

# Risk Factors of Recurrent Wheezing in Children Under 5 Years of Age

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**Objective:** To identify risk factors which may lead to the occurrence of recurrent wheezing in children under five years of age.

**Material and Method:** A cross-sectional study was conducted in children under 5 years old at the Out Patient Department at Naresuan University Hospital, from October 2013 to October 2014. Fifty-five children who had signs and symptoms of recurrent wheezing were assigned to the study group, whereas another fifty-five children matching on age and sex with the case who had no symptoms of recurrent wheezing were assigned to the control group. All of the parents completed the given questionnaires. Descriptive data analysis were statistically conducted to understand the characteristics of the study groups. The risk factors were analysed using both bivariate and multivariate statistical analyses which included all the important predictors with a statistically significant level of  $p < 0.05$ .

**Results:** Mean age in the study group was 36.1 months and in the control group 25.0 months. The mean weights and heights showed no difference between the case and control groups. Bivariate analysis showed that upper respiratory tract infection [odds ratio (OR) 7.273; 95% confidence interval (CI) 2.277-23.232], lower respiratory tract infection (OR 5.332; 95% CI 2.326-12.225), passive smoking (OR 2.368; 95% CI 1.094-5.129), and day care center attendance (OR 2.590; 95% CI 1.168-5.745) were the risk factors of recurrent wheezing. Multivariate logistic regression analysis indicate that lower respiratory tract infection [adjusted odds ratios (aOR) 0.241; 95% CI 0.088-0.659] was the most important risk factor leading to recurrent wheezing.

**Conclusion:** Lower respiratory tract infection, upper respiratory tract infection, passive smoking and day care center attendance were found to be risk factors of recurrent wheezing in children under five years of age, with lower respiratory tract infection being the most risk. Targeted surveillance of these risk factors should reduce the incidence of recurrent wheezing. This is especially important for high risk patients such as asthma patients.

**Keywords:** Recurrent wheezing, risk factors, asthma, lower respiratory tract infection, respiratory tract infection

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A wheeze is a continuous, coarse, whistling sound produced in the respiratory airways during breathing. For wheezes to occur, some parts of the respiratory tree must be narrowed or obstructed, or airflow velocity within the respiratory tree is heightened. Wheezing is commonly experienced by persons with lung disease; the most common cause of recurrent

wheezing is an asthmatic attack. In small children however, the etiologic diagnosis of recurrent wheezing varies considerably. Children with recurrent wheezing have a greater chance to develop asthma and can be depicted as an important cause of morbidity and mortality worldwide in both developed and developing countries<sup>(1)</sup>. Previous studies have shown the prevalence of recurrent wheezing between 14.3-36.6%<sup>(2,3)</sup>.

It is presumed that asthma can manifest early in children under 5 years of age. On the other hand, the diagnosis of asthma is difficult in this age group as complementary methods of investigation would rely on a pulmonary function test (not fully available),

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and a high number of possible etiologies. Prospective studies have suggested several risk factors for recurrent wheezing in children and its association with the subsequent development of asthma, such as a family history of asthma and allergies, A personal history of rhinitis or eczema<sup>(4,5)</sup>, maternal smoking during pregnancy or passive exposure after birth<sup>(6)</sup>, male gender<sup>(4,7)</sup>, viral respiratory infections by respiratory syncytial virus (RSV) or rhinovirus<sup>(8,9)</sup> and attending day care<sup>(10,11)</sup>.

Although risk factors for recurrent wheezing in children under 5 years of age have been identified, their analysis is complex due to genetic-environmental interactions. The development of methods to identify and quantify these factors is essential to a better understanding of the natural history of asthma in childhood. The epidemiology of asthma in school-age children, adolescents, and adults is generally known and understood. However, the risk factors of recurrent wheezing in infants and preschool children need to be further investigated.

The purpose of the present study was to evaluate the risk factors of recurrent wheezing in children under 5 years of age in Phitsanulok Province in lower northern Thailand.

## Material and Method

The study was conducted in the sick patients clinic of the Pediatrics Department at Naresuan University Hospital, from October 2013 to October 2014. The inclusion criteria were children under five years old coming in to the Outpatient Department. The exclusion criteria were children with congenital pulmonary abnormalities, chronic lung disease, bronchopulmonary dysplasia (BPD), pulmonary aspiration syndrome, and immunodeficiency disease. The Institutional Review Board for Human Studies of Naresuan University approved the protocols (IRB No. HE 55-Ep1-0100). Informed consent for every child included in the study was obtained from the parent or parents of the child.

At the time of enrollment, each parent was interviewed by the researchers for signs and symptoms of recurrent wheezing of the child. The recurrent wheezing in the present study was defined as three or more reported episodes of wheezing diagnosed by physical examination (every episode had to be confirmed by physician). Patients who had signs and symptoms of recurrent wheezing were assigned to the study group and patients matching of age and sex with

the study who had no symptoms of recurrent wheezing were assigned to the control group. Both study group and control group were outpatients who came to the O.P.D. Pediatric on the same day. The questionnaire was presented to all parents to complete all completed the given questionnaire. The questionnaire contained eight items as follow: detailed general data; history of respiratory symptoms during the last year; treatments during the last year; information on prenatal, perinatal periods and postnatal periods; risk factors; and domestic environment. The questionnaire was created by the researchers and confirmed by three specialists (one chest and two allergy experts). It was tested for validity and reliability with a group of parents of children attending the respiratory clinic at Naresuan University Hospital. The questionnaire was completed at the Outpatient Department by nurses, and subsequently confirmed by a pediatrician.

The collected data were analysed using a statistical program on descriptive data analysis through descriptive statistics (frequency, percentage, mean, standard deviation and range). To detect the risk factors of recurrent wheezing, a bivariate analysis was conducted using logistic regression models. The best model was defined by dropping covariates one by one from a saturated model that included all variables. Finally, a multivariate model was applied including all the important predictors with a statistically significant association ( $p < 0.05$ ). The results were expressed in odds ratios (OR) and adjusted odds ratios (aOR) calculated using methods of maximum likelihood with their corresponding confidence intervals of 95% (95%CI).

## Results

Five hundred and seventy children came to the general Outpatient Department of Pediatrics Naresuan University Hospital, from October 2013 to October 2014. In the present study, 460 children were excluded due to 3 main reason; 1) no informed consent in 254 children, 2) Children had underlying disease 109 case, and 3) incomplete questionnaires 97 case. Thus, 110 children were enrolled in the study: 55 children in the study group (who had recurrent wheezing) and 55 in the control group (no recurrent wheezing). Mean age in the case group was 36.1 months and 25.0 months in the control group. There were more females than males in both groups: for the study group 1.6:1 and in the control group 1.9:1. The mean weight of the

case group was 15.5 kg. whereas the control was 14.6 kg. The mean height in the study group was 97.5 cm. and 87.1 cm. in the control group. For the method of delivery, 58.2% of the study group were delivered by cesarean section, 40 % by normal delivery and 1.8% through vacuum extraction. In the control group 51.9% were by normal delivery, 46.2% by cesarean section, and 1.8% via vacuum extraction. The mean birth weight was 2,856.48 grams in the study group, and 2,881.78 grams in the control group, with a mean gestational age of 36.12 weeks for the study group and 33.73 weeks in the control group. The mean length of stay in hospital after birth in the study group was 8.0 days and for the control group 5.8 days, (Table 1).

Using the bivariate logistic regression analysis, risk factors of recurrent wheezing in children under 5 years of age were upper respiratory tract infection (OR 7.273; 95% CI 2.277-23.232), lower respiratory tract infection (OR 5.332; 95% CI 2.326-12.225), passive smoking (OR 2.368; 95% CI 1.094-5.129), and day care center attendance (OR 2.590; 95% CI 1.168-5.745) (Table 2). When analyzed via multivariate logistic regression analysis, the risk factor of recurrent wheezing was found to be lower respiratory tract infection (aOR 0.241; 95% CI, 0.088-0.659), (Table 3).

## Discussion

Recurrent wheezing is a common symptom of illness during infancy and early childhood<sup>(1,2)</sup>. Although the majority of children will out-grow their symptoms, some children go on to develop asthma. Recurrent wheezing is major public-health problem, because of the overuse of public health care funds/resources<sup>(12,13)</sup>. The prevalence of recurrent wheezing was 14.3-36.6% and the prevalence of wheezing associated with lower respiratory tract infection among children followed for the entire year was 32% in the first year of life, declined to 17.3% and 12% in the second and third year, respectively<sup>(14)</sup>. In Thailand, Wimuttigisol S. found risk factors of reactive airway disease in young children were having common cold more than 1 episode per month, lower respiratory tract infection or pneumonia, father or mother had allergic rhinitis, and using mosquito repellent spray or other kinds of smoke<sup>(15)</sup>. In 2006, Charutragulchai W. showed risk factors of asthma or recurrent wheezing in children 2-5 years old were lower respiratory tract infection and skin prick test positive for allergen more than 1 type.

On the other hand she found the protective factor was using air conditioner in bedroom<sup>(16)</sup>.

The present study showed the significant risk factors of recurrent wheezing in children under 5 years old through bivariate analysis were upper respiratory tract infections, lower respiratory tract infections, passive smoking, and day care attendance. This finding is in agreement with previous studies<sup>(4-10)</sup>.

The authors found upper and lower respiratory tract infection were risk factors of recurrent wheezing. The study with all International Study of Wheezing in Infants (EISL) centers and others showed that having a cold during the first 3-6 months of life and attending nursery school were the most important independent risk factors for wheezing<sup>(1-3,17)</sup>. Lower respiratory tract infection was demonstrated as the risk factor of recurrent wheezing in children under 5 years old in both bivariate and multivariate analysis, presenting in agreement with the other studies<sup>(3,5,7-9,14-18)</sup>. Lower respiratory tract infection in children under 5 years old, particularly those caused by virus, are common triggers of wheezing<sup>(8,19)</sup>. The complex mechanism of airway narrowing may result from the bronchospastic and inflammatory mediators locally released by inflammatory and parenchymal cells during viral infection which points to wheezing. As this was a cross-sectional study, the authors could not characterize the wheezing as a trigger or an outcome from pulmonary infections. Recurrent wheezing after lower respiratory tract infection subsequently results in permeability to antigens and allergens, exposure of bronchial cholinergic sensory nerve fibers to physical or chemical irritants, and loss of epithelial derived relaxant factors, including nitric oxide<sup>(19,23)</sup>.

Day care center attendance was a risk factors in the authors' study. In some study involving populations in European countries, there was also an association between day care center attendance and the risk of early wheezing<sup>(15,24,25)</sup>. A cohort study in England found that entering day care between 6 and 12 or after 12 months of age, respectively, was significantly and inversely associated with current wheeze (at 5 years of age)<sup>(18)</sup>.

Passive smoking in the present study showed that association with the risk of recurrent wheezing. In the other studies more frequent reports of the exposure to cigarette smoke at home was an independent and significant risk factors for wheezing<sup>(6,17)</sup>.

**Table 1.** Risk factors of recurrent wheezing in children under 5 years of age between the case and control group

Risk factors	Case group (n = 55)	Control group (n = 55)	p-value*
Age (months) Mean ± S.D.	36.13 (18.7)	25.00 (14.9)	0.343
Sex†			
Male	20 (36.4%)	17 (34.7%)	0.847
Female	35 (63.6%)	32 (65.3%)	
Prenatal/Perinatal/Post-natal			
Birth weight (grams)	2856.48	2881.78	0.195
Mean ± S.D.	(733.7)	(533.9)	
Mode of delivery‡			0.660
· normal delivery	22 (40.0%)	27 (51.9%)	
· cesarean section	32 (58.2%)	24 (46.2%)	
· vacuum extraction	1 (1.8%)	1(1.8%)	
Gestational age (weeks)			
Mean ± S.D.	36.12(3.5)	33.73(9.0)	0.228
Length of stay after birth (days)			
Mean ± S.D.	8.02 (18.794)	5.84 (6.303)	0.525
Complication after birth	15 (27.3%)	11 (20.0%)	0.428
Oxygen therapy after birth	12 (21.8%)	6 (10.9%)	0.140
On ventilator after birth	6 (10.9%)	4 (7.3%)	0.574

\*Pearson Chi-square test

† Missing data in control group = 6

‡ Missing data in control group = 3 (male 1, Female 1, unknown 1)

**Table 1.** (cont'd) Risk factors of recurrent wheezing in children under 5 years of age between the case and control group

Risk factors	Case group (n = 55)	Control group (n = 55)	p-value*
Breast feeding	30 (54.5%)	22 (40.0%)	0.830
Upper respiratory tract infection	48 (87.3%)	33 (60.0%)	0.001*
Lower respiratory tract infection	32 (61.5%)	16 (29.1%)	<0.001*
Passive smoking	31 (56.4%)	19 (34.5%)	0.027*
Cooking Method†			
· gas	49 (49.5%)	50 (50.5%)	0.751
· charcoal	19 (48.7%)	20 (51.3%)	0.842
· firewood	5 (62.5%)	3 (37.5%)	0.463
· microwave	23 (62.2%)	14 (37.8%)	0.069
· hobs	10 (52.6%)	9 (47.4%)	0.801
Electrical fan†	54 (50.0%)	54 (50.0%)	1.000
Air conditioner†	13 (76.5%)	4 (23.5%)	0.018*
Air purifier†	35 (52.2%)	32 (47.8%)	0.558
Day care center attendance	28 (52.8%)	16 (30.1%)	0.018*

\*Pearson Chi-square test

†Multiple response

**Table 2.** Risk factors of recurrent wheezing in children under 5 years of age between the case and control group (bivariate logistic regression analysis)

Risk factors	Odds ratio (OR)	95%CI	p-value
Upper respiratory tract infection	7.273	2.277-23.232	0.01
Lower respiratory tract infection	5.332	2.326-12.225	<0.001
Passive smoking	2.368	1.094-5.129	0.029
Air conditioner	0.79	0.362-1.721	0.552
Day care center attendance	2.590	1.168-5.745	0.019

**Table 3.** Risk factors of recurrent wheezing in children under 5 years of age between the case and control group (multivariate logistic regression analysis)

Risk factors	Adjusted Odds ratio (aOR)	95%CI	p-value
Upper respiratory tract infection	0.342	0.095-1.230	0.100
Lower respiratory tract infection	0.241	0.088-0.659	0.006
Passive smoking	1.222	0.454-3.285	0.691
Day care center attendance	0.555	0.221-1.396	0.211

Constant 2.386

R square 0.222

The authors did not observe a relationship between breastfeeding and risk factor of recurrent wheezing. Breastfeeding is widely promoted as an important factor in reducing the risk for atopy and asthma; however, the evidence for this effect is still controversy.

The present study had some limitations that should be considered for the interpretation of the results, as this was a cross-sectional study with a rather small sample size. Prospective studies are needed to clarify the correlation of risk factors for recurrent wheezing. In addition, interviewing with parents or caregivers about events that occurred when the children were under 5 years of age may depend on the ability of responders to recall.

### Conclusion

The present study demonstrated that risk factors associated with recurrent wheezing in children under 5 years of age were lower respiratory infection, upper respiratory infection, passive smoking and day care attendance. The identification of risk factors for wheezing in preschool children is crucial for the diagnosis of asthma, for the development of preventive strategies through public health policies that would minimize morbidity and mortality as well as improving the quality of life of these children and their families.

The knowledge on risk factors of recurrent wheezing in Thai children will be beneficial to find preventive solutions in connection with genetic-environmental factors that greatly affect the incidence of this disease.

### What is already known on this topic?

The recurrent wheezing is the first sign and symptom of the asthma. In children under 5 year old, diagnosis of asthma is very difficult because incoordination for pulmonary function test. The previous study showed risk factors of asthma in adult and adolescent, but in young children had limited data.

### What this study adds?

Although risk factors for recurrent wheezing in children under 5 years old have been identified, their analyses are complex due to genetic-environmental interactions. This study showed the risk factors of recurrent wheezing in children less than 5 year old. The development of methods to identify and quantify these factors are essential to a better understanding of the natural history and prevention of asthma in childhood.

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#### Potential conflicts of interest

None.

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## ปัจจัยเสี่ยงของการเกิดเสียงหายใจดังวี๊ดซ้ำในผู้ป่วยเด็กอายุน้อยกว่า 5 ปี

ไกลดา ศรีสิงห์, จิรพันธ์ วีรกุล, ศรัณญา ศรีจันทร์ทองศิริ, ธิติมา เงินมาก

**วัตถุประสงค์:** เพื่อหาปัจจัยเสี่ยงการเกิดเสียงหายใจดังวี๊ดซ้ำในผู้ป่วยเด็กอายุน้อยกว่า 5 ปี

**วัสดุและวิธีการ:** การศึกษาแบบตัดขวางในผู้ป่วยเด็กอายุน้อยกว่า 5 ปี ที่มารับการรักษาแบบผู้ป่วยนอกที่คลินิกกุมารเวชศาสตร์ โรงพยาบาลมหาวิทยาลัยนเรศวร ในช่วงเดือนตุลาคม พ.ศ. 2556 ถึง ตุลาคม พ.ศ. 2557 ผู้ป่วยเด็กที่มีอาการเสียงหายใจดังวี๊ดซ้ำถูกจัดให้เป็นกลุ่มผู้ป่วยจำนวน 55 ราย ส่วนผู้ป่วยที่ไม่มีอาการดังกล่าวจัดให้เป็นกลุ่มควบคุมจำนวน 55 ราย จากนั้นให้ผู้ปกครองเป็นผู้ตอบแบบสอบถาม โดยข้อมูลทั่วไปใช้สถิติเพื่ออธิบายลักษณะกลุ่มประชากร ส่วนปัจจัยเสี่ยงใช้สถิติ *bivariate* และ *multivariate logistic regression* โดยค่า *p-value* น้อยกว่า 0.05 ถือว่ามีนัยสำคัญทางสถิติ

**ผลการศึกษา :** อายุเฉลี่ยกลุ่มศึกษาและควบคุมเป็น 36.1 และ 25.0 เดือนตามลำดับ น้ำหนักและส่วนสูงของทั้ง 2 กลุ่มไม่มีความแตกต่างกัน ปัจจัยเสี่ยงการเกิดเสียงหายใจดังวี๊ดซ้ำโดยใช้สถิติ *bivariate logistic regression* พบการติดเชื้อทางเดินหายใจส่วนบน (OR) 7.273; 95% confidence interval (CI) 2.277-23.232), การติดเชื้อทางเดินหายใจส่วนล่าง (OR 5.332; 95% CI 2.326-12.225), การได้รับควันบุหรี่ (OR 2.368; 95% CI 1.094-5.129), และการอยู่ในสถานรับดูแลเลี้ยงเด็กเล็ก (OR 2.590; 95% CI 1.168-5.745) ส่วนการใช้สถิติ *multivariate logistic regression* พบปัจจัยเสี่ยงการเกิดเสียงหายใจดังวี๊ดซ้ำ คือ การติดเชื้อทางเดินหายใจส่วนล่าง [*adjusted odds ratios (aOR)* 0.241; 95% CI 0.088-0.659]

**สรุป:** การติดเชื้อทางเดินหายใจส่วนล่าง, การติดเชื้อทางเดินหายใจส่วนบน, การได้รับควันบุหรี่, และการอยู่ในสถานรับดูแลเลี้ยงเด็กเล็กเป็นปัจจัยเสี่ยงการเกิดเสียงหายใจดังวี๊ดซ้ำในเด็กอายุน้อยกว่า 5 ปี โดยเฉพาะอย่างยิ่งการติดเชื้อทางเดินหายใจส่วนล่างเป็นปัจจัยเสี่ยงที่สำคัญที่สุด อย่างไรก็ตามเป้าหมายการหาปัจจัยเสี่ยงดังกล่าวเพื่อช่วยลดอุบัติการณ์การเกิดเสียงหายใจดังวี๊ดซ้ำ และโดยเฉพาะอย่างยิ่งมีความสำคัญต่อการดูแลรักษาผู้ป่วยเด็กโรคหอบหืดในอนาคต