BMJ Open Respiratory Research

Association between antibiotics and asthma risk among adults aged over 40 years: a nationally representative retrospective cohort study

Jiwon Choi [1,2] Sun Jae Park [1] Young Jun Park,[3] Jaeyi Hong,[4] Seogsong Jeong,[5] Jooyoung Chang,[1] Sung Min Kim,[1] Jihun Song,[1] Yoosun Cho,[6] Sang Min Park[1,7]

Correspondence to
Professor Sang Min Park;
smpark.snuh@gmail.com

ABSTRACT

Introduction Several studies have reported that exposure to antibiotics can lead to asthma during early childhood. However, the association between antibiotic use and risk of asthma in the adult population remains unclear. This study aimed to investigate the association between antibiotic use and asthma in adults.

Methods We used data from the National Health Insurance Service (NHIS)-Health Screening Cohort, which included participants aged ≥40 years who had health screening examination data in 2005–2006. A total of 248 961 participants with a mean age of 55.43 years were enrolled in this retrospective cohort study. To evaluate antibiotic exposure from the NHIS database for 5 years (2002–2006), cumulative usage and multiclass prescriptions were identified, respectively. During the follow-up period (2007–2019), 42 452 patients were diagnosed with asthma. A multivariate Cox proportional hazard regression model was used to assess the association between antibiotic use and newly diagnosed asthma.

Results Participants with antibiotic use for ≥91 days showed a higher risk of asthma (adjusted HR (aHR) 1.84, 95% CI 1.72 to 1.96) compared with participants who did not use antibiotics (n=38 450), with a duration-dependent association (p_{trend}<0.001). Furthermore, ≥4 antibiotic class user group had an increased risk of asthma (aHR 1.44, 95% CI 1.39 to 1.49) compared with one class of antibiotic use (n=64 698). Also, one class of antibiotic use had a higher risk of asthma (aHR 1.21, 95% CI 1.17 to 1.26) compared with non-users, and it also showed a duration-dependent relationship in all classes, including 1, 2, 3 and ≥4 class group (p_{trend}<0.001). The duration-response relationship between antibiotic use and increased risk of asthma remained in our sensitivity analyses with the washout and shifting of the index date.

Conclusions The duration-response pattern observed in antibiotic use and asthma may suggest the implication of proper antibiotic use and management in adults.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Numerous studies have shown that antibiotic use in newborns and early childhood can cause allergic reactions such as asthma; however, studies on the effects of antibiotics on asthma in adults are limited.

WHAT THIS STUDY ADDS

⇒ Similar to the results of a study in early childhood, our study showed a duration-dependent relationship between the use of antibiotics and asthma in adults aged over 40 years.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study suggests that the cumulative use of antibiotics in adults is associated with asthma; therefore, it can be used to guide and manage the proper use of antibiotics.

variable airflow restriction with respiratory symptoms.[1 2] The prevalence of asthma has been steadily increasing worldwide across all age groups over the past four decades.[3 4] In adults aged >64 years, asthma is an increasingly serious health problem with improved longevity in the total population.[5] The mortality rates for asthma were the highest in the ≥65 years age group. In addition, 40% of older adult patients with asthma experience their first onset after the age of 40 years.[4] Nevertheless, the pathophysiology of asthma in adults is relatively understudied.[4 6 7] Thus, identifying and managing the risk factors for asthma to reduce the adverse effects and related mortality among middle-aged adults are important.

Previous studies have suggested that high antibiotic exposure increases the risk of asthma. Accumulating pathophysiological and clinical evidence suggests that antibiotic use increases the prevalence of asthma in

INTRODUCTION

Asthma is an inflammatory disorder characterised by airway hyper-responsiveness and

early childhood.[8–11] Antibiotics trigger dysbiosis of bacterial communities, and early microbiome composition skews the developing immune system towards dysfunctional allergic responses.[12–14] The association between antibiotic use and development of asthma in early childhood may be explained by the hygiene hypothesis, which states that exposure to endotoxins in early childhood can lead to a decrease in T-helper 2 (Th2)-biased responses with the continual production of IgE.[10] A large twin study investigated the relationship between antibiotics and asthma based on prescription claims data considering environmental and genetic factors.[15] However, these associations have not been found in previous studies, particularly in adult populations. Although some studies did not consider the use of antibiotics to reduce respiratory symptoms, indicating asthmatic prognosis,[16 17] other studies based on self-reported antibiotic usage databases could have a high risk of recall bias.[18 19] Further studies are required to address these limitations.

Given the growing need for epidemiological evidence on the relationship between antibiotic exposure and the risk of asthma in adults, we aimed to evaluate the risk of incident asthma. We conducted an analysis of asthma risk using data from the National Health Insurance Service-Health Screening Cohort (NHIS-HEALS) in Korean middle-aged to older-aged adults based on (1) the cumulative antibiotic prescription days and (2) the number of classes of antibiotics.

METHODS
Study population
We collected data from the NHIS-HEALS (NHIS-2022-2-088) from 2002 to 2019. The NHIS offers compulsory health insurance and covers approximately 97% of the population.[10] In South Korea, biennial health screening programmes are offered to individuals aged ≥40 years and their dependents by the NHIS. From these health-screening programmes, the NHIS-HEALS includes data such as demographic variables, laboratory results, health behaviours, drug prescriptions, healthcare visits and mortality information for 2002–2019.

We included 350 608 participants with health screening data from 2005 to 2006. The participants who passed away before the index date of 1 January 2007 (n=982), who had an asthma diagnosis before the index date (n=40 671), who received antibiotics for respiratory symptoms before the index date (n=29 878), who had a previous chronic obstructive pulmonary disease (COPD) diagnosis before the index date (n=8508) and participants with missing variables (n=21 608) were excluded (figure 1).

Asthma diagnosed before the index date of 1 January 2007 was excluded according to the International Classification of Diseases, 10th edition (ICD-10) with J45 or J46 codes in the main diagnosis. To avoid reverse causation and potential biases of confounding by indication, we excluded participants who received antibiotics for respiratory symptoms, such as cough, wheezing, chest and
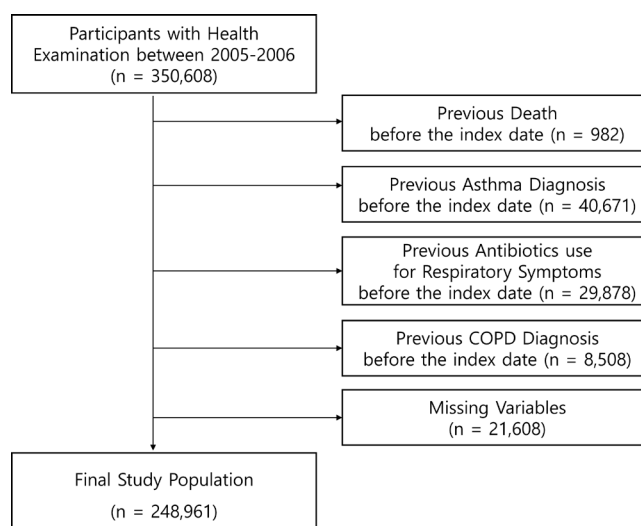

Figure 1 Selection of cohort study participants. COPD, chronic obstructive pulmonary disease.

acute upper or lower respiratory infections, including pneumonia.[9] Antibiotics for respiratory symptoms were identified with the J00-J22, R05, R062 and R0989 codes (ICD-10) with simultaneous prescriptions of antibiotics based on Anatomical Therapeutic Chemical (ATC) described in online supplemental table 1. COPD and asthma have similar overlapping symptoms, such as airway obstruction and inflammatory processes, making them difficult to diagnose in primary care settings.[20] Therefore, patients with COPD with the J44 code (ICD-10) were excluded. Ultimately, 248 961 participants were included in this retrospective cohort study as the baseline sample.

Key variables
Outcome variable
The main outcome of this study was newly diagnosed cases of asthma between 2007 and 2019. Asthma diagnoses were defined based on the medical treatment data using the ICD-10. Individuals newly diagnosed with asthma (ICD-10: J45) or status asthmaticus (ICD-10: J46) were considered with newly diagnosed asthma. We selected participants who were prescribed asthma medications, including tablet-based β2-agonists, inhaled β-agonists, leukotriene receptor antagonists, inhaled corticosteroids (ICSs) and ICSs with long-acting β2-agonists.[21–23] The participants were censored by an asthma event, death or 31 December 2019, whichever occurred first.

Exposure variable
The cumulative antibiotic prescription days and number of antibiotic classes from 2002 to 2006 were exposure variables that were defined individually in the NHIS database. Antibiotics were defined based on the ATC established by WHO. The antibiotics investigated in this study included *tetracyclines, macrolides, fluoroquinolones, penicillins, sulfonamides, lincosamides, vancomycin, carbapenems, cephalosporins,*

monobactams and *linezolid*, which are presented in . Antibiotic prescriptions for cumulative days were grouped into 0, 1–14, 15–30, 31–90 and ≥91 days, and the antibiotic classes were divided into 0, 1, 2, 3 and ≥4.

Covariates

The covariates included age, sex, residence, household income, smoking status, alcohol intake, physical activity, body mass index (BMI; kg/m^2), total cholesterol (mg/dL), systolic blood pressure (mm Hg), fasting serum glucose (mg/dL), number of healthcare visits, Carlson Comorbidity Index (CCI), previous atopic dermatitis (AD), previous allergic rhinitis (AR) and infectious diseases. To adjust for the indication of antibiotic use for infectious diseases, we included intra-abdominal infections; urinary tract infections; intestinal infectious diseases; skin, soft tissue, bone and joint infections and others[24 25] using ICD-10 codes along with the prescription of one or more antibiotics (Online supplemental table 2).

Household income was divided into quartiles based on insurance premium data and depicted from lowest to highest levels. BMI, blood pressure and total cholesterol levels were adjusted as surrogate markers for obesity and metabolic syndrome, which could be major risk factors for asthma.[26] The CCI, which considers a participant's health status based on various comorbid conditions, was adjusted using health claims records. The healthcare visit variable was the sum of the days the examinee visited a nursing institution for all types of treatment (first visit, revisit and admission) from 2002 to 2006.[10 27 28]

We drew a directed acyclic graph that included all covariates to determine the appropriate covariates and avoid duplicate variables (Online supplemental figure 1).

Statistical analysis

The clinical characteristics of the participants were compared with the cumulative number of days for which antibiotics were prescribed. The adjusted HRs (aHRs) and 95% CIs of asthma incidence and effects of antibiotic use were estimated using Cox proportional hazards regression. The proportional hazard assumption was tested statistically and visually using the Schoenfeld residual method. To identify the effects of antibiotic use on asthma incidence, we applied multivariate Cox proportional hazard regression analysis using two models.[24 25 29] Model 1 was adjusted for baseline characteristics, such as age, sex, residence, household income, smoking status, alcohol intake, physical activity, BMI, total cholesterol, systolic blood pressure, fasting serum glucose, CCI, number of healthcare visits, previous AD and previous AR. Last, we adjusted model 2 for the variables in model 1 plus infectious diseases such as intra-abdominal infections; urinary tract infections; intestinal infectious diseases; skin, soft tissue, bone and joint infections and others. In model 1, which did not incorporate infection adjustment that prompted antibiotic use, the analysis encompasses cases

without antibiotic prescriptions. In model 2, where infection adjustment was applied, the analysis did not include the antibiotic non-user but rather focused on the group who were prescribed antibiotics. Non-users of antibiotics were used as references to evaluate the risk of asthma and use of antibiotics. Additionally, each of the 1–14 antibiotic users and only one class of antibiotic users were used as references in all adjusted models, including infectious disease as an additional covariate (Online supplemental table 2).

For sensitivity analysis, we applied washout periods of 3, 4 and 5 years to minimise the likelihood of reverse causation and reduce protopathic bias. That is, we did not consider asthma events during the first 3–5 years of the follow-up period. We applied a washout period to prevent misinterpretation that the prestatus of the patient with asthma was prescribed antibiotics, which can be regarded as antibiotic use and can lead to asthma. In addition, we increased the exposure period to 6 and 7 years through shifting the index date and simultaneously shortening the follow-up period to adjust for antibiotic exposure after the index date. We attempted to verify whether the use of antibiotics after the index date showed the same tendency as an increased risk of asthma through increasing antibiotic exposure. Furthermore, stratified subgroup analyses were conducted for major covariates such as age, sex, residence, BMI, CCI, previous AD and history of AR. In addition, we conducted subgroup analyses for <2 and ≥2 years of asthma incidence based on cumulative days of antibiotics prescribed. Finally, we analysed a single specific class of antibiotic use and asthma risk compared with non-users of antibiotics. All statistical analyses were performed using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA) and R V.3.3.3 (www.r-project.org) software. Statistical significance was determined using a two-sided cut-off value of p<0.05.

Patient and public involvement statement

This study was a retrospective cohort study using data from the NHIS database, and because of the retrospective nature of the study, individual patients or the public were not allowed to access the study. The patients were not involved in the recruitment process or study. Data will be disseminated to the study participants through research publications and press release portals.

RESULTS

Table 1 shows the baseline characteristics of 248 961 cohort participants. During the observation period, 42 452 participants developed asthma. The median and IQR of follow-up times were summarised for each cumulative day of antibiotic administration. The antibiotic non-user group included 38 450 participants, and the antibiotic user groups categorised by cumulative days of antibiotic prescription consisted of 112 068 (1–14 days), 56 494 (15–30 days), 37 252 (31–90 days) and 4697 (≥91 days) participants. Compared with the antibiotic non-user

Table 1 Baseline characteristics of the study population

Characteristics	Total population	Cumulative days of antibiotics prescribed for 5 years before the index date				
		None	1–14 days	15–30 days	31–90 days	≥91 days
Number of participants, n	248 961	38 450	112 068	56 494	37 252	4697
Asthma events, n	42 452	3975	16 963	11 167	9058	1289
Median (IQR) of follow-up times	13.00 (12.93, 13.00)	13.00 (13.00, 13.00)	13.00 (13.00, 13.00)	13.00 (11.58, 13.00)	13.00 (9.25, 13.00)	13.00 (7.43, 13.00)
Age, years, mean±SD	55.43±8.91	54.51±8.75	55.07±8.79	55.82±8.97	56.62±9.14	57.21±9.32
Sex, n (%)						
Men	141 223 (56.72)	24 674 (64.17)	65 154 (58.14)	29 737 (52.64)	18 834 (50.56)	2824 (60.12)
Women	107 738 (43.28)	13 776 (35.83)	46 914 (41.86)	26 757 (47.36)	18 418 (49.44)	1873 (39.88)
Residence, n (%)						
Capital	41 843 (16.81)	6911 (17.97)	18 449 (16.46)	9407 (16.65)	6272 (16.84)	804 (17.12)
Metropolitan	112 290 (45.10)	17 293 (44.98)	50 672 (45.22)	25 475 (45.09)	16 751 (44.97)	2099 (44.69)
Rural	94 828 (38.09)	14 246 (37.05)	42 947 (38.32)	21 612 (38.26)	14 229 (38.20)	1794 (38.19)
Household income, n (%)						
First quartile (highest)	91 666 (36.82)	14 506 (37.73)	41 064 (36.64)	20 636 (36.53)	13 696 (36.77)	1764 (37.56)
Second quartile	73 016 (29.33)	10 791 (28.07)	32 969 (29.42)	16 875 (29.87)	10 997 (29.52)	1384 (29.47)
Third quartile	51 547 (20.70)	8063 (20.97)	23 255 (20.75)	11 693 (20.70)	7585 (20.36)	951 (20.25)
Fourth quartile (lowest)	32 732 (13.15)	5090 (13.24)	14 780 (13.19)	7290 (12.90)	4974 (13.35)	598 (12.73)
Smoking status, n (%)						
Never smoker	176 845 (71.03)	25 538 (66.42)	78 353 (69.92)	41 592 (73.62)	27 993 (75.14)	3369 (71.73)
Past smoker	22 918 (9.21)	3666 (9.53)	10 407 (9.29)	4956 (8.77)	3381 (9.08)	508 (10.82)
Current smoker	49 198 (19.76)	9246 (24.05)	23 308 (20.80)	9946 (17.61)	5878 (15.78)	820 (17.46)
Alcohol intake, times/week, n (%)						
0	181 804 (73.03)	26 596 (69.17)	80 521 (71.85)	42 254 (74.79)	28 769 (77.23)	3664 (78.01)
1–2	42 198 (16.95)	7528 (19.58)	19 690 (17.57)	8894 (15.74)	5403 (14.50)	683 (14.54)
3–4	16 000 (6.43)	2804 (7.29)	7588 (6.77)	3412 (6.04)	1974 (5.30)	222 (4.73)
≥5	8959 (3.60)	1522 (3.96)	4269 (3.81)	1934 (3.42)	1106 (2.97)	128 (2.73)
Physical activity, times/week, n (%)						
0	123 288 (49.52)	18 906 (49.17)	55 658 (49.66)	28 003 (49.57)	18 390 (49.37)	2331 (49.63)
1–2	68 684 (27.59)	11 336 (29.48)	31 168 (27.81)	15 222 (26.94)	9725 (26.11)	1233 (26.25)
3–4	31 045 (12.47)	4657 (12.11)	13 812 (12.32)	7132 (12.62)	4840 (12.99)	604 (12.86)
≥5	25 944 (10.42)	3551 (9.24)	11 430 (10.20)	6137 (10.86)	4297 (11.53)	529 (11.26)
Body mass index, kg/m^2, mean±SD	23.95±2.86	23.75±2.90	23.90±2.85	24.03±2.86	24.12±2.85	24.17±2.90
Total cholesterol, mg/dL, mean±SD	198.75±36.68	198.16±36.60	198.63±36.59	198.93±36.65	199.40±36.94	199.03±37.63
Systolic blood pressure, mm Hg, mean±SD	126.04±16.68	126.93±17.14	126.06±16.68	125.68±16.58	125.64±16.38	125.90±16.31
Fasting serum glucose, mg/dL, mean±SD	98.32±27.21	97.82±26.27	98.15±26.88	98.48±27.16	98.96±28.49	99.82±32.20
Number of healthcare visits*, mean±SD	73.13±75.99	39.05±51.99	58.47±60.32	85.02±74.26	121.36±94.51	176.03±120.70
Charlson Comorbidity Index, n (%)						
0	74 640 (29.98)	18 829 (48.97)	37 771 (33.70)	11 981 (21.21)	5472 (14.69)	587 (12.50)
1	67 324 (27.04)	9658 (25.12)	31 579 (28.18)	15 965 (28.26)	9109 (24.45)	1013 (21.57)
≥2	106 997 (42.98)	9963 (25.91)	42 718 (38.12)	28 548 (50.53)	22 671 (60.86)	3097 (65.94)
Previous atopic dermatitis, n (%)						
No	240 200 (96.48)	37 639 (97,89)	108 618 (96.92)	54 230 (95.99)	35 322 (94.82)	4391 (93.49)
Yes	8761 (3.52)	811 (2.11)	3450 (3.08)	2264 (4.01)	1930 (5.18)	306 (6.51)
Previous allergic rhinitis, n (%)						
No	108 289 (43.50)	25 039 (65.12)	53 410 (47.66)	19 342 (34.24)	9486 (25.46)	1012 (21.55)

Continued

Table 1 Continued

		Cumulative days of antibiotics prescribed for 5 years before the index date				
Characteristics	Total population	None	1–14 days	15–30 days	31–90 days	≥91 days
Yes	140 672 (56.50)	13 411 (34.88)	58 658 (52.34)	37 152 (65.76)	27 766 (74.54)	3685 (78.45)
Intra-abdominal infections, n (%)						
No	248 837 (99.95)	38 450 (100.00)	112 035 (99.97)	56 458 (99.94)	37 206 (99.88)	4688 (99.81)
Yes	124 (0.05)		33 (0.03)	36 (0.06)	46 (0.12)	9 (0.19)
Urinary tract infections, n (%)						
No	247 005 (99.21)	38 450 (100.00)	111 658 (99.63)	55 905 (98.96)	36 455 (97.86)	4537 (96.59)
Yes	1956 (0.79)		410 (0.37)	589 (1.04)	797 (2.14)	160 (3.41)
Intestinal infectious diseases, n (%)						
No	248 118 (99.66)	38 450 (100.00)	111 693 (99.67)	56 273 (99.61)	37 029 (99.40)	4673 (99.49)
Yes	843 (0.34)		375 (0.33)	221 (0.39)	223 (0.60)	24 (0.51)
Skin, soft tissue, bone and joint infections, n (%)						
No	247 457 (99.40)	38 450 (100.00)	111 604 (99.59)	56 018 (99.16)	36 772 (98.71)	4613 (98.21)
Yes	1504 (0.60)		464 (0.41)	476 (0.84)	480 (1.29)	84 (1.79)
Other infectious diseases, n (%)						
No	247 751 (99.51)	38 450 (100.00)	111 852 (99.81)	56 200 (99.48)	36 743 (98.63)	4506 (95.93)
Yes	1210 (0.49)		216 (0.19)	294 (0.52)	509 (1.37)	191 (4.07)

*The number of healthcare visits is the summation of days the examinee visited a nursing institution for all types of treatment (first visit, revisit and admission) from 2002 to 2006; n indicates number of people.

group, higher antibiotic use had an increased tendency of number of healthcare visits (none, 39.05±51.99; ≥91 days, 176.03±120.70), CCI with ≥2 (none, 25.91%; ≥91 days, 65.94%) and previous AR (none, 34.88%; ≥91 days, 78.45%).

Table 2 shows the relationship between the cumulative number of days of antibiotic prescription and incidence of asthma. The adjusted multivariable Cox proportional hazards model (model 1) showed an increased risk of

asthma in the ≥91 days of the antibiotic-exposed group, compared with the antibiotic non-user (aHR 1.84, 95% CI 1.72 to 1.96). The adjusted multivariable Cox proportional hazard model adjusting for infectious diseases (model 2) showed an increased risk of asthma in the ≥91 days of antibiotic exposure (aHR 1.46, 95% CI 1.38 to 1.55). In model 2, the cumulative days of 1–14 groups were used as a reference for the antibiotic user groups with the lowest usage. A clear duration-dependent

Table 2 Risk for asthma according to cumulative days of antibiotics prescribed

	Cumulative days of antibiotics prescribed for 5 years before the index date					P for trend
	None	1–14 days	15–30 days	31–90 days	≥91 days	
Number of participants, n	38 450	112 068	56 494	37 252	4697	
Events, n	3975	16 963	11 167	9058	1289	
Person-years	454 255	1 288 569	629 744	399 519	48 171	
Incidence/1000 person-years	8.75	13.16	17.73	22.67	26.76	
aHR (95% CI)						
Model 1*	1.00 (ref)	1.28 (1.23 to 1.32)	1.49 (1.44 to 1.55)	1.69 (1.63 to 1.76)	1.84 (1.72 to 1.96)	<0.001
Model 2†		1.00 (ref)	1.17 (1.15 to 1.20)	1.34 (1.30 to 1.37)	1.46 (1.38 to 1.55)	<0.001

The aHRs were calculated by Cox proportional hazards regression after adjustments for multivariate variables. Model 1 was adjusted for age, sex, residence, household income, smoking status, alcohol intake, physical activity, body mass index, total cholesterol, systolic blood pressure, fasting serum glucose, Charlson Comorbidity Index, the number of healthcare visits, previous atopic dermatitis and previous allergic rhinitis. Model 2 was adjusted for the variables in model 1 plus infectious diseases (intra-abdominal infections, urinary tract infections, intestinal infectious diseases, skin, soft tissue, bone and joint infections and others); n, indicates number of people.
*Antibiotics non-user group was set as a reference group.
†Antibiotics 1–14 days user group was set as a reference group.
aHR, adjusted HR; ref, reference.

Table 3 Sensitivity analysis of risk for asthma according to cumulative days of antibiotics prescribed

aHR (95% CI)	Total	Events	Cumulative days of antibiotics prescribed for 5 years before the index date					P for trend
			None	1–14 days	15–30 days	31–90 days	≥91 days	
Washout period (years)								
Model 1*								
3	237 630	31 121	1.00 (ref)	1.26 (1.21 to 1.31)	1.46 (1.40 to 1.52)	1.61 (1.54 to 1.69)	1.71 (1.58 to 1.84)	<0.001
4	234 170	27 661	1.00 (ref)	1.25 (1.20 to 1.31)	1.45 (1.39 to 1.52)	1.60 (1.53 to 1.68)	1.67 (1.54 to 1.82)	<0.001
5	230 763	24 254	1.00 (ref)	1.24 (1.19 to 1.30)	1.44 (1.37 to 1.51)	1.60 (1.52 to 1.68)	1.62 (1.48 to 1.78)	<0.001
Model 2†								
3	200 084	28 050		1.00 (ref)	1.17 (1.13 to 1.20)	1.30 (1.26 to 1.34)	1.38 (1.28 to 1.48)	<0.001
4	196 930	24 896		1.00 (ref)	1.16 (1.13 to 1.20)	1.29 (1.25 to 1.34)	1.35 (1.25 to 1.46)	<0.001
5	193 821	21 787		1.00 (ref)	1.16 (1.13 to 1.20)	1.30 (1.25 to 1.34)	1.32 (1.22 to 1.44)	<0.001
Shifting the index date								
Model 1*								
6-year exposure	233 495	36 462	1.00 (ref)	1.36 (1.29 to 1.43)	1.65 (1.57 to 1.73)	1.91 (1.82 to 2.01)	2.12 (1.99 to 2.27)	<0.001
7-year exposure	224 315	31 620	1.00 (ref)	1.38 (1.29 to 1.48)	1.64 (1.54 to 1.76)	2.00 (1.87 to 2.14)	2.33 (2.16 to 2.51)	<0.001
Model 2†								
6-year exposure	211 131	34 602		1.00 (ref)	1.22 (1.19 to 1.25)	1.42 (1.38 to 1.46)	1.58 (1.51 to 1.67)	<0.001
7-year exposure	210 207	30 671		1.00 (ref)	1.20 (1.16 to 1.24)	1.46 (1.42 to 1.51)	1.71 (1.63 to 1.79)	<0.001

The aHRs were calculated by Cox proportional hazards regression after adjustments for multivariate variables. Model 1 was adjusted for age, sex, residence, household income, smoking status, alcohol intake, physical activity, body mass index, total cholesterol, systolic blood pressure, fasting serum glucose, Charlson Comorbidity Index, the number of healthcare visits, previous atopic dermatitis and previous allergic rhinitis. Model 2 was adjusted for the variables in model 1 plus infectious diseases (intra-abdominal infections, urinary tract infections, intestinal infectious diseases, skin, soft tissue, bone and joint infections and others).
*Antibiotics non-user group was set as a reference group.
†Antibiotics 1–14 days user group was set as a reference group.
aHR, adjusted HR; ref, reference.

pattern between antibiotic use and asthma incidence was observed in both models (p<0.001).

Table 3 presents the sensitivity analysis of asthma risk based on the cumulative number of days antibiotics were prescribed. We conducted a washout period analysis using 3-year, 4-year and 5-year periods. Considering the 3-year, 4-year and 5-year washout periods, the aHRs in ≥91 days were 1.71 (95% CI 1.58 to 1.84), 1.67 (95% CI 1.54 to 1.82) and 1.62 (95% CI 1.48 to 1.78) in model 1. In model 2, with additional adjustments for infectious diseases, an increasing trend remained. We also conducted analyses through shifting the index date to consider exposure to antibiotics after the index date. Adjusted for 6-year and 7-year antibiotic exposure, the aHRs in ≥91 days were 2.12 (95% CI 1.99 to 2.27) and 2.33 (95% CI 2.16 to 2.51) when compared with non-users. It remained in model

2 with additional adjustments for infectious diseases. Compared with the 5-year baseline exposure, the 6-year and 7-year antibiotic exposure remained at an increased risk of asthma incidence based on the cumulative days of antibiotics prescribed.

Table 4 describes the association between the number of antibiotic classes and the incidence of asthma. In model 1, more than four antibiotic class users showed an increased risk of asthma (aHR 1.72, 95% CI 1.65 to 1.80) compared with the antibiotic non-user group. In model 2, participants who used ≥4 antibiotic classes showed a higher risk of asthma (aHR 1.44, 95% CI 1.39 to 1.49) compared with one class of antibiotic use.

Online supplemental table 3 depicts the subgroup analyses stratified by major covariates, such as age, sex, residence, BMI, CCI, previous AD and previous AR.

Table 4 Risk for asthma according to the number of antibiotic classes prescribed

	Number of antibiotic classes prescribed during 5 years before the index date					P for trend
	None	**1**	**2**	**3**	**≥4**	
Number of participants, n	38 450	64 698	69 746	50 420	25 647	
Events, n	3975	9023	12 196	10 800	6458	
Person-years	454 255	747 146	788 765	555 094	274 997	
aHR (95% CI)						
Model 1*	1.00 (ref)	1.21 (1.17 to 1.26)	1.39 (1.34 to 1.44)	1.56 (1.51 to 1.62)	1.72 (1.65 to 1.80)	<0.001
Model 2†		1.00 (ref)	1.15 (1.12 to 1.18)	1.30 (1.27 to 1.34)	1.44 (1.39 to 1.49)	<0.001

The aHRs were calculated by Cox proportional hazards regression after adjustments for multivariate variables. Model 1 was adjusted for age, sex, residence, household income, smoking status, alcohol intake, physical activity, body mass index, total cholesterol, systolic blood pressure, fasting serum glucose, Charlson Comorbidity Index, the number of healthcare visits, previous atopic dermatitis and previous allergic rhinitis. Model 2 was adjusted for the variables in model 1 plus infectious diseases (intra-abdominal infections, urinary tract infections, intestinal infectious diseases, skin, soft tissue, bone and joint infections and others); n indicates number of people.
Antibiotics were divided into 11 classes consisting of penicillin, cephalosporin, macrolide, fluoroquinolone, sulfonamides, tetracyclines and lincosamides or others.
*Antibiotics non-user group was set as a reference group.
†Antibiotics 1–14 days user group was set as a reference group.
aHR, adjusted HR; ref, reference.

In addition, regarding sex, a previous study reported that different directions exist for the modifiable risk of asthma; therefore, a stratified analysis for sex was conducted[7 30] (Online supplemental table 4). The risk of asthma showed an increasing trend in the overall stratified covariates as the cumulative days of antibiotic use increased (p<0.001). In the longer antibiotic use group (≥91 days), those who have CCI group (≥2) showed a higher risk of asthma (aHR 1.91, 95% CI 1.75 to 2.08) than those who do not have CCI (aHR 1.50, 95% CI 1.23 to 1.83). In all the antibiotic user groups, those who did not have previous AD or AR had a higher risk of asthma than those who had previous AD or AR.

Online supplemental table 5 presents the subgroup analyses for the <2 and ≥2 years of newly diagnosed asthma incidence based on the cumulative number of days of antibiotics prescribed. For ≥2 years, the ≥91 days of antibiotic exposure seemed to have a higher risk of asthma (aHR 1.37, 95% CI 1.28 to 1.47) compared with 1–14 days. The aHR was higher in the asthma incidence for ≥2 years than for <2 years for all cumulative days of antibiotic prescription.

Online supplemental table 6 describes the risk of a single specific class of antibiotics compared with the antibiotic non-user group. The results showed that only users of macrolides (aHR 1.14, 95% CI 1.07 to 1.23), fluoroquinolones (aHR 1.16, 95% CI 1.10 to 1.23), penicillins (aHR 1.20, 95% CI 1.15 to 1.26) and cephalosporins (aHR 1.18, 95% CI 1.12 to 1.24) had a higher risk of asthma compared with non-users of antibiotics.

DISCUSSION

In our retrospective cohort study comprising adults aged ≥40 years, increasing cumulative prescription days and the number of classes of antibiotic use increased the risk of asthma incidence. We also adjusted for potential confounders, including specific infectious diseases that could indicate antibiotic use. Our findings were consistent with those of additional analyses with different washout periods until asthma development or an extended duration of antibiotic exposure. To the best of our knowledge, this is the first study to report a positive relationship between antibiotic exposure and new-onset asthma in adults.

Our results correspond to those of previous cohort studies showing that antibiotic use in early life can induce the development of asthma, although most of them focused on asthma incidence in early childhood.[31–33] A prospective cohort study based on 493 785 children born in 2006–2010 by Örtqvist et al[34] showed an increasing relationship between exposure to antibiotics during infancy or childhood and subsequent asthma risk. However, our study stands out, as we considered a different age group (≥40 years) and investigated antibiotic exposures for 5 years and more (6 years, 7 years).

The relevant mechanism proposed for the relationship between antibiotics and asthma in adults has not been completely elucidated; however, the following mechanisms have been suggested. Antibiotics may affect global alterations in microbial communities[35 36] and can cause allergic reactions. The microbial diversity hypothesis suggests that a decline in the variability of microbiota consequently increases allergy.[37] Changes in the gastrointestinal microbiota composition, particularly

the reduction of *Lachnospira* and *Clostridium,* are associated with allergic diseases such as asthma.[38 39] The gut microbiota, such as *Bacteroides fragilis,* influences the balance between Th1 and Th2 and confers protection against allergic airway disorders.[40–42] The gut-lung axis strongly suggests a major role in respiratory diseases resulting from interactions between the different microbiome compositions of both the gut and lungs.[43] In addition, specific airway microbiome composition such as increased Proteobacteria, *Haemophilus parainfluenzae* and *Neisseria* may lead to bronchial hyper-responsiveness and airway allergic responses in adults with asthma.[44–46] The hygiene hypothesis states that exposure to endotoxins during early life can induce Th1 lymphocytes, reduce Th2-biased responses and produce persistent IgE.[10 47] Antibiotics administered in early childhood can induce allergic reactions through increasing IgE levels and Th2-mediated responses via reducing the Th1 response, which reacts competitively. Other studies have shown that both adult and neonatal mice treated with antibiotic have elevated IgE levels in the blood, and increased Th2 responses can result in severe airway inflammation that can be aggravated by basophil-bound IgE in a papain model of allergic airway inflammation.[8 48] However, these biological plausibilities have not been verified in humans. Further human-targeted studies are required to elucidate these pathophysiological mechanisms.

Our study had several strengths. We conducted a large population-based study using the NHIS database. It offers numerous precise prescriptions or medical records that can minimise the recall bias of antibiotic use. Sensitivity analyses, such as the washout period and shifting index date with a follow-up duration of >10 years, can strengthen the credibility of our results. In addition, we performed a stratified analysis of major covariates such as age, sex, residence, BMI, CCI, previous AD and previous AR. Furthermore, to increase the accuracy of new-onset asthma detection during the follow-up period, we defined asthma diagnosis based on ICD-10 codes and asthma drug prescriptions. In addition, we excluded previous COPD diagnoses and antibiotic use for respiratory symptoms from our sample selection process to exclude participants with possible underlying asthma precursor symptoms. Moreover, we examined both the cumulative use and number of classes of antibiotics, which fortified our hypothesis. We also described the association between a single specific class of antibiotics and asthma risk. Our findings are consistent with those of a previous study that reported an increased risk of asthma development associated with the use of penicillins and macrolides.[49]

In the stratified analysis, the residential area and BMI were unlikely to affect the relationship between antibiotics and asthma. However, age, sex, CCI, previous AD and previous AR may influence interactions between antibiotics and asthma. We included previous AD and AR as covariates because these factors are prerequisites for asthma development.[50 51] AD is generally considered a precursor to other atopic disorders,[52] and our study supports the hypothesis that AD is influenced by the association between antibiotics and asthma.

However, this study has some limitations. First, some risk factors for asthma, such as air pollution, occupational risk, genetics and family history, were not considered as the risk factors were not available in our claims data. Additionally, overcrowded living environments with air pollution or poor hygiene conditions can lead to antibiotic use and asthma.[53] To overcome air pollution and living environments as confounders, we used residence variables (capital, metropolitan and rural) as surrogate factors and conducted stratified analyses. Work environment is a potential risk factor for asthma; however, occupational asthma is often underdiagnosed.[54 55] Therefore, follow-up studies that include potential covariates of asthma are required. Second, although we excluded participants with antibiotic use for respiratory symptoms and a previous diagnosis of COPD, bias due to reverse causation in patients with undiagnosed asthma could exist. To overcome this shortcoming, we conducted a sensitivity analysis with an adjusted 3-year to 5-year washout period. Third, confusing viral infections and asthma symptoms with antibiotic use may lead to missed cases where antibiotics are wrongly prescribed for asthma, despite clinical guidelines stating otherwise. Viral infections could easily be confused with asthma symptoms, and they could occur simultaneously regarding the upper respiratory tract because they both invoke coughing, sneezing and even wheezing. Reversible airway limitation is the key pathophysiology of asthma, but this aspect could also easily be found in viral infections. Therefore, the misapplication of antibiotics for asthma may be a potential bias and limitation in our study. Fourth, accuracy uncertainty exists in the definition of asthma in the NHIS database. For example, differentiating the diagnosis of asthma and COPD is difficult in primary care[56 57] because COPD is a respiratory disease that is difficult to distinguish from asthma. In addition, inconsistencies between the diagnoses of infectious diseases and prescribed antibiotics may exist in the claims database. Finally, measures using self-reported questionnaires, such as health behaviours (drinking, smoking and physical activity), could be partially inaccurate. Therefore, this could lead to underreporting of risky health behaviours.

This retrospective cohort study showed an association between the cumulative use of antibiotics, number of antibiotics used and asthma incidence in adults aged ≥40 years. Our results suggest that antibiotic use could possibly increase the risk of asthma in a duration-response relationship; therefore, using antibiotics appropriately and responsibly with caution in clinical settings to prevent newly diagnosed asthma, particularly in adults, is necessary.

Author affiliations
[1]Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, The Republic of Korea

²Department of Public Health Science, Seoul National University, Gwanak-gu, The Republic of Korea

³Medical Research Center, Genomic Medicine Institute, Seoul National University, Seoul, The Republic of Korea

⁴Department of Statistics, University of Illinois at Urbana-Champaign, Urbana, Illinois, USA

⁵Department of Biomedical Informatics, CHA University School of Medicine, Seongnam, The Republic of Korea

⁶Total Healthcare Center, Kangbuk Samsung Hospital,Sungkyunkwan University School of Medicine, Seoul, The Republic of Korea

⁷Department of Family Medicine, Seoul National University Hospital, Jongno-gu, The Republic of Korea

ORCID iDs
Jiwon Choi http://orcid.org/0009-0003-2466-6229
Sun Jae Park http://orcid.org/0000-0001-8205-9556

REFERENCES

1. Hargreave FE, Nair P. The definition and diagnosis of asthma. *Clin Experimental Allergy* 2009;39:1652–8. 10.1111/j.1365-2222.2009.03321.x Available: https://onlinelibrary.wiley.com/toc/13652222/39/11
2. Mims JW. Definitions and pathophysiology. *Int Forum Allergy Rhinol* 2015;5. 10.1002/alr.21609 Available: https://onlinelibrary.wiley.com/toc/20426984/5/S1
3. Rodrigo GJ, Rodrigo C, Hall JB. Acute asthma in adults: a review. *Chest* 2004;125:1081–102.
4. Hanania NA, King MJ, Braman SS, et al. Asthma in the elderly: Current understanding and future research needs—a report of a national Institute on aging (NIA) workshop. *J Allergy Clin Immunol* 2011;128(3 Suppl):S4–24.
5. Gibson PG, McDonald VM, Marks GB. Asthma in older adults. *The Lancet* 2010;376:803–13.
6. Song W-J, Kang M-G, Chang Y-S, et al. Epidemiology of adult asthma in Asia: toward a better understanding. *Asia Pac Allergy* 2014;4:75–85.
7. Park S, Jung S-Y, Kwon J-W. Sex differences in the association between asthma incidence and Modifiable risk factors in Korean middle-aged and older adults: NHIS-HEALS 10-year cohort. *BMC Pulm Med* 2019;19:1–10.
8. Wypych TP, Marsland BJ. Antibiotics as Instigators of microbial dysbiosis: implications for asthma and allergy. *Trends Immunol* 2018;39:697–711.
9. Patrick DM, Sbihi H, Dai DLY, et al. Decreasing antibiotic use, the gut Microbiota, and asthma incidence in children: evidence from population-based and prospective cohort studies. *Lancet Respir Med* 2020;8:1094–105.
10. Han K, Kim SW. Effects of antibiotics on the development of asthma and other allergic diseases in children and adolescents. *Allergy Asthma Immunol Res* 2018;10:457–65.
11. Droste JHJ, Wieringa MH, Weyler JJ, et al. Does the use of antibiotics in early childhood increase the risk of asthma and allergic disease *Clin Experimental Allergy* 2000;30:1548–53.
12. Strzępa A, Lobo FM, Majewska-Szczepanik M, et al. Antibiotics and autoimmune and allergy diseases: causative factor or treatment? *Int Immunopharmacol* 2018;65:328–41.
13. Francino MP. Antibiotics and the human gut Microbiome: Dysbioses and accumulation of resistances. *Front Microbiol* 2015;6.
14. Tsakok T, McKeever TM, Yeo L, et al. Does early life exposure to antibiotics increase the risk of Eczema? A systematic review. *Br J Dermatol* 2013;169:983–91.
15. Slob EMA, Brew BK, Vijverberg SJH, et al. Early-life antibiotic use and risk of asthma and Eczema: results of a discordant twin study. *Eur Respir J* 2020;55.
16. Pitter G, Ludvigsson JF, Romor P, et al. Antibiotic exposure in the first year of life and later treated asthma, a population based birth cohort study of 143,000 children. *Eur J Epidemiol* 2016;31:85–94.
17. Ahmadizar F, Vijverberg SJH, Arets HGM, et al. Early life antibiotic use and the risk of asthma and asthma exacerbations in children. *Pediatr Allergy Immunol* 2017;28:430–7.
18. Risnes KR, Belanger K, Murk W, et al. Antibiotic exposure by 6 months and asthma and allergy at 6 years: findings in a cohort of 1,401 US children. *Am J Epidemiol* 2011;173:310–8.
19. Foliaki S, Pearce N, Björkstén B, et al. Antibiotic use in infancy and symptoms of asthma, Rhinoconjunctivitis, and Eczema in children 6 and 7 years old: International study of asthma and allergies in childhood phase III. *J Allergy Clin Immunol* 2009;124:982–9.
20. Postma DS, Rabe KF. The asthma–COPD overlap syndrome. *N Engl J Med* 2015;373:1241–9.
21. Kim SY, Lim H, Lim J-S, et al. Analysis of the relationship between adult asthma and stroke: a longitudinal follow-up study using the Korean national sample cohort. *Biomed Res Int* 2019.
22. Kim J-H, Wee J-H, Choi HG, et al. Association between Statin medication and asthma/asthma exacerbation in a national health screening cohort. *J Allergy Clin Immunol Pract* 2021;9:2783–91.
23. Kim SY, Min C, Oh DJ, et al. Bidirectional association between asthma and Migraines in adults: two longitudinal follow-up studies. *Sci Rep* 2019;9:1–9.
24. Park SJ, Park YJ, Chang J, et al. Association between antibiotics use and diabetes incidence in a nationally representative retrospective cohort among Koreans. *Sci Rep* 2021;11:1–10.
25. Kim M, Park SJ, Choi S, et al. Association between antibiotics and dementia risk: A retrospective cohort study. *Front Pharmacol* 2022;13.
26. Peters U, Dixon AE, Forno E. Obesity and asthma. *J Allergy Clin Immunol* 2018;141:1169–79.
27. Nguyen K, Zahran H, Iqbal S, et al. Factors associated with asthma control among adults in five New England States, 2006–2007. *J Asthma* 2011;48:581–8.

28 Mäkikyrö EMS, Jaakkola MS, Jaakkola JJK. Subtypes of asthma based on asthma control and severity: a latent class analysis. *Respir Res* 2017;18:24:24.:.

29 Kim M, Park SJ, Choi S, *et al*. Association of antibiotic use with risk of lung cancer: A nationwide cohort study. *J Infect Public Health* 2023;16:1123–30.

30 Kynyk JA, Mastronarde JG, McCallister JW. Asthma, the sex difference. *Curr Opin Pulm Med* 2011;17:6–11.

31 Celedón JC, Fuhlbrigge A, Rifas-Shiman S, *et al*. Antibiotic use in the first year of life and asthma in early childhood. *Clin Experimental Allergy* 2004;34:1011–6. 10.1111/j.1365-2222.2004.01994.x Available: https://onlinelibrary.wiley.com/toc/13652222/34/7

32 Kozyrskyj AL, Ernst P, Becker AB. Increased risk of childhood asthma from antibiotic use in early life. *Chest* 2007;131:1753–9.

33 Hoskin-Parr L, Teyhan A, Blocker A, *et al*. Antibiotic exposure in the first two years of life and development of asthma and other allergic diseases by 7.5 yr: a Dose-Dependent relationship. *Pediatr Allergy Immunol* 2013;24:762–71.

34 Örtqvist AK, Lundholm C, Kieler H, *et al*. Antibiotics in fetal and early life and subsequent childhood asthma: nationwide population based study with Sibling analysis. *BMJ* 2014;349:g6979.

35 Ding C, He J. Effect of antibiotics in the environment on microbial populations. *Appl Microbiol Biotechnol* 2010;87:925–41.

36 Modi SR, Collins JJ, Relman DA. Antibiotics and the gut Microbiota. *J Clin Invest* 2014;124:4212–8.

37 Legatzki A, Rösler B, von Mutius E. Microbiome diversity and asthma and allergy risk. *Curr Allergy Asthma Rep* 2014;14:466.

38 Gholizadeh P, Mahallei M, Pormohammad A, *et al*. Microbial balance in the intestinal Microbiota and its association with diabetes, obesity and allergic disease. *Microb Pathog* 2019;127:48–55.

39 Frati F, Salvatori C, Incorvaia C, *et al*. *The Role of the Microbiome in Asthma: The Gut* 2018;20:123.

40 Ni J, Friedman H, Boyd BC, *et al*. Early antibiotic exposure and development of asthma and allergic rhinitis in childhood. *BMC Pediatr* 2019;19.

41 Bengmark S. Gut Microbiota, immune development and function. *Pharmacol Res* 2013;69:87–113.

42 Russell SL, Gold MJ, Hartmann M, *et al*. Early life Antibiotic-Driven changes in Microbiota enhance susceptibility to allergic asthma. *EMBO Rep* 2012;13:440–7.

43 Enaud R, Prevel R, Ciarlo E, *et al*. The gut-lung axis in health and respiratory diseases: a place for inter-organ and inter-kingdom Crosstalks. *Front Cell Infect Microbiol* 2020;10:9.

44 Fujimura KE, Lynch SV. Microbiota in allergy and asthma and the emerging relationship with the gut Microbiome. *Cell Host & Microbe* 2015;17:592–602.

45 Hufnagl K, Pali-Schöll I, Roth-Walter F, *et al*. Dysbiosis of the gut and lung Microbiome has a role in asthma. *Semin Immunopathol* 2020;42:75–93.

46 Goleva E, Jackson LP, Harris JK, *et al*. The effects of airway Microbiome on corticosteroid responsiveness in asthma. *Am J Respir Crit Care Med* 2013;188:1193–201.

47 Renz H, Blümer N, Virna S, *et al*. The immunological basis of the hygiene hypothesis. *Allergy and Asthma in Modern Society: A Scientific Approach* 2006;91:30–48.

48 Russell SL, Gold MJ, Willing BP, *et al*. Perinatal antibiotic treatment affects murine Microbiota, immune responses and allergic asthma. *Gut Microbes* 2013;4:158–64.

49 Lin Y-C, Chen Y-C, Kuo C-H, *et al*. Antibiotic exposure and asthma development in children with allergic rhinitis. *J Microbiol Immunol Infect* 2020;53:803–11.

50 Spergel JM. From Atopic dermatitis to asthma: the Atopic March. *Annals of Allergy, Asthma & Immunology* 2010;105:99–106.

51 Zheng T, Yu J, Oh MH, *et al*. The Atopic March: progression from Atopic dermatitis to allergic rhinitis and asthma. *Allergy Asthma Immunol Res* 2011;3:67.

52 Lowe AJ, Leung DYM, Tang MLK, *et al*. The skin as a target for prevention of the Atopic March. *Ann Allergy Asthma Immunol* 2018;120:145–51.

53 Ayuk AC, Eze JN, Edelu BO, *et al*. The prevalence of allergic diseases among children with asthma: what is the impact on asthma control in South East Nigeria *Niger J Clin Pract* 2018;21:632–8.

54 Toskala E, Kennedy DW. Asthma risk factors. *Int Forum Allergy Rhinol* 2015;5 Suppl 1(Suppl 1):S11–6.

55 Chan-Yeung M, Malo J-L. Occupational asthma. *N Engl J Med* 1995;333:107–12.

56 Tho NV, Park HY, Nakano Y. Asthma–COPD overlap syndrome (ACOS): a diagnostic challenge. *Respirology* 2016;21:410–8.

57 Chang J, Mosenifar Z. Differentiating COPD from asthma in clinical practice. *J Intensive Care Med* 2007;22:300–9.