The Association between Humidifier disinfectant exposure and allergic diseases in Children

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The Association between Humidifier disinfectant exposure and allergic diseases in Children

The Doctoral Dissertation
Submitted to the Department of Medicine
and the Graduate School of Yonsei University
in Partial Fulfillment of the requirements for the degree of
Doctor of Philosophy in Medicine

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December 2024

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December 2024

Acknowledgements

First and foremost, I give all glory to God the Father, who has guided me to the completion of this degree program.

I would like to express my deepest gratitude to Professor Yeon-Soon Ahn for her guidance throughout the process, from selecting the topic of this dissertation to setting its direction and finally completing it. As a clinical physician working on my first research project, I faced many challenges, but with her mentorship, I was able to achieve this meaningful outcome. Reflecting on this journey, I am filled with gratitude for every step of the way. I am also sincerely thankful to Professors Sang Baek Koh, Kyoung Sook Jeong, Jeongmin Lee, and Sung-Kyung Kim for their invaluable advice and support in finalizing this dissertation.

Though the two years I spent in the Department of Preventive Medicine were short, I am deeply grateful to Professors Sei Jin Chang, Chun Bae Kim, and Hyun Joo Lee for their guidance and teaching. I also extend my heartfelt appreciation to Professors Young Myong Yoo, Tae Woo Shin, Eun Jung Lee, and the dedicated nurses of the neonatal intensive care unit for allowing me to gain valuable experience. Furthermore, I am profoundly grateful to Professors Hwang Min Kim, Mi Kyung Namgung, Byung-Ho Cha, Yong Hyuk Kim, Yun Koo Kang, and Jae Hee Seol, who greatly contributed to my growth as a pediatrician.

Lastly, I cannot express enough gratitude to my wife, Nam-Yun Kim, who steadfastly supported me throughout this journey, and to our precious blessing, Jae-Eun Choi, who was born during this time.

With deepest thanks,
Hyowon Choi

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ABSTRACT

The Association between Humidifier disinfectant exposure and allergic diseases in Children

Will Humidifier Disinfectant related allergic diseases
follow the path of atopy march?

Introduction: Humidifier disinfectants (HDs) have been associated with respiratory diseases such as interstitial lung disease and asthma (AS). However, limited research exists on the impact of HD exposure on overall allergic diseases. This study investigates the association between HD exposure and the incidence and aggravation of allergic diseases, as well as potential alterations in the typical progression of allergic comorbidities, so called "allergic march."

Material and Methods: I established a cohort of 1,655 children born between 2002 and 2012 who were registered as HD damage claimants. Allergic diseases were identified using matched National Health Insurance Service claim data, with follow-up until 119 months of age. To better capture changes in disease incidence and aggravation over time, exposure status was classified into three groups: 'pre-exposure', 'during exposure', and 'post-exposure'. A time-dependent Cox model assessed the incidence of allergic disease, and multilevel interrupted time series analysis assessed aggravation, as my longitudinal data included repeated measurements over time, allowing me to effectively capture changes in exposure status and their impacts. All analyses examined interactions with atopic dermatitis(AD) to assess whether impact on allergic march. Subgroup analyses of PHMG/PGH and CMIT/MIT exposure were performed to explore differences in

mechanisms.

Results: The cumulative incidence of AS, allergic rhinitis (AR), and AD was 67.9%, 71.1%, and 27.2%, respectively. In time-dependent Cox PH, during exposure significantly increased the incidence of AS (adjusted hazard ratio [aHR] 2.126, 95% confidence interval [CI] 1.681–2.688) and AR (aHR 1.671, 95% CI 1.250–2.234) compared to pre-exposure. In post-exposure, the incidence of AS and AR remained elevated (aHR 1.794, 95% CI 1.359–2.368, and aHR 1.559, 95% CI 1.135–2.141, respectively), while AD demonstrated no significant association. In multilevel ITS, during exposure, the level of the monthly number of office visits for AS and AR increased (adjusted utilization rate ratio [aURR] 1.218, 95% CI 1.051–1.410; aURR 1.143, 95%CI 1.031-1.279). In post-exposure, the level of the monthly number of office visits for AS and AR increased (aURR 1.171, 95% CI 1.011–1.356; aURR 1.148, 95% CI 1.031–1.279) then the slope of the monthly number of office visits for AS and AR decreased (aURR 0.849, 95% CI 0.754–0.956; aURR 0.815, 95% CI 0.755–0.880). HD exposure also independently increased both the incidence and monthly office visits for AS and AR, no significant interaction with AD. The results of the subgroup analysis were consistent with these findings, with no suggestion mechanistic differences between the two subgroups.

Conclusion: HD exposure was associated with a significant increase in both the incidence and aggravation of AS and AR, independent of the allergic march, with no differences observed among HD types. Further studies are needed to better understand the mechanisms underlying allergic diseases related to HD exposure, including the role of different HD types. Additionally, further research on exposed populations is necessary to address selection bias and overcome limitations due to the small sample size.

Keywords: Humidifier disinfectants; Allergic diseases; Time-dependent Cox proportional hazard model; Multilevel Interrupted Time Series

1. Introduction

1.1. Definition of Allergic diseases and Allergic comorbidities

Allergic diseases represent systemic IgE-mediated immune responses triggered by specific allergens and include conditions such as asthma (AS), allergic rhinitis (AR), atopic dermatitis (AD), and food allergy (FA) [1,2]. Upon exposure to allergens, T lymphocytes differentiate into Th2 cells, which in turn stimulate B lymphocytes to produce IgE. The produced IgE activates mast cells, basophils, and eosinophils through the release of cytokines like IL-4, IL-5, and IL-13. Consequently, patients with allergic diseases often exhibit elevated levels of eosinophils and IgE[3,4]. In this context, Th17 cells interacts with Th2 pathways, modulating the severity of allergic reactions[5].

The shared immunological mechanisms link various allergic diseases and are often reflected in the predictable progression known as the "allergic march," where AD frequently presents first, followed by other allergic diseases[6]. For instance, a meta-analysis by Ravnborg et al. demonstrated a significant association between AD and AS, with an odds ratio (OR) of 3.03 (95% CI, 2.64–3.47) when compared to non-AD[7].

However, it is important to note that not all individuals follow this classic allergic march. Some may experience allergic diseases at different stages of life, or in varying combinations, reflecting the variability in immune responses. This variability gives rise to the concept of “allergic comorbidities", where multiple allergic diseases coexist simultaneously rather than sequentially[8]. The co-occurrence of AD, AS, and AR, for example, may reflect an underlying systemic immune dysregulation, which could be influenced or aggravated by air pollutants, such as fine particulate, harmful gases, and greenhouse gases [9,10]. Humidifier disinfectants (HD), known as indoor toxicants, are

thought to potentially influence or aggravate allergic diseases, similar to the way chemical exposures act in this context

1.2. Chemical-induced allergic diseases

Various chemicals are known to induce allergic diseases, often affecting respiratory tract and skin sensitization[11]. Chemical-induced AS can be classified into two major categories: sensitizer-induced asthma (SIA) and irritant-induced asthma (IIA), each driven by different mechanisms[12]. SIA is further divided into high molecular weight (HMW)-induced SIA and low molecular weight (LMW)-induced SIA, depending on the sensitizing agent[12]. HMW agents, such as proteins, typically trigger Th2 immune responses, leading to IgE production and eosinophilic inflammation. [13] LMW agents, on the other hand, act as haptens, binding to host proteins and forming new allergenic complexes that initiate IgE sensitization[12]. SIA is often associated with AD, suggesting shared immunological pathways[12].

IIA, by contrast, is triggered by non-specific irritants that damage the airway epithelium, leading to bronchial hyperresponsiveness and inflammation. IIA is not driven by IgE production but by irritant-mediated pathways, which result in increased lung permeability, airway remodeling, and epithelial damage[14]. Unlike SIA, IIA is not typically linked to AD[15-17]. Chemical-induced AR follows a similar sensitizer or irritant mechanism[18]. One well-known chemical-induced skin condition is allergic contact dermatitis, which occurs when LMW agents bind to carrier proteins, leading to immune activation[19]. Both sensitizer and irritant mechanisms contribute to the aggravation of preexisting allergic conditions, making it challenging to distinguish between disease onset and symptom aggravation caused by chemical exposure[14,18,20,21]. In cases where allergic diseases are triggered by a sensitizer, even after exposure is discontinued, cross-reactivity may occur, leading to continuous healthcare utilization. However, in cases of irritant-induced allergic diseases, healthcare utilization tends to decrease once exposure is discontinued

.

1.3. Humidifier disinfectant and Allergic diseases

HDs have been strongly associated with severe respiratory diseases, such as HD-associated lung injury and interstitial lung disease (ILD) [22,23]. The major components of HDs include polyhexamethylene guanidine - oligo-(2-(2-ethoxy)-ethoxyethyl) guanidine chloride(PHMG/PGH), and chloromethylisothiazolinone/methylisothiazolinone (CMIT/MIT) [24].

The mixture of CMIT/MIT has been identified as a potent sensitizer, known to cause allergic contact dermatitis[25-27]. A study by Go et al. [28], suggested that CMIT/MIT epicutaneous exposure in mice models modulates Th2/Th17 immune responses, although its direct relationship with AD induction remains unclear. PHMG/PGH have been shown to increase Th17-mediated airway inflammation and induce airway hyperresponsiveness in mouse models via intranasal instillation, following a pathway similar to IIA[29,30]. In human based study, the HD-exposed AS group exhibited differences in decreased inducible T-cell costimulatory ligand, and decreased hepatocyte growth factor activator, compared to the non-HD-exposed AS group[31].

Based on mechanistic insights, PHMG/PGH likely affect allergic diseases through the irritant-induced pathway, while CMIT/MIT may act via the sensitizer-induced pathway. I anticipate that PHMG/PGH exposure is unlikely to be associated with the development of AD, and no significant interactions between AD and other allergic conditions are expected. Following the cessation of PHMG/PGH exposure, a reduction in the frequency of healthcare utilization is likely. In contrast, exposure to CMIT/MIT is associated with the onset of AD and an increase in healthcare utilization, along with significant interactions with other allergic conditions. Given that CMIT/MIT continue to be used in products such as cosmetics and hand sanitizers[32], it is likely that healthcare utilization will not decrease

even after the end of HD exposure. However, it is important to note that the CMIT/MIT study involved application on mice[28], which differs from the inhalation exposure method characteristic of HD exposure. Therefore, the mechanism of action may differ.

1.4. Previous studies about Humidifier disinfectant and Pediatric Allergic diseases

HDs were widely used in Korea, particularly among children and pregnant women. According to the Panel Study on Korean Children(PSKC), which investigated HD usage, among 1,577 randomly selected subjects born in 2008, 75.6% reported using a humidifier, and 31.1% reported using HDs[33]. Childhood asthma has been strongly linked to HD exposure[31,34,35]. However, there are few epidemiological studies on the relationship between HD and AR [35-37]. These studies [31,34-37] were based on populations from the PSKC[38] and the Cohort for Childhood Origin of Asthma and Allergic Diseases (COCOA) [39]. PSKC was investigated exposure to HDs through telephone surveys conducted, when the subjects were 7 to 8 years old. In the COCOA cohort, which recruited participants born since 2007, one study compared asthma prevalence in children born before and after 2011, the year HDs were withdrawn from the market [34]. This study lacked long-term follow-up and did not fully account for confounders such as comorbidities. Furthermore, there is no research exploring whether HD exposure aggravation preexisting allergic diseases in children.

To dates, there is only one study on the association between HD and AD, as well as the aggravation of allergic diseases. Kim et al. [40], using nationwide data from the National Health Insurance Service (NHIS) claims, reported that, in nationwide population, the relative risk for AS episodes tended to stabilize or decrease after the withdrawal of HD in 2013. In the cohort of individuals claiming health damage from HD, the ORs for AS were higher in the after-exposure start compared to pre-exposure, with no significant

association for AD. This analysis included only those who were eligible for follow-up at 1, 3, and 5 years before and after exposure, excluding individuals born during these periods. Since AD commonly occurs within the first year of life[1], it is likely that many cases were not captured in the analysis, particularly among younger children. In this analysis, only one AD case was included, making it difficult to conclude about childhood allergic disease (Table 1)

Previous studies focusing on pediatric populations have primarily demonstrated increases in the hazard ratios(HRs) and ORs for AS and AR, without thoroughly examining potential mechanisms[34-36]. Only Yoon et al[34]. reported that the development of AS following HD exposure likely follows an allergen-sensitization pathway. However, this contrasts with toxicology study findings suggested that HD exposure may follow either irritant or sensitizer pathway depending on HD type. Therefore, further epidemiological studies focusing on childhood populations are needed.

Table 1. Previous studies about Humidifier disinfectants and Childhood Allergic diseases

Author	Study populations	Results	Comments
Yon et al[35]	PSKC (HD exposed vs. Non-exposed)	AS: aHR, 1.35, 95%CI 1.01~1.80; AR: aHR, 1.22, 95%CI 1.03~1.44	- The exposure assessment and the diagnosis of allergic diseases were conducted through a telephone, and self-reported survey. -No classified the type of HD
	Seongnam atopic Project 2017 (HD exposed[≥ 3mo] vs. Non-exposed)	AS: aOR, 3.04, 95%CI 1.65~5.62; AR: aOR, 2.07, 95%CI 1.24~3.47	-The exposure assessment and the diagnosis of allergic diseases were conducted through a self-reported survey. -No classified the type of HD
Yoon et al[34]	PSKC (Bronchiolitis history * HD expose history)	HD(-)Br(-): aOR 1(REF); HD(+)Br(-): aOR 0.79, 95%CI 0.41~1.51; HD(-)Br(+): aOR 3.26, 95%CI 1.93~5.52; HD(+)Br(+): aOR 4.28, 95%CI 2.38~7.72	-The exposure assessment and the diagnosis of allergic diseases were conducted through a telephone, and self-reported survey. -No classified the type of HD
	COCOA (Annual trend)	Annually decreased in AS diagnosis, Trend P = 0.011	-Rather than analyzing the subjects' individual exposure relationships, an ecological approach was taken to examine the annual trends. -No classified the type of HD
Koh et al[36]	PSKC (HD exposed vs. Non-exposed)	AR: aOR 1.33, 95%CI 1.02~1.75 PHMG/PGH: aOR 1.41, 95%CI 1.02~1.95 CMIT/MIT: aOR 2.08, 95%CI 1.17~3.69(≥ 3mo)	-The exposure assessment and the diagnosis of allergic diseases were conducted through a telephone, and self-reported survey. - no significant in CMIT/MIT at exposed or not
Cho JH[37]	PSKC (HD exposed[≥12mo] vs Non-exposed)	AR: aOR 1.44, 95%CI 1.42~1.46	-The exposure assessment and the diagnosis of allergic diseases were conducted

			through a telephone, and self-reported survey. -No classified the type of HD
Kim et al[40]	Nationwide populations (Annually comparison)	aRR for AS episode of care stabilize or decrease in 2013	-Rather than analyzing the subjects' individual exposure relationships, an ecological approach was taken to examine the annual trends.
	Claimants of HD (Same intervals before exposed vs. After exposed)	AS: increased OR at 1, 3 and 5year PHMG/PGH: increased OR 1, 3, and 5year CMIT/MIT : increased OR 3, and 5year interval AD: no statistically significant	-The exposed and control groups were evaluated over the same intervals before and after exposure, but the analysis did not adequately address the subjects born during this interval. -Only one subject enrolled for AD patient

PSKC, Panel Study on Korean Children; COCOA, Cohort for Childhood Origin of Asthma and Allergic Diseases; HD, Humidifier disinfectants; AS, Asthma; AR, Allergic rhinitis; AD, Atopic dermatitis; Br, Bronchiolitis; aOR, adjusted odd ratios; aHR, adjusted Hazard ratio; PHMG/PGH, polyhexamethylene guanidine/oligo-(2-(2-ethoxy)-ethoxyethyl) guanidine chloride; CMIT/MIT, chloromethylisothiazolinone /methylisothiazolinone

1.5. Objectives of the study

Based on the current literature and the identified gaps, this study aims to investigate the association between HD exposure and allergic diseases during childhood. To achieve this, a birth cohort was established, allowing for the analysis of the incidence and aggravation of allergic diseases in relation to HD exposure, with comparisons made to previous studies.

Additionally, to examine the impact of HD exposure on the comorbidities of allergic diseases, I included AD as a covariate for my analysis, given that it is one of the earliest allergic conditions to manifest in children. By including an interaction term between HD exposure and AD, this study seeks to determine whether HD exposure influences the typical history of allergic comorbidities.

Finally, to explore the differential effects of specific HD components, I conducted subgroup analyses, dividing in PHMG/PGH group, and CMIT/MIT group. I aim to identify potential variations in allergic disease outcomes based on the toxicological profiles of these compounds, with a focus on epidemiological evidence

2. Materials and methods

2.1. Data source and Study populations

From 2011 to 2020, a total of 7,056 claimants registered with the Korean Environmental Industry and Technology Institute (KEITI) for relief related to damages caused by HD. These data have been systematically documented and stored within KEITI's comprehensive portal for HD damage support[41]. Utilizing this database, I selected a cohort of 1,835 subjects born between 2002 and 2012, which is one year after the cessation of HD sales. This cohort is designated as the Cohort for Survey of Pediatric Affected by HD (CoSPAHD). By linking the CoSPAHD with NHIS claims data, I were able to track the medical utilization of these subjects from 2002 to 2021, following them until they reached 119 months of age.

Due to the exclusion criteria, deceased subjects (N=178), and those born more than one year after the end of exposure (N=2) were excluded. Consequently, a total of 1,655 subjects were included in the analysis. (Figure 1).

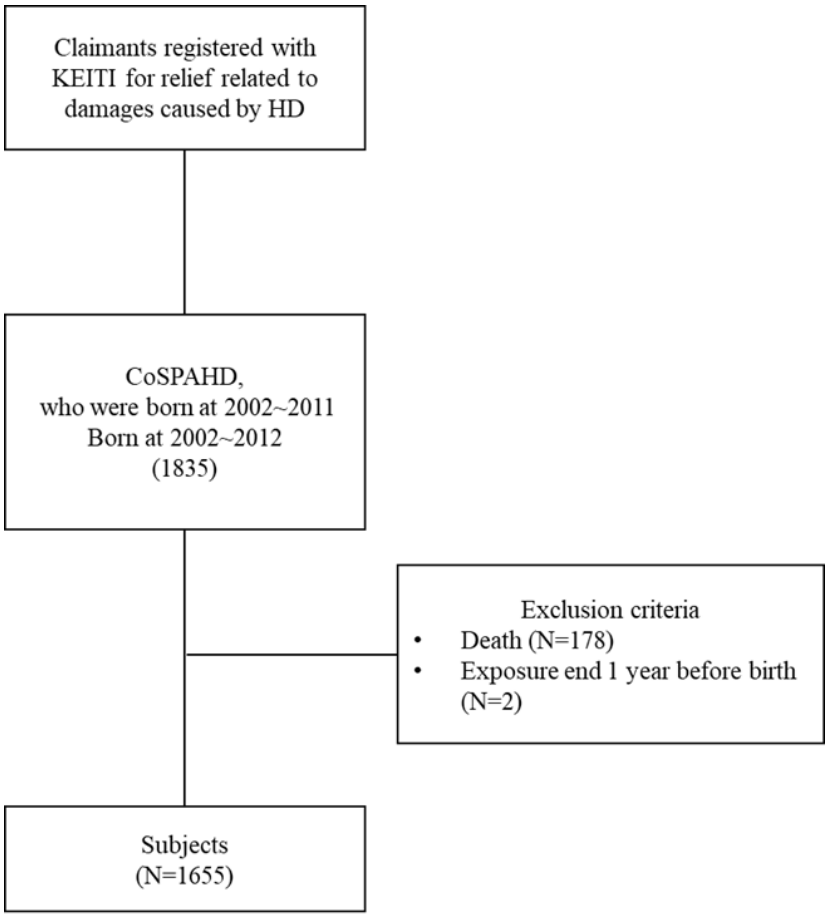


Figure 1. Study flowcharts

KEITI, Korean Environmental Industry and Technology Institute; CoSPAHD, Cohort for Survey of Pediatric Affected by Humidifier Disinfectants

2.2. Allergic diseases

The allergic diseases considered in this study include AS, AD, and AR. Each disease was defined according to the International Classification of Diseases-10 (ICD-10): AS was identified by codes J45.X (Asthma) and J46.X (Status asthmaticus); AD by L20.X (Atopic dermatitis); and AR by J30.1 (Allergic rhinitis due to pollen), J30.2 (Other seasonal allergic rhinitis), J30.3 (Other allergic rhinitis), and J30.4 (Allergic rhinitis, unspecified).

To identify the incidence of these diseases, diagnoses were confirmed when a subject was either hospitalized with one of the aforementioned codes as the primary diagnosis or visited an outpatient clinic with the same code at least twice within one year, based on the GINA guideline[42]. The date of diagnosis was defined as the first date that the condition was noted in the subject's medical records.

To assess disease aggravation, I considered any claims, among each incident cases, in which the primary or one of the first four additional diagnoses corresponded to the relevant disease codes. For AS, I calculated the number of monthly office visits and the number of hospital days per month due to admission. For AR and AD, I tracked the number of monthly office visits.

2.3. Humidifier disinfectant exposure history

For variables related to HD exposure, I used environmental exposure survey data from KEITI's comprehensive portal for HD damage support. The data was collected through self-administered questionnaire followed by 1:1 interview with victims who reported damage[41]. To verify exposure, HD receipts and photos of HD purchases provided by the subjects were cross-checked.

To better capture changes in disease incidence and aggravation over time, I classified each individual's exposure status over time into 'pre-exposure,' 'during exposure,' and 'post-exposure' periods, based on their birth date, exposure start date, and exposure end date. To estimate the cumulative exposure duration, the start and end ages (in months) of exposure were calculated based on the subject's date of birth. If exposure occurred before birth, the exposure start age was recorded as a negative value.

2.4. Covariates

Sociodemographic factors, including sex, birth year, status of HD exposure at birth, and residential area, were included as covariates. status of HD exposure at birth was categorized into three groups: pre-exposure, during exposure, and post-exposure. Residential area was categorized in two groups: ‘rural area’, and ‘urban area’. Rural areas were defined according to the Korean residential zoning classification, where regions classified as 'eup,' 'myeon,' or 'ri' were considered rural.

Perinatal comorbidities and congenital anomalies, known to influence allergic diseases[43], were defined according to the ICD-10 (Table 2). Additionally, ILD, which has been associated with HD, was defined by the presence of ICD-10 code J84 (Interstitial lung disease) as the primary diagnosis.

Table 2. Comorbidities for analysis

Definition of covariates	ICD-10 codes
Perinatal comorbidities	Disorders of newborn related to length of the gestation and fetal growth(P05-08); Birth trauma(P10-15); Respiratory and cardiovascular disorders specific to the perinatal period(P20-29); Infection specific to the perinatal period(P35-39); hemorrhagic and hematologic disorders of fetus and newborn(P50-61); Digestive system disorders of fetus and newborn(P75-78)
Congenital anomaly	Congenital malformations, deformations and chromosomal abnormalities(Q00-99)
Interstitial lung disease	Interstitial lung disease(J84.x)

ICD-10, International Classification of Diseases-10

2.5. Statistical analysis

2.5.1. Main analysis

First, descriptive statistics (mean ± standard deviation, proportion) were calculated for all subject characteristics. Stratified by exposure status, I calculated the incidence of allergic diseases and the counts of healthcare utilization. Incidence cases were defined as newly diagnosed allergic disease cases among subjects followed until the end of the observation. Incidence rates were calculated using stratified person-months, excluding subjects diagnosed in one period (pre-, during-, or post-exposure) from incidence and person-month calculations for subsequent periods to reflect only new cases in each timeframe (Figure2). Then stratified incidence rates were calculated by dividing the number of incident cases by person-months at risk, using Poisson regression models. A simple comparison of incidence rates and counts was conducted across different exposure states.

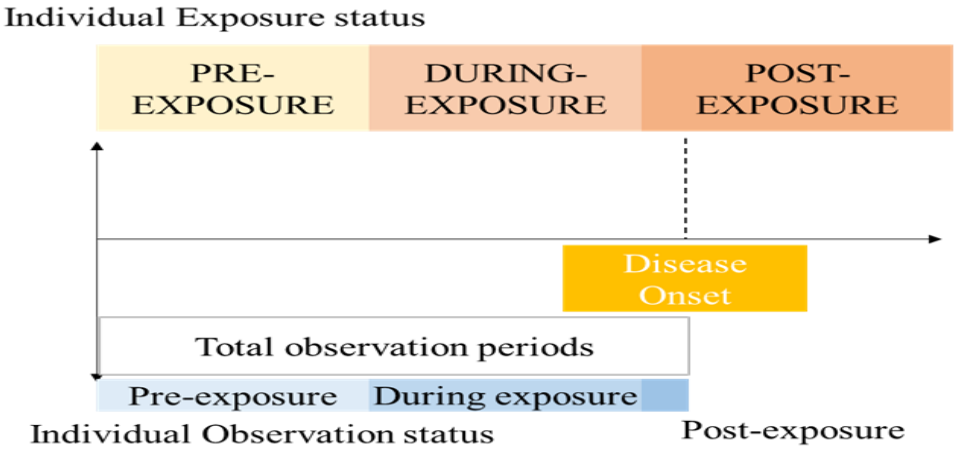


Figure 2 Examples of calculations of the Stratified person-month

The CoSPAHD consists of subjects who claimed respiratory diseases related to HD, making it a highly selected database. Therefore, comparing this cohort with a non-exposure group would likely introduce selection bias. Instead, my study analyzed changes within subjects over time, using repeated measurements to effectively capture changes in exposure status and their impacts. The time-dependent Cox proportional hazards (PH) model was used to analyze the effect of variables that change over time, making it suitable for use in a single exposed cohort[44] Additionally, the interrupted time series (ITS) method, a quasi-experimental approach, was used to evaluate both the short-term and long-term effects of exposure within a single cohort[45].

To examine the association between HD exposure and the incidence of allergic diseases, I applied time-dependent Cox PH models. To assess the association between HD exposure and the aggravation of allergic diseases, I employed multilevel ITS analysis. Given the varying start and end times of HD exposure in the dataset, I incorporated random effects at the individual level using multilevel regression models[45,46]. Additionally, the time variable was standardized to improve interpretation and model convergence. ITS modeling framework is illustrated in Figure 2. Poisson regression models were used, as healthcare utilization was a count variable. For the multilevel ITS models, I calculated the intraclass correlation coefficient for each model and compared them to the null model to evaluate the reduction in variation. This allowed me to quantify the proportion of total variance explained by the multilevel models and assess the improvement in model fit.

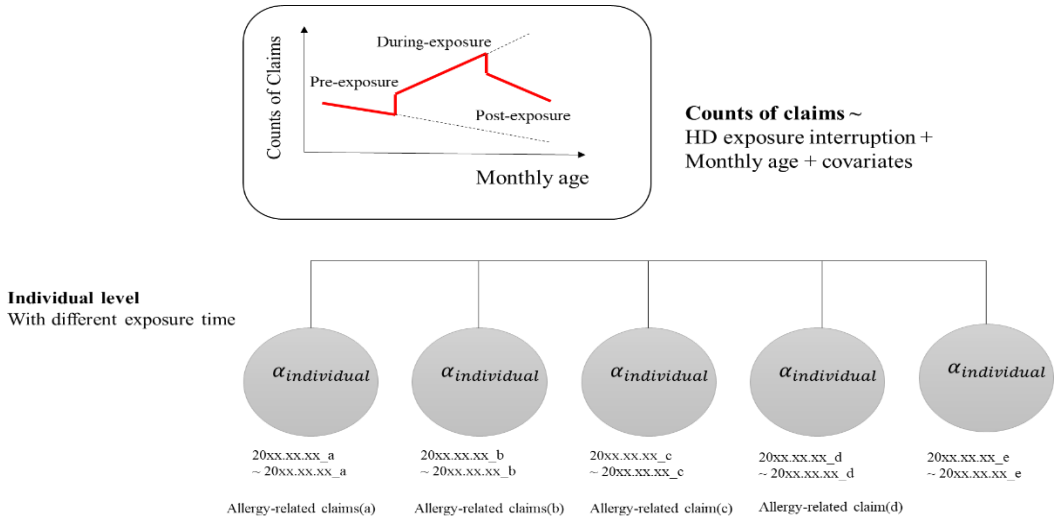


Figure 3. Modelling framework of Interrupted Time Series. HD, Humidifier disinfectants

All analyses were conducted using both crude and adjusted models. In the adjusted models, fixed variables included sociodemographic factors, and perinatal and congenital anomalies, while ILD was treated as a time dependent variable. Multicollinearity was assessed by calculating the variance inflation factor (VIF) for candidate covariates, with all variables demonstrating a VIF <10 (Appendix 1, 2).

Finally, I assessed the impact of HD on the atopic march. To investigate the interaction between AD and HD exposure, I included AD as a time- dependent factor in both the time-dependent Cox PH models and the multilevel ITS analyses to explore potential interactions.

Data analysis was performed using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as $p < 0.05$ for all analyses.

2.5.2. Subgroup analysis

I also conducted a subgroup analysis focusing on two groups: individuals who had been exposed to CMIT/MIT and those who had been exposed to PHMG/PGH' HD products were classified according to Park et al[24], (Table3) and categorized as either 'PHMG/PGH group' or ‘CMIT/MIT group’. The same analysis described above was then reapplied to these subgroups, except for the analysis of monthly hospital days for AS due to poor model fit and the small number of cases in the pre-exposure period. Additionally, I examined the VIF to assess multicollinearity in the analysis (Appendix 1, 2).

Table 3. Humidifier disinfectant types for Brands

Types	Brands
PHMG/PGH	Oxy Saksak(2000~), Lottemart Wiselect, Homeplus, Vegetable Clean up, Atorganic, Cefu etc.
CMIT/MIT	Aekyung Home Clinic Humidifier Mate, E-mart HD, Dongsan Humidifier Mate, Humidifier Homecare, SK Humidifier Mate, E-plus HD, Yukong Enclean Humidifier Mate, HD partner, HomeKeeper, Hambak HD, etc.
Others	N-with, Oxy Saksak(1996~2000), Oxy Saksak with solid type, etc.

PHMG, Polyhexamethylene guanidine; PGH, oligo- (2-(2-ethoxy)-ethoxyethyl) guanidine chloride; CMIT/MIT, Chloromethylisothiazolinone/ methylisothiazolinone

2.5.3. Sensitivity analysis

Since healthcare utilization cannot occur before birth, there were no medical records during the pre-exposure period for subjects born during or after exposure. Therefore, I conducted a sensitivity analysis on subjects born prior to the exposure. This analysis utilized both time-dependent Cox PH models and multilevel ITS analysis. However, interaction terms and the analysis of monthly hospital days for AS were not performed due to poor model fit and the small number of cases.

3. Results

3.1. Subject characteristics

The characteristics of the study population were as follows: the mean birth year was 2006.7 ± 2.8, and the mean total exposure duration was 32.0 ± 26.2 months. The mean age at the start of exposure was 5.3 ± 15.5 months, while the mean age at the end of exposure was 37.3 ± 28.1 months. The male-to-female ratio was 1.4, and 13.1% of subjects resided in rural areas. Of the subjects, 44.5% were born prior to exposure, 52.7% during exposure, and 2.7% after exposure. Furthermore, 64.3% of subjects were exposed to only PHMG/PHG type, 9.4% experienced exposure to only CMIT/MIT types, and 24.3% experienced exposure to both types. Perinatal comorbidities were present in 31.0% and 18.7% had congenital anomalies. The proportion of ILD was 5.1% of the subjects. The cumulative incidence of AS, AD, and AR were 67.9%, 27.2%, and 71.1%, respectively (Table 4).

Table 4 Characteristics of Study populations

Characteristics	mean ± SD or n(%)
Total(n)	1,655
Birth year	2006.7 ± 2.8
Sex	
- M	966 (58.4%)
- F	689 (41.6%)
Residential areas	
- Rural area	217 (13.1%)
- Urban area	1438 (86.9%)
Total exposure duration(month)	32.0 ± 26.2
Exposure start age at month	5.3 ± 15.5
Exposure end age at month	37.3 ± 28.1
Status of HD exposure at birth	
- Pre-exposure	737 (44.5%)
- During exposure	873 (52.7%)
- Post-exposure	45 (2.7%)
Perinatal comorbidities*	
- Y	513 (31.0%)
- N	1142 (69.0%)
Congenital anomaly	
- Y	310 (18.7%)
- N	1345 (81.3%)
Interstitial lung disease	
- Y	85 (5.1%)
- N	1570 (94.9%)
Asthma	
- Y	1123 (67.9%)
- N	532 (32.1%)
Atopic dermatitis	
- Y	450 (27.2%)
- N	1205 (72.8%)
Allergic rhinitis	
- Y	1176 (71.1%)
- N	479 (28.9%)

*Perinatal comorbidities: Disorders of newborn related to length of the gestation and fetal growth(P05-08); Birth trauma(P10-15); Respiratory and cardiovascular disorders specific to the perinatal period(P20-29); Infection specific to the perinatal period(P35-39); hemorrhagic and hematologic disorders of fetus and newborn(P50-61); Digestive system disorders of fetus and newborn(P75-78)

The peak monthly incidence of asthma (AS) occurred at 5 months of age, for atopic dermatitis (AD) at 1 month, and for allergic rhinitis (AR) at 25 months. The incidence of AS was significantly elevated during the exposure period, with a rate of 17.049 cases per 1,000 person-months (95% CI: 16.089–18.966). The incidence of AR peaked post-exposure, with a rate of 11.828 cases per 1,000 person-months (95% CI: 10.988–12.698). Conversely, AD incidence was significantly higher in the pre-exposure period, with a rate of 7.821 cases per 1,000 person-months (95% CI: 6.239–9.569), all with p-values <0.001(Table5). When stratified by age group (0–12 months, 13–24 months, 25–60 months, and 61–119 months), there were significant differences in the incidence of AS and AR within the 0–12 and 13–24 month age groups. In contrast, no significant differences in AD incidence were observed across the age groups (Figure 4, Appendix 3).

During the exposure period, the number of office visits for AS and AR increased significantly, with mean monthly visits of 0.324 ± 0.964 and 0.395 ± 1.080, respectively. In the post-exposure period, AR visits remained relatively high at 0.676 ± 1.360 per month. However, the number of office visits for AD decreased throughout the exposure phases, with the lowest mean observed during the post-exposure period at 0.034 ± 0.281. Hospital days of admissions for AS were also higher during exposure (0.117 ± 1.143) compared to the pre-exposure (0.035 ± 0.559) and post-exposure (0.040 ± 0.603) period (p<0.001 for all comparisons, Table 5). Figure 5 illustrates the healthcare utilization by monthly ages.

Table 5. Incidence and Healthcare utilization of allergic disease stratified by exposure status

	Pre	During	Post
Incidence (1000/Person-month, 95%CI)			
AS*	8.130 (6.512 ~ 9.914)	17.049 (15.670 ~ 18.485)	8.254 (7.525 ~ 9.015)
AD*	7.821 (6.239 ~ 9.569)	4.709 (4.071 ~ 5.390)	1.586 (1.355 ~ 1.833)
AR*	4.647 (3.471 ~ 5.979)	9.532 (8.607 ~ 10.502)	11.828 (10.988 ~ 12.698)
Number of Office visits, or Hospital days of admission (mean + SD/Month)			
AS, office visits*	0.103 ± 0.524	0.324 ± 0.964	0.3 ± 0.94
AS, admission*	0.035 ± 0.559	0.117 ± 1.143	0.04 ± 0.603
AD*	0.048 ± 0.283	0.042 ± 0.276	0.034 ± 0.281
AR*	0.167 ± 0.673	0.395 ± 1.08	0.676 ± 1.36

AS, Asthma; AD, Atopic dermatitis; AR, Allergic rhinitis

*, $p<0.001$

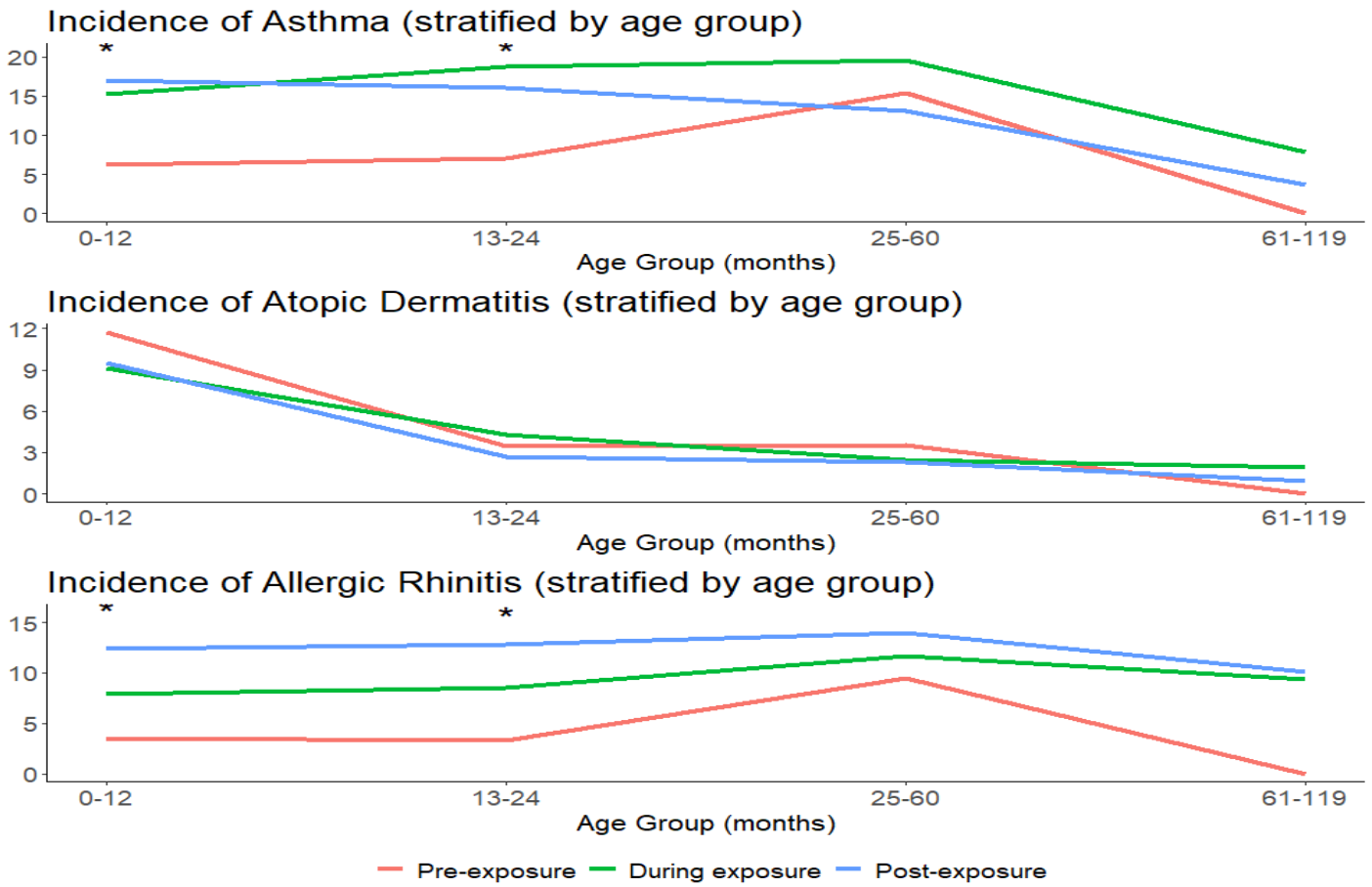


Figure 4. Incidence of allergic diseases by Age group *p<0.005

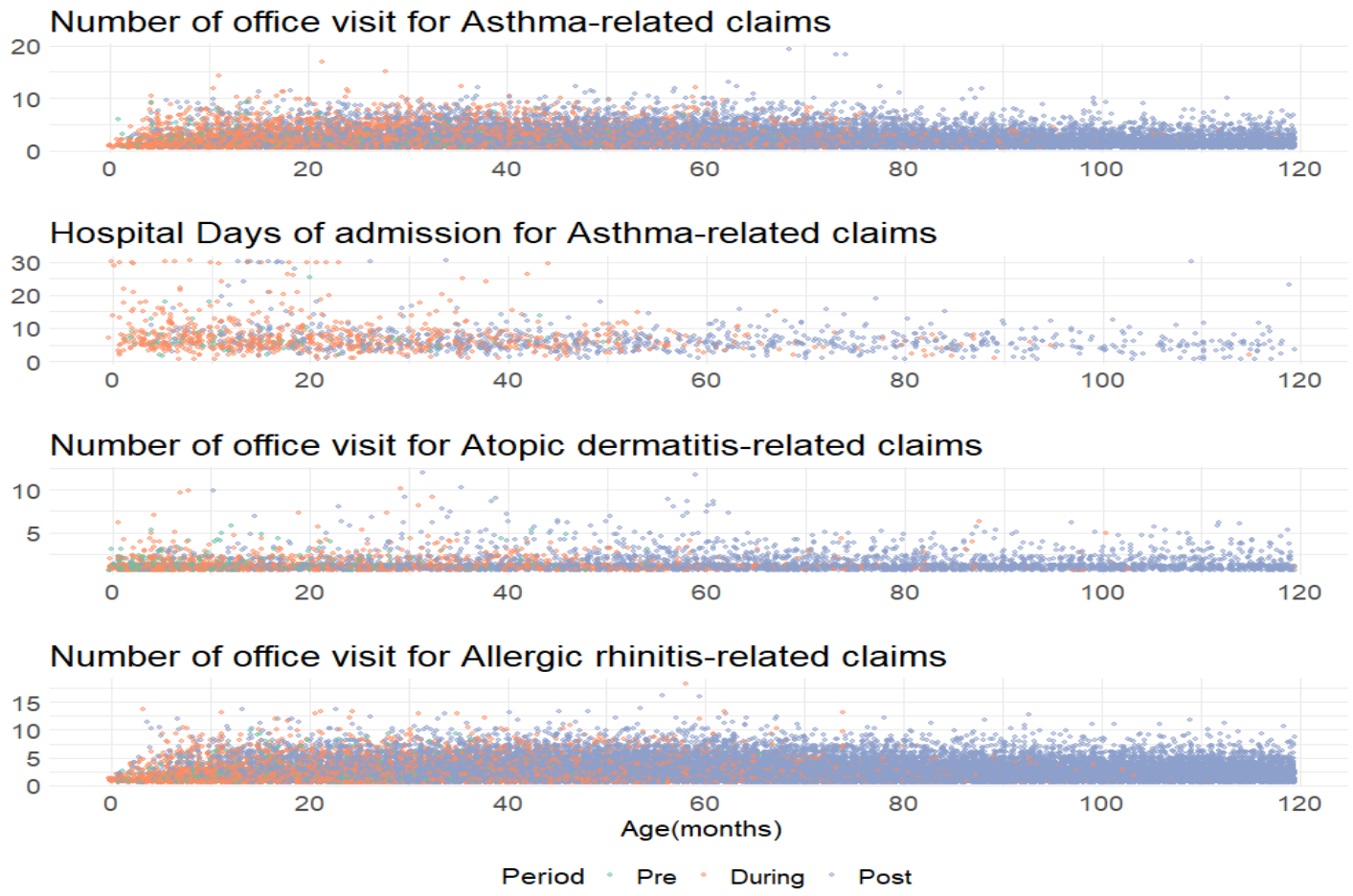


Figure 5. Healthcare Utilizations of Allergic Diseases by Age (months)

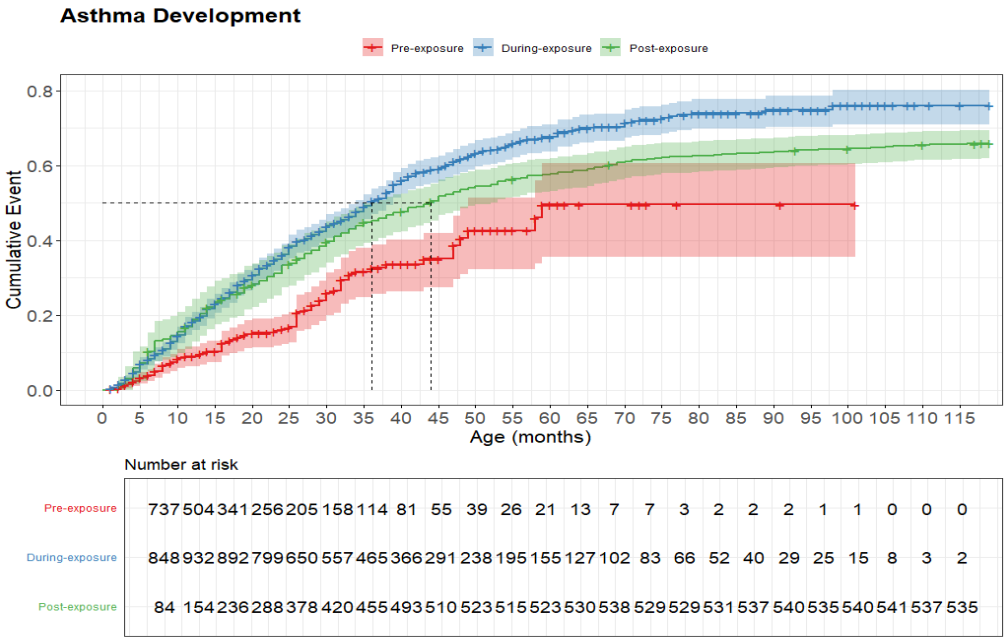
3.2. Time-dependent effects of HD exposure on allergic disease incidence

Table 6 presents the results of the time-dependent Cox proportional hazards analysis, demonstrating the incidence of allergic diseases in relation to HD exposure. During exposure and post exposure were observed significant increased adjusted hazard ratio (aHR) for AS (During exposure: aHR, 2.126, 95%CI 1.681-2.688; Post-exposure: aHR, 1.794, 95%CI 1.359~2.368). In AR, a significant increase in aHR was also observed during exposure and post-exposure(During exposure: aHR, 1.671, 95%CI 1.250-2.234; Post-exposure: aHR 1.559, 95%CI 1.135-2.141, respectively). Meanwhile, AD did not demonstrate statistically significant results. And figure 4 demonstrate Kaplan-Meier plot of each allergic disease

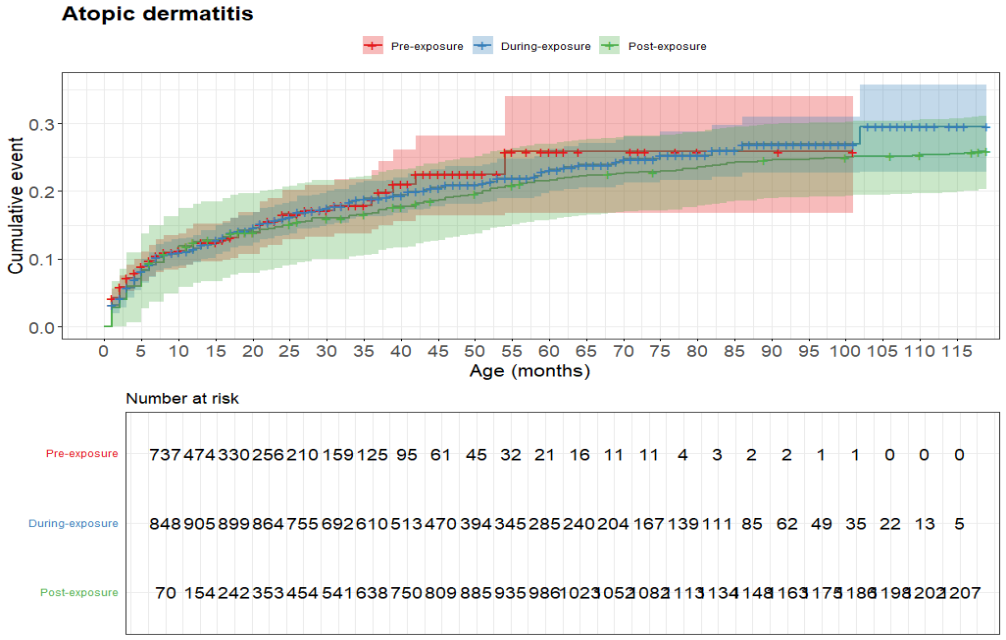
Table 6. Effects of Humidifier disinfectants on Incidence of Allergic diseases, Time-dependent Cox Proportional hazard models

HR(95%CI)	Crude	Adjusted
Asthma		
Pre	1 (REF)	1 (REF)
During	2.034 (1.633 - 2.533)	2.126 (1.681 - 2.688)
Post	1.496 (1.176 - 1.903)	1.794 (1.359 - 2.368)
Atopic dermatitis		
Pre	1 (REF)	1 (REF)
During	0.958 (0.740 - 1.238)	1.004 (0.731 - 1.379)
Post	0.828 (0.594 - 1.155)	0.905 (0.593 - 1.380)
Allergic rhinitis		
Pre	1 (REF)	1 (REF)
During	1.772 (1.341 - 2.343)	1.671 (1.250 - 2.234)
Post	2.262 (1.696 - 3.017)	1.559 (1.135 - 2.141)

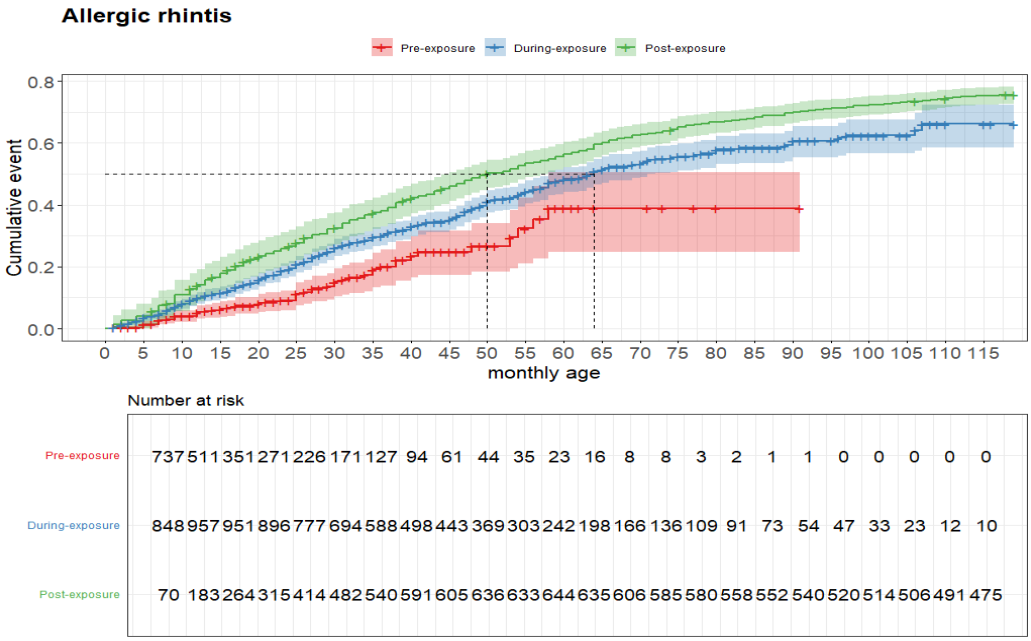
HR, Hazard Ratio; CI, Confidential intervals; Crude model, unadjusted; Adjusted model, adjusted with sex, birth year, residential area, time at birth, Perinatal comorbidities, Congenital anomaly, Interstitial lung diseases



a. HD exposure and Asthma development



b. HD exposure and Atopic dermatitis development



c. HD exposure and Allergic rhinitis development

Figure 6. Cumulative incidences of allergic diseases by exposure status

a. Asthma; b. Atopic dermatitis; c. Allergic rhinitis

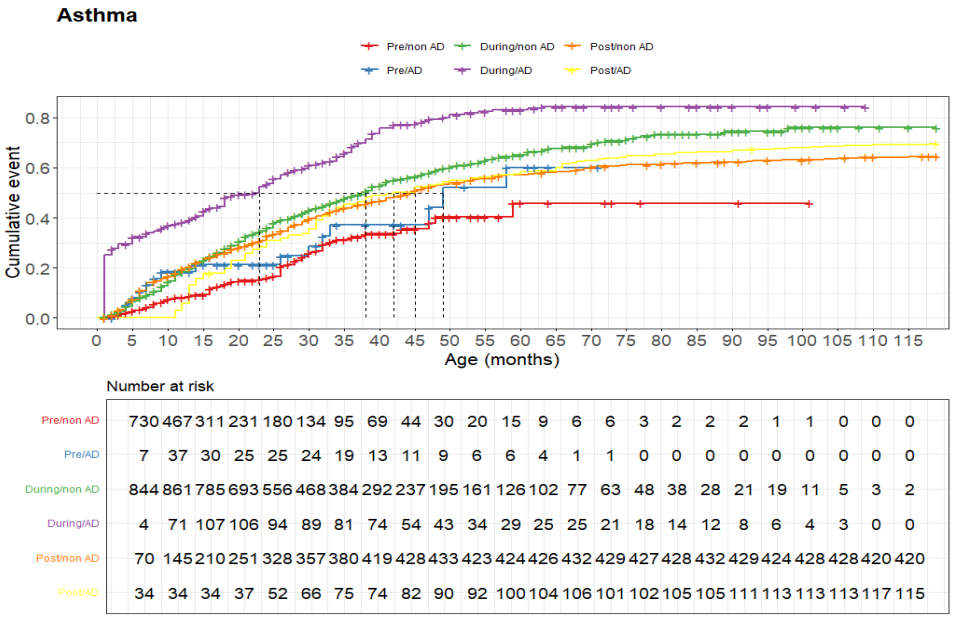
3.3. Interaction between AD and HD exposure in relation to incidence of other allergic diseases

Table 8 and Figure 7 presents the results of the interaction between AD and HD exposure on the incidence of AS and AR. In the case of AS, significant increases in the HR were observed during and after exposure in the absence of AD (During exposure: aHR 2.214, 95% CI 1.715-2.857; Post-exposure: aHR 1.852, 95% CI 1.378–2.488). For AR, a significant increase in the HR were observed during exposure in the absence of AD (During exposure: aHR 1.760, 95% CI 1.282–2.417; Post-exposure aHR 1.665 95%CI 1.183 - 2.345). However, the interaction between AD and HD exposure did not demonstrate significant results.

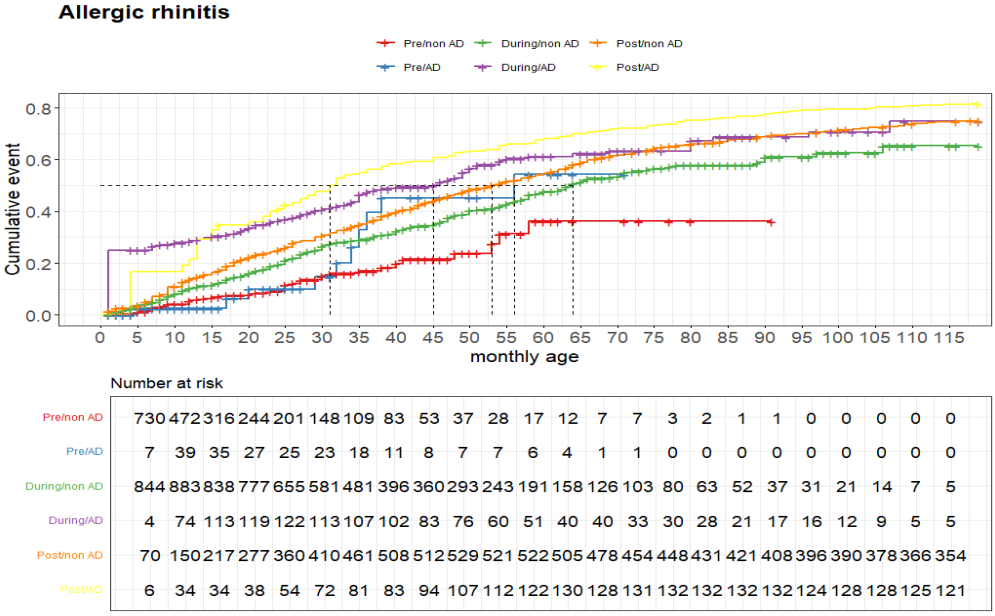
Table 7. Interaction of Atopic dermatitis and Humidifier disinfectants on Incidence of Allergic diseases, Time-dependent Cox Proportional hazard models

HR (95%CI)	Crude	Adjusted
Asthma		
Pre, REF	1 (REF)	1 (REF)
During	2.078 (1.635 - 2.641)	2.214 (1.715 - 2.857)
Post	1.540 (1.187 - 2.000)	1.852 (1.378 - 2.488)
AD	1.538 (0.885 - 2.675)	1.526 (0.877 - 2.655)
During*AD	0.846 (0.468 - 1.528)	0.841 (0.465 - 1.520)
Post*AD	0.834 (0.458 - 1.520)	0.853 (0.468 - 1.555)
Allergic rhinitis		
Pre, REF	1 (REF)	1 (REF)
During	1.913 (1.409 - 2.598)	1.760 (1.282 - 2.417)
Post	2.422 (1.770 - 3.315)	1.665 (1.183 - 2.345)
AD	1.750 (0.884 - 3.463)	1.711 (0.864 - 3.388)
During*AD	0.582 (0.280 - 1.209)	0.610 (0.294 - 1.267)
Post*AD	0.616 (0.304 - 1.250)	0.623 (0.307 - 1.264)

AD, Atopic dermatitis; Crude unadjusted; Adjusted, adjusted with sex, birth year, residential area, time at birth, Type of Humidifier disinfectants, Perinatal comorbidities, Congenital anomaly, Interstitial lung diseases



a. Interaction HD exposure and Atopic dermatitis on incidence of Asthma



b. Interaction HD exposure and Atopic dermatitis on incidence of Allergic rhinitis

Figure 7. Cumulative incidences of allergic diseases by Interaction HD exposure and Atopic dermatitis. AD, Atopic dermatitis

3.4. Time-dependent effects of HD exposure on allergic disease aggravations

Table 7 and Figure 6 present the results of medical utilization according to exposure status. For AS, the number of office visits showed a significant increase during the exposure period (aURR[adjusted utilization rate ratio]: 1.218, 95% CI: 1.051–1.41), followed by a significant increase post-exposure (aURR: 1.171, 95% CI: 1.011–1.356), compared to pre-exposure. However, the slope effect post-exposure significantly declined (aURR: 0.849, 95% CI: 0.754–0.956).

For AR, a secular increase in office visits was observed over age (months) (aURR: 1.104, 95% CI: 1.023–1.192). Significant level effects were identified both during exposure (aURR: 1.143, 95% CI: 1.024–1.275) and post-exposure (aURR: 1.148, 95% CI: 1.031–1.279), compared to pre-exposure. Similar to AS, the slope effect post-exposure demonstrated a significant decline (aURR: 0.815, 95% CI: 0.755–0.88). After adjustment in all analyses, the variance attributed to the random factor decreased, reflecting improved model fit.

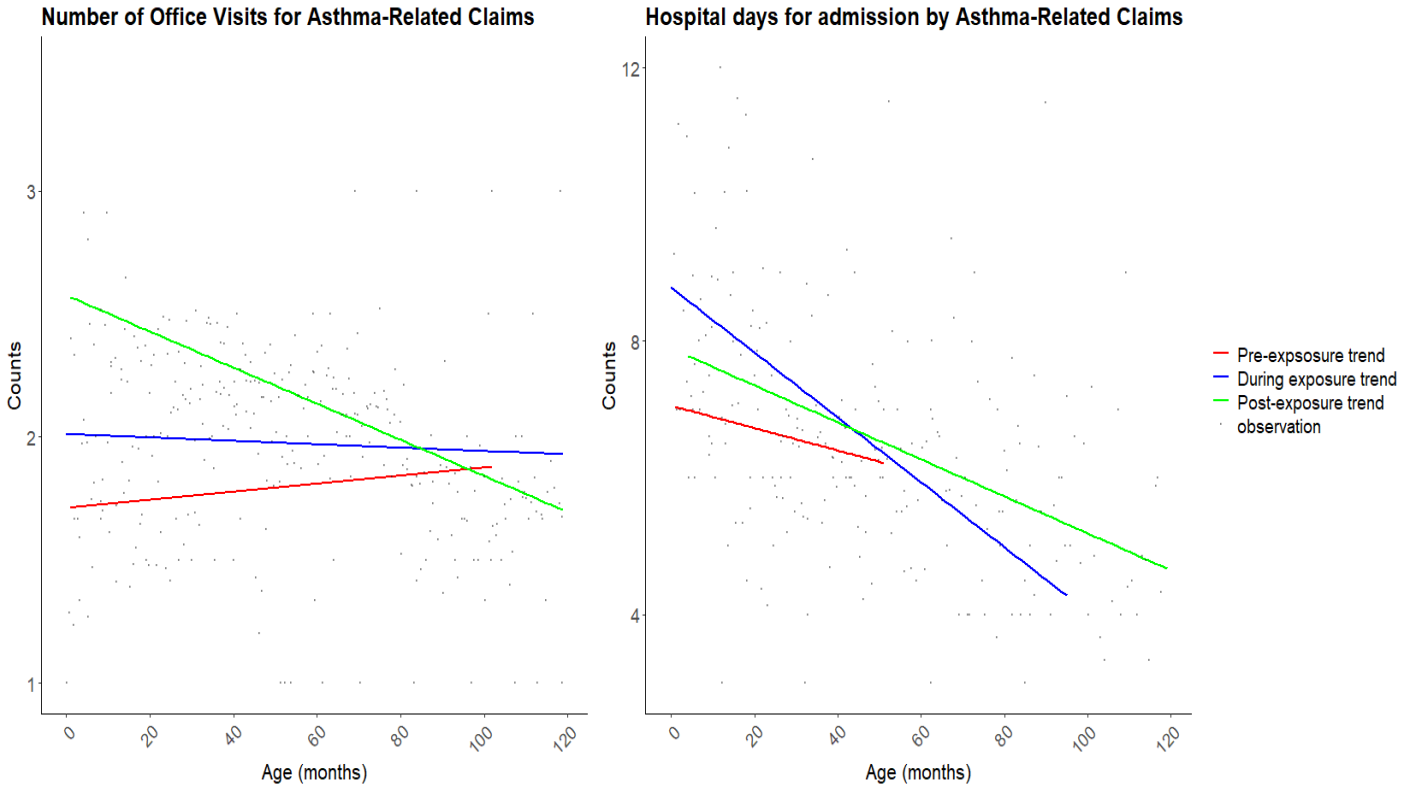


Figure 8. Effects of Humidifier disinfectants on Aggravation of Allergic diseases, Multilevel interrupted time series(1)

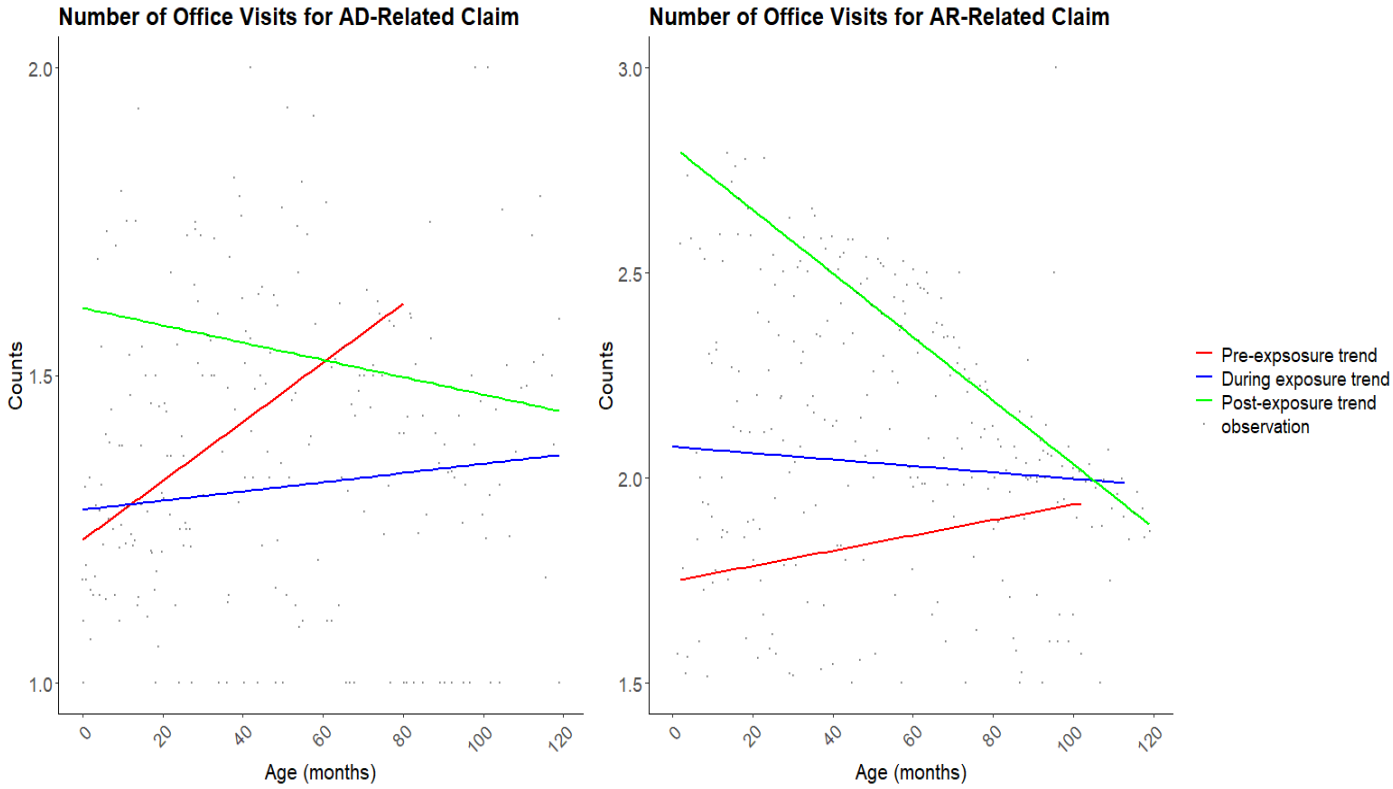


Figure 9. Effects of Humidifier disinfectants on Aggravation of Allergic diseases, Multilevel interrupted time series(2)

AD, Atopic dermatitis; AR, Allergic rhinitis

Table 8. Effects of Humidifier disinfectants on Aggravation of Allergic diseases, Multilevel interrupted time series

URR(95%CI)	Crude	Adjusted
AS, Number of office visits		
Intercept	1.601 (1.383~ 1.854)	1.627 (1.401~ 1.891)
Age (months)	1.042 (0.926~ 1.173)	1.068 (0.949~ 1.202)
During exposure	1.234 (1.065~ 1.429)	1.218 (1.051~ 1.41)
Post-exposure	1.236 (1.068~ 1.431)	1.171 (1.011~ 1.356)
Age (months) * During exposure	0.991 (0.879~ 1.118)	0.986 (0.874~ 1.112)
Age (months) * Post-exposure	0.863 (0.766~ 0.972)	0.849 (0.754~ 0.956)
proportion reduction in variance	2.96%	11.85%
AS, Hospital days of admission		
Intercept	6.201 (4.767~ 8.066)	6.151 (4.705~ 8.042)
Age (months)	1.049 (0.795~ 1.385)	1.176 (0.894~ 1.547)
During exposure	0.971 (0.745~ 1.265)	0.929 (0.716~ 1.206)
Post-exposure	0.95 (0.728~ 1.239)	0.929 (0.714~ 1.209)
Age (months) * During exposure	0.756 (0.571~ 1.002)	0.684 (0.518~ 0.903)
Age (months) * Post-exposure	0.858 (0.65~ 1.131)	0.773 (0.588~ 1.017)
proportion reduction in variance	4.76%	12.99%
AD, Number of office visits		
Intercept	1.415 (1.078~ 1.857)	1.542 (1.164~ 2.044)
Age (months)	1.131 (0.894~ 1.431)	1.14 (0.902~ 1.443)
During exposure	0.901 (0.681~ 1.192)	0.905 (0.682~ 1.2)
Post-exposure	1.002 (0.761~ 1.318)	0.96 (0.725~ 1.27)
Age (months) * During exposure	0.871 (0.68~ 1.114)	0.894 (0.699~ 1.143)
Age (months) * Post-exposure	0.859 (0.677~ 1.09)	0.862 (0.68~ 1.093)
proportion reduction in variance	3.13%	18.75%
AR, Number of office visits		
Intercept	1.776 (1.595~ 1.979)	1.743 (1.559~ 1.948)
Age (months)	1.09 (1.01~ 1.177)	1.104 (1.023~ 1.192)
During exposure	1.152 (1.032~ 1.285)	1.143 (1.024~ 1.275)
Post-exposure	1.181 (1.061~ 1.315)	1.148 (1.031~ 1.279)
Age (months) * During exposure	0.96 (0.887~ 1.039)	0.957 (0.885~ 1.036)
Age (months) * Post-exposure	0.823 (0.763~ 0.889)	0.815 (0.755~ 0.88)
proportion reduction in variance	3.60%	7.19%

AS, Asthma; AD, Atopic dermatitis; AR, allergic rhinitis; URR, Utilization rate ratio; CI, Confidential index; Crude unadjusted; Adjusted, adjusted with sex, birth year, residential area, time at birth, Perinatal comorbidities, Congenital anomaly, Interstitial lung diseases

3.5. Interaction between AD and HD exposure in relation to aggravations of other allergic diseases

Table 9 and Figure 8 details the results regarding the aggravation of AS and AR in relation to AD and HD exposure. For AS, the level during exposure demonstrated a significantly higher aURR(1.305, 95% CI: 1.09–1.563), with a significant increase post-exposure (aURR: 1.245, 95% CI: 1.04–1.49). No significant interaction between AD and HD exposure was observed during or after the exposure period in relation to the number of AS office visits.

For AR, the number of office visits demonstrated a significant increase during exposure (aURR: 1.22, 95% CI: 1.063–1.4) and post-exposure (aURR: 1.216, 95% CI: 1.062–1.392), compared to pre-exposure. The post-exposure slope effect was observed a significant decline (aURR: 0.859, 95% CI: 0.781–0.946). Similar to AS, no significant interaction was found between AD and HD exposure in relation to AR office visits.

After adjustment in all analyses, the variance attributed to the random factor decreased, reflecting improved model fit.

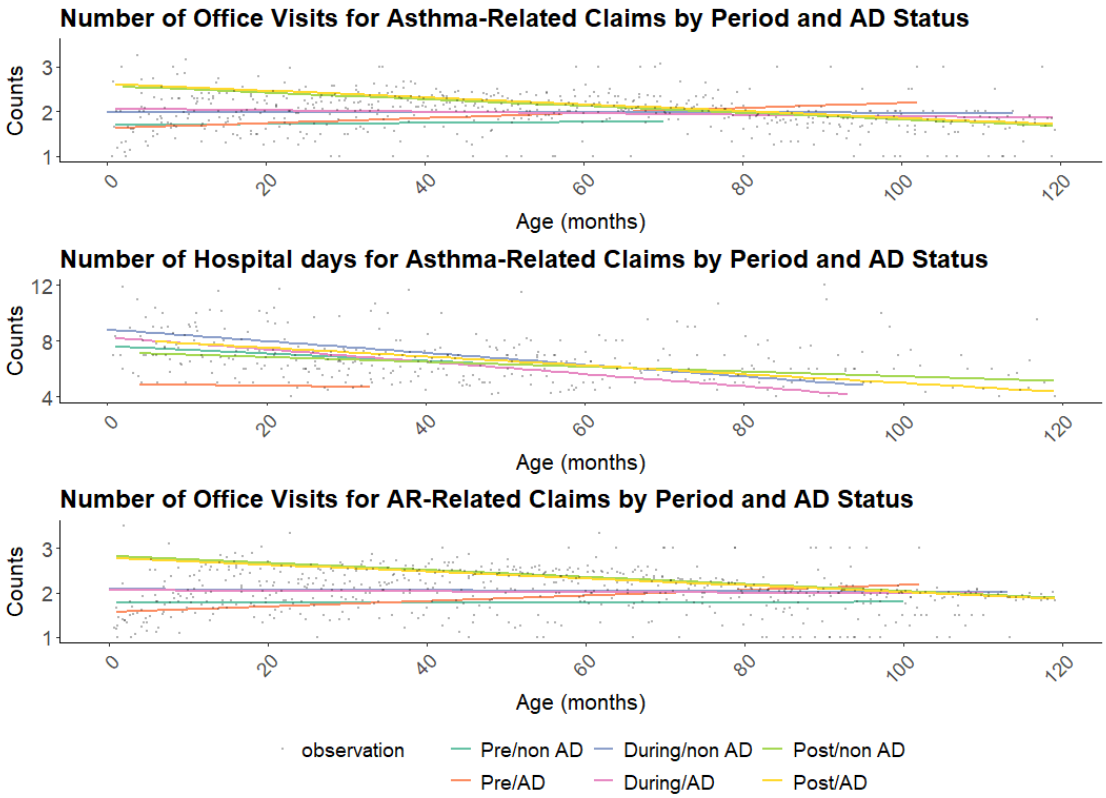


Figure 10. Interaction of Humidifier disinfectant exposure and Atopic dermatitis on Aggravation of Allergic diseases, Multilevel interrupted time series

AD, Atopic dermatitis; AR, Allergic rhinitis

Table 9. Interaction of Atopic dermatitis and Humidifier disinfectants on Aggravation of Allergic diseases, Multilevel interrupted time series

URR(95%CI)	Crude	Adjusted
AS, Number of office visits		
Intercept	1.509 (1.26~ 1.806)	1.521 (1.267~ 1.825)
Age (months)	1.013 (0.873~ 1.175)	1.033 (0.891~ 1.199)
During exposure	1.312 (1.095~ 1.572)	1.305 (1.09~ 1.563)
Post-exposure	1.306 (1.091~ 1.563)	1.245 (1.04~ 1.49)
Age (months)* During exposure	1.027 (0.883~ 1.194)	1.025 (0.881~ 1.192)
Age (months)* Post-exposure	0.892 (0.768~ 1.035)	0.882 (0.76~ 1.023)
AD	1.229 (0.9~ 1.678)	1.262 (0.926~ 1.719)
Age (months)*AD	1.097 (0.858~ 1.401)	1.111 (0.87~ 1.417)
During exposure*AD	0.809 (0.592~ 1.107)	0.789 (0.578~ 1.077)
Post-exposure*AD	0.827 (0.605~ 1.13)	0.809 (0.593~ 1.102)
Age (months)* During exposure*AD	0.894 (0.696~ 1.147)	0.884 (0.69~ 1.134)
Age (months) * Post-exposure*AD	0.902 (0.705~ 1.153)	0.889 (0.696~ 1.135)
proportion reduction in variance	2.96%	11.85%
AS, Hospital days of admission		
Intercept	6.605 (4.98~ 8.762)	6.503 (4.884~ 8.659)
Age (months)	1.054 (0.785~ 1.416)	1.189 (0.888~ 1.593)
During exposure	0.932 (0.702~ 1.238)	0.898 (0.679~ 1.188)
Post-exposure	0.87 (0.654~ 1.159)	0.862 (0.65~ 1.144)
Age (months) * During exposure	0.76 (0.563~ 1.026)	0.681 (0.507~ 0.916)
Age (months) * Post-exposure	0.889 (0.662~ 1.193)	0.79 (0.591~ 1.057)
AD	0.794 (0.36~ 1.755)	0.788 (0.362~ 1.717)
Age (months) *AD	1.156 (0.484~ 2.763)	1.039 (0.441~ 2.446)
During exposure*AD	1.189 (0.537~ 2.635)	1.194 (0.546~ 2.608)
Post-exposure*AD	1.366 (0.615~ 3.034)	1.341 (0.612~ 2.938)
Age (months) * During exposure*AD	0.849 (0.353~ 2.042)	0.949 (0.4~ 2.25)
Age (months) * Post-exposure*AD	0.768 (0.321~ 1.837)	0.874 (0.371~ 2.06)
proportion reduction in variance	5.63%	13.64%

(continue)

AR, Number of office visits		
Intercept	1.68 (1.466~ 1.925)	1.64 (1.428~ 1.884)
Age (months)	1.041 (0.945~ 1.146)	1.051 (0.955~ 1.156)
During exposure	1.225 (1.067~ 1.407)	1.22 (1.063~ 1.4)
Post-exposure	1.246 (1.088~ 1.427)	1.216 (1.062~ 1.392)
Age (months) * During exposure	1.004 (0.909~ 1.109)	1.004 (0.91~ 1.108)
Age (months) * Post-exposure	0.865 (0.786~ 0.953)	0.859 (0.781~ 0.946)
AD	1.162 (0.929~ 1.455)	1.18 (0.944~ 1.475)
Age (months)*AD	1.14 (0.971~ 1.337)	1.149 (0.98~ 1.348)
During exposure*AD	0.846 (0.673~ 1.062)	0.837 (0.667~ 1.05)
Post-exposure*AD	0.868 (0.694~ 1.085)	0.859 (0.687~ 1.072)
Age (months) * During exposure*AD	0.886 (0.75~ 1.046)	0.878 (0.744~ 1.036)
Age (months) * Post-exposure*AD	0.868 (0.739~ 1.019)	0.861 (0.734~ 1.01)
proportion reduction in variance	2.88%	7.19%

AS, Asthma; AD, Atopic dermatitis; AR, allergic rhinitis; URR, Utilization rate ratio; CI, Confidential index; Crude unadjusted; Adjusted, adjusted with sex, birth year, residential area, time at birth, Type of Humidifier disinfectants, Perinatal comorbidities, Congenital anomaly, Interstitial lung diseases

3.6. Subgroup analysis

Table 10 presents the characteristics of the subgroups. A simple comparison revealed statistically significant differences between the PHMG/PGH and non-PHMG/PGH in birth year, total exposure duration, exposure start age at month, and exposure end age at month($p=0.003$, $p<0.001$, $p=0.033$, and $p<0.001$). Also, significantly differences observed between CMIT/MIT and non-CMIT/MIT in total exposure duration, exposure start age at month, exposure end age at month, and time at birth($p=0.001$, $p=0.047$, $p=0.044$, and $p=0.046$).

Table 10 Characteristics of Subgroups

Subgroup	PHMG/PGH	Non-PHMG/PGH	CMIT/MIT	Non-CMIT/MIT
	(N=1466)	(N=189)	(N=558)	(N=1097)
Birth year	2006.7 ± 2.8*	2007.3 ± 2.7	2006.6 ± 2.7	2006.8 ± 2.8
sex				
- M	862 (58.8%)	104 (55.0%)	328 (58.8%)	638 (58.2%)
- F	604 (41.2%)	85 (45.0%)	230 (41.2%)	459 (41.8%)
Residential areas				
- Rural area	1273 (86.8%)	165 (87.3%)	494 (88.5%)	944 (86.1%)
- Urban area	193 (13.2%)	24 (12.7%)	64 (11.5%)	153 (13.9%)
Total exposure duration(month)	33.4 ± 26.6**	21.1 ± 19.6	35.0 ± 26.1**	30.5 ± 26.1
Exposure start age at month	4.9 ± 15.2*	7.8 ± 17.2	4.2 ± 14.4*	5.8 ± 16.0
Exposure end age at month	38.4 ± 28.3*	28.9 ± 24.8	39.2 ± 27.8*	36.3 ± 28.1
Time at birth			*	
- Pre-exposure	783 (53.4%)	90 (47.6%)	318 (57.0%)	555 (50.6%)
- During exposure	38 (2.6%)	7 (3.7%)	13 (2.3%)	32 (2.9%)
- Post-exposure	645 (44.0%)	92 (48.7%)	227 (40.7%)	510 (46.5%)
Perinatal comorbidities				
- Y	446 (30.4%)	67 (35.4%)	161 (28.9%)	352 (32.1%)
- N	1020 (69.6%)	122 (64.6%)	397 (71.1%)	745 (67.9%)
Congenital anomaly				
- Y	269 (18.3%)	41 (21.7%)	118 (21.1%)	192 (17.5%)
- N	1197 (81.7%)	148 (78.3%)	440 (78.9%)	905 (82.5%)
Interstitial lung disease				
- Y	80 (5.5%)	5 (2.6%)	23 (4.1%)	62 (5.7%)
- N	1386 (94.5%)	184 (97.4%)	535 (95.9%)	1035 (94.3%)
Asthma				
- Y	985 (67.2%)	138 (73.0%)	390 (69.9%)	733 (66.8%)
- N	481 (32.8%)	51 (27.0%)	168 (30.1%)	364 (33.2%)
Atopic dermatitis				
- Y	397 (27.1%)	53 (28.0%)	160 (28.7%)	290 (26.4%)
- N	1069 (72.9%)	136 (72.0%)	398 (71.3%)	807 (73.6%)
Allergic rhinitis				
- Y	1046 (71.4%)	130 (68.8%)	409 (73.3%)	767 (69.9%)
- N	420 (28.6%)	59 (31.2%)	149 (26.7%)	330 (30.1%)

PHMG, Polyhexamethylene guanidine; PGH, oligo- (2-(2-ethoxy)-ethoxyethyl) guanidine chloride; CMIT/MIT, Chloromethylisothiazolinone/ methylisothiazolinone;

*p<0.05; **p<0.01

Figures 10 present the results of the subgroup analysis, showing aHRs for allergic diseases and their interactions with AD across subgroups. The aHRs of allergic diseases and the interaction with AD by subgroup. In the PHMG/PGH group, like in the total cohort, the aHRs for a AS and AR in during post-exposure were increased. In the CMIT/MIT group, the aHR for AS post-exposure was also not significant. aHR for AS during exposure, AR during and post exposure were increased. In the interaction with AD, the results of subgroup were mirrored by overall HD's results. Detail results were on the appendix 4.

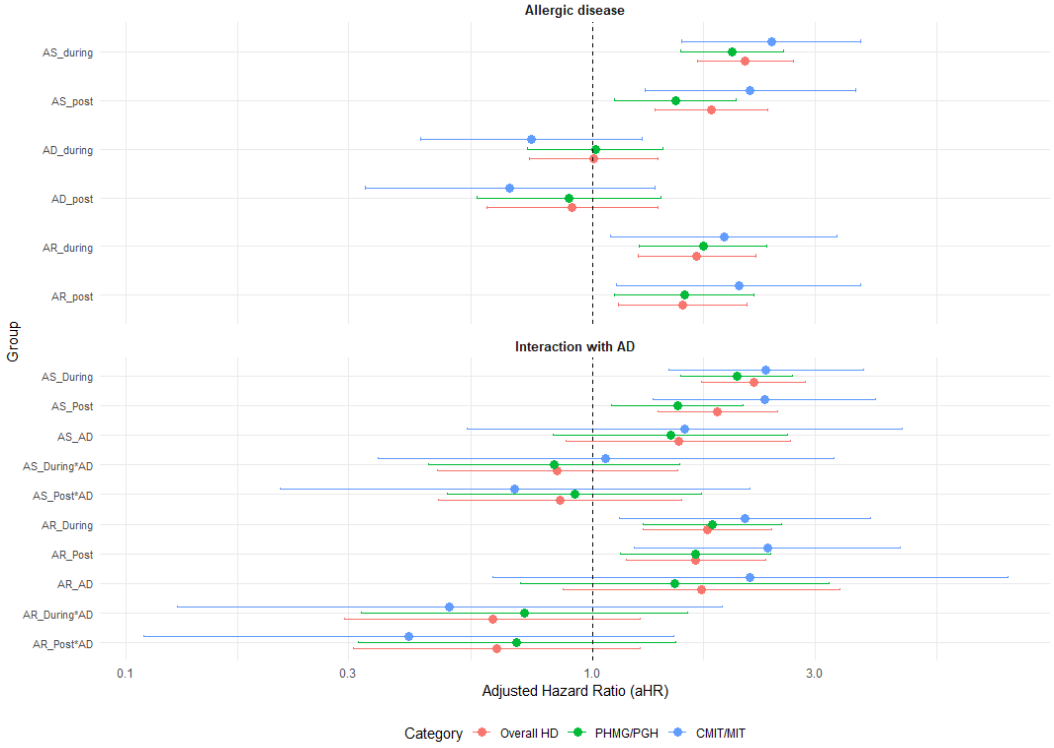


Figure 11. Results of the Time dependent Cox model for subgroup

AS, Asthma; AD, Atopic dermatitis; AR, Allergic rhinitis; aHR, Adjusted hazard ratio; HD, Humidifier disinfectant; PHMG, Polyhexamethylene guanidine; PGH, oligo- (2-(2-ethoxy)-ethoxyethyl) guanidine chloride; CMIT/MIT, Chloromethylisothiazolinone/ methylisothiazolinone;

Figures 11 present the results of the subgroup analysis, showing aURRs for allergic diseases and their interactions with AD across subgroups. In the PHMG/PGH group, the level effect of the number of office visits for AS was increased on during exposure, and post-exposure. For AR, the number of office visits similarly demonstrated a secular increase in pre-exposure. And the intercept effect of the number of office visits for AS was increased on during exposure, and post-exposure, followed by a significant decline in the slope at post-exposure. After adjusting for all analyses, the variance of the random factor decreased. The interaction analysis with AD was also conducted. The number of office visits for AS demonstrated a level effect on during and post exposure independent with AD, with increased level effect of AD. In the number of office visits for AR, the level effect at during and post-exposure. And level and slope effects of AD were increased. All the analyses were decreased of the variance of random factor.

In the CMIT/MIT group, the number of office visits for AS were observed a secular decline in post-exposure. For AR, there were no significant level effects in the number of office visits. And slope effect of post-exposure was significant decreased. The interaction analysis with AD was also conducted. The level effects of office visits for AS and AR were not statistically significant. The slope effects of post-exposure in AS and AR were significant decreased, independent with AD. All the analyses were decreased of the variance of random factor. The detailed aURR values, confidence intervals, and variance reductions for random factors are provided in the appendix5 and 6.

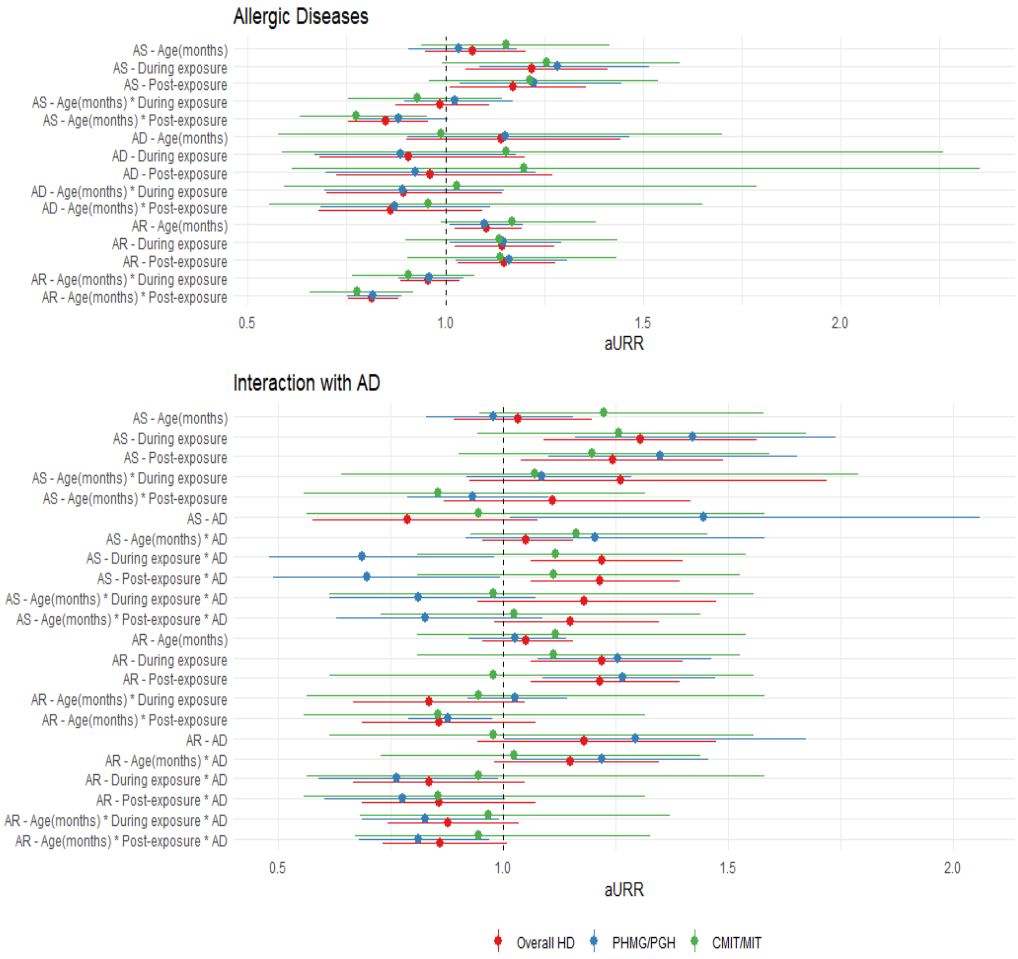


Figure 12 Results of the multilevel ITS for subgroup

AS, Asthma; AD, Atopic dermatitis; AR, Allergic rhinitis; aURR, Adjusted utilization rate ratio; HD, Humidifier disinfectant; PHMG, Polyhexamethylene guanidine; PGH, oligo-(2-(2-ethoxy)-ethoxyethyl) guanidine chloride; CMIT/MIT, Chloromethylisothiazolinone/ methylisothiazolinone;

3.7. Sensitivity analysis

Figure 9 demonstrates the results of the sensitivity analysis. The time-dependent Cox PH model demonstrated results similar to the main outcomes for the incidence of AS, AD, and AR. Additionally, the time-dependent Cox PH did not show statistically significant results in AR' aHR at post-exposure; however, the aHR values were elevated.

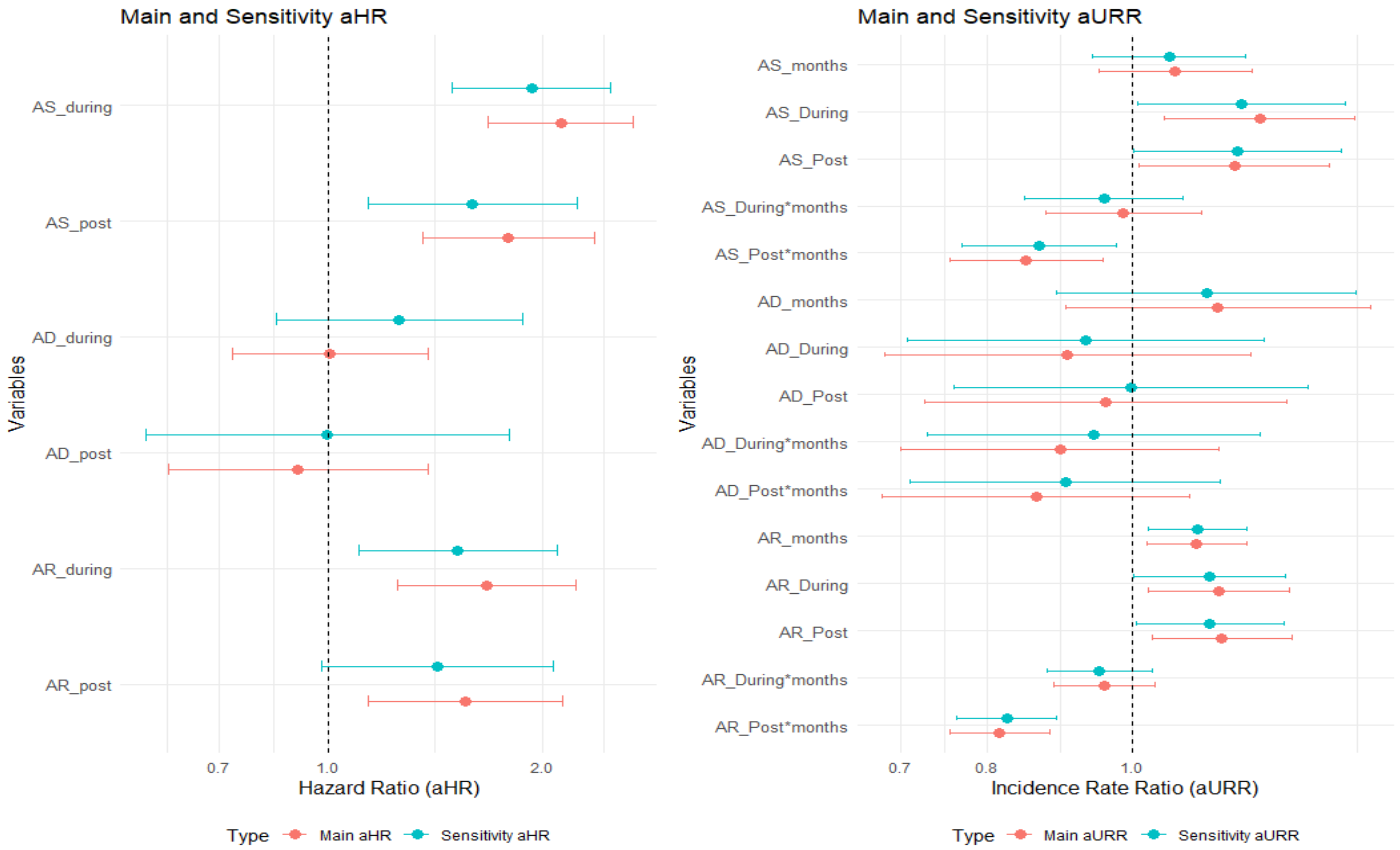


Figure 13. Results of Sensitivity analysis

PH, Proportional Hazard; ITS, interrupted time series; aHR, Adjusted Hazard ratio; aURR, adjusted utiliztion rate ratio; AS, Asthma; AD, Atopic dermatitis; AR, Allergic rhinitis

4. Discussion

4.1. Main findings

Findings from CoSPAHD indicate that HD exposure had a statistically significant effect on the incidence and aggravation of AS and AR, while no significant association was found with AD. Specifically, during and post-exposure periods, the incidence of AS and AR increased. In terms of aggravation, the level effect for monthly office visits for AS increased during the exposure period, while the slope effect for monthly office visits for both AS and AR decreased in the post-exposure period. However, no interactive effect was observed between HD exposure and AD. Although hospital admission days for AS were analyzed, no significant differences were observed, likely due to the relatively small number of admissions (627 subjects with 1,725 admission cases). Also, when analyzing specific subgroups, I found that the incidence and aggravation of allergic diseases in PHMG/PGH and CMIT/MIT group mirrored the overall results from CoSPAHD, independent with AD.

4.2. Findings and Implications

4.2.1. Using data from NHIS claim data

My analysis utilized data from the NHIS claims database, which encompassed 97% of the Korean population. This dataset provides comprehensive information on demographics such as age, sex, residential regions, healthcare services, and diagnoses classified using ICD-10 codes[47]. The NHIS claims data has been constructed since 2002,

ensuring that the majority of allergic disease cases within the CoSPAHD cohort were captured in my study. To gain a broader understanding of allergic diseases, I made efforts to ensure a comprehensive approach when defining the conditions. Consequently, I applied the long-term management criteria for AS[42].

Since I utilized ICD-10 codes from NHIS claims data for my analysis, I could not account for FA. In studies using NHIS claims data, the ICD-10 codes used to define FA vary widely[43,48-50]. Depending on the study, the prevalence of FA in this cohort ranged from 0.1% to 17.1% (Appendix 7). Due to the substantial variation in defining FA using ICD-10 codes, it was not feasible to include them in my analysis.

4.2.2. Characteristics of COSPAHD

According to the Global Burden of Disease Study 2021, the incidence of AS in Korean children aged 0–14 years ranged from 902.29 to 999.02 per 100,000, while the incidence of AD ranged from 940.27 to 1,048.35 per 100,000 between 2002 and 2021[51]. However, the CoSPAHD cohort exhibited higher incidences of AS and AD, which can be attributed to the fact that CoSPAHD was designed as a database for claiming respiratory diseases, including HD-related lung injury, ILD, and AS. To address this selection bias, I conducted an internal comparison analysis using time-dependent Cox PH and multilevel ITS to examine the differences in incidence and aggravation according to time- dependent exposure status.

4.2.3. Contact dermatitis

In this study, I did not include a separate analysis for contact dermatitis, such as irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). The decision was based on the very low prevalence of contact dermatitis among young children, as reported

in the Global Burden of Disease Study 2021[51]. Specifically, the prevalence of contact dermatitis in Korea from 2002 to 2021 was 0 cases per 100,000 persons in the 0–5 years age group and only 39.0 cases per 100,000 persons in the 5–9 year age group. However, in adults aged 20 and above, the prevalence is significantly higher, ranging from 1,051.67 to 1,151.82 cases per 100,000 persons. These findings suggest that examining the relationship between contact dermatitis and HD exposure in adult populations could be more informative and may help in understanding the characteristics of HD-related skin reactions. Therefore, future studies focusing on adults could provide valuable insights into the dermatological effects of HD exposure

4.3. Comparison to Previous studies

Several studies have evaluated the impact of HD exposure on allergic diseases, including AS, AR, and AD. Yon et al. [35] reported an aHR for HD-exposed individuals with AS (aHR 1.35, 95% CI: 1.01–1.80) and AR (aHR 1.22, 95% CI: 1.03–1.44). Additionally, this study analyzed cross-sectional data from the Seongnam Atopic Project 2017 and found that for those exposed to HD for more than three months, the adjusted odds ratio (aOR) for AS was 3.04 (95% CI: 1.65–5.62) and for AR, it was 2.07 (95% CI: 1.24–3.47). Koh et al[36] reported that HD and PHMG/PGH type increased the aOR for AR(HD: aOR 1.33, 95%CI 1.02~1.75; PHMG/PGH: aOR 1.41, 95%CI 1.02~1.95). Similarly, a study by Cho JH[37] using PSKC data reported that HD exposure increased the aOR for AR to 1.43 (95% CI: 1.37–1.49). My study also demonstrated elevated aHRs for both AS and AR during the exposure period, suggesting an increased risk associated with HD exposure.

In another study by Yoon et al. [34] using the PSKC cohort, the aOR for AS diagnosis between ages 5 and 7 years in children HD exposure without a history of bronchiolitis was 0.79 (95% CI: 0.41–1.51), indicating no significant association with HD exposure. However, for those with a history of bronchiolitis and HD exposure, the aOR was 4.28 (95%

CI: 2.38–7.72), suggesting a significant interaction between HD exposure and prior allergic condition. In contrast, my study found that using AD as a prior allergic condition did not demonstrate a significant interaction effect on the development of AS or AR. Additionally, HD exposure did not significantly increase the aHR for the development of AD itself. These findings indicate that, independently to AD, HD exposure may affect the development of AS and AR, suggesting a deviation from the so-called 'allergic march'.

Additionally, In a report by Kim et al[40] based on NHIS claim data, the relative risk for episodes of care for AS was high before the withdrawn of the HD, but after 2013, a reduction and stabilization in the relative risk were observed in an age-period cohort study. This trend resonates with my observation of declining AS and AR healthcare utilization after HD use ceased, suggesting that exposure status play crucial roles in the course of allergic disease. Also, in a study of individuals who applied claims for HD exposure, the OR for AS was 4.23 (95% CI 2.71–6.59) when comparing the three-year periods before and after the use of the HD, while AD did not show statistically significant values. Among PHMG/PGH users, the OR for AS was higher (OR 4.30, 95%CI 2.33~7.94), also among CMIT/MIT users, the OR for AS was also elevated (5.56, 95%CI 1.57~19.63), with no significant association observed for AD in either group. Additionally, in my study, even with sufficient enrollment of childhood subjects, there was no association between HD exposure and the incidence or aggravation of AD.

Overall, HD exposure was not related to the occurrence, aggravation of AD, nor with interactions involving AD. This is consistent with findings from PHMG/PGH toxicology studies, which pointed to an irritant-induced mechanism.

4.4. Type of Humidifier disinfectants and Allergic diseases

In my study, PHMG/PGH appears to induce and aggravate allergic diseases through the irritant pathway. In the multilevel analysis, the slope effect of post-exposure on office visits for AS was not statistically significant. Supporting this, it has been reported that prolonged exposure to such substances leads to chronic inflammation and airway remodeling, resulting in irreversible changes[14]. Furthermore, Lee et al[31]. reported no significant difference in AD prevalence and reduction in forced expiratory volume in 1 second without airway hyperresponsiveness between PHMG/PGH-exposed AS patients and healthy controls in PSKC. Also, this study demonstrated differences in inducible T-cell costimulatory ligand, and hepatocyte growth factor activator in PHMG/PGH-exposed AS compared to non-exposed AS.

Inducible T-cell costimulatory ligand is one of the proteins involved in the activation of T cells and plays a role in the differentiation of Th2 cells, which are elevated in allergic diseases[52]. Additionally, hepatocyte growth factor activator is involved in tissue repair and regeneration[53] and is known as a potent blocker of lung fibrosis[54]. A study that PHMG/PGH was administered as an aerosol to mice demonstrated an increase in gene expression related to TGF-β[55], which is a key factor in the tissue remodeling pathway and IIA[56].

In this human epidemiological study, CMIT/MIT also appears to act as an irritant in the development of allergic diseases. In this study, it was observed that CMIT/MIT exposure did not significantly affect the incidence or aggravation of AD and independently influenced the incidence and aggravation of AS and AR. According to Song et al. [57], an analysis of bronchoalveolar lavage fluid from mice instilled with CMIT/MIT for 48 hours showed an increase in eosinophil counts, and Th2 cytokines (IL-4, IL-5, and IL-13), suggesting a pathway similar to SIA. However, a notable finding was the increased levels of neutrophils and gene expressions associated with TGF-ß, suggesting that CMIT/MIT may also act as an irritant. Supporting this, Pak et al[58] reported that adults with any type

of HD-exposed AS had significantly lower DLCO values compared to non-HD-exposed AS patients. The differences observed between the Go et al[28], which investigated CMIT/MIT through topical application on mice and found Th2/Th17 dysregulation via skin biopsy, and this study on human inhalation exposure may stem from variations in exposure methods and species differences.

4.5. Strengths and Limitations

4.5.1 Strengths

This study has several strengths. It is the first to comprehensively analyze the relationship between HD exposure and allergic diseases in children and adolescents, demonstrating statistically significant findings for the incidence of AS and AR, as well as the aggravation of AS, independent of AD. I also utilized multilevel ITS to analyze individual factors and assess the effects of HD exposure on disease aggravation. Also, I established the CoSPAHD birth cohort to differentiate between chemical-induced allergic diseases and the aggravation of pre-existing allergic conditions due to HD exposure. Furthermore, subgroup analyses were conducted to identify the distinct characteristics of different substances, and sensitivity analyses were performed to ensure the robustness of my findings. Lastly, I minimized selection bias by conducting internal comparisons, enabling me to distinguish the effects of exposure status.

4.5.2. Limitations

This study has some limitations. First, I lacked data on other potential confounding factors, such as family history, environmental tobacco exposure, and body mass index. Second, the retrospective nature of HD exposure data collection may introduce information bias, though it is likely non-differential. Third, I used NHIS claims data, which

inherently lacks detailed clinical information, and therefore may not capture the full scope of allergic disease diagnoses. Fourth, although I examined incidence and aggravation by age, this design makes it difficult to clearly differentiate between the natural course of allergic diseases and the effects of HD exposure. Lastly, this retrospective design identifies associations between HD exposure and allergic diseases but does not establish causality. Further experimental studies on pathophysiology, particularly involving AD models, are needed.

5. Conclusions

In conclusion, this study is the first to elucidate the overall association between HD exposure and allergic diseases in children and adolescents. I found that HD exposure alone significantly association with the increased incidence of AS and AR and aggravation of AS, independent of AD. These findings underscore the need for future research to account for confounding factors, focus on exposed individuals, and explore the mechanisms underlying HD-related allergic disease risk.

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Appendix1. Multicollinearity evaluations for Covariates

VIF for Cox PH	Asthma	AD	AR
Total subjects			
Exposure status	1.385	1.316	1.324
Sex	1.006	1.006	1.005
Rural residence	1.002	1.006	1.004
Birth year	1.154	1.139	1.138
Birth time	1.408	1.355	1.365
Congenital anomalies	1.013	1.015	1.012
Perinatal comorbidities	1.086	1.090	1.087
ILD	1.028	1.025	1.021
mean VIF	1.135	1.119	1.119
Subgroup - only-PHMG/PGH users			
Exposure status	1.393	1.323	1.330
Sex	1.007	1.007	1.006
Rural residence	1.002	1.004	1.003
Birth year	1.151	1.135	1.134
Birth time	1.407	1.360	1.369
Congenital anomalies	1.011	1.013	1.011
Perinatal comorbidities	1.086	1.090	1.087
ILD	1.032	1.026	1.023
mean VIF	1.136	1.120	1.120

(Continued)

Subgroup - only-CMIT/MIT users			
Exposure status	1.392	1.342	1.344
Sex	1.012	1.008	1.012
Rural residence	1.010	1.022	1.012
Birth year	1.184	1.180	1.170
Birth time	1.479	1.424	1.434
Congenital anomalies	1.022	1.025	1.022
Perinatal comorbidities	1.085	1.106	1.090
ILD	1.018	1.027	1.017
mean VIF	1.150	1.142	1.138

VIF, variance inflation factor; ILD, Interstitial lung disease; AS, Asthma; AD, Atopic dermatitis; AR, Allergic rhinitis

Appendix2. Multicollinearity evaluations for Covariates, Multilevel interrupted Time series

VIF for Cox PH	No. of office visits for AS	Hospital days for AS	No. of office visits for AD	No. of office visits for AR
Total subjects				
Time_z	1.538	1.496	1.995	1.514
Exposure status	1.733	1.594	2.660	1.720
Sex	1.067	1.121	1.085	1.058
Rural residence	1.024	1.054	1.029	1.029
Birth year	1.008	1.047	1.020	1.008
Birth time	1.006	1.037	1.025	1.003
Congenital anomalies	1.149	1.179	1.330	1.173
Perinatal comorbidities	1.339	1.156	1.311	1.400
ILD	1.013	1.041	1.114	1.039
mean VIF	1.209	1.192	1.397	1.216
Subgroup -PHMG/PGH users				
Time_z	1.562	1.579	2.035	1.519
Exposure status	1.775	1.688	2.727	1.757
Sex	1.081	1.131	1.108	1.060
Rural residence	1.025	1.062	1.034	1.030
Birth year	1.009	1.043	1.028	1.009
Birth time	1.010	1.035	1.045	1.003
Congenital anomalies	1.160	1.191	1.333	1.182
Perinatal comorbidities	1.368	1.171	1.319	1.425
ILD	1.013	1.045	1.123	1.049
mean VIF	1.222	1.216	1.417	1.226

Subgroup - CMIT/MIT users				
Time_z	1.615	1.503	2.086	1.655
Exposure status	1.744	1.592	2.441	1.798
Sex	1.069	1.279	1.072	1.092
Rural residence	1.040	1.246	1.036	1.039
Birth year	1.031	1.134	1.078	1.026
Birth time	1.057	1.176	1.103	1.054
Congenital anomalies	1.187	1.336	1.246	1.202
Perinatal comorbidities	1.276	1.220	1.202	1.430
ILD	1.055	1.144	1.018	1.038
mean VIF	1.231	1.292	1.365	1.259

VIF, variance inflation factor; ILD, Interstitial lung disease; AS, Asthma; AD, Atopic dermatitis; AR, Allergic rhinitis

Asthma									
Age (months) at the end of follow-up	Pre-exposure			During exposure			Post exposure		
	Incident	Obs-months	Incidence (/1,000 obs-months)	Incident	Obs-months	Incidence (/1,000 obs-months)	Incident	Obs-months	Incidence (/1,000 obs-months)
0-12	37	5923	6.247	183	11939	15.328	41	2407	17.034
13-24	18	2557	7.039	157	8354	18.793	71	4402	16.129
25-60	33	2081	15.858	205	10439	19.638	241	18439	13.070
61-119	0	140	0.000	18	2290	7.860	118	31814	3.709
Total	87	10701	8.130	563	33022	17.049	353	57062	6.186
Atopic dermatitis									
Age (months) at the end of follow-up	Pre-exposure			During exposure			Post exposure		
	Incident	Obs-months	Incidence (/1,000 obs-months)	Incident	Obs-months	Incidence (/1,000 obs-months)	Incident	Obs-months	Incidence (/1,000 obs-months)
0-12	67	5709	11.736	108	11801	9.152	23	2420	9.504
13-24	9	2579	3.490	40	9366	4.271	14	5179	2.703
25-60	8	2265	3.532	38	15509	2.450	69	30308	2.277
61-119	0	187	0.000	9	4738	1.900	62	68044	0.911
Total	84	10740	7.821	195	41414	4.709	168	105951	1.586
Allergic rhinitis									

Age (months) at the end of follow-up	Pre-exposure			During exposure			Post exposure		
	Incident	Obs-months	Incidence (/1,000 obs-months)	Incident	Obs-months	Incidence (/1,000 obs-months)	Incident	Obs-months	Incidence (/1,000 obs-months)
0-12	21	5999	3.501	97	12341	7.860	31	2499	12.405
13-24	9	2745	3.279	83	9672	8.581	62	4827	12.844
25-60	22	2318	9.491	170	14636	11.615	312	22284	14.001
61-119	0	128	0.000	38	4055	9.371	329	32445	10.140
Total	52	11190	4.647	388	40704	9.532	734	62055	11.828

Appendix3. Time- dependent Cox Proportional hazard models for Subgroup

HR(95%CI)	PHMG/PGH		CMIT/MIT	
	Crude	Adjusted	Crude	Adjusted
Each Allergic disease				
Asthma(Pre, REF)				
During	1.957 (1.545 - 2.477)	1.989 (1.545 - 2.560)	2.313 (1.523 - 3.512)	2.415 (1.551 - 3.760)
Post	1.302 (1.003 - 1.690)	1.504 (1.113 - 2.033)	1.970 (1.252 - 3.098)	2.177 (1.296 - 3.657)
AD(Pre, REF)				
During	0.924 (0.706 - 1.211)	1.013 (0.725 - 1.417)	0.758 (0.486 - 1.185)	0.739 (0.427 - 1.278)
Post	0.746 (0.521 - 1.069)	0.889 (0.564 - 1.402)	0.729 (0.418 - 1.271)	0.665 (0.326 - 1.358)
AR(Pre, REF)				
During	1.849 (1.367 - 2.501)	1.726 (1.261 - 2.362)	1.984 (1.156 - 3.404)	1.911 (1.094 - 3.339)
Post	2.364 (1.728 - 3.233)	1.573 (1.115 - 2.220)	2.765 (1.586 - 4.821)	2.059 (1.127 - 3.761)
Interaction with AD				
Asthma(Pre, REF)				
During	2.022 (1.560 - 2.621)	2.037 (1.547 - 2.683)	2.279 (1.444 - 3.598)	2.355 (1.455 - 3.811)
Post	1.332 (1.001 - 1.771)	1.519 (1.099 - 2.098)	2.125 (1.302 - 3.469)	2.333 (1.346 - 4.044)
AD	1.538 (0.863 - 2.740)	1.469 (0.824 - 2.619)	1.595 (0.547 - 4.657)	1.575 (0.538 - 4.610)
During*AD	0.809 (0.436 - 1.501)	0.828 (0.446 - 1.536)	1.058 (0.345 - 3.242)	1.068 (0.347 - 3.284)
Post*AD	0.877 (0.468 - 1.643)	0.915 (0.488 - 1.715)	0.707 (0.223 - 2.244)	0.681 (0.214 - 2.169)
AR (Pre, REF)				
During	1.948 (1.400 - 2.709)	1.808 (1.285 - 2.543)	2.197 (1.205 - 4.008)	2.123 (1.144 - 3.941)
Post	2.498 (1.778 - 3.508)	1.662 (1.148 - 2.405)	3.154 (1.705 - 5.835)	2.369 (1.228 - 4.572)
AD	1.502 (0.703 - 3.209)	1.500 (0.702 - 3.205)	2.073 (0.583 - 7.370)	2.174 (0.610 - 7.748)
During*AD	0.692 (0.310 - 1.545)	0.713 (0.319 - 1.595)	0.515 (0.134 - 1.971)	0.494 (0.129 - 1.896)
Post*AD	0.688 (0.314 - 1.507)	0.688 (0.314 - 1.509)	0.436 (0.118 - 1.612)	0.403 (0.109 - 1.495)

HR, Hazard ratio;CI, HD, Humidifier disinfectant; AD, Atopic dermatitis; AR, Allergic rhinitis; PHMG, Polyhexamethylene guanidine; PGH, oligo- (2-(2-ethoxy)-ethoxyethyl) guanidine chloride; CMIT/MIT, Chloromethylisothiazolinone/ methylisothiazolinone

Appendix4. Multilevel interrupted time series for PHMG/PGH group

URR(95%CI)	HD and each Allergic disease		Interaction with AD	
	Crude	Adjusted	Crude	Adjusted
AS, Number of office visits				
Intercept	1.526 (1.292~ 1.802)	1.55 (1.308~ 1.837)	1.394 (1.139~ 1.707)	1.402 (1.142~ 1.721)
Age (months)	1.009 (0.883~ 1.152)	1.034 (0.906~ 1.181)	0.961 (0.814~ 1.134)	0.979 (0.829~ 1.156)
During exposure	1.299 (1.099~ 1.534)	1.282 (1.085~ 1.514)	1.425 (1.163~ 1.746)	1.421 (1.16~ 1.74)
Post-exposure	1.294 (1.095~ 1.528)	1.224 (1.037~ 1.446)	1.415 (1.156~ 1.732)	1.35 (1.102~ 1.653)
Age (months) * During exposure	1.029 (0.899~ 1.177)	1.023 (0.895~ 1.17)	1.088 (0.919~ 1.287)	1.087 (0.919~ 1.286)
Age (months) * Post-exposure	0.896 (0.784~ 1.023)	0.882 (0.772~ 1.007)	0.941 (0.797~ 1.111)	0.932 (0.789~ 1.101)
AD			1.394 (0.976~ 1.991)	1.446 (1.015~ 2.059)
Age (months) *AD			1.184 (0.9~ 1.558)	1.205 (0.917~ 1.582)
During exposure*AD			0.711 (0.497~ 1.017)	0.687 (0.482~ 0.981)
Post-exposure*AD			0.719 (0.503~ 1.027)	0.698 (0.49~ 0.995)
Age (months) * During exposure*AD			0.827 (0.626~ 1.092)	0.813 (0.616~ 1.073)
Age (months) * Post-exposure*AD			0.844 (0.641~ 1.111)	0.828 (0.63~ 1.088)
proportion reduction in variance	1.3%	15.0%	1.3%	15.0%
AR, Number of office visits				
Intercept	1.765 (1.564~ 1.991)	1.728 (1.525~ 1.958)	1.623 (1.396~ 1.886)	1.58 (1.355~ 1.842)
Age (months)	1.086 (0.998~ 1.181)	1.099 (1.011~ 1.196)	1.016 (0.915~ 1.129)	1.026 (0.923~ 1.14)
During exposure	1.153 (1.021~ 1.303)	1.145 (1.012~ 1.294)	1.261 (1.083~ 1.469)	1.256 (1.078~ 1.464)
Post-exposure	1.191 (1.056~ 1.343)	1.16 (1.027~ 1.309)	1.295 (1.115~ 1.504)	1.266 (1.089~ 1.472)
Age (months) * During exposure	0.963 (0.883~ 1.05)	0.959 (0.88~ 1.047)	1.026 (0.921~ 1.144)	1.026 (0.921~ 1.144)
Age (months) * Post-exposure	0.825 (0.758~ 0.898)	0.817 (0.751~ 0.889)	0.884 (0.795~ 0.982)	0.878 (0.79~ 0.976)
AD			1.27 (0.984~ 1.638)	1.295 (1.003~ 1.673)
Age (months) *AD			1.208 (1.013~ 1.442)	1.22 (1.021~ 1.457)
During exposure*AD			0.775 (0.599~ 1.003)	0.764 (0.59~ 0.99)
Post-exposure*AD			0.789 (0.611~ 1.017)	0.778 (0.603~ 1.004)
Age (months) * During exposure*AD			0.835 (0.696~ 1.002)	0.827 (0.688~ 0.993)
Age (months) * Post-exposure*AD			0.82 (0.687~ 0.98)	0.813 (0.68~ 0.971)
proportion reduction in variance	2.1%	7.1%	6.2%	13.1%

(Continued)

AD, Number of office visits		
Intercept	1.526 (1.292~ 1.802)	1.55 (1.308~ 1.837)
Age (months)	1.009 (0.883~ 1.152)	1.034 (0.906~ 1.181)
During exposure	1.299 (1.099~ 1.534)	1.282 (1.085~ 1.514)
Post-exposure	1.294 (1.095~ 1.528)	1.224 (1.037~ 1.446)
Age (months) * During exposure	1.029 (0.899~ 1.177)	1.023 (0.895~ 1.17)
Age (months) * Post-exposure	0.896 (0.784~ 1.023)	0.882 (0.772~ 1.007)
proportion reduction in variance	2.1%	7.1%

AS, Asthma; AD, Atopic dermatitis; AR, allergic rhinitis; URR, Utilization rate ratio; CI, Confidential index; Crude unadjusted; Adjusted, adjusted with sex, birth year, residential area, time at birth, Type of Humidifier disinfectants, Perinatal comorbidities, Congenital anomaly, Interstitial lung diseases

Appendix 5. Multilevel interrupted time series for CMIT/MIT group

URR(95%CI)	HD and each Allergic disease		Interaction with AD	
	Crude	Adjusted	Crude	Adjusted
AS, Number of office visits				
Intercept	1.589 (1.254~ 2.014)	1.656 (1.299~ 2.111)	1.587 (1.194~ 2.108)	1.652 (1.237~ 2.206)
Age (months)	1.14 (0.928~ 1.4)	1.152 (0.938~ 1.415)	1.216 (0.943~ 1.569)	1.224 (0.949~ 1.579)
During exposure	1.259 (0.992~ 1.597)	1.256 (0.99~ 1.593)	1.253 (0.941~ 1.669)	1.257 (0.944~ 1.673)
Post-exposure	1.254 (0.99~ 1.588)	1.214 (0.958~ 1.538)	1.236 (0.931~ 1.641)	1.199 (0.903~ 1.593)
Age (months) * During exposure	0.926 (0.752~ 1.142)	0.928 (0.754~ 1.144)	0.895 (0.69~ 1.16)	0.9 (0.694~ 1.166)
Age (months) * Post-exposure	0.779 (0.633~ 0.957)	0.775 (0.631~ 0.953)	0.735 (0.569~ 0.949)	0.735 (0.569~ 0.948)
AD			1.071 (0.641~ 1.791)	1.071 (0.641~ 1.789)
Age (months) *AD			0.847 (0.55~ 1.303)	0.857 (0.557~ 1.317)
During exposure*AD			0.956 (0.571~ 1.603)	0.945 (0.565~ 1.582)
Post-exposure*AD			0.987 (0.59~ 1.651)	0.983 (0.589~ 1.643)
Age (months) * During exposure*AD			1.082 (0.699~ 1.675)	1.072 (0.693~ 1.659)
Age (months) * Post-exposure*AD			1.155 (0.749~ 1.779)	1.142 (0.741~ 1.759)
proportion reduction in variance	-0.6%	9.3%	1.2%	10.5%
AR, Number of office visits				
Intercept	1.832 (1.453~ 2.309)	1.797 (1.418~ 2.278)	1.851 (1.349~ 2.539)	1.824 (1.323~ 2.516)
Age (months)	1.16 (0.981~ 1.371)	1.168 (0.988~ 1.381)	1.152 (0.921~ 1.44)	1.163 (0.929~ 1.455)
During exposure	1.136 (0.899~ 1.435)	1.136 (0.899~ 1.435)	1.119 (0.814~ 1.54)	1.117 (0.811~ 1.539)
Post-exposure	1.15 (0.913~ 1.448)	1.137 (0.903~ 1.433)	1.127 (0.822~ 1.546)	1.112 (0.81~ 1.527)
Age (months) * During exposure	0.907 (0.764~ 1.076)	0.905 (0.763~ 1.073)	0.914 (0.728~ 1.147)	0.911 (0.725~ 1.144)
Age (months) * Post-exposure	0.78 (0.66~ 0.923)	0.776 (0.657~ 0.918)	0.792 (0.634~ 0.991)	0.787 (0.629~ 0.985)
AD			0.987 (0.621~ 1.57)	0.979 (0.615~ 1.558)
Age (months) *AD			1.03 (0.734~ 1.446)	1.025 (0.73~ 1.44)
During exposure*AD			1.027 (0.643~ 1.641)	1.029 (0.644~ 1.646)
Post-exposure*AD			1.046 (0.659~ 1.661)	1.054 (0.663~ 1.674)
Age (months) * During exposure*AD			0.966 (0.683~ 1.367)	0.968 (0.683~ 1.37)
Age (months) * Post-exposure*AD			0.941 (0.67~ 1.323)	0.945 (0.672~ 1.328)
proportion reduction in variance	-2.9%	1.5%	-2.9%	1.5%

(Continued)

AD, Number of office visits		
Intercept	1.191 (0.612~ 2.319)	1.297 (0.662~ 2.542)
Age (months)	1.022 (0.594~ 1.758)	0.989 (0.576~ 1.699)
During exposure	1.1 (0.56~ 2.161)	1.152 (0.587~ 2.26)
Post-exposure	1.189 (0.608~ 2.325)	1.199 (0.612~ 2.351)
Age (months) * During exposure	0.977 (0.562~ 1.701)	1.028 (0.592~ 1.787)
Age (months) * Post-exposure	0.919 (0.532~ 1.587)	0.957 (0.555~ 1.65)
proportion reduction in variance	30.0%	50.0%

AS, Asthma; AD, Atopic dermatitis; AR, allergic rhinitis; URR, Utiliztion rate ratio; CI, Confidential index; Crude unadjusted; Adjusted, adjusted with sex, birth year, residential area, time at birth, Type of Humidifier disinfectants, Perinatal comorbidities, Congenital anomaly, Interstitial lung diseases

Appendix 3. number of Food allergy by definitions of other studies

Studies	**ICD-10 codes**	**n(%) in my study**
Oh et al 2024	Z910, T780, T781	2 (0.1%)
Noh et al 2023	T78.0, T78.1, L27.2, L23.6, K52.2, K52.3, K52.8, K52.9, Z91.0	284 (17.1%)
Oh et al 2024	T78.0, T78.1, L27.2, L23.6,K52.2, K52.3, K52.8, K52.9, Z91.0	284 (17.1%)
Kim et al 2023	T78.0, T78.1, L23.6, L24.6, L25.4, L27.2, K52.2	14 (0.8%)

ICD-10, International Classifications of Diseases-10th revision

ABSTRACT in Korean

소아에서 가습기 살균제 노출과 알레르기 질환과의 관련성 분석

서론: 가습기 살균제는 간질성 폐질환과 천식과 같은 호흡기 질환과 연관되어 있지만, 가습기 살균제 노출이 전체적인 알레르기 질환에 미치는 영향에 대한 연구는 제한적이다. 본 연구는 가습기 살균제 노출과 알레르기 질환의 발생 및 악화 간의 연관성을 조사하고, 가습기 살균제 노출이 흔히 “알레르기 행진”이라 불리는 알레르기 동반 질환의 자연 경과를 변경시키는지 평가하고자 한다.

방법: 2002년에서 2012년 사이에 태어나 가습기 살균제 피해자로 신고된 1,655명의 소아를 대상으로 코호트를 구성하였다. 알레르기 질환은 국민건강보험공단 청구 데이터를 이용해 확인하였으며, 120개월까지 추적 관찰을 진행하였다. 질병 발생 및 악화의 변화를 더 잘 파악하기 위해 노출 상태는 ‘노출 전’, ‘노출 중’, ‘노출 후’ 세 그룹으로 분류하였다. 알레르기 질환 발생은 시간 의존적 콕스 모델을 사용하여 분석하였고, 악화는 반복 측정 데이터를 활용해 다수준 단절 시계열 분석으로 평가하였다. 모든 분석에서는 아토피 피부염의 상호작용을 평가하였다. 또한 PHMG/PGH 및 CMIT/MIT에 대한 하위 그룹 분석을 통해 기전의 차이를 탐색하였다.

결과: 천식, 알레르기 비염, 아토피 피부염의 누적 발생률은 각각 67.9%, 71.1%, 27.2%로 나타났다. 시간 의존적 콕스 모델에서, 노출 중 천식(조정 위험비 [aHR] 2.126, 95% 신뢰구간 [CI] 1.681–2.688)과 알레르기 비염(aHR 1.671, 95% CI 1.250–2.234)의 발생이 유의하게 증가한 반면, 아토피 피부염은 유의한 연관성을 보이지 않았다. 노출 후에도 천식(aHR 1.794, 95% CI 1.359–2.368)과 알레르기 비염(aHR 1.559, 95% CI 1.135–2.141)의 발생률은 여전히 높았다. 다수준 단절 시계열 분석에서 AS와 AR의 월별 외래 방문 횟수는 노출 전과 비교하여, 노출 중에 각각 증가하였으며(aURR 1.218, 95% CI 1.051–1.410; aURR 1.143, 95% CI 1.031–1.279), 노출 후에도 증가가 관찰되었다(aURR 1.171, 95% CI 1.011–1.356; aURR 1.143, 95% CI 1.024–1.275). 그러나 노출 후 천식과 알레르기 비염의

월별 외래 방문 횟수 경향은 감소하였다 (aURR 0.849, 95% CI 0.754–0.956; aURR 0.815, 95% CI 0.755–0.880). 가습기 살균제 노출은 천식과 알레르기 비염의 발생 및 월별 외래 방문 횟수를 독립적으로 증가시켰으나, 아토피 피부염과의 유의한 상호작용은 관찰되지 않았다. 하위 그룹 분석에서도 이와 일관된 결과가 나타났으며, 두 그룹 간 기전의 차이는 관찰되지 않았다.

결론: 가습기 살균제 노출은 알레르기 질환의 전형적인 경과와는 독립적으로 천식과 알레르기 비염의 발생 및 악화를 유의하게 증가시키는 것으로 나타났으며, 가습기 살균제 유형 간의 차이는 관찰되지 않았다. 가습기 살균제와 관련된 알레르기 질환의 기전을 더 잘 이해하기 위한 추가 연구가 필요하며, 노출된 인구를 대상으로 선택 편향을 해결하고 작은 표본 크기의 한계를 극복할 수 있는 추가 연구도 필요하다.

키워드: 가습기 살균제; 알레르기 질환; 시간 의존적 Cox 비례 위험 모델; 다수준 단절 시계열 분석