보건학 석사 학위논문

Effect of antibiotic use on the incidence of asthma and atopic dermatitis in infants

- For the 2011-13 births of Republic of Korea -

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2017 년 2 월

서울대학교 보건대학원

보건학과 보건학전공

이 문 규

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Abstract

Effect of antibiotic use on the incidence of asthma and atopic dermatitis in infants

- For the 2011-13 births of Republic of Korea -

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Background: Previous studies have shown that both asthma and atopic dermatitis are caused by allergic marching in the childhood, with their cooccurrence or with some pre-existing relationship. Because of these relationship, the behavior of both diseases and their risk factors have been jointly investigated. Asthma and atopic dermatitis are from the complex interplay various factors such as demographic factors, infectious disease related factors, medicinal use factors, dietary related factors, and atmospheric environmental factors are mixed and acting together. Among the various risk factors, the use of antibiotics has been studied to cause long-term changes in intestinal microorganisms such as decreased actinomycetes, increased bacteria, and decreased enzymes. It has also been studied to increase the incidence of allergic sensitization to allergies such as asthma and atopic dermatitis by inhibiting the proper growth of infantile immune system and inhibiting the development of immune tolerance because it causes an increase in the immature microbial growth. Nevertheless, due to the difficulty in diagnosing asthma and atopic dermatitis of less than 5 years old, there have been few studies about disease status and on the risk factors including antibiotic use.

Objective: The purpose of this study is to investigate the effect of antibiotics use in infants on the risk of asthma and atopic dermatitis with the current status of asthma and atopic dermatitis of newborns between 2011 and 2013 in Korea.

Method: This study used claims data of the Health Insurance Review and Assessment

Service of newborns born in 2011, 2012, and 2013 in Korea. The registered analysis number of the data requested by the Health Insurance Review and Assessment Service is M2016082442, which is applied to the remote access system and granted access to data. The data to be used in this study were composed by combining the general information, healthcare information, diagnostic information and prescriptions information based on the patient identification code and the key code. The directed acyclic graph (DAG) was made through literature review, and was used to choose confounding variables. Frequency analyses were performed to examine the characteristics of the data, and the prevalences and incidence rates of asthma and atopic dermatitis were estimated. Incidence was estimated by person-month. Kaplan-Meier survival curves were estimated for subjects with the antibiotic use before the diseases, with the antibiotic use before the disease and the respiratory disease, and with the respiratory disease in the antibiotic use and pyelonephritis. Finally, the cox proportional hazard model was used to estimate the hazard ratio for the use of antibiotics in the development of asthma and atopic dermatitis. This study also estimated the hazard ratio for the development of asthma and atopic dermatitis according to the type of antibiotics proposed by WHO.

Results: The prevalence of asthma was about 60% and its incidence rate was 0.0238 per person-month who were less than one year old in 2011-2013, and the prevalence of atopic dermatitis was about 80% and incidence rate was 0.0845 per person-month. Both diseases were found to have higher prevalence and incidence rates for subjects using antibiotics before the diseases. DAG reveals that respiratory disease is a main confounder between asthma, atopic dermatitis and antibiotics, and the subjects were categorized into four different groups based on the antibiotics use and respiratory diseases. Kaplan-Meier survival curves show that both asthma and atopic dermatitis were associated with the highest risk in the group of antibiotic use and respiratory disease. The log-rank test also showed that there was a substantial difference in the survival functions between groups because the significance probability was less than 0.0001. Finally, the hazard ratio of antibiotic use before asthma in the Cox proportional hazards model was estimated to be 1.556 (95% CI: 1.543 - 1.569) for the development of asthma, and hazard ratio of antibiotic use before atopic was estimated to be 1.369 (95% CI: 1.360 - 1.378) for the occurrence of atopic dermatitis. The hazard ratio of antibiotic use for asthma among subjects with respiratory diseases was estimated to be 1.518 (95% CI: 1.510 - 1.527) and the hazard ratio for atopic dermatitis was estimated to be 1.210 (95% CI: 1.205 - 1.215). Effects of different antibiotics were estimated with the Cox proportional hazards model, and hazard ratios of the beta-lactam antibacterials and penicillins for asthma was 1.682 (95% CI: 1.668-1.695), and those for atopic dermatitis was 1.408 (95% CI: 1.399 – 1.417).

Conclusion: In this study, the use of antibiotics before the onset of asthma and atopic dermatitis was found to be an important risk factor affecting the incidence of asthma and

atopic dermatitis. Especially, the effect of beta-lactam antibacterials, penicillins on the incidence of asthma and atopic dermatitis was found to be the largest among antibiotics, and thus we can conclude that careful prescription for those antibiotics may be necessary to minimize the risk of asthma and atopic dermatitis in infants.

Keywords : Asthma, Atopic dermatitis, Antibiotics, Cox proportional hazard model, Kaplan-Meier curve

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Ⅰ. Introduction

1. Background & Necessity

Asthma is one of the most common chronic diseases in the world. The 2014 ISAAC study reported that around 344 million people worldwide suffered from asthma as of 2008-2010. This is higher than the 2000-2002 report, estimated at about 242 million people, indicating that the rate of asthma growth has increased faster than the rate of global population growth. The prevalence of global asthma in childhood is estimated to be about 14% in 2008-2010, and the prevalence of asthma in Korean children is estimated to be 8.7%.

A recent epidemiological survey based on the ISAAC protocol shows the estimates of the prevalence of allergic diseases in Korea in 2010. This study involved 4,000 children who are 6-7 years, and 13-14 years old in Korea. The prevalence of asthma was estimated to be approximately 10.3% (95% confidence interval [CI]: 9.2-11.4) in the former group and 8.3% (95% CI: 7.4-9.2) in the latter. The prevalence of eczema, a symptom of atopic dermatitis, was estimated to be 17.9% (95% CI 16.6-19.3) in children 6-7 years, and 11.2% (95% CI 10.1-12.3) in 13-14 years of age.

Research on the prevalence of asthma and atopic dermatitis in Korea using data from Korea National Health and Nutrition Examination Surveys (KNHNES) is also actively being conducted. Their estimates for the prevalence of adult asthma were 3.1% in 2011, 2.8% in 2012, 3.0% in 2013 and 3.0% in 2014, showing no big difference.

However, the prevalence of asthma in elementary school students is estimated to be 10.2% in 2010, a 2.5%p increase from 7.7% in 1995. The proportion of experienced patients in elementary school increased from 17% in 1995 to 18.7% in 2010. In adult

atopic dermatitis, the prevalence was 3.0% in 2011, 2.9% in 2012, 3.0% in 2013 and 3.0% in 2014.

Korea is one of the countries with the highest antibiotic consumption per capita in the world. According to a 2004 study using the Insurance Claims Data of Korea National Health Insurance Service, 23.62 people per 1,000 people were taking antibiotics in Korea. It was found that males tend to use more antibiotics, and the dose of antibiotics was the highest in children under 7 years of age (47.13 per 1,000). In comparison, the US and EU (27 countries) antibiotics usage rates in 2004 were 24.92 and 19.04 per 1,000 respectively. In particular, amount of antibiotics consumption is increasing in BRICS (Brazil, Russia, India, China, South Africa) in developing countries. They found that antibiotics with the highest use in children were beta-lactam antibacterials, penicillins, followed by cephalosporins and macrolides. People in the metropolitan areas tend to use more antibiotics than people in the small cities or rural areas.

Previously, there were efforts to clarify the link between the use of antibiotics and asthma & atopic dermatitis. Various studies investigated effects of antibiotics during infancy and childhood on the incidence of pediatric asthma and the effects of maternal antibiotics during pregnancy on the incidence of pediatric asthma and atopic dermatitis to clarify the association between the use of antibiotics and the occurrence of asthma and atopic dermatitis. However, due to limitations caused by the complex interplay among multiple risk factors for asthma and atopic dermatitis with multiple risk factors and small sample size, some inconsistency of their results have been found among them. Recent studies found associations between antibiotic use and asthma through a case-sibling study design, and they showed that antibiotics during pregnancy can lead to the higher incidence of asthma in school-aged children.

Health insurance claims data records which medical services an insurer, such as a

hospital, a clinic, or a health center, provided to patients. Many health policy decision makers are creating policies that incorporate evidence from a variety of studies. In particular, real world data is used to make health policy decisions because it contains the patient's actual treatment records and can be used to assess long-term safety and effectiveness as well as economic efficiency. Due to the health insurance system in Korea, claims data have detailed medical data including diagnosis data and prescription drugs. The data also include information about the health services of all citizens. In this thesis, I focused on the medical claims data managed by Health Insurance Review & Assessment Service (HIRA) in Korea, which is dataset for the whole nation. This data includes most Koreans on births, and the details of medical use, drug use and disease code were included. Therefore, the general conclusion about associations between asthma, atopic dermatitis and antibiotics in Koreans can be obtained.

2. Objectives

The aim of this study is to investigate the prevalence and incidence rate of asthma and atopic dermatitis and the status of antibiotic use in 2011-2013 using the claims data of HIRA in Korea. In addition, this study will investigate the effect of antibiotic use on the risk of asthma and atopic dermatitis. To do this, this study explored the complex risk factors associated with asthma and atopic dermatitis and analyzed the effects of antibiotic use on asthma by appropriately controlling and correcting risk factors. In particular, this study will estimate the effect by the different types of antibiotics. An appropriate statistical model will be presented to clarify the association between antibiotics and asthma & atopic dermatitis by correcting covariates and confounders. Especially, the main goal is to reduce the incidence of asthma and atopic dermatitis by presenting appropriate prescriptions of antibiotics when infant has respiratory disease.

To summarize, the results of the prevalence of asthma, the use of antibiotics, and the effects of antibiotics on the occurrence of asthma are used to suggest ways to reduce the risk of developing asthma and atopic dermatitis in children due to proper antibiotic prescription in infancy and childhood.

The detail purposes of this study are as follows:

1. To estimate the current state of asthma, and atopic dermatitis and antibiotic use in Korea's 2011-2013 birth infant.
2. To assess the association between the use of antibiotics, and the incidence of asthma and atopic dermatitis in infancy.
3. To assess the association between the use of antibiotics, and the incidence of asthma and atopic dermatitis in infancy by different antibiotics type

Ⅱ. Theoretical background

1. Asthma, atopic dermatitis and antibiotics

According to the 2007 report by National Heart, Lung, and Blood Institute (NHLBI) in the United States, asthma is defined as a chronic inflammatory disorder of the airways in which many cells and cellular element play a role. The cells and cellular refer to mast cells, eosinophils, neutrophils, T lymphocytes, macrophages and epithelial cells. Symptoms such as wheezing, difficulty breathing, and coughing (especially early morning or evening) can be caused by inflammation. The characteristics of asthma include bronchoconstriction, airway hyperresponsiveness, and Airway edema. The airflow obstruction of the airway caused by such inflammation can be said to induce the aforementioned symptoms.

Atopic dermatitis is defined as chronic disease that affects the skin according to the National Institutes of Health (NIH) for 2014. Atopy means that the allergic condition worsens, and dermatitis means swelling of the skin. Symptoms of atopic dermatitis include dry, cracking skin, rash, eczema and characteristics of atopic dermatitis are common in children and can be improved naturally when grown up (National Institute of Arthritis and Musculoskeletal and Skin Diseases, 2013). However, if they are constantly in a dry environment or are exposed to irritation, they may become affected. Particularly, children suffering from atopic dermatitis disease are known to be more likely to suffer from fever and asthma due to the allergy march. An allergy march is the concept that atopic dermatitis occurs in 1 to 3 years after birth, and the occurrence of asthma is likely to continue thereafter.

Antibiotics are substances that inhibit the growth microbiome and remove them to make antimicrobial action. Antibiotics were found in 1928 when Alexander Fleming did

not cultivate bacteria around the fungus in a fungal incubator during a staphylococcal culture experiment (Fleming, 1929). Fleming studied the substance contained in the fungus and that was named penicillin, which opened the era of antibiotics opening the era of antibiotics (Song, 2012). Antibiotics are divided into tetracycline, beta-lactam. Beta-lactam is divided into penicillin, 1-4th generation cephalosporin and so on. In this study, the types of antibiotics were classified into 16 categories according to world health organization (WHO) guidelines. The classified antibiotics were paired with the International Classification of Diseases, 10th revision (ICD-10) codes in the claims data of HIRA.

2. Risk factors of asthma and atopic dermatitis

The incidence of asthma and atopic dermatitis is known to be affected by a combination of various and complex risk factors such as demographic factors, infectious disease, medication, dietary factors, and atmospheric environment (Beasley, 2015). In demographic factors, age, sex, family history and my other factors are known. Infectious diseases are respiratory infections caused by viruses. Examples of medication factors are paracetamol, which is a component of antipyretic drugs, and antibiotics, which are antimicrobial (Beasley, 2015). Dietary factors such as vitamins, magnesium, and nutrients are known to be ingested, and the atmospheric environment factors include parental smoking, air pollution are known to be factors of asthma and atopic dermatitis (Beasley, 2015).

The effect of sex on asthma and atopic dermatitis incidence may be related to age. The prevalence of asthma and atopic dermatitis is high in men before age 13, but after that it is known that the prevalence of asthma in women is higher (Melgert, 2007). The reason that age-specific gender differences are the main causes of asthma is not only

sociological and environmental differences but also biological differences. The biological difference between male and female refers to the change in hormones after the secondary sex characteristics. Estrogen, a female hormone, is secreted by women in the secondary sex, estrogen has an alpha receptor gene (ESR1). It has been studied that the alpha receptor gene (ESR1) is known to be reactive with bronchial tubes, which can increase the risk of asthma incidence (Dijkstra, 2006).

Family history of asthma and atopic dermatitis is also a major risk factor for pediatric asthma (Guerra, 2008). The genetic impact of asthma does not clearly follow Mendelian's laws. The reason for this is that it is difficult to unambiguously identify at the genetic level, as several genes affect asthma, methodological limitations and chronic factors.

3. The association of asthma and atopic dermatitis with antibiotics

Antibiotics are characterized by indiscriminate suppression of microbiomes that have positive effects as well as negative effects of antibiotic users. These features break the balance in intestinal microorganisms, which cause long-term changes in intestinal microbial composition, such as increasing actinomycetes, enzymes and decreasing bacteria (Blaser, 2011). These changes cause T cells to destroy insulin secreted from the pancreatic beta cells. Beta cells play a role in killing the causative bacteria of complex diseases. It has studied that the destruction affects the development of comorbid diseases such as asthma, atopic diseases, autoimmune diseases such as type 1 diabetes, familial Mediterranean fever and colitis.

Previous studies (Strachan, 1989) have suggested a "hygiene hypothesis" of asthma incidence. Hygiene hypothesis is that factors such as individual hygiene status, birth order, and antibiotic use increase the prevalence of diseases such as atopic dermatitis

and asthma in western cultures. Recent some studies (Noverr, 2005) suggest that the hypothesis should be modified to include the role of gastrointestinal microorganisms. This is called a microflora hypothesis. One hypothesis states that diet and the use of antibiotics resulted in a decrease in microbiome and that changes in intestinal microbes resulted in an unmatured microbial growth (Noverr, 2005). Immature microbial growths increase the incidence of allergic sensitization by interfering with the proper growth of the immune system and by inhibiting the development of general immune tolerance.

In the study (Ortqvist, 2014), codes of antibiotics were separated by the classification method of Anatomical Therapeutic Chemical (ATC) into three broad categories, A, B and C. A contains all type of antibiotics, B which was known to be the highest hazard ratio is an antibiotic group used to treat respiratory infections such as penicillin and C is a group of antibiotics used in the treatment of urinary or skin, all of which three groups significantly increased the risk of asthma incidence.

4. Directed acyclic graphs

As mentioned above, asthma and atopic dermatitis have complex risk factors. In adults, asthma can be diagnosed more clearly through diagnostic methods such as pulmonary function test, whereas pediatric asthma is difficult to perform pulmonary function tests. This makes diagnosis of childhood asthma less than 5 years old difficult. Therefore, it is more desirable to estimate the disease by using operational definition rather than using the result of diagnosis in childhood asthma. This operational definition should be used to estimate risk factors through appropriate modeling of the major risk factors for asthma. Appropriate modeling of risk factors should precede proper search of causal graphs.

A graph with causal directional information among causal graphs for analysis of factors is called a directional graph. Among them, graphs with no circulating arrows are called directed acyclic graphs (DAGs), a concept used in computer science, probability theory, statistics, and so on. DAGs are often used in epidemiology because it allows causal reasoning for each factor by decomposing information about relations into probability distribution using conditional independence and joint probability distribution. In epidemiological studies, the precedence of DAGs can identify component of bias and selection of covariates or confounder for statistical correction and can help interpretation of causal inference (Vanderweele, 2011). Particularly, the analysis of causal direction can be made more precisely by analyzing covariates, confounders, and colliders. Developing DAGs for research is difficult and can be bullish. Nevertheless, DAGs should be clarified through appropriate literature review and advice from clinical specialists. Therefore, the selection of the variables mentioned above and the interpretation of the analysis results can be carried out according to the purpose of the study.

Ⅲ. Method

1. Study design

This study used the claims data of HIRA from Korean children born in 2011-2013 in order to investigate the effects of antibiotics used in infancy on the incidence of asthma and atopic dermatitis. The registered analysis number of the data requested by HIRA is M2016082442, which is applied to the remote access system and granted access to data on the demographic information, the medical care and prescription of the newborn child in 2011-2013. Afterwards, analyses were carried out after eliminating the personally identifiable information from the result of remote analysis.

In the claims data of HIRA, Table 20 provides its general information, Table 40 includes diagnostic information, and specific information on healthcare services provided, outpatient prescriptions and birth registration data can be obtained from Table 30 and 53. Thus demographic factors are extracted from the data in Table 20 and the data combining the birth registration data with the patient ID. Then, the data of the individual's disease history (main disease and sub disease) and individual drug use history are extracted from Table 40, Table 30, and Table 53 by matching the billing statement identification code (key ID). Finally, they were merged by patients' ID. By merging in the same order as above, it is possible to identify outliers or missing values at the beginning of the merging phase and reduce the resources used for the analysis. The outliers were defined as foreigners or those born with diseases corresponding to exclusion criteria whose information can be found in Table 2. The missing values were defined as the absence of information about the year of birth and month, or the absence of socioeconomic status (SES). In addition, errors of measurement in defining asthma disease could be reduced by combining disease code and drug code rather than only

using the disease code. The pipeline for the dataset configuration is shown in the following Figure 1.

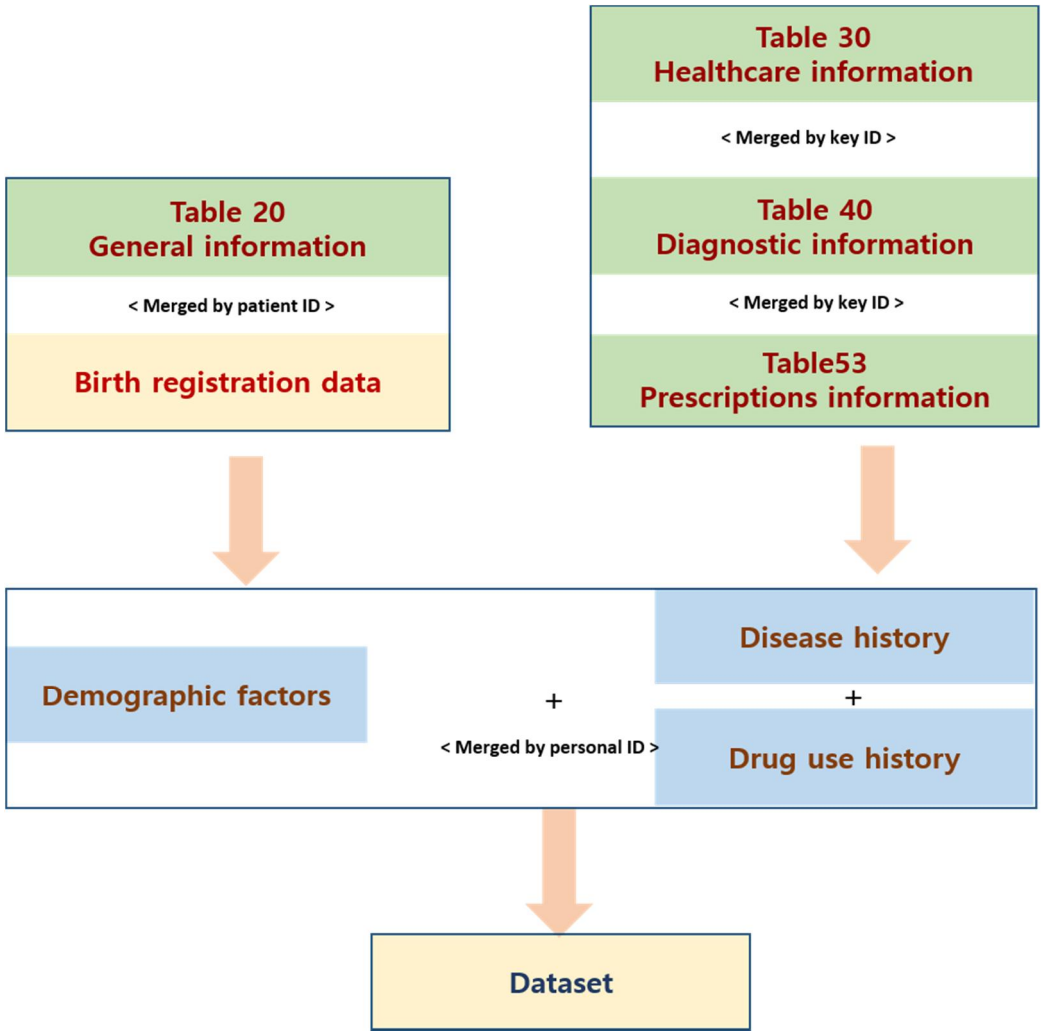


Figure 1 The pipeline for the dataset configuration

The selection criteria of variables can be confirmed in Figure 2. The DAG was developed with following studies around antibiotics which are main exposure, asthma

and atopic dermatitis which are main outcome, and respiratory diseases which are confounder. The use of antibiotics is known to break down the balance of the microbiome and cause asthma and atopic dermatitis (Sekirov, 2010). Respiratory infections are treated with antibiotics and cause asthma and atopic deramtitis if they are caused by respiratory infections (Beasley, 2015). In childhood, asthma, atopic dermatitis and pyelonephritis have a high prevalence in boys (Melgert, 2007; Raszka, 2005). Because the incidence of pyelonephritis causes high temperature, prescription of paracetamol is made, and that may cause asthma and atopic dermatitis (Farquhar, 2009). In areas where birth area is urbanized, air pollution is severe, causing respiratory diseases, asthma and atopic dermatitis (Robinson, 2011). In the winter of the year, there are fewer outdoor exposures to vitamin D deficiency, and the nutritional status and stress of the mother cause asthma (Hollams, 2011).

Diagnostic and drug prescription codes for the operational definition of asthma and atopic dermatitis, which are outcomes of this study, were extracted from the disease history and drug use history stage. The main exposure of antibiotic use was extracted from the drug use history stage, and the main confounder respiratory disease was extracted from the disease history. In order to control covariates affecting asthma and dermatitis, this study extracted sex, birth season, residential area, and health insurance status at the demographic factor stage.

The FEV test in infancy was not provided in the claims data of HIRA and subjects were considered as asthma patients if they satisfy the following three requirements:

1. Subjects should be diagnosed three times or more within a year and intervals of any two consecutive diagnoses should be larger than or equal to one month.

2. Subjects should be prescribed three times or more asthma medications within a

year, and intervals of any two consecutive diagnoses should be larger than or equal to one month.

3. Dates for asthmatic diagnoses and medications should be same.

Diagnosis of asthma in the first requirement of operational definition can be obtained by a standard ATC code J45, J46, J21, and R062. Medications in the second requirement of operational definition can be obtained by a wide medication criteria which include about 360 different asthma-related medications. As a third requirement, we considered subjects with one-month interval or more between any two consecutive diagnoses and medications in order to detect chronic asthma. Furthermore, there are some possibility that the asthma diagnose code can be used to treat, and thus unless three detections occur within one year, we assume that asthma diagnoses were attributable to other diseases. The atopic dermatitis can be operationally defined by the diagnosis code L20 which is much less complicated than the operational definition of asthma.

The WHO-designated ATC code is commonly used to study disease occurrence by antibiotics type. However, claims data of HIRA is classified by ingredient code, not ATC code. The ingredient code is 9 digits and contains information on the active ingredient, drug strength & unit, route of administration, and dosage form (Jang, 2011). So, approximately 2,000 antibiotics were converted from ingredient codes to ATC codes according to WHO guidelines (WHO Collaborating Centre for Drug Statistics Methodology, 2016).

This study was conducted to investigate the effect of antibiotics on asthma and atopic dermatitis. Only the antibiotics taken prior to the date of asthma and atopic dermatitis as defined above were extracted. Sex is composed of two levels, male and female. In the case of the birth season, births were classified by quarter. The first quarter is winter, the

second quarter is spring, the third quarter is summer, and the fourth quarter is autumn. In the case of the residential area, it was assumed that the first medical service of the newborn was provided because there was no data corresponding to the residential area. For the analysis, it was necessary to classify the residential area and it was divided into Seoul, metropolitan, Medium sized city, and small town to reflect the characteristics of Korea. Seoul is the capital of Korea, and metropolitan was classified as metropolitan cities or cities with a population of over 900,000. Medium sized cities are more than 100,000 and less than 900,000, and small towns were classified as less than 100,000. Estimates of the number of population by municipal or district refer to the data on the website of the Statistics Korea. In order to estimate the SES, this study used the variables of health insurance subscribers or medical care receivers. This is because people who had difficulties in living were subscribed to medical benefits rather than health insurance, so SES could be estimated using these variables.

In addition, antibiotics were classified into 17 categories by using the taxonomy suggested in the WTO guidelines to analyze the effects of antibiotics on atopic dermatitis and asthma. The classification of antibiotics is shown in the following table.

ATC code	Antibiotic types
J01A	Tetracyclines
J01B	Amphenicols
J01C	Beta-Lactam antibacterials, Penicillins
J01D	Other Beta-Lactam antibacterials
J01DB	First-generation Cephalosporins
J01DC	Second-generation Cephalosporins
J01DD	Third-generation Cephalosporins
J01DE	Fourth-generation Cephalosporins

J01DF	Monobactams
J01DH	Carbapenems
J01DI	Other Cephalosporins and Penems
J01E	Sulfonamides and Trimethoprim
J01F	Macrolides, Lincosamides and Streptogramins
J01G	Aminoglycoside antibacterials
J01M	Quinolone antibacterials
J01R	Combinations of antibacterials
J01X	Other antibacterials

Table 1 Types of antibiotics according to ATC code

As mentioned in the theoretical background, in epidemiological studies, it is necessary to clarify DAG prior to the analysis of the research through appropriate literature review and consultation with clinical experts. Especially, in case of atopic dermatitis and asthma, the factors of disease are complex, so it is important to clarify the DAGs and control the factors one by one.

The DAG for antibiotics of asthma and atopic dermatitis is as follows:

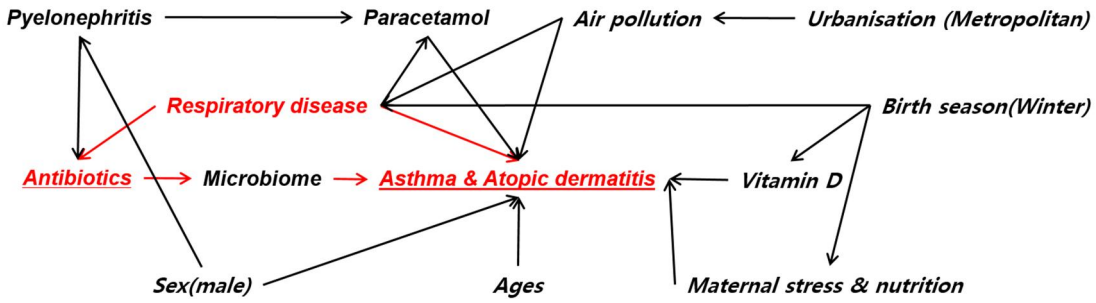


Figure 2 DAG of asthma and atopic dermatitis.

As shown in the DAG, the major confounder of antibiotics and pediatric asthma and atopic dermatitis is respiratory disease. The prevalence of pyelonephritis, asthma and atopic dermatitis are high in males. The higher the air pollution level in the birth area, the higher the risk of asthma and atopic dermatitis incidence. The lower the exposure dose of sunlight in the winter and the worse the mother's psychological state and nutrition, the higher the prevalence of asthma and dermatitis in children.

In addition to the risk factors presented in the graph above, other factors such as low birth weight, musculoskeletal disorders, and congenital heart disease are also known to be risk factors for asthma and dermatitis incidence. However, the final goal of this study is to provide an appropriate prescription of antibiotics for infants with respiratory disease. It is not appropriate to control and analyze other diseases, and the prevalence of the diseases is also low. So this study set up exclusion criteria.

The list of exclusion criteria and the ICD-10 code are as follows:

Disease	ICD-10 code
Low birth weight infant	P070, P071, P0711, P0712, P0713, P0714
Premature	P072
Intrauterine growth retardation	P059
Obstructive bronchitis	J44
Congenital heart disease	Q2
Congenital malformations of the respiratory system	Q3
Respiratory and cardiovascular disorders Specific to the perinatal period	P220
Muscular skeletal disease	G7, Q7
Inborn error of metabolism	Q8, Q9
Immune deficiency diseases	D8

Table 2 list of ICD-10 code for exclusion criteria

2. Hypotheses

The hypotheses for achieving the above objectives in this study are as follows:

1. The use of antibiotics in infancy may affect the incidence of asthma.

2. The use of antibiotics in infancy may affect the incidence of atopic dermatitis.

3. The use of antibiotics by type of infant may affect the incidence of asthma.

4. The use of antibiotics by type of infant may affect the incidence of atopic dermatitis.

3. Statistical methods

Frequency analysis, prevalence and incidence estimation, and survival analysis were conducted. Frequency analysis was carried out to estimate the distributions of basic demographic variables such as gender and birth area in 2011-2013 and to confirm the use of antibiotics in Korean children. In the case of prevalence, the percentage of patients with asthma and atopic dermatitis was calculated based on the period within one year of birth. Since subjects available for the birth claims data of HIRA in Korea are very large, the standard errors are very small and CI estimates are not included. The incidence rate was calculated on the basis of person-month rather than person-year, and their 95% CIs were estimated by assuming Poisson distribution for disease occurrence. Time to asthma and atopic dermatitis onsets was analyzed with the crude Kapan-Meier curve analysis, which is a method of estimating the survival function by major groups until the asthma and atopic dermatitis incidence respectively, and the Cox proportional hazards model, which estimates the effect of only antibiotic use on diseases by adjusting the effects of confounders in DAGs.

The Kaplan-Meier analysis estimates subjects' conditional probability at each time point that asthma and atopic dermatitis occur, and they were used to calculate the survival rate by multiplying the estimated probabilities. For the Kaplan-Meier analysis, occurrence time of the event should be clarified and the starting point of the survival time is defined by the time of birth. Events are defined by the occurrence of asthma and atopic dermatitis. Specifically, for atopic dermatitis, the first diagnosis of L20 diagnosis among main diagnosis and sub-diagnosis is defined as the time point of occurrence of atopic dermatitis by operational definition. For asthma, the date of the first prescription and diagnosis was defined as the point in time of asthma, during the three prescriptions and diagnoses at intervals of one month or more in the operational definition.

If times to onset of asthma or atopic dermatitis are $t_1, t_2, \cdots, t_n$, the numbers of events at time points are $d_1, d_2, \cdots, d_n$, and the number of people who can develop disease at time points are $r_1, r_2, \cdots, r_n$, the hazard rate at time point t_i can be defined as $\mathrm{h}(t_i) = d_i/r_i$. The survival function $\mathrm{S}(t_i)$ can be estimated to be $\mathrm{S}(t_i) = S(t_{i-1}) \times \big(1 - h(t_i)\big), \mathrm{S}(t_0) = 1$ for each time point. The Kaplan-Meier Curve is a graph of the survival function $\mathrm{S}(t)$ at each point in time. The survival function $\mathrm{S}(t)$ is as follows:

$$\mathrm{S}(t) = \mathrm{P}[\mathrm{T} > t] = 1 - \mathrm{P}[\mathrm{T} \leq t] = 1 - \mathrm{F}(t)$$

T is the random variable of the disease occurrence time and $\mathrm{F}(t)$ is the cumulative probability distribution.

Kaplan-Meier analyses were conducted for three different goals. First, the crude Kaplan-Meier curves for the disease-free antibiotic-treated subjects, the antibiotic-untreated subjects, and all subjects were separately generated, and the differences among three groups was tested. Second, subjects are separated into four groups depending on the respiratory disease status before the onset of the diseases because

respiratory diseases are often known as confounder of asthma and atopic dermatitis and the effect of respiratory diseases should be adjusted. Third, subjects were divided into two groups according to the presence or absence of respiratory disease in patients who had pneumonia prior to the disease and took antibiotics.

Differences of survival functions between different groups were tested by log-rank test. The log-rank test is a non-parametric method and can test whether events occurs in proportion to the number of subjects in both groups. That is. In the Kaplan-Meier analysis, it is often used to test the differences of survival function among groups.

The Cox proportional hazards model was used to estimate the effect of antibiotics on the incidence of asthma and atopic dermatitis when effects of confounders and covariates are adjusted. The Cox proportional hazard model (Cox, 1972) can be modeled by

$$\mathrm{h}(t; X_i) = \mathrm{h}_0(t) \times \exp(\beta_1 X_{i1} + \cdots + \beta_k X_{ip})$$

Here $\mathrm{h}(t)$ is the baseline risk function at each time point in time, and $X_1, \cdots, X_p$ indicates covariates. The logistic model uses the disease status as response variable but the Cox proportional hazard model can estimate the effect of covariates on time to onset. Therefore, Cox proportional hazard model is useful if disease status is unclear. Disease status is often unclear for controls because they have a chance to be affected. In the case of the claims data used in this study, the study period was set up until the first year after birth or when the follow-up was not made. For this reason, this data can be considered to be right-censored. So, the effects of antibiotics were estimated using the Cox proportion hazard model. The use of antibiotics was limited to pre-asthma use to estimate the effect of antibiotics taken prior to asthma. The use of antibiotics was limited to pre-asthma use to estimate the effect of antibiotics taken prior to asthma.

Ⅳ. Results

1. Characteristics of study population

Subjects who were born in Korea in 2011, 2012 and 2013 were used for analyses. There are 1440,836 subjects available in the claims data of HIRA in Korea, and some subjects who satisfy the following conditions were excluded. First, the foreigner or subjects with missing information about date of birth were excluded. Second, subjects whose SES are unknown are excluded. Last, subjects who satisfies the exclusion criteria are removed. See the Table 2 for exclusion criteria. Figure 3 shows the summary for subject filtering described so far.

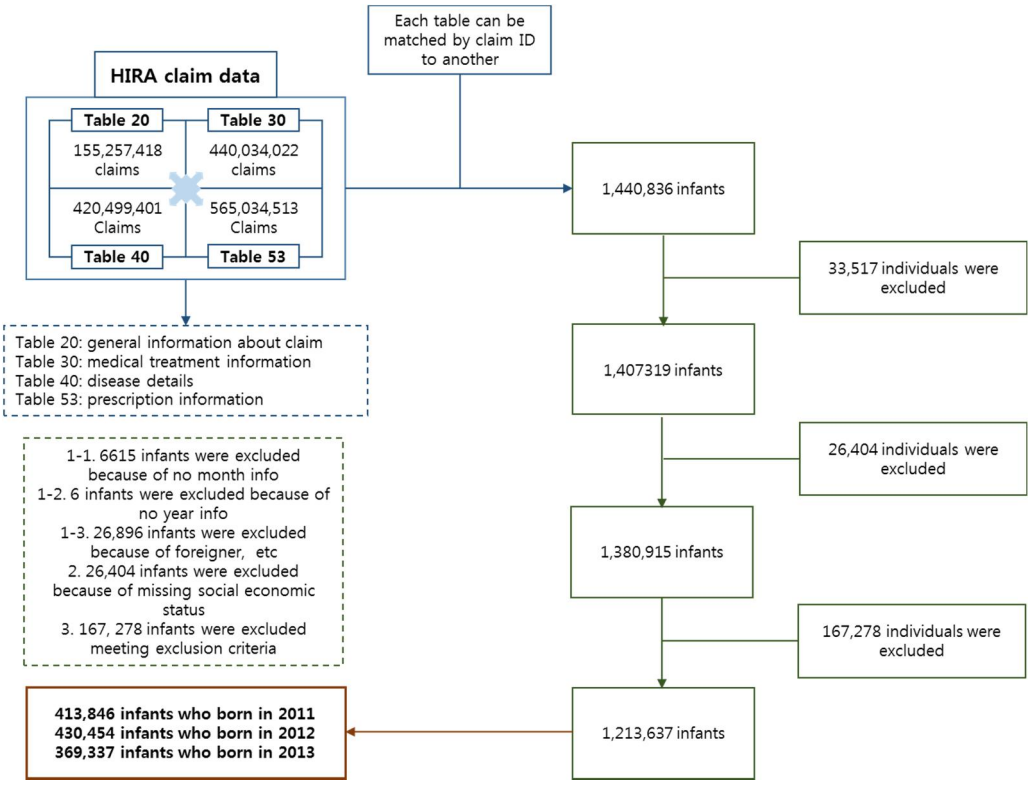


Figure 3 Procedure of data preparation

Before investigating the effect of antibiotics on the incidence of asthma and atopic dermatitis, the use of antibiotics by type of antibiotics was summarized. The 17 antibiotics mentioned in the method were categorized based on the types of antibiotics used. The use of antibiotics by the type of antibiotics in the claims data was confirmed in healthcare information (table 30) and prescriptions information (Table 53). When studying drug exposure research, it is known that it is necessary to utilize information about healthcare and prescriptions to study more accurate drug use status.

Beta-Lactam antibacterials, penicillins was the most popularly used, and it was followed by third-generation cephalosporins and macrolides, lincosamides and streptogramins among infants born between 2011 and 2013 according to the claims data of HIRA. The use of antibiotics by type is shown in Table 3.

ATC code	Antibiotic types	Healthcare information (table 30)	Prescriptions information (table 53)
J01A	Tetracyclines	209	168
J01B	Amphenicols	0	0
J01C	Beta-Lactam antibacterials, Penicillins	2,949,472	45,668,863
J01D	Other Beta-Lactam antibacterials	1,609	4,921
J01DB	First-generation Cephalosporins	122,388	785,519
J01DC	Second-generation Cephalosporins	448,266	8,850,048
J01DD	Third-generation Cephalosporins	1,967,133	10,538,545
J01DE	Fourth-generation Cephalosporins	6,933	0
J01DF	Monobactams	211	0
J01DH	Carbapenems	21,067	0

J01DI	Other Cephalosporins and Penems	0	0
J01E	Sulfonamides and Trimethoprim	25,332	686,916
J01F	Macrolides, Lincosamides and Streptogramins	1,094,479	12,370,868
J01G	Aminoglycoside antibacterials	733,576	319
J01M	Quinolone antibacterials	3,789	2,773
J01R	Combinations of antibacterials	6	7,659
J01X	Other antibacterials	39,713	8,199

Table 3 The number of use by type of antibiotics

In the claims data of HIRA in Korean children born in 2011-2013, variables were collected for the risk factors in DAG. The risk factors identified in the claims data were sex, birth date, SES, birth area, diseases and medications. In our data 51% of subjects are males and 49% of them are females, and it is almost identical to gender ratio in Korea. Medium sized cities were the most common birth places (40.25%) followed by Metropolitan (37.21%). The birth quarter is mostly distributed evenly at 25%, but there is a slight imbalance between the first quarter (31.87%) and the fourth quarter (18.79%) in 2011. SES has been confirmed by the presence of Health insurance, and most of the subjects can be confirmed to be in Health insurance (99.35%). The medical care receiver case is used as an indicator of the poor. The major diseases, including asthma and atopic dermatitis, were identified by frequency and prevalence by year in operational definitions mentioned in the research method. The prevalence of asthma and respiratory diseases is similar to 60%, and atopic dermatitis is about 80% and pyelonephritis is about 2%. The frequency and percentage of the above-mentioned variables by year are shown in Table 4.

	Newborn in 2011		Newborn in 2012		Newborn in 2013		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Demographics								
Sex								
Male	212,021	(51.23)	219,095	(50.90)	187,705	(50.82)	618,821	(50.99)
Female	201,824	(48.77)	211,359	(49.10)	181,631	(49.18)	594,814	(49.01)
Birth area								
Seoul (Capital)	75,480	(18.24)	79,918	(18.57)	67,943	(18.40)	223,341	(18.40)
Metropolitans	150,742	(36.42)	161,661	(37.56)	139,144	(37.67)	451,547	(37.21)
Medium sized cities	169,326	(40.92)	171,594	(39.86)	147,508	(39.94)	488,431	(40.25)
Small town	18,294	(4.42)	17,281	(4.01)	14,741	(3.99)	50,316	(4.15)
Birth quarter								
1st	131,886	(31.87)	101,182	(23.51)	88,429	(23.94)	321,497	(26.49)
2nd	106,979	(25.85)	102,449	(23.80)	86,868	(23.52)	296,296	(24.41)
3rd	97,216	(23.49)	117,402	(27.27)	95,048	(25.73)	309,666	(25.52)
4th	77,764	(18.79)	109,421	(25.42)	98,991	(26.80)	286,176	(23.58)
SocioEconomic Status								
Health insurance	411,120	(99.34)	427,709	(99.36)	366,872	(99.33)	1,205,701	(99.35)
Medical care	2,725	(0.66)	2,745	(0.64)	2,464	(0.67)	7,934	(0.65)
Major disease								
Asthma								
Yes	246,323	(59.52)	266,156	(61.83)	224,746	(60.85)	737,225	(60.75)
No	167,522	(40.48)	164,298	(38.17)	144,590	(39.15)	476,410	(39.25)
Atopic dermatitis								
Yes	329,386	(79.59)	349,223	(28.77)	297,838	(80.64)	976,447	(80.46)
No	84,459	(20.41)	81,231	(6.69)	71,498	(19.36)	237,188	(19.54)
Respiratory disease								
Yes	294,572	(71.18)	251,074	(58.33)	212,256	(57.47)	757,902	(62.45)
No	119,273	(28.82)	179,380	(41.67)	157,080	(42.52)	455,733	(37.55)
Pyelonephritis								
Yes	6,606	(1.60)	7,581	(1.76)	6,717	(1.82)	20,904	(1.72)

No	407,239	(98.40)	422,873	(98.24)	362,619	(98.18)	1,192,731	(98.28)
Drugs under 1 year								
Antibiotics								
Yes	356,899	(86.24)	369,496	(85.84)	315,637	(85.46)	1,042,032	(85.86)
No	56,946	(13.76)	60,958	(14.16)	53,699	(14.54)	171,603	(14.14)
Paracetamol								
Yes	299,541	(72.38)	325,758	(75.68)	279,605	(75.70)	904,904	(74.56)
No	114,304	(27.62)	104,696	(24.32)	89,731	(24.30)	308,731	(25.44)

Table 4 Characteristics of newborn between 2011 and 2013 in Korea by the claims data of HIRA

2. Prevalence and Incidence rate of asthma and atopic dermatitis

Prevalence and incidence of asthma and atopic dermatitis were estimated in order to examine the overall status of asthma and atopic dermatitis in the period from 2011 to 2013. The prevalence was calculated by setting the period to be less than 1-year-old between 2011 and 2013. The prevalence of asthma in all subjects by year was about 60%, and the prevalence of asthma was higher in the group taking antibiotics before the onset of asthma than in the group not taking antibiotics. The prevalence of atopic dermatitis in all subjects was about 80%, which was higher than the prevalence of asthma. Similar to the prevalence of asthma, prevalence of atopic dermatitis is high in the group taking antibiotics before atopic dermatitis than in those not taking antibiotics.

Because the data on birth date were composed of quarters, the incidence of asthma and atopic dermatitis was determined by setting the person-month. The overall incidence of asthma was estimated to be 0.0238 (CI: 0.0238 to 0.0239), while the overall incidence of atopic dermatitis was estimated to be 0.0845 (CI: 0.0843 to 0.0847) higher than that of asthma. The prevalence of asthma and atopic dermatitis, as well as prevalence, was higher in the group taking antibiotics than in those not taking antibiotics. More

information on prevalence and incidence rate can be found from Table 5 and Table 6. They show that antibiotic use is a risk factor for the development of asthma and atopic dermatitis. However, this does not consider respiratory diseases, which are important confounders of asthma and atopic dermatitis. Therefore, we analyzed the effects of antibiotics use and respiratory diseases on subsequent analysis.

	Prevalence		
	2011	2012	2013
Asthma			
Total	59.52%	61.83%	60.85%
Non-Antibiotics	7.39%	6.63%	6.47%
Antibiotics before incidence of asthma	52.13%	55.20%	53.38%
Atopic dermatitis			
Total	79.59%	81.13%	80.64%
Non-Antibiotics	10.27%	10.36%	10.50%
Antibiotics before incidence of atopic dermatitis	69.32%	70.77%	70.14%

Table 5 Prevalence of asthma and atopic dermatitis in infants under 1 year between 2011 and 2013 by antibiotics

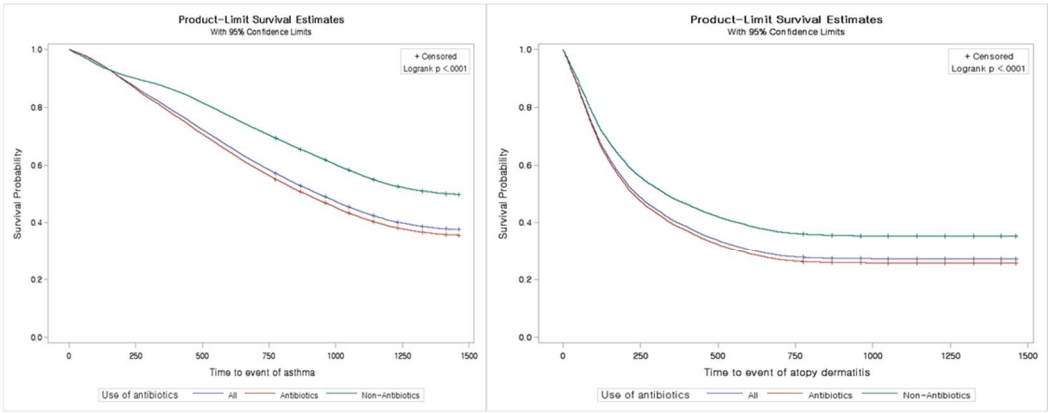
	The number of event	Incidence rate	95% CI	
Asthma				
Total	737,225	0.0238	0.0238	0.0239
Non-Antibiotics	83,021	0.0170	0.0169	0.0171
Antibiotics before incidence of asthma	654,204	0.0251	0.0250	0.0252
Atopic dermatitis				
Total	976,447	0.0845	0.0843	0.0847
Non-Antibiotics	125,868	0.0591	0.0588	0.0594
Antibiotics before incidence of atopic dermatitis	850,579	0.0903	0.0901	0.0905

Table 6 Incidence rate of asthma and atopic dermatitis by antibiotics

3. Kaplan-Meier curve of asthma and atopic dermatitis by antibiotics, respiratory disease and pyelonephritis

As mentioned in the method, the Kaplan-Meier curves were generated for three purposes about asthma and atopic dermatitis.

The first Kaplan-Meier curves among the three groups which consist of total, antibiotics use before the onset of asthma and non-use antibiotics. Both asthma and atopic dermatitis were found to occur more rapidly and frequently in subjects who use antibiotics before onset of asthma than in those who did not use antibiotics according to Figure 4. ‘a’ is the Kaplan-Meier curve of asthma and ‘b’ is the Kaplan-Meier curve of atopic dermatitis. The log-rank test was significant for both 'a' and 'b'. This is also the same in Figure 5 and Figure 6.

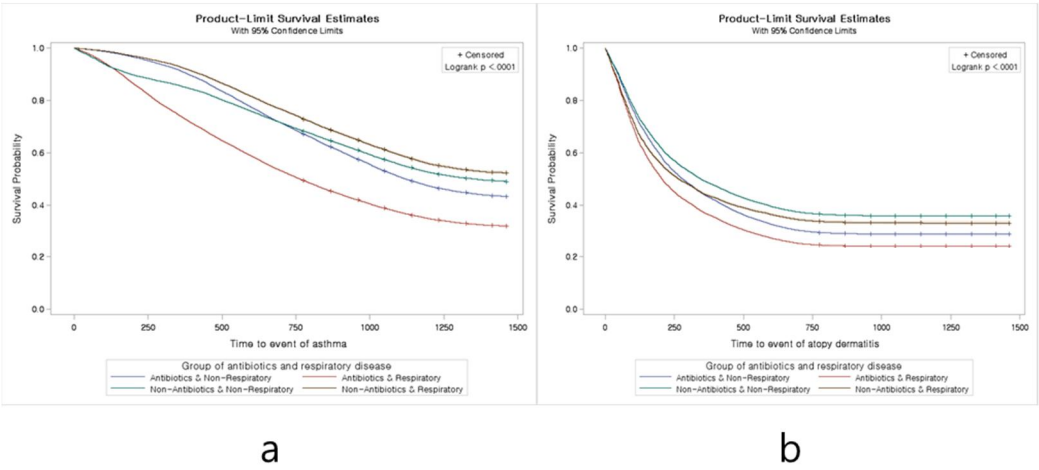


a b

Figure 4 Kaplan-Meier curve of asthma and atopic dermatitis according to antibiotics use

respiratory disease is known as a confounder of asthma and atopic dermatitis and

Kaplan-Meier curve analysis was provided in Figure 5 for four groups according to use of antibiotics and respiratory diseases. In the case of asthma, asthma occurred most frequently in subjects who had antibiotic use and respiratory diseases before the onset of asthma. This tendency was similar in 'b', atopic dermatitis. The incidence of atopic dermatitis was the highest in subjects who had antibiotics prior to disease and developed respiratory diseases. In both Kaplan-Meier curves, log-rank tests were significant.

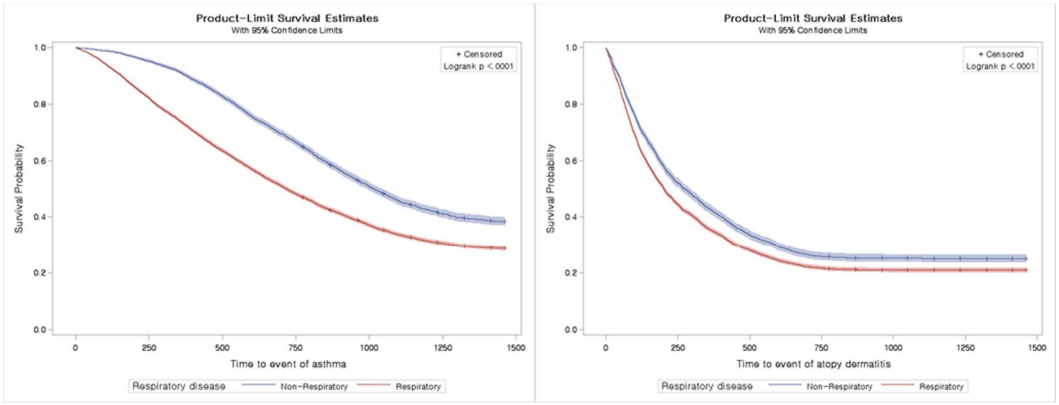


a b

Figure 5 Kaplan-Meier curve of asthma and atopic dermatitis grouped by antibiotics use and respiratory disease

Figure 6 depicted Kaplan-Meier curves of asthma and atopic dermatitis in groups of patients who developed pyelonephritis and who were taking antibiotics before each disease. Although pyelonephritis is not a direct risk factor for asthma, it is one of the representative diseases that use antibiotics in childhood. Therefore, the subjects who had pyelonephritis and used antibiotics were divided into groups according to respiratory

disease criteria. Both asthma and atopic dermatitis were found to be highly associated with respiratory diseases in those subjects.



a b

Figure 6 Kaplan-Meier curve of asthma and atopic dermatitis grouped by respiratory disease in Pyelonephritis and antibiotics

4. Cox proportional hazard model of asthma and atopic dermatitis

To assess the status of asthma and atopic dermatitis in 2011-2013, the prevalences and incidence rates were estimated, and the Kaplan-Meier curves were generated to compare the risks of asthma and atopic dermatitis according to antibiotic use before onset of diseases and respiratory diseases. As can be seen from DAGs, asthma is affected not only by antibiotics and respiratory diseases, but also by other risk factors. Therefore, effects of sex, birth time, and birth area affecting asthma and atopic dermatitis in DAGs need to be adjusted and the Cox proportional hazard models are

applied.

For Cox proportional hazard model, the use of antibiotics was set as the main exposure and fitted to the Cox proportional hazards model (Table 7). The hazard ratios according to the use of antibiotics before the disease were found to be 1.556 and 1.369 for asthma and atopic dermatitis, respectively. This means that taking antibiotics before the onset of the illness increases the risk of disease. Men also had higher risk of developing asthma and atopic dermatitis (hazard ratio 1.139, 1.107), respiratory disease before the onset of the disease, and higher risk of asthma and atopic dermatitis (hazard ratio 1.518 1.205). For birth area, the hazard ratio was higher in metropolitan compared to small town, but the hazard ratio in Seoul, the capital city of Korea, is low. For the birth quarter, the hazard ratio of the 4th quarter (reference) is higher than the others. The hazard ratio of paracetamol before the onset of the asthma and atopic dermatitis was 0.541 and 0.681, respectively.

	Asthma				Atopic dermatitis			
	HR	95%CI		P-value	HR	95%CI		P-value
Antibiotics before each disease								
Yes	1.556	1.543	1.569	<.0.0001	1.369	1.360	1.378	<.0.0001
No (Reference)								
Sex								
Male	1.139	1.134	1.145	<.0.0001	1.107	1.103	1.112	<.0.0001
Female (Reference)								
Respiratory disease before each disease								
Yes	1.518	1.510	1.527	<.0.0001	1.210	1.205	1.215	<.0.0001
No (Reference)								
Birth area								
Seoul	0.954	0.942	0.967	<.0.0001	1.016	1.005	1.028	0.0052
Metropolitans	1.065	1.052	1.078	<.0.0001	1.073	1.062	1.085	<.0.0001
Medium sized cities	1.125	1.111	1.139	<.0.0001	1.109	1.097	1.121	<.0.0001
Small town (reference)								
Birth quarter								
1st	0.969	0.962	0.975	<.0.0001	0.870	0.865	0.875	<.0.0001
2nd	0.984	0.977	0.991	<.0.0001	0.910	0.905	0.915	<.0.0001
3rd	1.002	0.995	1.009	0.5666	0.960	0.954	0.965	<.0.0001
4th (Reference)								
Paracetamol before each disease								
Yes	0.541	0.538	0.544	<.0.0001	0.681	0.677	0.684	<.0.0001
No (reference)								

Table 7 Cox proportional hazard model of the risk factors of asthma and atopic dermatitis

Second, the effects of types of antibiotics were tested with the Cox proportional hazards model (Table 8). Effects of each antibiotic types were estimated with subjects who took the antibiotic before the onset of the disease. Hazard ratios of J01C (Beta-Lactam antibacterials, Penicillins), J01DB (First-generation Cephalosporins), J01DD (Third-generation Cephalosporins), J01F (Monobactams), and J01G (Aminoglycoside

antibacterials) are significantly greater than 1 for asthma and atopic dermatitis. Among them, hazard ratios of J01C were 1.682 and 1.408 in asthma and atopic dermatitis, respectively, and it has the highest hazard ratios among antibiotics. The hazard ratio estimates for other risk factors are almost identical to estimates of antibiotic use. However, in the cox proportional hazard model estimated by antibiotic type, the hazard ratio for respiratory disease was somewhat smaller than that estimated from antibiotic use.

	Asthma				Atopic dermatitis			
	HR	95%CI		P-value	HR	95%CI		P-value
J01C - Beta-Lactam antibacterials, Penicillins								
Yes	1.682	1.668	1.695	<.0001	1.408	1.399	1.417	<.0001
No (Reference)								
J01DB - First-generation Cephalosporins								
Yes	1.129	1.117	1.141	<.0001	1.103	1.093	1.114	<.0001
No (Reference)								
J01DD - Third-generation Cephalosporins								
Yes	1.435	1.428	1.443	<.0001	1.312	1.306	1.318	<.0001
No (Reference)								
J01F - Monobactams								
Yes	1.477	1.470	1.485	<.0001	1.295	1.289	1.301	<.0001
No (Reference)								
J01G - Aminoglycoside antibacterials								
Yes	1.176	1.165	1.188	<.0001	1.128	1.118	1.138	<.0001
No (Reference)								
Sex								
Male	1.110	1.105	1.115	<.0001	1.089	1.085	1.094	<.0001
Female (Reference)								
Respiratory disease before each disease								
Yes	1.250	1.243	1.257	<.0001	1.063	1.058	1.068	<.0001
No (Reference)								

Birth area								
Seoul	0.980	0.967	0.993	0.0022	1.032	1.021	1.044	<.0001
Metropolitans	1.037	1.024	1.050	<.0001	1.055	1.043	1.066	<.0001
Medium sized cities	1.089	1.076	1.103	<.0001	1.087	1.075	1.098	<.0001
Small town (reference)								
Birth quarter								
1st	0.989	0.982	0.996	0.0016	0.883	0.878	0.888	<.0001
2nd	0.978	0.971	0.984	<.0001	0.906	0.901	0.911	<.0001
3rd	0.995	0.988	1.002	0.1541	0.957	0.951	0.962	<.0001
4th (Reference)								
Paracetamol before each disease								
Yes	0.501	0.499	0.504	<.0001	0.638	0.635	0.642	<.0001
No (reference)								

Table 8 Cox proportional hazard model of the risk factors of asthma and atopic dermatitis by type of antibiotics

Ⅴ. Conclusion

In this thesis, I investigated the effects of antibiotics on the incidence of asthma and atopic dermatitis. Asthma and atopic dermatitis are similar to those caused by the allergic march, so it is necessary to study both diseases together rather than studying only one disease. Because the risk factors are complex in both diseases, it is difficult to estimate the exact effect of the risk factors. Among them, the use of antibiotics has been known to be a major risk factor for asthma and atopic dermatitis because it causes obstacles to intestinal microbiomes in the newborn infant or changes the composition of intestinal microbiomes in the long term. Therefore, this study examined the effect of antibiotics use in Korea on the incidence of asthma and atopic dermatitis in 2011-2013, and further examined the effect of type by antibiotics on the incidence of asthma and atopic dermatitis. To do this, this study made efforts to divide dependent variables, independent variables, covariates, confounders into the model by clarifying DAG using previous research. The Kaplan-Meier analysis, log-rank test and Cox proportional hazard model were used to estimate the effect.

The major difference from previous studies is the fact that the subjects are set as infants Prevalence and incidence of asthma and atopic dermatitis less than 1-year-old were presented and the effect of antibiotic use was estimated. Most of the previous studies on pediatric asthma have been conducted on subjects aged 5-18 years. Children aged 5 years or older were able to use the questionnaire method as in the ISAAC study, so pediatric asthma was mainly studied at 5-18 years of age. On the other hand, subjects who are less than 5 years cannot use the questionnaire method and pediatric asthma under 5years of age can be difficult to estimate because it appears in the form of temporary wheezing in children under 5 years of age. However, this study was able to study pediatric asthma in subjects less than 5 years of age because it gave operational

definition more than adequate period in order to reduce the bias that regards temporary wheezing as pediatric asthma.

In this study I also examined the effect of different types of antibiotics on the incidence of asthma and atopic dermatitis, as well as the presence or absence of comprehensive antibiotics. There are very few studies to classify antibiotics by type and to determine the relationship with asthma and atopic dermatitis. A representative study on the occurrence of asthma according to the use of antibiotics was conducted (Ortqvist, 2014). The study based on Swedish children, used about 500,000 people in 2006.

The results of this study showed that the use of antibiotics and their types have an influence on the incidence of asthma and atopic dermatitis. Similar to previous studies, the risk of asthma and atopic dermatitis is higher in males in the pediatric population, and in the respiratory disease, similar results were obtained as in previous studies. The prevalence and incidence rate of asthma and atopic dermatitis were higher in antibiotics group. In the analysis, this study used an analysis to correct major confounder of respiratory diseases or to control the other risk factors in DAG. Survival curves were estimated using the Kaplan-Meier curve. The first Kaplan-Meier curve was divided into three groups: pre-asthma antibiotics, antibiotic-free, and all subjects. Both asthma and antibiotics showed a rapid decrease in survival function in patients with antibiotics before disease. In the second Kaplan-Meier curve, the survival function of the four groups was estimated by dividing into the use of antibiotics as well as respiratory diseases. The results showed that the group with antibiotic and respiratory disease had a high risk of developing asthma and atopic dermatitis. However, the results of antibiotic-free and respiratory disease-free groups were slightly different from those anticipated.

In the Cox proportional hazard model, only the effects of antibiotics on asthma and atopic dermatitis were estimated by controlling the effects of the risk factors identified

in the DAG. The hazard ratios of antibiotic use in both asthma and atopic dermatitis ere estimated. Hazard ratios were also estimated for antibiotic use by type. Among them, the hazard ratio for the use of J01C, beta-lactam antibacterials and penicillins was estimated to be the highest. It should be noted that the p-value can be significant even though it is not actually significant because the number of subjects used in the model is large. In this case, the effect of asthma and atopic dermatitis on the occurrence of asthma and atopic dermatitis should be interpreted by considering the estimated effect size (hazard ratio) as well as hypothesis testing by p-value.

The claims data used in this study does not include prescriptions for drugs that can be purchased without prescription, such as non-paying medical care or over the counter (OTC). In addition, there may be an error because it is difficult to exclude the diagnosis, the individual difference in the procedure, and the customary factors. There is a study that there is an error in the accuracy of the claims data about 70% of the degree of agreement between the medical records. The family history information, which is an important covariate of the risk factors of the disease, is missing and the possibility of bias cannot be excluded in the estimation. As a limitation of the analysis, Survival analysis was carried out from the time of birth to the time of illness. The data of the received claim is not composed of data on the date of birth, but consists of quarterly data. Since the date of birth is set to a representative value with a median date of the quarter, there may be an error in the estimation of the survival function.

In this study I confirmed the association between the use of antibiotics and the incidence of asthma and atopic dermatitis. However, it is very difficult to consider all risk factors for asthma and atopic dermatitis with complex risk factors and results depend on the characteristics of the data. Nevertheless, the almost entire Korean subject born between 2011 and 2013 were used for the analyses and the frequency analysis of

this study and the estimation of the effect of antibiotic use may provide informative results even though results depend on the operational definition of appropriate asthma and atopic dermatitis. The results of this study suggest that the use of antibiotics in infancy be causal factors for asthma and atopic dermatitis incidence. Further studies are needed to confirm the effects of antibiotics use on asthma and atopic dermatitis in infants.

Ⅵ. Reference

김지애. (2014). 의료보건 연구를 위한 건강보험심사평가원 청구 데이터의 소개 및 활용. **폐쇄성폐질환 연구원, 2**(1) 3-9.

장혜민, & 이의경. (2011). 서방형제제 분할처방에 대한 건강보험심사제도의 효과와 장애요인. **한국임상약학회지, 21**(4), 347-352.

통계청 (2016). 2011-2013 한국의 사회 지표, http://kostat.go.kr/에서 검색

Ahn, K., Kim, J., Kwon, H. J., Chae, Y., Hahm, M. I., Lee, K. J., ... & Kim, W. K. (2011). The prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in Korean children: Nationwide cross-sectional survey using complex sampling design. *Journal of the Korean Medical Association/Taehan Uisa Hyophoe Chi, 54*(7).

Asher, M. I., Montefort, S., Björkstén, B., Lai, C. K., Strachan, D. P., Weiland, S. K., ... & ISAAC Phase Three Study Group. (2006). Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *The Lancet, 368*(9537), 733-743.

Beasley, R., Semprini, A., & Mitchell, E. A. (2015). Risk factors for asthma: is prevention possible?. *The Lancet, 386*(9998), 1075-1085.

Blaser, M. (2011). Antibiotic overuse: stop the killing of beneficial bacteria. *Nature, 476*(7361), 393-394.

Boyle, P., & Parkin, D. M. (1991). *Statistical methods for registries.Cancer registration: principles and methods, 95*, 126-158.

Cox, D. R. (1972). Regression models and life-tables. *JR Stat Soc, 34*(2), 187-220.

Dijkstra, A., Howard, T. D., Vonk, J. M., Ampleford, E. J., Lange, L. A., Bleecker, E. R., ... & Postma, D. S. (2006). Estrogen receptor 1 polymorphisms are associated with airway hyperresponsiveness and lung function decline, particularly in female subjects with asthma. *Journal of allergy and clinical immunology, 117*(3), 604-611.

Farquhar, H., Crane, J., Mitchell, E. A., Eyers, S., & Beasley, R. (2009). The acetaminophen and asthma hypothesis 10 years on: a case to answer. *Journal of Allergy and Clinical Immunology, 124*(4), 649.

Fleming, A. (1929). On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of B. influenzae. *British journal of experimental pathology, 10*(3), 226.

Goossens, H., Ferech, M., Coenen, S., Stephens, P., & European Surveillance of Antimicrobial Consumption Project Group. (2007). Comparison of outpatient systemic antibacterial use in 2004 in the United States and 27 European countries. *Clinical infectious*

diseases, 44(8), 1091-1095.

Greenland, S., Pearl, J., & Robins, J. M. (1999). Causal diagrams for epidemiologic research. *Epidemiology*, 37-48.

Guerra, S., & Martinez, F. D. (2008). Asthma genetics: from linear to multifactorial approaches. *Annu. Rev. Med., 59*, 327-341.

Hollams, E. M., Hart, P. H., Holt, B. J., Serralha, M., Parsons, F., De Klerk, N. H., ... & Holt, P. G. (2011). Vitamin D and atopy and asthma phenotypes in children: a longitudinal cohort study. *European Respiratory Journal, 38*(6), 1320-1327.

Kaplan, E. L., & Meier, P. (1958). Nonparametric estimation from incomplete observations. *Journal of the American statistical association, 53*(282), 457-481.

Kim, D. S., Jang, S. M., & Kim, N. S. (2010). Epidemiologic investigation on antibiotic use using defined daily dose. *J Korean Acad Manag Care Pharm, 2*, 47-59.

Martinez, F. D., Wright, A. L., Taussig, L. M., Holberg, C. J., Halonen, M., & Morgan, W. J. (1995). Asthma and wheezing in the first six years of life. *New England Journal of Medicine, 332*(3), 133-138.

Mahajan, R. (2015). Real world data: Additional source for making clinical decisions. *International Journal of Applied and Basic Medical Research, 5*(2), 82.

Melgert, B. N., Ray, A., Hylkema, M. N., Timens, W., & Postma, D. S. (2007). Are there reasons why adult asthma is more common in females?. *Current allergy and asthma reports, 7*(2), 143-150.

Mulder, B., Pouwels, K. B., Schuiling-Veninga, C. C. M., Bos, H. J., De Vries, T. W., Jick, S. S., & Hak, E. (2016). Antibiotic use during pregnancy and asthma in preschool children: the influence of confounding. *Clinical & Experimental Allergy*.

National Heart, Lung, and Blood Institute. (2007). Expert panel report 3: guidelines for the diagnosis and management of asthma: full report. *US Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute.*

Noverr, M. C., & Huffnagle, G. B. (2005). The 'microflora hypothesis' of allergic diseases. *Clinical & Experimental Allergy, 35*(12), 1511-1520.

Örtqvist, A. K., Lundholm, C., Kieler, H., Ludvigsson, J. F., Fall, T., Ye, W., & Almqvist, C. (2014). Antibiotics in fetal and early life and subsequent childhood asthma: nationwide population based study with sibling analysis. *Bmj, 349*, g6979.

Raszka, W. V., & Khan, O. (2005). Pyelonephritis. *Pediatrics in Review, 26*(10), 358.

Robins, J. (1987). A graphical approach to the identification and estimation of causal parameters in mortality studies with sustained exposure periods. *Journal of chronic diseases, 40*, 139S-161S.

Robinson, C. L., Baumann, L. M., Romero, K., Combe, J. M., Gomez, A., Gilman, R. H., ... & Barnes, K. C. (2011). Effect of urbanisation on asthma, allergy and airways inflammation in a developing country setting. *Thorax, 66*(12), 1051-1057.

Sekirov, I., Russell, S. L., Antunes, L. C. M., & Finlay, B. B. (2010). Gut microbiota in health and disease. *Physiological reviews, 90*(3), 859-904.

Shin, J. E., Cheon, B. R., & Shim, J. W. (2012). A Comparative Study to Analyze the Proportion of Highrisk Neonates from Mothers Residing in Metropolitan Cities and Small-to-Medium-Sized Cities in Korea. *Journal of the Korean Society of Neonatology, 19*(3), 140-145.

Song, Y. G. (2012). The History of Antimicrobial Drug Development and the Current Situation. *Infection & Chemotherapy, 44*(4).

Strachan, D. P. (1989). Hay fever, hygiene, and household size. *BMJ: British Medical Journal, 299*(6710), 1259.

National Institute of Arthritis and Musculoskeletal and Skin Diseases. (2013). *Handout on Health: Atopic Dermatitis,* 13-4272

Network, G. A. (2014). *The global asthma report 2014.* Auckland, New Zealand.

Van Boeckel, T. P., Gandra, S., Ashok, A., Caudron, Q., Grenfell, B. T., Levin, S. A., & Laxminarayan, R. (2014). Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *The Lancet infectious diseases, 14*(8), 742-750.

VanderWeele, T. J., & Shpitser, I. (2011). A new criterion for confounder selection. *Biometrics, 67*(4), 1406-1413.

Wahn, U. (2000). What drives the allergic march?. *Allergy, 55*(7), 591-599.

WHO Collaborating Centre for Drug Statistics Methodology. (2016). *Guidelines for ATC classification and DDD assignment.*

Yeo, J. E. (2001). *Comparison of the logistic regression model and the Cox proportional hazards regression model* (Doctoral dissertation, Master's thesis, Yonsei University).

국문 초록

영아기 항생제 사용이 천식 및 아토피 피부염 발생에 미치는 영향

- 한국의 2011-13 년도 출생아를 대상으로 -

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연구 배경: 천식과 아토피 피부염은 신생아 시기에 알레르기 행진(allergic march)에 의해 두 질환이 함께 발병하거나 어느정도의 선후 관계를 가지며 함께 발생한다고 알려져 있다. 이러한 관계 때문에 두 질환에 대해 분석을 같이 실시하여 두 질환의 행태와 위험요인을 연구해야 한다. 천식과 아토피 피부염은 다양하고 복합적인 위험요인을 가진다고 알려져 있다. 인구학적 요인, 감염성 질병 관련 요인, 약제 사용에 따른 요인, 식이 관련요인, 대기 환경 요인 등의 여러 요인들이 혼재되어 복합적으로 작용한다고 알려져 있다. 여러 위험 요인 중 항생제의 복용은 방선균의 감소, 박테리아의 증가, 효소의 감소 등과 같은 장내 미생물에 대한 장기적인 변화를 야기한다고 알려져 있다. 또한 성숙하지 않은 미소 생물상 증가를 야기하기 때문에 유아기 면역 체계의 적절한 성장을 방해하고 면역 내성의 발달을 저해함으로써 천식이나 아토피 피부염과 같은 알러지에 대한 과민성 발생을 증가시킨다고 알려져 있다. 그럼에도 불구하고, 5 세 미만의 천식 및 아토피 피부염의 진단 방법의 어려움으로 인해 질병 현황 및 항생제를 포함한 위험 요인에 대한 연구가 활발히 이루어 지지 않았다.

연구 목적: 우리나라의 2011 년도부터 2013 년도의 출생아를 대상으로 천식 및 아토피 피부염 발생 현황을 파악하고 영아기 항생제의 복용에 따른 천식과 아토피 피부염의 발생 위험에 미치는 영향을 탐색하고자 한다. 또한, 항생제 종류 별

복용에 따른 천식과 아토피 피부염의 발생 위험에 미치는 영향도 분석하고자 한다.

연구 방법: 본 연구는 한국의 1 세 미만 영아의 항생제 복용에 따른 천식 및 아토피 피부염 발생의 위험을 파악하여 두 요인의 연관성을 밝히고자 2011 년도와 2012 년도, 2013 년도에 출생한 신생아의 건강보험심사평가원 청구데이터를 활용하였다. 건강 보험 심사 평가원 청구 자료의 분석 과제 번호는 M2016082442 로 원격 접속 시스템 신청 과정을 거쳐 자료 접속 권한을 부여 받았다. 명세서, 진료내역, 처방전 관련 자료를 환자 식별 번호와 key 번호를 기준으로 통합하여 본 연구에 활용 될 자료를 구성하였다. 문헌 조사를 통해 방향성 비 순환 그래프를 제시하였고, 이를 활용하여 이후 분석에서 교란 요인의 설정 및 설명 변수의 선택을 실시 하였다. 자료의 특성을 알아보기 위해 빈도분석을 실시하였고, 천식과 아토피 피부염의 현황을 알아보기 위해 유병률과 발생률을 추정하였다. 발생률의 추정은 인-월을 기준으로 추정하였다. 카플란-마이어의 생존 곡선을 통해 질환 발생 이전 항생제 사용 군, 질환 발생 이전 항생제 사용과 호흡기 질환 유무로 나눈 군, 신우신념 발생과 항생제 사용 대상자에서의 호흡기 질환 유무로 나눈 군에 대해 위험 함수를 추정하였다. 마지막으로, 항생제의 사용이 천식 및 아토피 피부염 발생에 대한 위험비를 추정하기 위하여 콕스 비례 위험 모형을 활용하였다. 교란변수및 설명변수는 위에서 언급한 DAG 를 통하여 정할 수 있었다. 또한 WHO 에서 제시한 항생제 종류로 종류 별 천식 및 아토피 피부염 발생에 대한 위험비를 추정 하였다.

연구 결과: 천식의 경우 2011-2013 년의 생후 1 년 미만의 대상자에게서 약 60%의 유병률과 0.0238 의 발생률(인-월)이 확인되었고, 아토피 피부염의 경우는 약 80%의 유병률과 0.0845 의 발생률(인-월)이 확인되었다. 두 질병 모두 질환 발생 이전에 항생제를 사용한 군에서 유병률과 발생률이 높음을 확인 할 수 있었다. DAG 에서 항생제의 복용과 천식 및 아토피 피부염의 주된 교란요인이 호흡기 질환이므로 항생제의 복용과 호흡기 질환 유무를 기준으로 군을 나누어 카플란 마이어 생존 곡선을 추정하였다. 천식과 아토피 피부염 모두 항생제 사용과 호흡기 질환 군에서 질환 발생 위험이 가장 높았다. 로그-순위 검정 또한 유의확률이 0.0001 보다 작으므로 군간 생존 함수의 차이가 있다고 볼 수 있었다. 마지막으로, 콕스 비례 위험 모형에서 천식 발생 이전 항생제 사용은 천식 발생에 대해 위험비가 1.556 (신뢰구간 : 1.543 – 1.569)로 추정되었고, 아토피 피부염 발생 이전 항생제 사용은 아토피 피부염 발생에 대해 위험비가 1.369 (신뢰구간 : 1.360 – 1.378)로 추정 되었다. 호흡기 질환의 천식 발생에 대한 위험비는 1.518 (신뢰구간 : 1.510 – 1.527), 아토피 피부염 발생에 대한 위험비는 1.210 (신뢰구간 :1.205 – 1.215)로 추정되었다. 항생제 종류별 사용에 대해서 콕스 비례 위험 모형에 적합 시킨 결과 중, J01C 에 해당하는 베타락탐-페니실린 계가 천식과

아토피 피부염 모두의 위험비에서 각각 1.682 (신뢰구간 : 1.668 – 1.695), 1.408 (신뢰구간 : 1.399 – 1.417)으로 가장 높은 것을 확인 할 수 있었다.

결론: 본 연구에서는 천식과 아토피 피부염의 발생 이전의 항생제의 사용이 천식과 아토피 피부염의 발생에 영향을 미치는 요인임을 확인 할 수 있었다. 특히 항생제의 종류 중 베타-락탐, 페니실린계의 질환 발생 위험 영향이 가장 큰 것을 확인 할 수 있었다. 따라서 신생아의 항생제 사용에 있어서 천식 및 아토피 피부염의 발생 위험을 고려한 처방 및 사용이 필요하다.

주요어: 천식, 아토피 피부염, 항생제, 콕스 비례 위험 회귀 모형, 카플란 마이어 생존 곡선

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