (62.5% with 95% CI: 48.6% - 75.2%) of the children. The study revealed that recurrent wheezing in preschool children was strongly associated with male gender (AOR = 2.6, 95% CI: 1.2-9.1), indoor cooking exposure (AOR = 3.2, 95% CI: 1.3-8.2), and history of Neonatal Intensive Care Unit admission (AOR = 3.4, 95% CI: 1.5-7.8).

Conclusion and recommendation: This study highlights the significant prevalence of multi-trigger and atopic wheezing in preschool children, with male gender, indoor cooking exposure, and a history of NICU admission identified as strong independent risk factors. Therefore, it better to reduce indoor cooking exposure, particularly in households with young children. Moreover, clinicians should also be aware of the increased risk in male children and incorporate these findings into their assessment and management of preschool wheezing.

Keyword: Wheezing, Phenotype, preschool, Risk Factors, Addis Ababa, Ethiopia

1. Introduction

1.1 Background

Wheezing is a musical high-pitched whistling sound that occurs due to narrowed airway causing turbulence of air flow. It requires sufficient flow to generate airway oscillation and produce sound in addition to narrowing or compression of the airway (1).

Wheezing is one of the commonest presentations in children age less than six year. One in three children had one episode of wheezing before their third birthday and half prior to the age of six years (2, 3). Wheezing that occur in children aged below six years in more than one episode and has current/prior documented objective confirmation is defined as preschool wheeze. Wheezing which occurs more than three times per year is also referred as recurrent wheezing (4).

Multiple causes of wheezing are described in literatures. Acute episode of wheeze commonly occur with viral associated respiratory problems while recurrent and chronic wheezing usually occur due to asthma (5). However, whether the child has an asthmatic pattern of airway inflammation or not in young children a large population of wheezing is virally induced. Other triggering factors like passive exposure to tobacco smoke or vaping, indoor and outdoor pollutants, and indoor allergens also have their shares (6).

Before considering any pharmacotherapy, evidence shows it is important to address relevant risk factors and triggers for recurrent preschool wheezing (7). As is true to childhood asthma, preschool wheeze is a heterogeneous disease in terms of phenotypic classification and pathogenesis/endotyping which are related with the treatment outcome. Various features have been used to group these children in terms of temporal pattern, severity, triggering factors and presence of Atopy (4).

The main objective of these study is to identify risk factors associated with recurrent preschool wheezing and, determinants of its evolution into childhood asthma. Early initiations of target therapies based on their phenotypic classification are also the keys in preventing the future unwanted outcomes in terms of symptom control as well as future risk of exacerbation.

1.2 Literature review

1.2.1 Phenotypic classification of recurrent wheezing in preschool children

Wheezing is heterogeneous in clinical presentation as well as its pathophysiology. Various features have been used to group preschool children with wheezing. These distinctions are mainly based on clinical observations which is called wheezing phenotype (8).

The first phenotypic classification reported by the Tucson childhood respiratory study of Martinez et al. in which children were classified into four main subtypes, including never wheezing, early transient wheezing, persistent wheezing, and late-onset wheezing has been used for epidemiologic purpose (2). Similar phenotypic classification was also used in the cohort study done in South Africa to assess the determinants of preschool wheeze. This is a retrospective classification which has no role in preventing or treating children during preschool age (9).

Further classification was made based on triggering factor as episodic wheezing and multi-triggered wheeze. Episodic wheeze is wheezing during discrete time periods, often in association with URTI, with symptoms absent between episodes. Multi-triggered wheeze is episodic wheezing with symptoms also occurring between these episodes, e.g., during sleep or with triggers such as activity, laughing, or crying (10).

The other phenotypic classification is based on the presence or absence of type 2 inflammation markers as atopic and non-atopic. The atopic patients have family history of asthma, other allergic diseases like allergic dermatitis, eosinophilia and early sensitization for food and aeroallergen. These phenotypic classifications have been used to predict the risk of developing asthma (11). Blood eosinophil and/or aeroallergen sensitization identifies children who will preferentially respond to maintenance inhaled corticosteroid in preschool recurrent wheezing (2, 12).

1.2.3 Risk factors associated with recurrent wheezing in preschool children

Perinatal risk factor, such as maternal smoking and second-degree exposure to smoking during pregnancy shows an association with recurrent wheezing early in childhood (13, 14). A Pooled analysis of eight birth cohort study which focus exclusively on smoking during pregnancy but not in the first year after birth result found that maternal smoking increases the risk of wheezing and asthma at age 4-6 year with adjusted odds ratios of 1.39 (95% confidence interval, 1.08– 1.77) and 1.65 (95% confidence interval, 1.18–2.31), respectively. The risk even increases in a linear dose dependent manner on the number of cigarette per day consumption during the first trimester pregnancy (14).

Another risk factor identified in relation to maternal smoking and risk of recurrent wheezing is prematurity. Premature children have increased risk of developing recurrent wheeze (15). Jointly both maternal smoking and prematurity increase the risk of the odds from 2.0 with 95% CI (1.3-3.1) to 95% CI 3.8(1.8-8.0) according to the cohort study done in Boston (13).

The study which tries to assess the effects of early onset asthma and in utero exposure to maternal smoking on childhood lung function concluded that those children who were diagnosed with asthma in early childhood and who have in utero exposure to smoking have lower lung function results compared to those who were diagnosed to have asthma later in childhood (16).

Different socio demographic factors like sex, ethnicity, site and level of income, and educational status affect the risk of recurrence. Wheezing and asthma is commonly seen in male sex during preschool and childhood and the relationship is reversed to female patients during and after adolescence. The reason is unknown, but can relate to environmental and biological factors (17, 18).

Low socioeconomic class and low maternal schooling also affect the recurrence and severity of wheezing. In one cross sectional multicenter study which identifies associated factor for recurrent with based on their sex, the odds of developing recurrent wheeze in male preschool children is 1.8x higher in children with low schooling (19).

Parental asthma is among the three major factors that predict the future risk of having childhood asthma, according to the modified asthma predictive tool. These also supported by different literatures. Maternal asthma had a higher risk than paternal asthma (hazard ratio 1.72 (95% confidence interval 1.72 to 1.77) versus 1.51 (1.48 to 1.53). Having two parents with asthma was associated with a 2.40-fold (2.34-fold to 2.47-fold) increased risk of asthma and persistent wheezing based on the match case control study done in Danish children (20).

Other allergic diseases including allergic rhinitis, eczema, food allergy and biomarker such as blood eosinophilia mostly present in association with recurrent wheeze and asthma (21). In addition the treatment outcome also depends on the control of these comorbidities (22). Analysis of predicting factors of recurrent wheezing infants done in Tianjin children's hospital result shows the presence of eczema is higher in recurrent wheezes than control group (23, 24). Bronchiolitis is commonly the first episode of wheeze during infancy. The presence of allergic history, atopic dermatitis, atopic rhinitis and atopic family history with odds of 4.0,3.7, 7.8, and 10.9 respectively, were identified as independent risk factor for recurrent wheeze after bronchiolitis (25).

Allergic diseases may share common mechanisms in the pathogenesis. As a result, eosinophil plays key role in the development of recurrent wheeze, asthma and the other allergic diseases. Data from 1074 children with recurrent with found that each eosinophil cut point was associated with increased odds of exacerbation, higher exacerbation rate and greater hospitalization occurrence in preschool children with recurrent wheezing (26). However, the cut points are difficult to use in developing countries where blood eosinophilia are commonly due to diagnosis of helminthiasis (27).

Wheezing is usually caused by bronchospasm, which can worsen by inflammation of the small and medium airways. In young children, viral infections are the most important triggers of wheezing. Some children are more prone to severe infection because of dysregulation of the innate immune response or bronchial hyper responsiveness which further put them at risk of developing the symptom frequently (28).

The commonest identified virus associated with severe and recurrent wheeze and asthma is

rhinovirus. Hemophilus influenza, Moraxella catarrhalis, Streptococcus pneumoniae are also cultured from lower airway samples of children with persistent severe wheeze episode (29, 30).

Conceptual framework

1.3 Rationale of the study

Recurrent attacks and hospital admission are frequent in children who have specific risk factors. Identifying these factors will help in prevention as well in assessing the treatment response. The phenotypic classification of the recurrent wheeze also predicts their feature risk of developing asthma and level of lung function impairment.

Literatures show an association between the phenotypic classification of wheeze and risk of having recurrent attack and response to treatment. Therefore, determining the phenotypic classification of these patients and associated risk factors, which were not previously assessed in our setup, will fulfill the information gap and help us to recommend possible medical intervention to improve the quality of life and functional capacity of the preschool children.

2. Objective

2.1 Main objective

- To identify risk factor associated with recurrent wheeze in a Tertiary Teaching Hospital in Addis Ababa, Ethiopia

2.2 Specific Objective

- To describe the phenotypic classification of recurrent wheeze among preschool children in a Tertiary Teaching Hospital in Addis Ababa, Ethiopia
- To determine risk factor associated with recurrent wheeze among preschool children in a Tertiary Teaching Hospital in Addis Ababa, Ethiopia

3. Methods

3.1 Study setting and period

The study was conducted in Tikur Anbessa Specialized Hospital (TASH), which is the largest public hospital in the country, located in the capital city Addis Ababa. The hospital provides comprehensive health care services for around half a million patients per year through specialty clinics and inpatient service departments. It has over 600 beds, and about 1,200 health professional in-patient, outpatient and emergency units.

The study was conducted in the pediatric respiratory clinic at TASH which consists of a team of clinicians including a pediatric pulmonologist, pediatric pulmonology fellow and pediatric residents rotating to the clinic, and nursing staff. In average, 75 patients visit the clinic each month.

Team of clinicians from pediatric emergency ward at TASH were also recruited and hematology malignancy, congenital heart diseases and pediatrics surgical emergency cases contribute the major emergency admission. In average 245 patients admitted each month.

The study was conducted from October 2024-Februray 2024 G.C.

3.2 Study design

- Institution based unmatched case control study was employed to assess the risk factor associated with recurrent wheeze among preschool children in a Tertiary Teaching Hospital in Addis Ababa, Ethiopia.

3.2.1 Population

3.3.1 Source population

- The source population includes patients who received services at the pediatric emergency and respiratory clinic.

3.3.2 Study population

- All children diagnosed with recurrent wheeze below age 6year and on follow up at pediatrics respiratory clinic and their age matched children with no wheezing episode who were admitted during the data collection period was included in the study.

3.3.3 Inclusion criteria

- All children diagnosed with recurrent wheeze below age 6years and on follow up at pediatrics respiratory clinic and their age matched children with no wheezing episode who were admitted to pediatrics emergency during the data collection period whose

parents/ guardian given consent to participate in this study.

3.3.4 Exclusion criteria

- Children with pre-existing comorbidities that involve or are associated with respiratory complaints, infrequent wheezes (< 3 per year), cases where incomplete data renders the participant's information unusable, or instances where parents or legal guardians do not provide informed consent for their child to participate in the study were excluded.

3.4 Sample size determination

$$n = \frac{(r+1)}{r} \frac{(\bar{p})\ (1-\bar{p})(Z_{\beta+}\ Z_{\alpha/2})^2}{(p_1 - p_2)^2}$$

Double population proportion exposure difference formula used by taking breast feeding practice on the first six month as independent predictor exposure variable (31). The proportion of not exclusively breast feed preschool children among controls was 23.33% and the proportion of not exclusively breast feed among cases was 56.6%. One to two cases to controls ratio was recruited to achieve 95% power at 5% significance level. Adding 10% non-response rate, the total sample size is 145 with 48 cases and 97 controls.

3.5 Sampling

- Cases was consecutively selected among those preschool children who are in follow up at pediatrics respiratory clinic. The corresponding controls was selected by simple random method from admission to pediatrics emergency ward during the data collection period.

3.6 Data collection procedure

A questionnaire was prepared by reviewing different literatures and other checklists which were related to risk factors of recurrent wheeze in preschool children. A comprehensive early allergy questionnaire was used to assess allergic dermatitis, Food allergy and recurrent wheezing (32, 33) and the Young Children Allergic Rhinitis Questionnaire (YCAR-Q) to assess allergic rhinitis (33).

These data collection tools were translated in to local language (Amharic) and then translated back to English. Review was made by Amharic; English language experts and health professionals checked for consistency of the language translation.

Data was collected through face to face interview of the index parent /guardian and record review using pretested structured and interviewer administered questionnaires by trained

experienced health professionals.

3.7 Operational definition

- Preschool wheeze -Wheezing that occur in children aged below six years in more than one episode and has current/prior documented objective confirmation (4).
- Recurrent wheezing also defined as wheezing which occurs more than three times per year (4).
- Upper respiratory tract infection-includes the common cold, laryngitis, pharyngitis/tonsillitis, acute rhinitis, acute rhinosinusitis and acute otitis media (34).
- Lower respiratory tract infection- includes acute bronchitis, bronchiolitis, pneumonia and tracheitis (34).

3.8 Data Management

Data entry and analysis was done by the principal investigator. Before analysis is done data was coded and cleaned. Data entry was done using Epi info version 7 and analysis was done using SPSS version 27.

3.9 Data analysis

Descriptive analysis was performed to describe numbers and percentage of the variables. The mean was used to describe the participant's characteristics for continuous variable. Categorical variables were described as frequency or percentage. Bivariate analysis was performed to identify potential associated factors for the recurrent wheeze. Variables with P<0.25 on bivariate analysis was entered on multivariate logistic regression to identify independently risk factors associated with recurrent wheeze in preschool children. The significance of Odds Ratio (OR) was determined with 95% CI and P<0.05.

3.10 Ethical consideration

Proposal approval was obtained before beginning of data collection. Written consent was obtained from the child's guardian. The information in the questionnaire was used solely for the intended purpose. The questionnaire was safely stored by the principal investigator. The final proposal was submitted to institutional research board (IRB) of pediatrics and child health department, for ethical clearance.

3.11 Dissemination of results

The results of this study will be publicly defended at Tikur Anbessa Specialized Hospital in the department of pediatrics and child health and Internal medicine. Hard copies will be availed at TASH library. The results will further be disseminated to wider scientific community through abstract presentation at conferences and through publication in a peer-reviewed scholarly journal.

4. Results

4.1 Sociodemographic characteristics

A total of 145 preschool children, including 48 with recurrent wheezing and 97 with non-recurrent wheezing, participated in the study conducted at a tertiary teaching hospital in Addis Ababa. Regarding the age distribution of the participants, children with recurrent wheezing (Mean of 42 months, SD ±17 months) were, on average, older than those without recurrent wheezing (Mean of 34 months, SD ±17 months). In terms of sex distribution, among the total participants, 30 (81.1%) females had non-recurrent wheezing compared to 7 (18.9%) with recurrent wheezing. In contrast, among males, 67 (62.0%) experienced non-recurrent wheezing while 41 (38.0%) had recurrent wheezing. The majority of children with non-recurrent wheezing had fathers with a college education, 41 (68.3%), and mothers who could read and write, 18 (85.7%). In contrast, among children with recurrent wheezing, the highest percentage had fathers with secondary education, 14 (37.8%), and mothers with primary education, 15 (41.7%).

Additionally, the average parental income was higher among children with recurrent wheezing (Mean of 10,044 birr, SD ±4,934 birr) compared to those without recurrent wheezing (Mean of 7,780 birr, SD±2,854 birr). Finally, when considering residence status, urban dwellers showed a notable difference in wheezing patterns, with a frequency of 70 (81.4%) experiencing non-recurrent wheezing compared to just 16 (18.6%) with recurrent cases. In contrast, rural residents displayed an opposite trend, where only 27 (45.8%) had non-recurrent versus a higher count of 32 (54.2%) experiencing recurrent wheezing. Among the aforementioned socio-demographic variables, only sex showed a significant difference between children with recurrent and non-recurrent wheezing during the chi-square analysis, with a P-value of 0.034 **(Table 1).**

Table 1: Socio-demographic characteristics of study participants in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2024 (N=145)

Variables		Non-recurrent wheezing		Recurrent wheezing		P-value
		Freq	%	Freq	%	
Age Category	2 years and Younger	38	79.2	10	20.8	0.23
	3 and 4 years	39	67.2	19	32.8	
	5 years and older	20	51.3	19	48.7	
Sex	Female	30	81.1	7	18.9	0.034
	Male	67	62.0	41	38.0	
Paternal Education	Read and write	13	72.2	5	27.8	0.88
	Primary	20	66.7	10	33.3	
	Secondary	23	62.2	14	37.8	

	College	41	68.3	19	31.7	
Maternal education	Read and write	18	85.7	3	14.3	0.28
	Primary	21	58.3	15	41.7	
	Secondary	25	69.4	11	30.6	
	College	33	63.5	19	36.5	
Parental Income	Up to 5000 birr	21	77.8	6	22.2	0.38
	5000 to 10,000 birr	67	69.1	30	30.9	
	More than 10,000 birr	9	42.9	12	57.1	
Residence	Urban	70	81.4	16	18.6	0.12
	Rural	27	45.8	32	54.2	

4.2 Birth and Infancy history

Regarding the participants birth history, 74 (70.5%) of children with non-recurrent wheezing were delivered vaginally (SVD), while 31 (29.5%) had recurrent wheezing through this method. For those delivered via C-section, 23 (57.5%) experienced non-recurrent wheezing compared to 17 (42.5%) with recurrent wheezing. Among non-recurrent wheezing 85 (73.3%) and 31 (26.7%) recurrent wheezing had a normal birth weight while the remining children were born with low birth weight (less than 2500g). However, the gestational age revealed a significant difference during chi-square analysis as 9 (36.0%) had non-recurrent wheezing compared to a higher proportion of 16 (64.0%) with recurrent wheezing and conversely, among term infants, the figures were 88 (73.3%) for non-recurrent and 32 (26.7%) for recurrent wheezing. NICU admission status also showed a strong association with wheezing patterns as well; among those admitted to NICU, 25 (47.2%) had non-recurrent wheezing compared to 28 (52.8%) with recurrent wheezing, with a highly significant P-value of 0.001. In contrast, among those not admitted to NICU, a higher percentage experienced non-recurrent wheezing at 72 (78.3%), while only 20 (21.7%) had recurrent cases.

Immunization status did not show a significant difference; among fully vaccinated children, 93 (66.0%) experienced non-recurrent wheezing compared to 48 (34.0%) with recurrent cases, resulting in a P-value of 0.138. Among partially vaccinated children, all four participants had non-recurrent wheezing. Finally, regarding feeding practices in the first six months, exclusive breastfeeding (EBF) was reported by 49 (60.5%) of children with non-recurrent wheezing compared to 32 (39.5%) with recurrent wheezing which also did not show a significant difference **(Table 2).**

Table 2: Birth and Infancy history of study participants in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2024 (N=145).

Variables		Non-recurrent wheezing		Recurrent wheezing		P-value
		Freq	%	Freq	%	
Mode of delivery	SVD	74	70.5	31	29.5	0.13
	C/Section	23	57.5	17	42.5	
Birth weight	<2500	12	41.4	17	58.6	0.01
	2500-4000	85	73.3	31	26.7	
Gestational age	Preterm	9	36.0	16	64.0	0.00
	Term	88	73.3	32	26.7	
NICU admission	Yes	25	47.2	28	52.8	0.001
	No	72	78.3	20	21.7	
Immunization status	Fully vaccinated	93	66.0	48	34.0	0.138
	Partially vaccinated	4	100.0	0	.0	
Feeding in the first 6 month	EBF	49	60.5	32	39.5	0.65
	Mixed feeding	48	75.0	16	25.0	

4.3 History of Allergy

The allergic history findings showed clear differences between children with non-recurrent and recurrent wheezing. Among those with recurrent wheezing, 20 (95.2%) had an AR score of less than 3, while only 1 (4.8%) had a score of 3 or more. The mean blood eosinophilia count for children with non-recurrent wheezing was 76 (Standard Deviation = 96), while for children with recurrent wheezing, the mean count was notably higher at 289 (Standard Deviation = 257). The blood eosinophilia counts revealed significant differences between children with non-recurrent wheezing and those with recurrent wheezing as 14 (82.4%) of children with recurrent wheezing having eosinophil levels above 4%, compared to only 3 (17.6%) in the non-recurrent group. Additionally, food allergy scores revealed that only 7 children with recurrent wheezing experience food allergy. Allergic dermatitis was also exclusively observed among those with recurrent wheezing. While parental history of asthma did not show a significant difference **(Table 3).**

Table 3: Allergic History of study participants of study participants in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2024 (N=145).

Variables		Non-recurrent wheezing		Recurrent wheezing		P-value
		Freq	%	Freq	%	
Allergic Rhinitis	No	1	4.8	20	95.2	0.00
	Yes	96	77.4	28	22.6	
Blood Eosinophilia Percentage	Less than 4%	94	73.4	34	26.6	0.00
	4% and above	3	17.6	14	82.4	
Food allergy	Yes	97	70.3	41	29.7	0.00
	No	0	.0	7	100.0	
Allergic dermatitis	Yes	0	.0	15	100.0	0.00
	No	97	74.6	33	25.4	
Family history of Asthma	Yes	14	51.9	13	48.1	0.066
	No	83	70.3	35	29.7	
Family affected by Asthma	Mother	0	.0	3	100.0	0.00
	Father	0	.0	2	100.0	

	Grandparents	0	.0	5	100.0	
	Sibling	1	50.0	1	50.0	
	Aunt and uncle	0	.0	3	100.0	
	None	96	73.8	34	26.2	

4.4 Environmental Risk factors

The findings regarding environmental risk factors showed that parental smoking was reported in 1 (33.3%) child with non-recurrent wheezing and 2 (66.7%) with recurrent wheezing. Maternal passive smoking was observed in 1 (50.0%) child with recurrent wheezing. Indoor cooking practices showed a significant association; 52 (57.8%) children with non-recurrent wheezing were exposed to indoor cooking, whereas 38 (42.2%) with recurrent wheezing were also exposed. Conversely, among those who did not cook indoors, a higher percentage of children doesn't have wheezing experience at 45 (81.8%), while only 10 (18.2%) had recurrent cases. Among cooking

Variable		**Non-recurrent wheezing**		**Recurrent wheezing**		**P-value**
		Freq	**%**	**Freq**	**%**	
Paternal Smoking	Yes	1	33.3	2	66.7	0.212
	No	96	67.6	46	32.4	
Maternal smoking	Yes	0	.0	0	.0	
	No	97	66.9	48	33.1	
Maternal passive smoking	Yes	1	50.0	1	50.0	0.69
	No	96	67.1	47	32.9	
Indoor cooking	Yes	52	57.8	38	42.2	0.003
	No	45	81.8	10	18.2	
Method	Stove	20	54.1	17	45.9	0.100
	Charcoal	14	87.5	2	12.5	
	stove and charcoal	59	67.8	28	32.2	
	stove and biomass	4	80.0	1	20.0	
Separated kitchen	Yes	52	70.3	22	29.7	0.609
	No	45	63.4	26	36.6	

methods, stove use was reported in 20 (54.1%) children with non-recurrent wheezing and 17 (45.9%) with recurrent wheezing, while the combination of stove and charcoal was used by 59 (67.8%) children with non-recurrent wheezing and 28 (32.2%) with recurrent cases. Additionally, among children without a separated kitchen, 45 (63.4%) had non-recurrent wheezing, while 26 (36.6%) had recurrent cases **(Table 4).**

Table 4: Environmental Risk factors of study participants in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2024 (N=145).

4.5 Characteristics of recurrent wheezing

The characteristics of recurrent wheezing were assessed in a total of 48 children experiencing at least three wheezing episode per year. A significant majority, 42 (87.5%), had a history of hospital admissions due to severity, while 6 (12.5%) did not. The timing of the first wheezing episode varied, with 19 (39.6%) occurring in infancy and 29 (60.4%) after infancy. Regarding frequency of admission, 14 (33.3%) children were admitted once, twice, or more than twice.

During wheezing episodes, additional diagnoses were common, with upper respiratory tract infections (URTI) affecting 28 (58.3%), lower respiratory tract infections (LRTI) seen in 5 (10.4%), and both types in 15 (31.3%). Wheezing symptoms during sleep or triggered by activities such as laughing or crying were reported by 27 (56.3%) children, while 21 (43.8%) did not experience these symptoms **(Table 5).**

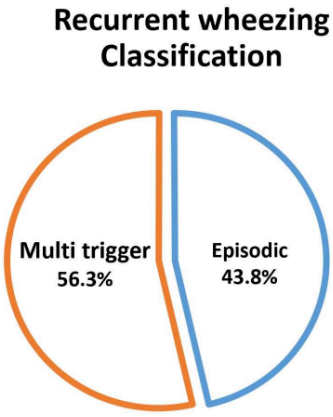
Table 5: Characteristics of recurrent wheezing in of study participants in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2024 (n=48).

Characteristics		Freq	%
Any wheezing episode	Yes	48	33.1
	No	97	66.9
Frequency	<3/year	0	.0
	>=3/year	48	100.0
Severity/History of admission	Yes	42	87.5
	No	6	12.5

Time at first episode	Infancy	19	39.6
	After infancy	29	60.4
Frequency of Admission	Once	14	33.3
	Twice	14	33.3
	More than twice	14	33.3
Additional diagnosis during the wheezing episode	URTI	28	58.3
	LRTI	5	10.4
	Both	15	31.3
Multi triggered wheeze	Yes	27	56.3
	No	21	43.8

4.6 Phenotypic classification of children with recurrent Whizzing

The phenotypic characteristics of recurrent wheezing among the study population revealed that multi-trigger wheezing was present in 27 (56.3% with 95% CI: 41.5%-71.1%) of the participants, while 21 (43.8%) were Episodic wheezing. Atopic wheezing was observed in 30 (62.5% with 95% CI: 48.6% - 75.2%) of the children, with 18 (37.5%) not presenting this phenotype **(Figure 1).**



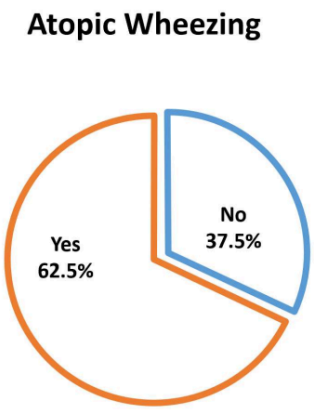


Figure 1: Phenotypic classification of children with recurrent Wheezing among children in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2024 (n=48).

Regarding the relationship between atopic wheezing and Multi trigger wheezing; among children with atopic wheezing, 20 (66.7%) experienced the symptoms apart from the time of URTI, while 10 (33.3%) did not. In contrast, among children without atopic wheezing, only 7 (38.9%) experienced symptoms, while 11 (61.1%) did not. Even though, the Pearson correlation results indicate a moderate positive relationship between atopic wheezing and multi-trigger wheezing, with a Pearson correlation coefficient of 0.271. This suggests that as the incidence of atopic wheezing increases, there is a tendency for multi-trigger wheezing to also increase. However, the significance level (p = 0.062) indicates that this correlation is not statistically significant **(Table 6).**

Table 6: Relationship between atopic wheezing and Multi trigger and episodic wheezing of study participants in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2024 (n=48).

		Multi trigger and episodic wheezing				Pearson Correlation	P-Value
		Yes		No			
		Freq	%	Freq	%		
Atopic wheezing	Yes	20	66.7	10	33.3	0.271	0.062
	No	7	38.9	11	61.1		

4.7 Factors associated with Recurrent Wheezing

A binary logistic regression analysis was conducted to identify factors associated with recurrent wheezing in children. During the bivariate analysis, six variables (sex, indoor cooking, day care attendance, gestational age, birth weight, and NICU admission) were found to be associated with recurrent wheezing with a p-value less than 0.05. These variables were selected as candidates for multivariate analysis. In the multivariate analysis, three variables (sex, indoor cooking, and NICU

admission) were found to be significantly associated with recurrent wheezing with a p-value less than 0.05.

In this study, the odds of recurrent wheezing among male children were 2.6 times higher than female children [AOR = 2.6, 95% CI: 1.2-9.1]. The second significant variable associated with recurrent wheezing was indoor cooking exposure. Children exposed to indoor cooking were 3.2 times more likely to experience recurrent wheezing compared to those not exposed [AOR = 3.2, 95% CI: 1.3-8.2]. Finally, the odds of recurrent wheezing among children who had been admitted to the NICU were 3.4 times higher than those who had not been admitted [AOR = 3.4, 95% CI: 1.5-7.8] **(Table 7).**

Table 7: Factors associated with Recurrent Wheezing among children in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2024 (N=145).

Variable	Recurrent wheezing		COR	AOR
	Yes Frequency (%)	No Frequency (%)	(95% CI)	(95% CI)
Sex				
Female	7 (18.9)	30 (81.1)	1	1
Male	41 (38.0)	67 (62.0)	2.6 (1.1-6.5)	**2.6 (1.2-9.1)***
Indoor Cooking				
Yes	38 (42.2)	52 (57.8)	3.2 (1.5-7.3)	**3.2 (1.3-8.2)***
No	10 (18.2)	45 (81.8)	1	1
Day Care Attendance				
Yes	11 (61.1)	7 (38.9)	3.3 (1.4-7.4)	2.7 (0.8-9.6)
No	37 (29.1)	90 (70.9)	1	1
Gestational Age				

Preterm	16 (64.0)	9 (36.0)	4.8 (1.9-12.2)	1.6 (0.8-5.2)
Term	32 (26.7)	88 (73.3)	1	1
Birth Weight				
<2500	17 (58.6)	12 (41.4)	3.8 (1.6-9.0)	2.8 (0.9-8.7)
2500-4000	31 (26.7)	85 (73.3)	1	1
NICU Admission				
Yes	28 (52.8)	25 (47.2)	4.0 (1.9 – 8.4)	**3.4 (1.5-7.8) ***
No	20 (21.7)	72 (78.3)	1	1

Note: *P-value less than 0.05.

5. Discussion

In this study, we tried to assess the phenotypic classification of recurrent wheeze among preschool children and identify the risk factor associated with recurrent wheeze among preschool children in a Tertiary Teaching Hospital in Addis Ababa, Ethiopia. The findings of this study provide valuable insights into the phenotypic characteristics of recurrent wheezing among the study population.

Multi-trigger wheezing was present in 56.3% (95% CI: 41.5%-71.1%) of the participants. This finding is comparable with study conducted in Switzerland identified multi-trigger wheezing as a common phenotype among children with recurrent wheezing, with a prevalence of 52.4% in their cohort (35). Multi-trigger wheezing is a common phenotype in the study population, suggesting that a significant proportion of children with recurrent wheezing experience symptoms triggered by multiple factors such as physical activity, laughing, crying, or environmental exposures.

Atopic wheezing was observed in 62.5% (95% CI: 48.6% - 75.2%) of the children. Atopy (allergic sensitization) plays a significant role in recurrent wheezing in the study population, as evidenced by the high prevalence of atopic wheezing. This finding is consistent with a study by conducted in Australia reported that atopic wheezing was present in 65.2% of children with recurrent wheezing, emphasizing the role of atopy as a significant risk factor (36). In general, the high prevalence of multi-trigger wheezing and atopic wheezing in this study imply that recurrent wheezing in the study population is a heterogeneous condition and the importance of phenotype-specific management strategies, early intervention, and environmental modifications to improve outcomes for children with recurrent wheezing (37).

The second objective of the study was identifying factors associated with recurrent wheezing. In this study, the odds of recurrent wheezing among male children were 2.6 times higher than female children [AOR = 2.6, 95% CI: 1.2-9.1] which is consistent with findings from studies in the United States, United Kingdom, and Brazil. A study conducted in USA found that male children had 2.3 times higher odds of recurrent wheezing compared to females (38). A longitudinal study conducted in UK reported that male children were 1.8 times more likely to experience recurrent wheezing than females. The study suggested that genetic and immunological factors, such as differences in immune responses to respiratory viruses, may contribute to this disparity (39). Similarly, study

conducted in Brazil also found that male children had 2.5 times higher odds of recurrent wheezing, aligning closely with our findings (40).

The higher incidence of recurrent wheezing in male children can be attributed to a combination of biological, environmental, and behavioral factors. Biologically, males tend to have narrower airways, making them more prone to obstruction and wheezing, and they may have a heightened immune response to respiratory viruses. Additionally, hormonal differences, such as the protective effects of estrogen in females, may lower the risk of wheezing in girls (31). Environmentally and behaviorally, male children often engage more in outdoor activities, increasing exposure to dust, pollen, and air pollution. They may also be more exposed to indoor pollutants like secondhand smoke due to cultural norms, further increasing their risk of recurrent wheezing (41).

The study also identified indoor cooking exposure is significantly associated with recurrent wheezing, with exposed children being 3.2 times more likely to experience recurrent wheezing compared to those not exposed [AOR = 3.2, 95% CI: 1.3–8.2], underscores the critical role of environmental factors in the development of respiratory conditions. A study conducted in Mexico also found that children exposed to indoor cooking with wood or charcoal had 3.1 times higher odds of recurrent wheezing, which is nearly identical to our findings (42). Similarly, a study conducted in Nepal reported that children in households using solid fuels for cooking had 2.8 times higher odds of recurrent wheezing. The authors emphasized the role of chronic exposure to indoor air pollution in causing airway inflammation and hyperreactivity (43). This finding is also similar with study conducted in Addis Ababa, Ethiopia, reported that children exposed to indoor cooking with biomass fuels had 3.4 times higher odds of recurrent wheezing, closely matching our findings (44). Another study conducted in rural Ethiopia found that children in households using solid fuels for cooking had 2.9 times higher odds of recurrent wheezing (45).

The strong association between indoor cooking exposure and recurrent wheezing can be attributed to the release of harmful pollutants from biomass fuels, such as particulate matter (PM2.5), carbon monoxide, and nitrogen dioxide, which irritate the airways and lead to inflammation and hyperreactivity (46). Children, with developing respiratory systems, are particularly vulnerable to these effects (47). Prolonged exposure to indoor air pollution can cause chronic airway inflammation, increasing susceptibility to recurrent wheezing episodes. Additionally, inflammatory mediators released in response to pollutant exposure can contribute to airway remodeling, further exacerbating respiratory symptoms (48).

Finally, the finding of this study identified that children who had been admitted to the Neonatal Intensive Care Unit (NICU) were 3.4 times more likely to experience recurrent wheezing compared to those who had not been admitted [AOR = 3.4, 95% CI: 1.5–7.8] highlights the long-term respiratory consequences of neonatal complications. This finding is consistent with studies from the United States, Netherlands, Brazil, and Ethiopia. A study conducted in USA found that children with a history of NICU admission had 3.2 times higher odds of recurrent wheezing compared to those without such a history by (15). A study conducted in Netherland reported that NICU-admitted children had 3.5 times higher odds of recurrent wheezing, which is nearly identical to our findings. The authors emphasized the role of mechanical ventilation and oxygen therapy in causing airway injury and inflammation, which can predispose children to recurrent wheezing (49). The study in Brazil identified that children with a history of NICU admission had 3.1 times higher odds of recurrent wheezing (50). Similarly, A study conducted in Addis Ababa, Ethiopia, reported that children with a history of NICU admission had 3.3 times higher odds of recurrent wheezing, closely matching our findings (51). Another study conducted in Hawassa, Ethiopia, found that NICU-admitted children had 2.9 times higher odds of recurrent wheezing. The authors suggested that the lack of follow-up care for NICU survivors in low-resource settings may contribute to the persistence of respiratory symptoms (52).

The strong association between NICU admission and recurrent wheezing can be explained by several mechanisms. Impaired Lung Development: Preterm or low birth weight infants often experience incomplete lung development and reduced lung function, predisposing them to recurrent wheezing. Conditions like bronchopulmonary dysplasia (BPD) can cause long-term airway damage, increasing wheezing risk (53). Airway Injury and Inflammation can also lead to recurrent wheezing in later life of the children as Mechanical ventilation and oxygen therapy in the NICU can lead to airway injury and inflammation, causing hyperreactivity and wheezing (15). Neonatal Infections such as pneumonia and sepsis are common in NICU settings and can lead to long-term respiratory complications, including recurrent wheezing, especially in low-resource settings like Ethiopia (52).

6. Strength and Limitation of the study

6.1 Strength of the study

- The study design is a case control study which helps to identify risk factors for the outcome variable and also helps to determine cause and effect relationship.
- The study also identifies the phenotypic classification of recurrent wheezing which help to highlights the need for targeted interventions to address the underlying triggers and risk factors

6.2 Limitation of the study

- The study conducted in a single a tertiary teaching hospital with small sample which makes it difficult to generalize to all the children with recurrent wheezing in Addis Ababa.
- The study also lacks longitudinal data to assess the progression of wheezing phenotypes over time.
- Lack of objective evidence of allergy with Allergic test panel.

7. Conclusion

The study finds out that high prevalence of multi-trigger wheezing and atopic wheezing among children with recurrent wheezing. that highlights the phenotypic heterogeneity of recurrent wheezing in the study population, with multi-trigger wheezing and atopic wheezing being the most common phenotypes. This study also identified key factors associated with recurrent wheezing among children, emphasizing the interplay of biological, environmental, and neonatal influences. Male children were found to be at a higher risk of recurrent wheezing compared to females, likely due to a combination of biological differences and greater exposure to environmental triggers. Indoor cooking exposure emerged as a significant environmental risk factor, with children in households with indoor cooking exposure more susceptible to recurrent wheezing, highlighting the detrimental effects of indoor air pollution on respiratory health. Additionally, a history of NICU admission was strongly linked to recurrent wheezing, reflecting the long-term respiratory consequences of neonatal complications such as preterm birth, low birth weight, and neonatal infections.

8. Recommendations

i. For Clinicians:

- Recognize the phenotypic heterogeneity of recurrent wheezing, particularly the high prevalence of multi-trigger wheezing and atopic wheezing, and tailor treatment plans accordingly.
- Provide education to parents and caregivers on reducing exposure to environmental triggers, such as improving ventilation, using clean cooking technologies, and avoiding secondhand smoke.
- Establish specialized follow-up programs for NICU survivors to monitor and manage long-term respiratory outcomes, including recurrent wheezing. Early intervention in this high-risk group can improve lung health and reduce the burden of respiratory diseases.

ii. For Policymakers:

- Launch public health campaigns to raise awareness about the health risks of indoor air pollution and the importance of reducing exposure to environmental triggers.
- Strengthen neonatal care services, particularly in low-resource settings, to reduce the incidence of neonatal complications such as preterm birth and neonatal infections.
- Establish follow-up programs for NICU survivors to monitor and manage long-term health outcomes, including recurrent wheezing.
- Develop gender-sensitive strategies to address the higher risk of recurrent wheezing among male children, including targeted interventions to reduce exposure to environmental triggers and improve access to healthcare services.

iii. For Researchers

- Conduct longitudinal studies to better understand the progression of different wheezing phenotypes, particularly multi-trigger wheezing and atopic wheezing, and their long-term outcomes.
- Investigate the genetic, immunological, and environmental factors contributing to phenotypic heterogeneity in recurrent wheezing.
- Explore the long-term respiratory outcomes of NICU-admitted children, focusing on the impact of neonatal complications such as preterm birth, low birth weight, and neonatal infections.

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Annex
I: Information sheet

Research Project: To determine phenotypic classification and risk factor associated with recurrent wheeze in preschool children, Addis Ababa Ethiopia.

Name of principal investigator-Melat Tesfaye

Introduction: This information sheet and consent form is prepared by the investigator whose main aim is to determine the phenotype classification and risk factor associated with recurrent wheeze in a Tertiary Teaching Hospital.

Purpose: The research will determine the phenotype of children with recurrent wheeze and try to identify factors that can be prevented or treated to decrease the unwanted outcome of preschool children with recurrent wheeze.

Procedure; you are kindly invited to take part in our research because we believe you can provide the necessary information for the research. Participation into the study is on voluntary basis. If you are willing for you and your child to be part of this study, you need to understand and sign the consent form and then the data collectors will ask you some questions about you and yourchild. All responses and results will be kept anonymous and confidential. No one other than the research team will have access to your response.

Risk and/discomfort- you will not face any risk in participating in this research but it might take your time (15 to30 minutes).

Benefit- Your child might not directly benefit from this study but your participation in this study will help other children in the future. But any new information found will be

relayed to the doctor(s) taking care of the child so that your child gets the relevant treatment. Right to refuse; you have full right to refuse from participating in this research if you do not wish to participate; and this will not affect you.

Person to contact for any information;
Melat Tesfaye Email:melattesfaye1990@gmail.com

Annex II Consent form

I am giving my consent to participate in the study entitled as "Phenotypic classification and risk factor associated with recurrent wheeze in preschool children in a tertiary hospital Addis Ababa Ethiopia, A case control study". I have understood that participation in this study is entirely voluntarily. I have been told that my answers to the questions and the finding from the child will not be given to anyone else and no reports of this study ever identify me in any way. I have also been informed that my participation or non-participation or my refusal to answer questions will have no effect on me. I understood that participation in this study does not involve risks.

Do you agree to proceed?

Participant's Signature _____Date

Researcher's Signature _____Date

If yes continue, if no stop, Thank you!

የመረጃወረቀት

የምርምርፕሮጄክት፡-

በቅድመትምህርትቤትህጻናትላይበተደጋጋሚከሚከሰትየትንፋሽትንፋሽጋርየተዛመደፍኖታይፒክምደባእናየአደጋመን
ስኤንለመወሰን፣አዲስአበባኢትዮጵያ።

የዋናመርማሪውስም - ሜላትተስፋዬ

መግቢያ፡ይህየመረጃወረቀትእናየስምምነትፎርምየተዘጋጀውበመርማሪውነውዋናውአላማው በ
ከፍተኛትምህርትሆስፒታልውስጥከተደጋጋሚየትንፋሽጋርየተያያዘውንየፊኖታይፕምደባእናየአ
ደጋመንስኤንለመወሰንነው።

ዓላማው፡ጥናቱበተደጋጋሚየትንፋሽመተንፈስያለባቸውንሕጻናትፍኖታይፕይወስናልእናመከላከልወይምመ
ታከምየሚቻልባቸውንሁኔታዎችለመለየትይሞክራል።

አሰራር;

ለምርምሩአስፈላጊውንመረጃመስጠትችላላችሁብለንስለምናምንበጥናታችንእንድትሳተፉበአክብሮትተጋ
ብዘዋል።በጥናቱውስጥመሳተፍበፈቃደኝነትላይየተመሰረተነው.

እርስዎእናልጅዎየዚህጥናትአካልእንዲሆኑፍቃደኛከሆኑ፣የስምምነትቅጹንተረድተውመፈረምእናመረጃሰብሳ
ቢዎቹስለእርስዎእናስለልጅዎአንዳንድጥያቄዎችንይጠይቃሉ።ሁሉምምላሾችእናውጤቶችማንነታቸውሳይገ
ለጽእናሚስጥራዊሆነውይቀመጣሉ።ከተመራማሪውቡድንሌላማንምሰውየእርስዎንምላሽማግኘትአይችል
ም።

ስጋትእና/መመቸት-

በዚህጥናትውስጥለመሳተፍምንምአይነትአደጋአይጋለጥምነገርግንጊዜዎንሊወስድይችላል (ከ15 እስከ 30
ደቂቃዎች)።

ጥቅማጥቅሞች-

ልጅዎከዚህጥናትበቀጥታተጠቃሚላይሆንይችላልነገርግንበዚህጥናትውስጥመሳተፍዎወደፊት
ሌሎችልጆችንይረዳል።ነገርግንማንኛውምአዲስየተገኘመረጃልጅዎተገቢውንህክምናእንዲያገኝል
ጁንለሚንከባከበውዶክተር(ዎች) ይተላለፋል።

እምቢየማለትመብት; መሳተፍካልፈለጉበዚህጥናትውስጥላለመሳተፍሙሉመብትአለዎት;
እናይህአይነካዎትም
ለማንኛውምመረጃለማነጋገርሰው;
ሜላትተስፋዬኢሜል፦melattesfaye1990@gmail.com
የፍቃድቅፅ
“Phenotypic classification and risk factor with recurrent wheeze in preschool children in a tertiary hospital Addis Ababa Ethiopia, A case control study” በሚልርዕስበጥናቱለመሳተፍፈቃዴንእየሰጡሁነው።በዚህጥናትውስጥመሳተፍሙሉበሙሉበፈ
ቃደኝነትእንደሆነተረድቻለሁ።ለጥያቄዎቹየእኔመልሶችእናከልጁየተገኘውግኝትለሌላሰውእንደማ
ይሰጥተነግሮኛልእናምየዚህጥናትዘገባበምንምመልኩእኔንለይቶአያውቅም።የእኔተሳትፎወይም
አለመሳተፍወይምለጥያቄዎችመልስአለመስጠትበእኔላይምንምተጽእኖእንደሌለውተነግሮኛል.
በዚህጥናትውስጥመሳተፍአደጋዎችንእንደማያካትትተረድቻለሁ።
ለመቀጠልተስማምተሃል?

የተሳታፊፈርማ _____ቀን

የተመራማሪፈርማ _____ቀን

አዎከቀጠሉ፣ማቆሚያከሌለ፣አመሰግናለሁ!

Annex III Questionnaire

Part 1 Chart number

	Question	Response	Specify
1) Sociodemographic			
1	Age	months	
2	Sex	1. Female 2. Male	
3	Paternal education level	1. Illiterate 2. Read and write 3. Primary 4. Secondary 5. College	
4.	Maternal education level	1. Illiterate 2. Read and write 3. Primary 4. Secondary 5. College	
5	Parent Income		
6	Address	1. Urban 2. Rural	
2) Nutritional Assessment		**Kilogram/Centimeter**	**Z score**
7	Weight		

8	Length/Height		
9	Weight/Length		
10	Interpretation	1. Underweight 2. Stunted 3. Wasted 4. Overweight 5. Obesity	
3) Risk Factors			
3.1 Presence of Atopy			**Specify**
3.1.1 The Young Children Allergic Rhinitis Questionnaire (YCAR-Q)			
11.	blocked nose	1. Yes 2. No	
12.	Sneezing	1. Yes 2. No	
13.	Itchy nose?	1. Yes 2. No	
14.	Runny nose?	1. Yes 2. No	
15.	Itchy throat?	1. Yes 2. No	
16.	Itchy or irritated eyes?	1. Yes 2. No	

17	Aero allergy Sensitization? if yes specify	1. Yes 2. No	• Dust mite • Cockroach • Cat • Dog • Mold • Grass • Trees/weeds • other

18	Parental History of Asthma	1. Yes 2. No	• Mother • Father • other
19	Blood eosinophilia	1. < 4% 2. > =4%	• Count • Percentage
3.2 Indoor exposure			
20	Passive smoker	1. Yes 2. No	
21	Pack per year		
21	Indoor cooking	1. Yes 2. No	
22	If yes for question number 16, method?	1. Stove 2. Charcoal 3. other	
23	Day care attendance	1. Yes 2. No	
3.3 Perinatal history			

24	Maternal smoking	1. Yes 2. No	
25	Maternal passive smoking	1. Yes 2. No	
26	Mode of delivery	1. Yes 2. No	
27	Gestational age	1. Preterm 2. Term	
28	Birth weight	1. <2500gm 2. >=2500gm	
29	NICU admission	1. Yes 2. No	

30	Immunization	1. Fully vaccinated 2. Partially vaccinated 3. Unvaccinated	
31	Feeding in the first 06 month	1. EBF 2. Mixed feeding 3. Bottle feeding	
	4) Wheezing Episode		
32	Any wheezing episode?	1. Yes 2. No	
33	If yes for question number 23, Frequency?	1. < 3/Year 2. >= 3/Year	
34	Severity/History of admission?	1. Yes 2. No	
35	If yes, when was the first episode?	1. Infancy 2. After infancy	
36	Frequency of admission over the past one year?		

37	Additional diagnosis during the wheezing episode?	1. URTI 2. LRTI 3. Other 4. None	
38	Any symptoms occur during sleep or with triggers such as activity, laughing, or crying apart from U/LRTI?	1. Yes 2. No	

Part 2 Comprehensive allergy questionnaire

1. Hasyourchildeverhadanyofthefollowing**WITHINTWOHOURS**aftereatinganyfood(s)?

Itchyrash(hives)	1.Yes 2.No
Swellingoflips,eyes,tongue	1.Yes

	2.No
Breathingdifficulties(cough/hoarsevoice/wheezing)	1.Yes 2.No
Vomiting/Diarrhea	1.Yes 2.No

2. If **YES**, did these problems go away **WITHINADAY?**

A. YES

B. NO

C. Don't remember

3. Whichofthefollowingfoodshasyourchildreactedto**WITHIN2HOURS**aftereatingit?

A. Cow's milk

B. Egg

C. Peanut

D. Soy

E. Wheat

F. Fruits

G. Don't know

H. other

4. Hasadoctoreversaidyourchildhasa**foodallergy**?

A. Yes

B. No

5. Hasyourchildhadanitchyorredrashcomingandgoing**inthepast12months**?

A. Yes

B. No

6. Ifyouanswered**YES**to**Question9**,howmanytimeshasyourchildhadthisrash?

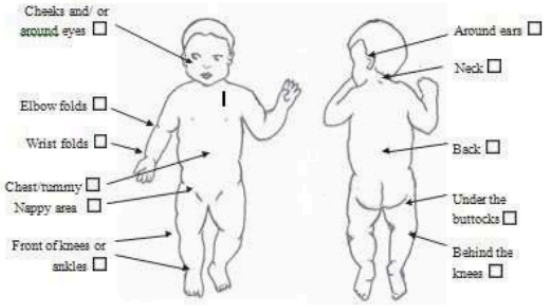
A. Once

B. 2-3

C. 4 or more

D. All the times

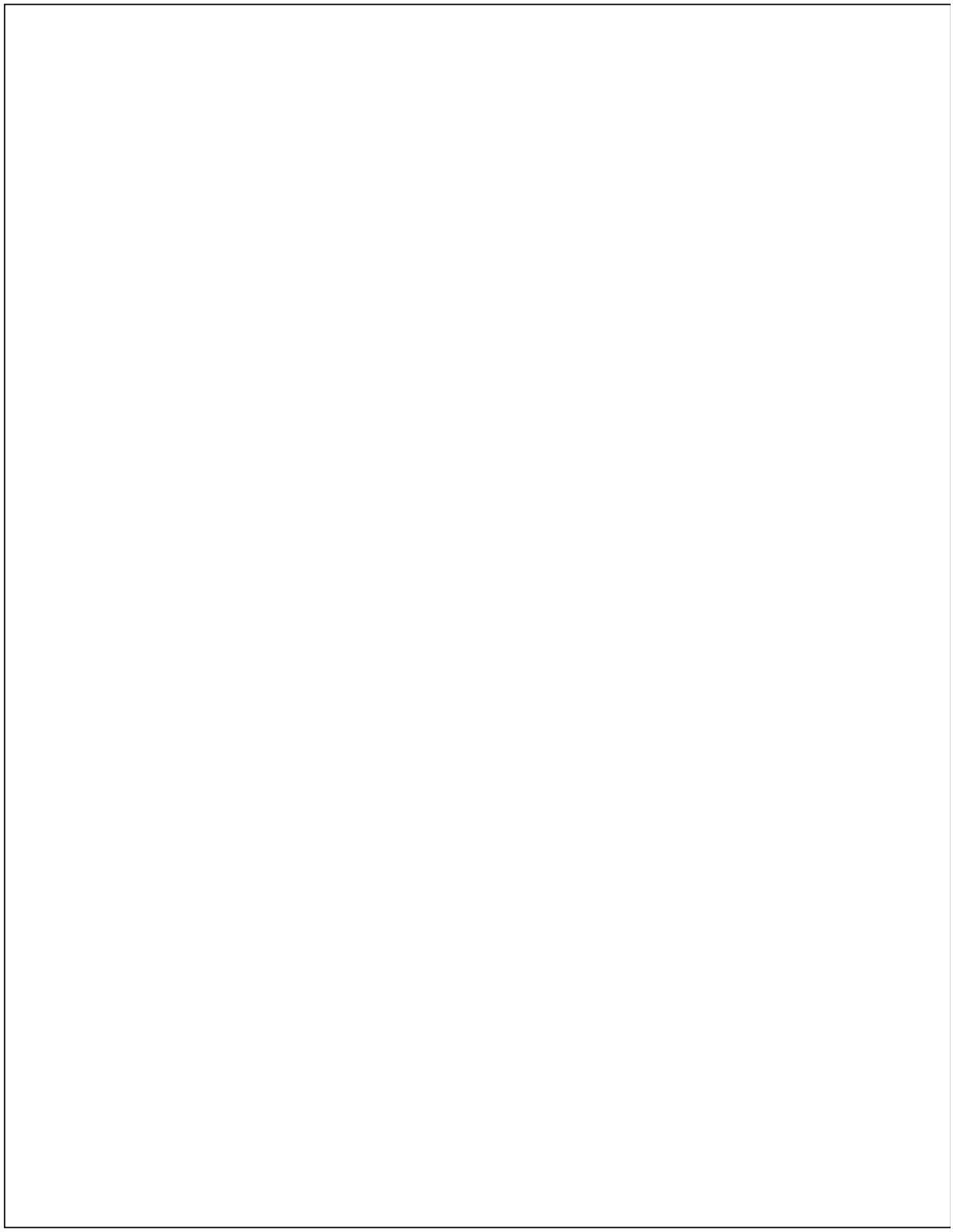
7. Has the rash affected any of the areas below? (please tick all affected areas)



8. Has a doctor ever said you child has **eczema**?

A. Yes

B. N



PHENOTYPIC CLASSIFICATION AND RISK FACTORS ASSOCIATED WITH RECURRENT WHEEZE AMONG PRESCHOOL CHILDREN IN A TERTIARY TEACHING HOSPITAL IN ADDIS ABABA, ETHIOPIA; A CASE CONTROL STUDY By Melat Tesfaye

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