



中國醫藥大學  
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碩士學位論文

氣喘兒童睡眠品質與細胞激素的研究

Sleep Quality and Cytokines in Asthmatic Children

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## 中文摘要

氣喘兒童常有睡眠的困擾,不管是因氣喘症狀或是所使用藥物而引起。氣喘的症狀(如咳嗽、喘鳴)常在夜間或清晨時更易惡化,所以病童常有半夜醒來或清晨提早醒來的情形。許多研究都已證實細胞激素在氣喘的病因扮演重要角色。近年來細胞激素在人類睡眠的調控功能也漸被重視,文獻上則少有氣喘兒童的睡眠品質、細胞激素和疾病控制狀況的相關性研究。

### 研究目的:

本研究針對門診氣喘兒童進行有關睡眠品質、氣喘控制程度及血中細胞激素的相關研究。

### 研究方法:

本研究從 2007 年七月到十二月,在小兒過敏科門診,共收案 90 位年齡從 6 歲到 12 歲,患有氣喘病史超過 6 個月以上的兒童參加本研究。每位參加者均填寫一份氣喘控制測驗(Asthma Control Test)和一份氣喘兒童睡眠品質問卷。同時採集血液做細胞激素 interleukin(IL)-4、IL-6、IL-10、IL-12, prolactin 和免疫球蛋白 E(IgE)的定量。

### 研究結果:

氣喘控制測驗得分 20 或 20 分以上者歸為控制良好組

(well-controlled group, 68 人), 19 分或 19 分以下者則歸為控制不佳組(inadequately- controlled group, 22 人), 比較兩組的睡眠困擾得分顯示兩者沒有明顯的差異存在( $8.14 \pm 7.193$  vs.  $4.91 \pm 4.203$ ,  $P = 0.063$ )。主觀睡眠感受在控制良好組則明顯比控制不佳組為好( $4.59 \pm 1.149$  vs.  $3.95 \pm 1.090$ ,  $p = 0.028$ ), 在這兩組的 IgE 和 IL-6、IL-10、IL-12 則無統計學上有意義的差別。進一步分析控制良好組, 發現睡眠品質好的兒童(11 人)較睡眠品質不好的兒童(57 人)血中 IL-10 濃度較低( $1.78 \pm 1.05$  pg/mL vs.  $3.92 \pm 3.81$  pg/mL,  $p = 0.026$ ), 泌乳激素(prolactin) 濃度較高( $10.03 \pm 7.15$  ng/mL vs.  $7.73 \pm 4.63$  ng/mL,  $p = 0.037$ )。IL-12/ IL-10 比值在睡眠品質好的兒童則明顯較睡眠品質不好者高( $0.93 \pm 1.17$  vs.  $0.41 \pm 0.26$ ,  $p = 0.03$ )。IL-6、IL-12、IgE 在這兩組中則沒有明顯差異。

#### 研究結論:

此研究結果顯示良好的氣喘控制可明顯改善兒童的睡眠品質, 同時好的睡眠品質則有較低的 IL-10 濃度及較高的  $T_H1/T_H2$  的比值, 這有利於氣喘的控制。泌乳激素在這免疫的轉變中扮演一個重要的角色。

## Abstract

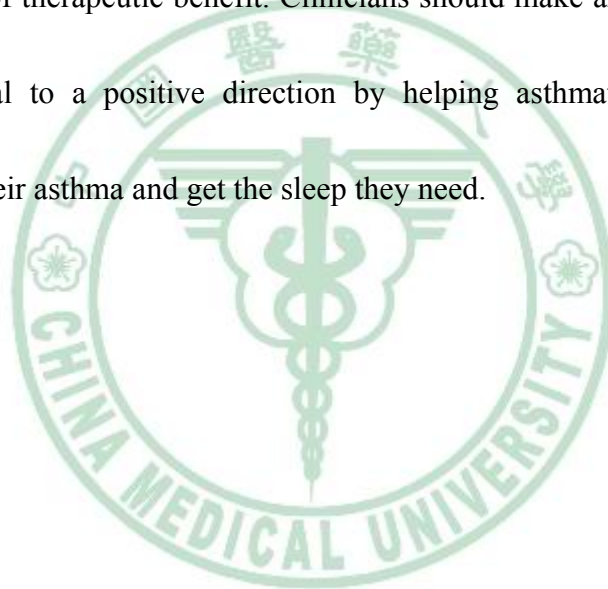
**Background:** According to the International Study of Asthma and Allergies in Childhood study phase III, there has been an increasing trend of asthma prevalence in Taiwan during the last 30 years. Recently, a national survey in Taiwan demonstrated the general hospitalization rate of asthma in the children group (<18 yr old) increased significantly from 1996 to 2002. Asthmatic children have been reported to complain about poor sleep quality. Recent research has demonstrated the relationship between sleep and circulating cytokines. There are few studies delineating the relationship between immune mediators and sleep quality in asthmatic children. This cross-sectional study aims to assess the relationship of serum cytokine level and sleep quality in asthmatic children.

**Methods and materials:** After an initial screening phase at allergic clinic visits, 90 asthmatic children aged 6 through 12 years were enrolled to complete one Chinese version of the (Childhood) Asthma Control Test. A specially-design questionnaire concerning sleep quality of asthmatic children was administered to all subjects and parents. We assessed the serum level of certain immunological parameters, including interleukin (IL)-4, IL-6, IL-10, IL-12, total immunoglobulin (Ig) E, and prolactin at enrollment.

**Results:** Subjects with an ACT score of 20 or more were assigned as the well-controlled group (N = 68) and those with a score of 19 or less were assigned as the inadequately-controlled group (N = 22). Mean scores for level of sleep disturbance did not have a significant difference between the well-controlled group and inadequately-controlled group ( $8.14 \pm 7.193$  vs.  $4.91 \pm 4.203$ , respectively;  $p = 0.063$ ). Mean scores for the subjective sleep perception showed a significant difference between the well-controlled group and inadequately-controlled group ( $4.59 \pm 1.149$  vs.  $3.95 \pm 1.090$ , respectively;  $p = 0.028$ ). Mean levels of assessed cytokines IL-6, IL-10, IL-12 and total IgE did not show a significant difference in relation to the level of asthma control. In the well-controlled group, the good sleepers had a significantly lower mean level of IL-10 ( $1.78 \pm 1.05$  pg/mL vs.  $3.92 \pm 3.81$  pg/mL, respectively,  $p = 0.026$ ) and higher mean ratio of IL-12/IL-10 ( $0.93 \pm 1.17$  vs.  $0.41 \pm 0.26$ , respectively,  $p = 0.03$ ) compared to the poor sleepers. Additionally, there was a significantly enhanced serum prolactin level in the good sleeper subgroup, in comparison with the poor sleeper subgroup ( $10.03 \pm 7.15$  ng/mL vs.  $7.73 \pm 4.63$  ng/mL, respectively,  $p = 0.037$ ). Of both subgroups, the concentrations of IL-6, IL-12 and total IgE did not reach a significant difference.

**Conclusion:** These results suggested an improvement in asthma control would promote better sleep quality. Good sleep is associated with a lower IL-10 level, a

higher prolactin concentration, and a higher  $T_{H1}/T_{H2}$  ratio. Prolactin may have a potential role in this immunity shift. Furthermore, this pattern of immune profile may have therapeutic benefits on asthma management. Thus, it can be anticipated that further insight into the functional role of cytokines on sleep quality of asthmatic sufferers will result in novel therapeutic perspectives. Nonetheless, more research is warranted to see whether the reduced IL-10 level and elevated IL-12/IL-10 ratio in the good sleepers is of therapeutic benefit. Clinicians should make an effort and do more to shift the spiral to a positive direction by helping asthmatic children to gain well-control of their asthma and get the sleep they need.



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## Chapter 1 Introduction

### 1.1 Background

According to the International Study of Asthma and Allergies in Childhood study phase III, there has been an increasing trend of asthma prevalence in Taiwan during the last 30 years (1). Recently, a national survey in Taiwan demonstrated the general hospitalization rate of asthma in the children group (<18 yr old) increased significantly from 1996 to 2002 (2). Many inflammatory mediators and cells play a key role in the development of the chronic processes of asthma, ultimately contributing to the release of mediators such as histamine and leukotrienes, and remodeling of the airway wall, resulting in a number of structural changes and clinically heterogeneous phenotypic expression (3). The exact functional role of an individual signaling mediator, as cytokine, in the inflammatory process of asthma may not be easy to predict because each cytokine has many overlapping functions, with each function potentially mediated by more than one cytokine. In the profile of  $T_H1/T_H2$  (helper T cell, type 1 and type 2) balance, allergic diseases have been well known as a  $T_H2$ -dominant disorder. In recent years there has been increasing recognition of the central role of  $T_H2$  cytokines, such as IL-4, -5, and -13, in the context of asthma. An increased expression of pro-inflammatory cytokines such as tumor necrosis factor (TNF)- $\alpha$ , IL-6, and IL-1 $\beta$  can further enhance the inflammatory process. It is important to note that allergic airway inflammation might be induced by

not only an increased expression of T<sub>H</sub>2 cytokines but also a decreased expression of counteracting ones, including IL-12, IL-10, and interferon gamma (IFN- $\gamma$ ).

We spend a third of our lives asleep, but despite a century of study, we have very little understanding of why we sleep. Sleep is hypothesized to have a restorative function on the immune system. A network of mutually interacting cytokines regulates the human sleep-wake cycle. Recently, new and emerging molecular technologies have become available to investigate the physiologic role of various cytokines in the regulation of sleep. The circadian rhythm of various cytokines has been reported in both normal and sleep-deprived individuals, yet the exact functional role of each individual cytokine in the regulation of sleep remains to be fully established. An important aspect when assessing the functional role of cytokines in a complex behavior such as the sleep-wake cycle is the interaction with other cytokines in the microenvironment. There has been an emerging body of evidences from animal studies suggesting that sleep is closely intertwined with three classes of cytokines: T<sub>H</sub>1 cytokines (e.g. IFN- $\gamma$ ), anti-inflammatory/T<sub>H</sub>2 cytokines (e.g. IL-10), and pro-inflammatory cytokines (e.g. IL-6). An increased expression of pro-inflammatory cytokines such as TNF, IL-6 and IL-1  $\beta$  can enhance sleep. In addition, an increased expression of anti-inflammatory cytokines, including IL-4 or IL-10 can also inhibit the slow-wave sleep (4, 5).

Chronic diseases in children, such as asthma, may impair sleep quality and contribute to the development of emotional problems both in the children and their family. The symptoms usually become worse at night and in the early morning, accompanying sleep interruption. Accumulating data suggest that the presence of nocturnal symptoms, such as cough and shortness of breath, is related to asthma severity. Despite modern therapeutic advances, patients who are afflicted with asthma often suffer sleep interruption, caused either by diseases or side effects of medicines. To date, many studies have demonstrated that asthma is associated with decreased subjective sleep quality and increased daytime sleepiness. Even clinically stable asthmatic children report frequent nocturnal symptoms and sleep disturbances (6). Vir et al. reported that more than 90% of young adults with clinically stable bronchial asthma had sleep disturbance (7). Janson et al. showed that difficulties inducing sleep and early morning awakenings were about twice as common and daytime sleepiness 50% more common in asthmatics compared with healthy normal subjects (8). It has been proposed that a bidirectional relationship exists between sleep and behavioral/emotional regulation. Inadequate sleep interferes with learning and memory in the broadest sense. Moreover, sleep is vital for cognitive processing and emotional learning. In the study of morbidity in nocturnal asthma, Fitzpatrick et al. concluded that hospital outpatients with stable nocturnal asthma have impaired sleep

quality and daytime cognitive performance (9).



## 1.2 Objective

The goals of asthma control in the 2006 GINA guidelines were for the patient to have no daytime or nocturnal symptoms and to have no limitations in daytime activities or social function (10). It is recognized that the expression of cytokines plays a role in view of the bi-directional relationship between cytokines and sleep. An improved understanding of the role of cytokines during the sleep-wake cycle among asthmatic subjects would further advance the knowledge of the pathophysiology of asthma and suggest new strategies for intervention into this disease entity. We hypothesized that well-controlled asthma would improve sleep quality because cytokine response may influence both sleep and asthma. Therefore, the objectives of the present study were to investigate the relationships among asthma control, cytokine levels and sleep quality of asthmatic children.



## Chapter 2 Materials and Methods

### 2.1 Study population

Potential subjects, ranging in age from six to 12 years, were invited from an allergy clinic of the Pediatrics Department of Tungs' Taichung Metroharbor Hospital during a screening period. Subjects were eligible if they had a history of self-reported physician-diagnosed asthma with current asthma-related symptoms for more than six months. All subjects were free of physical illness by examination and none had a history of recent febrile infection disease. In addition, potential subjects who were receiving systemic glucocorticosteroids, sleep medications, and psychotropic medications were excluded from participating in this study. The Tungs' Taichung Metroharbor Hospital Ethics Committee approved this study. Informed written consent was obtained from each subject and from a parent or legal guardian of the eligible children.

### 2.2.1 Study design

In this cross-sectional study, 90 asthmatic children were enrolled. They completed one (Childhood) Asthma Control Test and a questionnaire concerning sleep quality.

Peripheral blood samples were collected for laboratory analyses.

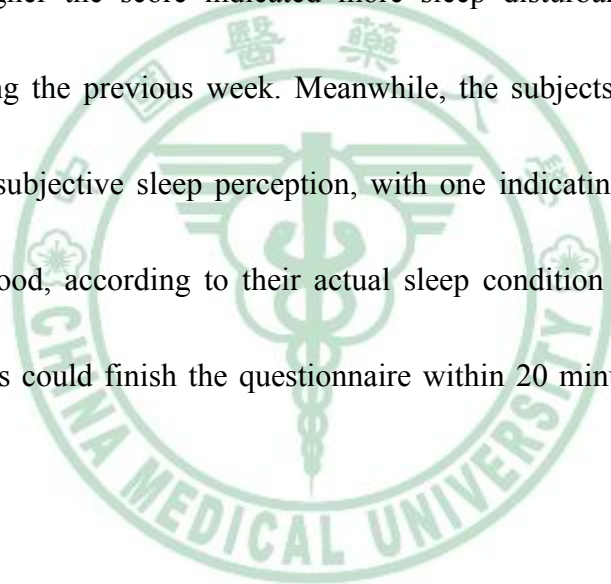


### 2.2.2 Procedures and questionnaire

At the allergy clinic visit, we recorded characteristics of all the subjects enrolled. A comprehensive medical history was taken for eligible subjects, especially including a history of allergic diseases of family members and comorbid allergic diseases. A comprehensive physical examination, including check of body weight and height, was performed. The body mass index (BMI) was calculated as weight (kg)/height (m<sup>2</sup>).

According to age, subjects finished a Chinese version of the Asthma Control Test (ACT) (subjects older than 11 yr) or Childhood Asthma Control Test (C-ACT) (subjects aged between 6 and 11 yr). Subjects with a score of 20 or more were assigned as the well-controlled group and those with a score of 19 or less were assigned as the inadequately-controlled group. A self-rated questionnaire was administered for the assessment of sleep quality during the last week before entering this study. The questionnaire is a three-page, Chinese survey designed to assess the subjective sleep quality in addition to requesting demographic information such as age, gender, school grades, and comorbid allergic diseases. Parents and children were encouraged to answer the questions and to return the questionnaire. This Chinese version of the questionnaire was specially designed for assessment of sleep quality of asthmatic school children and had been shown to have both high validity and high reliability in a previous study (not published). Subjects were asked to score symptoms

that they had experienced over the previous week. The questionnaire consists of two domains (sleep disturbance and subjective sleep perception) and 10 items corresponding to the sleep disturbance domain. The scores are indexed on a five-point scale for each item. Subjects rated the frequency of sleep disturbance as zero indicating none to four indicating daily over the previous week. The possible scores range from zero (no problems at all) to 40 (presence of all problems within the domain). The higher the score indicated more sleep disturbance the subject had experienced during the previous week. Meanwhile, the subjects were also asked to rate the level of subjective sleep perception, with one indicating very poor and six indicating very good, according to their actual sleep condition during the previous week. All subjects could finish the questionnaire within 20 minutes with or without help from parents.

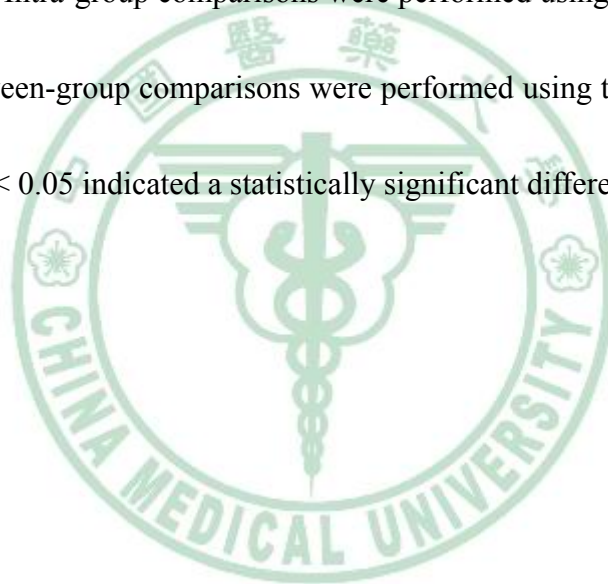


### 2.2.3 Blood samplings and laboratory tests

Peripheral blood samples were obtained by venipuncture from subjects at the start. For each subject, 4 mL of blood was collected. The blood samples were then centrifuged, separated, and sera frozen immediately at -80 °C until thawed for later cytokine batch analysis. Each cytokine (IL-4, IL-6, IL-10 and IL-12) was quantified by an enzyme-linked immunosorbent assay (ELISA) method with high sensitivity kit (R&D Systems, Minneapolis, MN). The results were quantified against the standard curves generated using known amounts of recombinant cytokines, according to the instructions of the manufacturer. The mean minimum detectable dose was 0.11 pg/mL and 0.039 pg/mL for IL-4 and IL-6, respectively. The mean minimum detectable dose for both IL-10 and IL-12 assay was 0.5 pg/mL. The intraassay coefficient of variation for all variables ranged from 2.5% to 8.5%. All assays were performed in duplicate and the mean value was used for interpretation. The specimens were also assayed for quantitative measurement of total IgE level (IMMULITE<sup>®</sup> 2000 Total IgE assay, Diagnostics Products Corporation, USA). The limit of detection was 1 IU/mL. The quantitative measurement of serum prolactin was performed (IMMULITE<sup>®</sup> 2000 Prolactin Reagent, Diagnostics Products Corporation, USA). The analytical sensitivity was 0.16 ng/mL.

### 2.3 Statistical analyses

All statistical analyses were performed using SPSS software (version 14.0 for MS-Windows). Descriptive statistics were used for demographic characteristics. Inferential statistics were conducted on the scores of sleep quality and cytokine levels. Data are reported as means  $\pm$  SD. Because the scores of sleep quality and the sera level of cytokines might have been non-normally distributed, we used nonparametric tests for analyses. Intra-group comparisons were performed using the Wilcoxon's rank sum test and between-group comparisons were performed using the Mann-Whitney *U* test. A value of  $p < 0.05$  indicated a statistically significant difference.



## Chapter 3 Results

### 3.1 Subjects and demographic characteristics

From June 2007 to December 2007, a total of 90 subjects (60 boys and 30 girls) were enrolled to this study. The characteristics of the participants are described as means and standard deviations for quantitative variables. Table 1 summarizes the demographic characteristics, severity of asthma, and history of comorbid allergy and family allergic diseases of the enrolled subjects. According to the ACT or C-ACT scores, there were 68 children categorized in the well-controlled group and 22 in the inadequately-controlled group. There were no significant differences in age, body weight, height, and body mass index between the two groups. All subjects in the well-controlled group had mild asthma, and 3 of the 22 had moderate persistent asthma in the inadequately-controlled group. Subjects of both groups had high rate of comorbid allergic diseases (> 95%). The majority (> 80%) of the subjects had positive family history of allergic diseases (e.g. asthma, allergic rhinitis, and atopic eczema).

### 3.2.1 Asthma control and laboratory tests

The first objective of this study was to examine sera cytokine levels in well-controlled and inadequately-controlled asthmatic children. Means and standard deviations for each group on the cytokine and total IgE levels are presented in Table 2. Of the four cytokines assessed, IL-4 had a negligible level in the blood samples of 80 subjects and was excluded from further analysis. The T<sub>H</sub>1 (IL-12), anti-inflammatory/T<sub>H</sub>2 (IL-10), and pro-inflammatory (IL-6) cytokines were analyzed as individual cytokine and as the ratio of IL-12/IL-10. The ratio of IL-12/IL-10 reflects the relative balance of T<sub>H</sub>1/T<sub>H</sub>2 cytokines with effects on the regulation of allergy. There were no significant differences in the sera level of IL-6, IL-10, IL-12 and total IgE between the two groups ( $p > 0.05$ ), suggesting that achieving well-controlled asthma failed to demonstrate a significant effect on the mean sera level of cytokines and total IgE. For the mean ratio of IL-12/IL-10, there was no significant difference between the two groups.



### 3.2.2 Asthma control and subjective sleep quality

The second objective was to investigate the relationship between subjective sleep quality and level of asthma control in all subjects. A comparison of the two groups revealed that well-controlled asthmatic children had a significantly higher rating scale of subjective sleep perception ( $4.59 \pm 1.149$  vs.  $3.95 \pm 1.090$ ,  $p = 0.028$ ). In contrast, both groups had similar values of sleep disturbance ( $4.91 \pm 4.203$  vs.  $8.14 \pm 7.193$ ,  $p = 0.063$ ) (Table 3).



### 3.2.3 Subjective sleep quality and laboratory tests

The third aim was to examine the relationship between subjective sleep quality and cytokine levels. There was no significantly statistical correlation of sleep disturbance and assessed laboratory parameters in either group (data not shown). The subjects in the good sleeper subgroup were those who rated subjective sleep perception as 4, 5, or 6, and those who rated subjective sleep perception as 1, 2, or 3 were assigned as the poor sleeper subgroup. In the inadequately-controlled group, there were no significant differences in mean cytokine levels, ratio of IL-12/IL-10, or total IgE level between the two subgroups (data not shown). In the well-controlled group, mean IL-10 levels were significantly lower in the good sleepers subgroup compared to the poor sleepers subgroup ( $1.78 \pm 1.05$  pg/mL, vs.  $3.92 \pm 3.81$  pg/mL, respectively,  $p = 0.026$ ). There were no significant differences in IL-6 ( $0.99 \pm 1.02$  pg/mL, vs.  $2.05 \pm 4.42$  pg/mL, respectively,  $p = 0.236$ ), IL-12 ( $1.19 \pm 1.10$  pg/mL, vs.  $0.99 \pm 0.72$  pg/mL, respectively,  $p = 0.726$ ), total IgE level ( $1075.27 \pm 1586.63$  IU/mL, vs.  $893.60 \pm 920.39$  IU/mL, respectively,  $p = 0.449$ ) between the two subgroups (Fig 1). The ratio of IL-12/IL-10 ( $T_H1/T_H2$ ) was significantly higher in the good sleepers compared to the poor sleepers ( $0.93 \pm 1.17$ , vs.  $0.66 \pm 0.98$ , respectively,  $p = 0.03$ ). Additionally, there was a significantly enhanced sera prolactin level in the good sleepers, in comparison with that of the poor sleepers ( $10.03 \pm 7.15$  ng/mL vs.  $7.73 \pm 4.63$  ng/mL,

respectively,  $p = 0.037$ ). These findings suggested that better subjective sleep perception was significantly associated with a reduced IL-10 level, a higher prolactin concentration, and a higher  $T_H1/T_H2$  ratio.



## Chapter 4 Discussion

### 4.1 Discussion of results

To our knowledge, this was the first study that evaluated the relationship of subjective sleep quality and cytokine level in well-controlled asthmatic children. Several important findings are of interest in this study. First, as expected, well-controlled asthmatic children had higher sleep quality than those inadequately controlled. Additionally, this study demonstrated that the level of T<sub>H</sub>2 cytokine IL-10 is lower in the good sleepers of asthmatic children with clinical stability. However, no statistically significant differences of individual IL-12 and IL-6 level were proved between the two subgroups. In the present study, the mean ratio of IL-12/IL-10 (T<sub>H</sub>1/T<sub>H</sub>2) of the good sleepers was significantly higher in comparison with that of the poor sleepers. The present results demonstrated that the good sleepers had a significantly higher sera prolactin level than the poor sleepers. Finally, there was no significant association between level of asthma control and assessed cytokines. In line with this view, our analysis showed that the poor sleepers had higher T<sub>H</sub>2 cytokines activity. This will have a negative impact on asthma control.

## 4.2 Discussion of other studies

Asthma is a frequently overlooked and misdiagnosed medical condition in young child patients. Proper management of asthma aims at improving health and well being and reducing limitation in daily living (10). However, clinicians often target symptoms of asthma and comorbid allergies and do not think about the sleep disturbance that children suffer. Meanwhile, the sleep problems of children remain an area of asthma-related quality of life that is often neglected in both research and clinical practice. Hitherto no treatment has been shown to improve sleep quality in patients with nocturnal asthma. The data from the Childhood Asthma Management Program demonstrated that 351 of 1041 (33.7%) children with relatively stable asthma experienced one or more night awakenings caused by asthma during the 28-day screening period (11). In the present study, nevertheless, 57/68 (84.6%) of the subjects with well-controlled asthma reported poor sleep perception. These findings underscore that asthma-related problems in sleep represent an important aspect of quality of life for children with asthma. It is worthy of note that limitations in the sleep quality of children, like other limitations on quality of life, indicate that asthma is not well controlled. Pediatric clinicians, patients, and parents or caregivers need to discuss sleep as part of an asthma control assessment. Further research needs to examine the risk factors for both asthma-related sleep quality and asthma control.

Individually, several cytokines have a role in both asthma and sleep regulation. Accumulating data suggest that allergic diseases are characterized by a predominant  $T_H2$  response to antigens. Lower IL-10 level ( $T_H2$ ) may have benefit on asthma management. In vitro studies, in turn, have demonstrated that IL-10 can inhibit the expression of pro-inflammatory cytokines (IL-1, IL-6, IL-12, and TNF- $\alpha$ ) by macrophages/monocytes (12, 13, 14). These results indicate that IL-10 has anti-inflammatory activities and may act as a critical factor of allergic reactions. IL10, IL-4, and IL13 have been reported to inhibit spontaneous non-rapid eye movement sleep (NREMS). In contrast, other cytokines such as IL6, IL18, and interferon gamma (IFN  $\gamma$ ) promote NREMS (15). These observations suggest that the role of IL-10 in inhibiting sleep is skewing of the  $T_H$  response towards  $T_H2$  dominance. In a clinical pilot study, Krouse et al. failed to demonstrate any significant associations between sleep quality and cytokines assessed in their study, including IL-2, IL-4, IL-10, and IL-12 for patients suffering from allergic rhinitis (16). For IL-6, this is difficult to explain. Total sleep deprivation has been shown to elevate certain inflammatory cytokines (IL-6, TNF) in healthy young adults (17). In a study in which healthy young adults had sleep restricted to six hours per night, the 24-h production profile of IL-6 was enhanced (18). These findings suggested that pro-inflammatory cytokines IL-6 and TNF daytime secretion is elevated after poor nocturnal sleep. Further research

regarding the roles of IL-6 and IL-12 in the sleep of asthmatic children might shed light on new strategies of asthma management.

The underlying mechanisms accounting for the associations between sleep quality and alterations of immunity are currently not well known, but it is possible that sleep works through certain immunological and endocrine mediators. The study conducted by Born et al. showed that nocturnal levels of the T<sub>H</sub>1 cytokines, as IL-12 and IFN- $\gamma$ , increase during sleep with declines in the production of these T<sub>H</sub>1 cytokines after sleep loss (19). However, the effect of sleep loss on the profile of T<sub>H</sub>2 cytokines or the ratio of T<sub>H</sub>1 /T<sub>H</sub>2 cytokines in humans is not known. Previous studies have suggested that disordered sleep and sleep loss are associated with nocturnal elevations of sympathetic tone with elevated production of norepinephrine and epinephrine (20, 21). In an animal model, stress and the release of sympathetic neurotransmitters shift the expression of T<sub>H</sub> cytokines toward a T<sub>H</sub>2-dominant profile (22). However, the sympathetic neurotransmitters may not be the only neuroendocrinal hormone that entrains cytokine shift; other candidates not examined herein, including cortisol and growth hormone, may also have potential roles in this immunity shift. Recently, Lange et al. demonstrated that high prolactin and low cortisol levels are factors contributing to the shift in the IL-12/IL-10 ratio toward T<sub>H</sub>1 cytokine activity during sleep (23). It is known that prolactin and growth hormone synergistically act to shift

the  $T_H1$  /  $T_H2$  balance toward  $T_H1$  cytokine activity dominance, whereas cortisol and norepinephrine can shift it toward  $T_H2$  (24, 25). If these are replicated in a cohort with asthma, our present finding may provide limited evidence of management of asthmatic children with sleep disturbance.

The chronic and acute inflammatory process observed in the airways of atopic asthma could result from the excessive expression of cytokines, which has been observed in an experimental induction of asthma by allergen challenge (26), or in the airways of symptomatic episodes (27). Considerable evidence has shown that both ACT and C-ACT were responsive to changes in specialist ratings of asthma control, the need for change in a patient's therapy, and to clinically meaningful changes in the percentage of predicted  $FEV_1$  (28, 29). Nevertheless, there is no established evidence suggesting that ACT is responsive to cytokine change or  $T_H1/T_H2$  immune response. Further clinical studies are needed to determine whether improved asthma management, as assessed by ACT, predicts a shift of immune profiles.



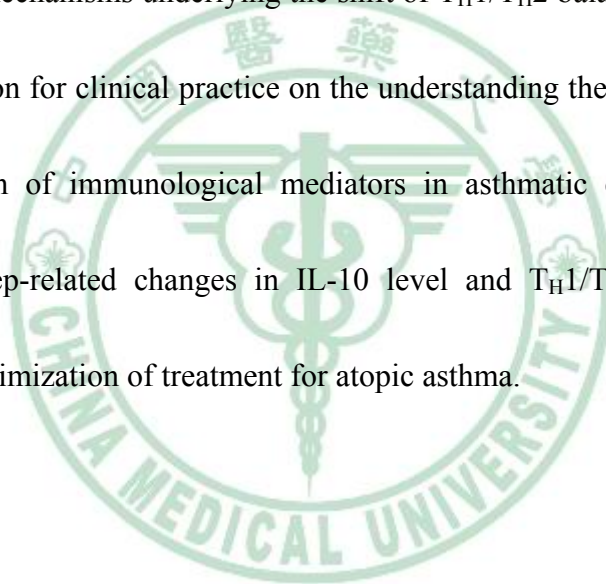
### 4.3 Study limitations

There are several limitations to the present study. First, an asthmatic population was exclusively studied because evidence suggests that asthmatic sufferers, as compared with healthy controls, have decreased sleep quality. Thus, it is not known whether differences of sleep quality and cytokine patterns generalize to the healthy children. Second, since the study was cross-sectional in nature, a conclusion of causal relationships cannot be made. This study was also limited in its generalizability to other patient populations. Further prospective longitudinal studies are needed. Third, considering that the cytokine production in human whole blood exhibits circadian rhythmicity, more data should be obtained with serial blood samplings during sleep. It is difficult and not ethical to collect large volumes of blood samples from young children, as done in adult subjects. However, Krouse et al. reported that serum cytokine levels (IL-1 $\beta$ , IL-1ra, IL-2, IL-4, IL-10, and IL-12) measured 5 times overnight were relatively stable at each collected sample from allergic rhinitis sufferers (16). Another limitation is the lack of objective data (such as polysomnography) on sleep, preventing us from fully describing the sleep architecture and assessing differences in sleep and asthma between well-controlled and inadequately-controlled subgroups.

## Chapter 5 Conclusion and suggestion

### 5.1 Conclusion

In conclusion, it can be said that the main findings of the present study are that the sleep quality in stable asthmatic children has effect on cytokine production and  $T_H1/T_H2$  immunity balance. The good sleepers had significantly lower sera levels of IL-10 and higher ratio of  $T_H1/T_H2$  immunity. More studies are needed to elicit the neurobiological mechanisms underlying the shift of  $T_H1/T_H2$  balance. These data may have an implication for clinical practice on the understanding the role of sleep quality on the expression of immunological mediators in asthmatic children. It may be possible that sleep-related changes in IL-10 level and  $T_H1/T_H2$  balance may be relevant to the optimization of treatment for atopic asthma.



## 5.2 Suggestion

Herein, looking for underlying or comorbid sleep problems in any child who presents with inadequately-controlled asthma is an important issue before deciding the new strategy for asthma management (such as adding anti-inflammatory agents or increasing the dosage of anti-inflammatory agents). Achieving good sleep could become a therapeutic option to enhance the success in the management of diseases that are characterized by  $T_H2$  cytokine predominance, such as atopic asthma. Thus, it can be anticipated that further insight into the functional role of cytokines on sleep quality of asthmatic sufferers will result in novel therapeutic perspectives. Nonetheless, more research is warranted to see whether the reduced IL-10 level and elevated IL-12/IL-10 ratio in the good sleepers is of therapeutic benefit. Clinicians should make an effort and do more to shift the spiral to a positive direction by helping asthmatic children to gain well-control of their asthma and get the sleep they need.

Fig 1 Cytokines and total IgE level of the good sleepers (■, n =11) and the poor sleepers (□, n = 57) in the well-controlled group (N = 68). \*:  $p < 0.05$

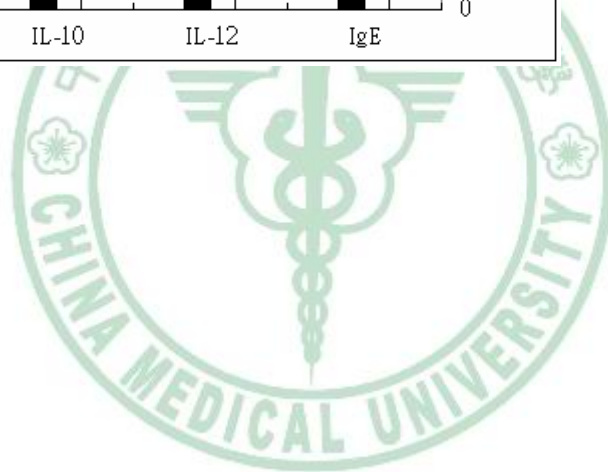
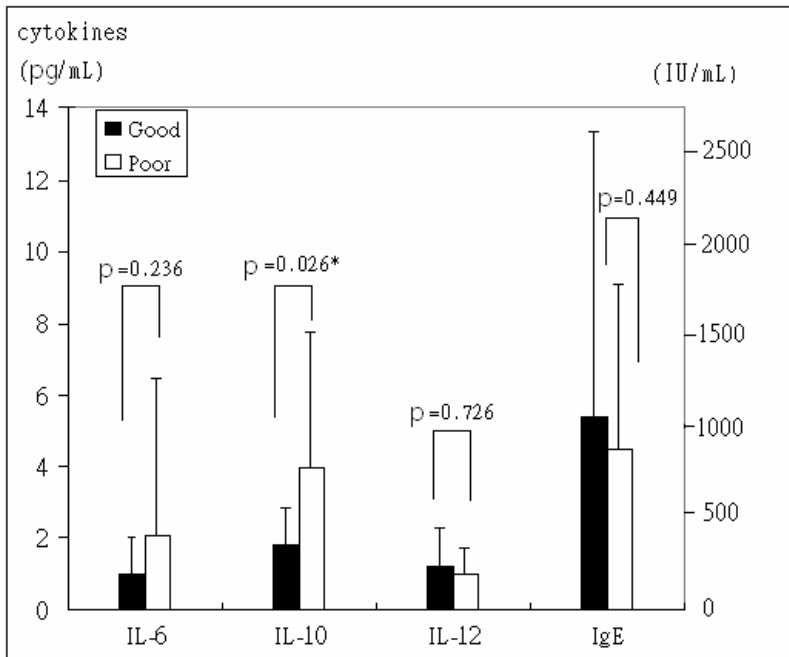


Table 1 Demographic characteristics

		Well-controlled (N=68) n(%)	Inadequately-controlled (N=22) n(%)	Total (N=90) n(%)
Gender	Boy	43(63.2%)	17(77.3%)	60(66.7%)
	Girl	25(36.8%)	5(22.7%)	30(33.3%)
Age (year)		8.88 ± 2.02	8.45 ± 2.2	8.78 ± 2.07
Height (cm)		132.79 ± 14.42	131.52 ± 15.7	132.48 ± 14.66
Weight (kg)		32.81 ± 11.14	34.06 ± 14.9	33.11 ± 12.09
Body mass index		18.31 ± 3.11	18.87 ± 4.2	18.44 ± 3.38
Family history of allergy	No	12(17.6%)	3(13.6%)	15(16.7%)
	Yes	56(82.4%)	19(86.4%)	75(83.3%)
Comorbid allergic diseases	No	2(2.9%)	1(4.5%)	3(3.3%)
	Yes	66(97.1%)	21(95.5%)	87(96.7%)
Severity of asthma	Grade 1	42(61.8%)	6(27.3%)	48(53.3%)
	Grade 2	26(38.2%)	13(59.1%)	39(43.3%)
	Grade 3	0(0%)	3(13.6%)	3(3.3%)

Data presented as Mean ± SD

Grade 1: Intermittent, Grade 2: Mild persistent, Grade 3: Moderate persistent

Table 2 Asthma control and laboratory tests

	Inadequately-controlled (N = 22)	Well-controlled (N = 68)	p value
IL-6(pg/mL)	1.43 ± 1.228	1.89 ± 4.084	0.46
IL-10(pg/mL)	3.78 ± 3.494	3.57 ± 3.593	0.529
IL-12(pg/mL)	0.77 ± 0.229	1.02 ± 0.788	0.081
IL-12/IL-10*	0.34 ± 0.228	0.49 ± 0.547	0.108
IgE(IU/mL)	812.91 ± 734.542	922.99 ± 1,043.219	0.721

\* IL-12/ IL-10 : T<sub>H</sub>1/T<sub>H</sub>2 ratio

Data presented as Mean ± SD



Table 3 Asthma control and subjective sleep quality

	Inadequately-controlled (N = 22)	Well-controlled (N = 68)	p value
Sleep disturbance	8.14 ± 7.193	4.91 ± 4.203	0.063
Subjective sleep perception	3.95 ± 1.090	4.59 ± 1.149	0.028*

\* p < 0.05



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## 附錄

### 1 Asthma Control Test 氣喘控制測驗 (ACT™)

以下的測驗可以幫助有氣喘的人（12 歲或 12 歲以上）評估氣喘的控制程度。

請在每個問題，圈選出適當的分數。

1. 在過去 4 週中，您的氣喘會讓您無法完成一般的工作、課業或家事嗎？

總是如此	1	經常如此	2	有時如此	3	很少如此	4	不曾如此	5
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2. 在過去 4 週中，您多常發生呼吸急促的情形？

一天超過 1 次	1	一天 1 次	2	一週 3 至 6 次	3	一週 1 或 2 次	4	完全沒有發生過	5
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3. 在過去 4 週中，您多常因氣喘症狀(喘鳴、咳嗽、呼吸急促、胸悶或胸痛)而讓您半夜醒來或提早醒來？

一週 4 次或 4 次以上	1	一週 2 至 3 次	2	一週 1 次	3	1 或 2 次	4	完全沒有發生過	5
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4. 在過去 4 週中，您多常使用急救性藥物或噴霧式藥物 (例如 Albuterol®(舒坦寧®)、Ventolin®(泛得林®)、Berotec®(備勞喘®) 或 Bricanyl®(撲可喘®) 等氣喘藥物)？

一天 3 次或 3 次以上	1	一天 1 或 2 次	2	一週 2 或 3 次	3	一週 1 次或更少	4	完全沒有使用過	5
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5. 在過去 4 週中，您自認為氣喘控制程度如何？

完全沒有受到控制	1	控制不好	2	稍微受到控制	3	控制良好	4	完全受到控制	5
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## 2 Childhood Asthma Control Test 兒童氣喘控制測驗(4到11歲兒童專用)

讓您小孩回答前四題(1到4)。如果您小孩在閱讀或瞭解問題上需要協助，您可以協助，但讓您小孩自己來選擇答案。剩下的三題(5到7)則由您自己完成，不要讓您小孩的答案影響了您的作答。答案並無對錯之分。

讓您的小孩完成以下問題

1. 今天你的氣喘狀況怎樣？



非常不好

0

不好

1

好

2

非常好

3

2. 當你跑步、運動或玩耍時，你的氣喘會造成多大的問題？



那是個大問題，  
我無法做我想做的

0

那是個問題，  
我並不喜歡

1

是有點問題，  
但還好

2

並不會  
造成問題

3

3. 你會因為你的氣喘而咳嗽嗎？



會，一直如此

0

會，大部分時候

1

會，有些時候

2

不會，從來不會

3

4. 你會因為你的氣喘而在夜間醒來嗎？



會，一直如此

0

會，大部分時候

1

會，有些時候

2

不會，從來不會

3

以下問題請由您自己來完成

5. 在過去四星期，平均每個月有幾天您的小孩在白天出現了氣喘症狀？

⑤完全沒有 ④1~3天 ③4~10天 ②11~18天 ①19~24天 ①每天都有

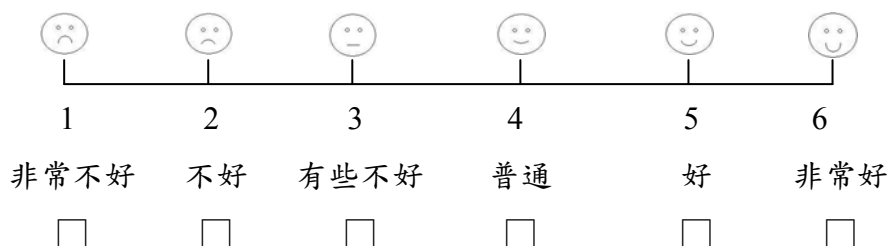
6. 在過去四星期，平均每個月有幾天您的小孩在白天因氣喘而發出哮喘聲？

⑤完全沒有 ④1~3天 ③4~10天 ②11~18天 ①19~24天 ①每天都有

7. 在過去四星期，平均每個月有幾天您的小孩在夜間因氣喘(夜咳)而醒來？

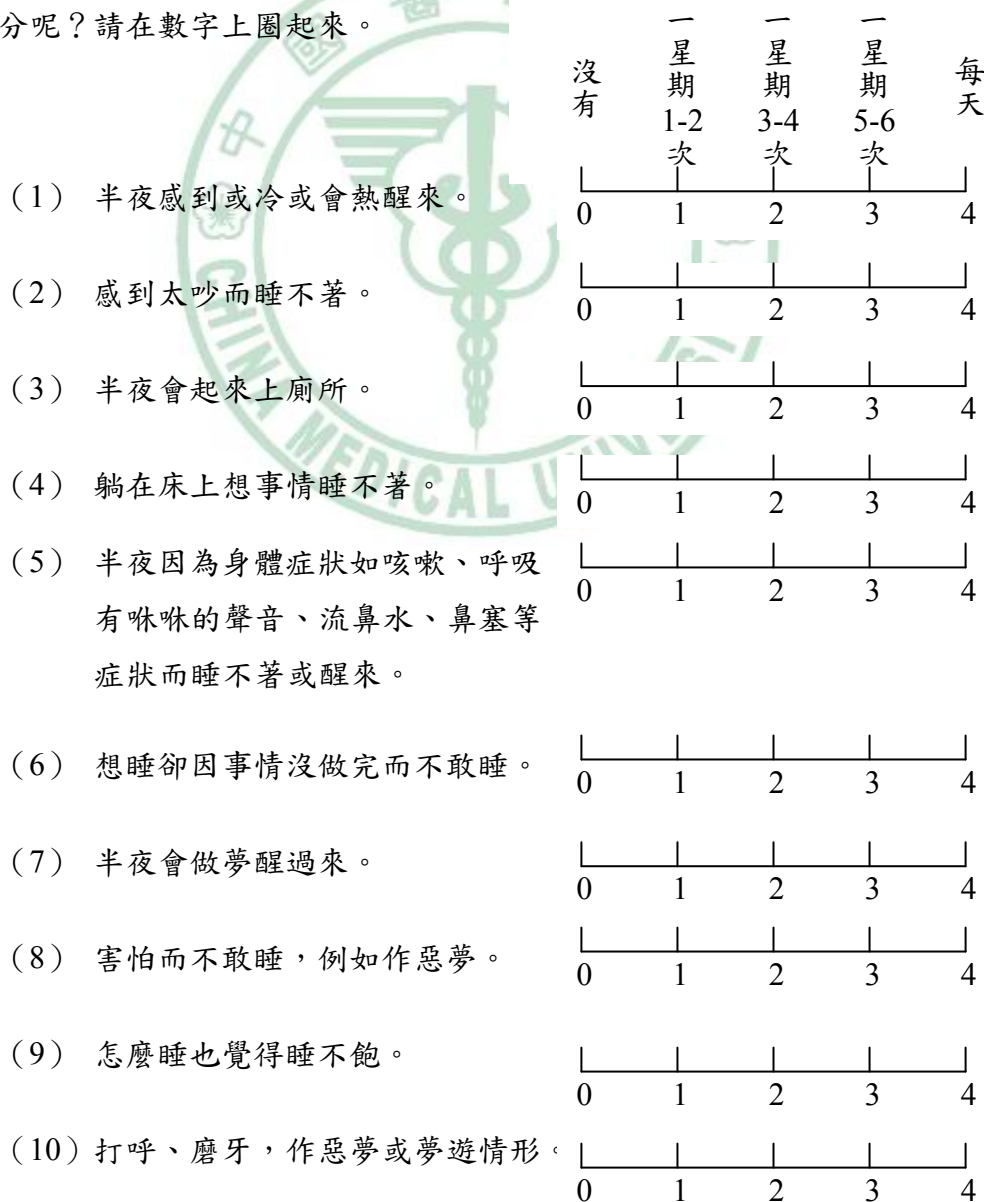
⑤完全沒有 ④1~3天 ③4~10天 ②11~18天 ①19~24天 ①每天都有

### 3. 氣喘兒童睡眠品質問卷 第一部分



1. 若上面娃娃最左邊哀傷的臉代表睡的非常不好(1分)，最右邊笑臉代表睡的非常好(6分)。那請問你這一個星期睡覺的感覺跟哪一個娃娃的臉最像呢？請在上打勾✓。

2. 下面題目是想知道你這一個星期晚上睡覺會不會因為下面所說的情形而無法睡覺或是睡到一半醒來嗎？如果看下面的尺，最左邊0分是說『沒有』，最右邊4分是說『每天』，那請問你這一個星期晚上睡覺有遇到的情形是幾分呢？請在數字上圈起來。



第二部分 基本資料 病歷號碼：\_\_\_\_\_ 個案編號：\_\_\_\_\_

1. 姓名：\_\_\_\_\_
2. 性別：男生 女生。家中排行？\_\_\_\_\_
3. 年齡，生日：民國\_\_\_\_年\_\_\_\_月\_\_\_\_日 \_\_\_\_\_歲 \_\_\_\_\_月
4. 身高：\_\_\_\_\_ 公分；體重：\_\_\_\_\_ 公斤，BMI：\_\_\_\_\_
5. 你讀幾年級？國小 \_\_\_\_\_ 年級 國中 \_\_\_\_\_ 年級
6. 你父母親的教育程度？  
父親 不識字 國小 國中 高中 大學 碩士 博士。  
母親 不識字 國小 國中 高中 大學 碩士 博士。
7. 家中有其他人過敏嗎？（可複選）  
無 父親 母親 兄弟姊妹 爺爺奶奶。

氣喘嚴重度

1. 有無其他過敏疾病？（可複選）  
沒有 過敏性鼻炎 異位性皮膚炎 過敏性結膜炎。
2. 依GINA分級標準，氣喘嚴重度分級  
等級1 等級2 等級3 等級4。
3. 過去一星期裡有無使用尖峰呼氣流速器？有 沒有（沒有者下題4. 無需作答）
4. 過去一星期裡個人最佳的尖峰呼氣流速值（PEF）\_\_\_\_\_。
5. FEV1/FVC 比值為 \_\_\_\_\_；>80% 60-80% <60%。
6. 過去一星期裡有無使用支氣管擴張劑或類固醇的氣喘藥物：  
有 沒有（沒有者下題7. 無需作答）
7. 過去一星期裡支氣管擴張劑或類固醇的氣喘藥物使用情形  
\_\_\_\_\_
8. 過去12個月內氣喘發作次數？有 沒有 \_\_\_\_\_ 次。
9. 過去12個月內因氣喘晚上發作而住院或上學請假？  
有 沒有，住院或上學請假有 \_\_\_\_\_ 天。
10. 晚上氣喘最常發作的時間？（可複選）12-1點 凌晨2-3點 凌晨4-5點 凌晨6-7點。



#### 4. 授 權 書

本授權書所授權之「兒童睡眠品質問卷」，乃為本人於國立臺灣大學護理學研究所，撰寫碩士學位論文過程所自行研發測試之問卷工具。本人同意授予中國醫藥大學臨床醫學研究所王銘甫醫師，以為其進行碩士學位論文「氣喘兒童的疾病控制、細胞激素、睡眠品質相關研究」，冀能提供學術研究及臨床照護之參考應用。

立授權書人/簽名：葉曉萍

論文名稱：氣喘學齡兒童睡眠品質及其相關因素之研究

指導教授/簽名：高碧霞

中華民國 九十六 年 三 月 十 日