

## Supplementary Material

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

**Supplementary Figure 1. Directed acyclic graph of the relation between antibiotics, asthma, and all covariates.**

**Supplementary Table 1. Examples of antibiotics for each class based on the World Health Organization Anatomical Therapeutic Chemical (WHO ATC) guidelines.**

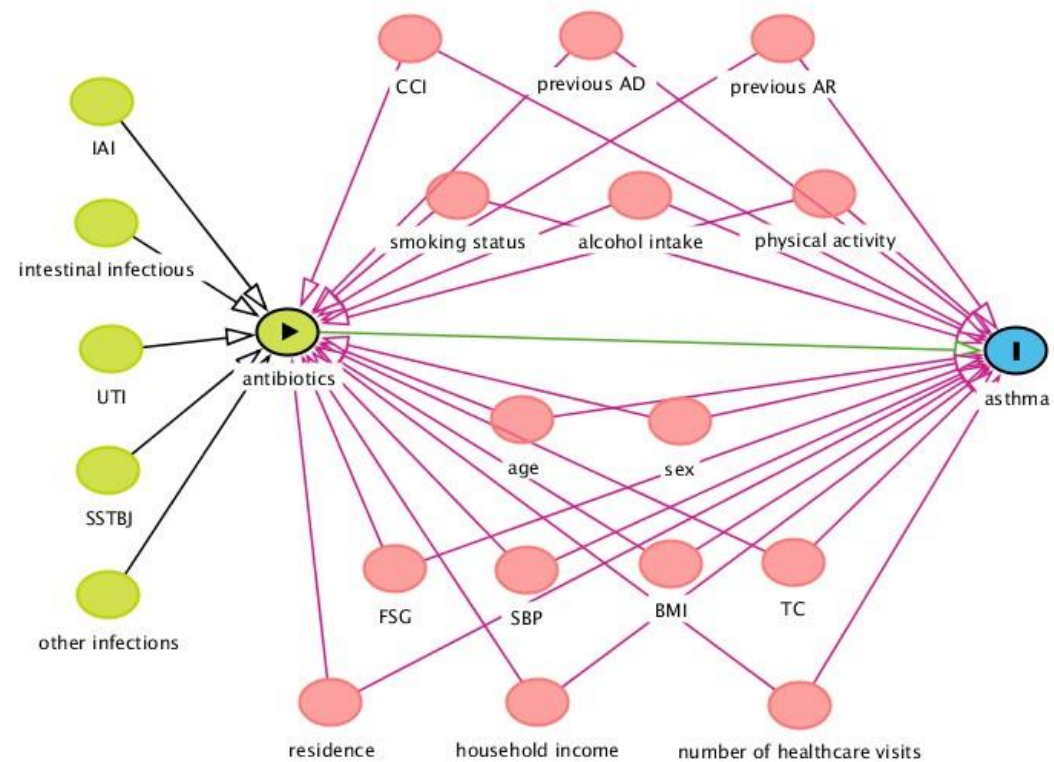
**Supplementary Table 2. Representative sources of infection according to the ICD-10 codes, mainly categorized by systems.**

**Supplementary Table 3. Stratified analysis of risk for asthma according to cumulative days of antibiotics prescribed.**

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**Supplementary Table 5. Risk by follow-up period of asthma incidence according to cumulative days antibiotics prescribed.**

**Supplementary Table 6. Risk of according to a single specific class of antibiotics compared to antibiotics non-user group.**

**Supplementary Figure 1. Directed acyclic graph of the relation between antibiotics, asthma, and all covariates.**

Abbreviation: IAI, intra-abdominal infections; UTI, urinary tract infections; SSTBJ, skin, soft tissue, bone, and joint infections; CCI, Charlson comorbidity index; Previous AD, previous atopic dermatitis; Previous AR, previous allergic rhinitis; FSG, fasting serum glucose; SBP, systolic blood pressure; BMI, body mass index; TC, total cholesterol;

**Supplementary Table 1. Examples of antibiotics for each class based on the World Health Organization Anatomical Therapeutic Chemical (WHO ATC) guidelines.**

<b>Antibiotics class</b>	<b>Types of antibiotics for each class</b>
Tetracyclines	doxycycline, tetracycline
Macrolides	erythromycin, spiramycin, midecamycin, oleandomycin, roxithromycin, josamycin, troleandomycin, clarithromycin, azithromycin, miocamycin, rokitamycin, dirithromycin, flurithromycin, telithromycin, solithromycin
Fluoroquinolones	ofloxacin, ciprofloxacin, pefloxacin, enoxacin, temafloxacin, norfloxacin, levofloxacin, moxifloxacin, gemifloxacin, gatifloxacin, sitafloxacin
Penicillins	ampicillin, pivamicillin, carbenicillin, amoxicillin, amoxicillin and clavulanate, azlocillin, mezlocillin, mecillinam, piperacillin, ticarcillin, metampicillin, talampicillin, dicloxacillin, oxacillin
Sulfonamides	sulfaisodimidine, sulfamethizole, sulfadimidine, sulfapyridine, sulfafurazole, sulfanilamide, sulfathiazole, sulfathiourea, sulfamethoxazole and trimethoprim, sulfadiazine, sulfasalazine, sulfamoxole
Lincosamides	clindamycin, lincomycin
Vancomycin	vancomycin
Carbapenems	meropenem, ertapenem
Cephalosporins	cefalexin, cefaloridine, cefalotin, cefazolin, cefatrizine, ceftazolidime, cefotaxime, cefonicid, cefotaxime, ceftazidime, ceftriaxone, cefmenoxime, cefdinir, cefteteram, cefepime, cefpirome, cefaclor, cefuroxime
Monobactams	aztreonam, carumonam
Linezolid	linezolid

**Supplementary Table 2. Representative sources of infection according to the ICD-10 codes, categorized by systems.**

<b>Infectious diseases</b>	<b>ICD-10 codes</b>
Intra-abdominal infections (IAI)	
Cholecystitis & Cholangitis	K80, K81, K83
Appendicitis	K35, K36, K37
Diverticulitis	K57
Peritonitis	K65
Pancreatitis	K85
Urinary tract infections (UTI)	
Cystitis	N30
Acute pyelonephritis	N10
Urethritis	N34, N37
Intestinal infectious diseases	A00, A01, A02, A03, A04, A05, A06, A07, A08, A09
Skin, soft tissue, bone, and joint infections (SSTBJ)	
Cellulitis	L03
Erysipelas	A46
Impetigo	L01
Folliculitis	L66.2, L66.4
Furuncle & Carbuncle	L02
Osteomyelitis	M86
Synovitis	M65, M67, M68, M70
Others	
Acute/chronic otitis media	H65, H66
Sepsis	A40, A41
Central nervous system infection	A81, A89

**Supplementary Table 3. Stratified 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	P for interaction
			None	1-14 days	15-30 days	31-90 days	≥91days		
<b>Age</b>									<0.001
40-49 years	81,834	11,098	1.00 (ref)	1.32 (1.24-1.41)	1.49 (1.39-1.60)	1.72 (1.59-1.86)	1.70 (1.48-1.96)	<0.001	
50-59 years	92,883	16,202	1.00 (ref)	1.23 (1.17-1.30)	1.46 (1.38-1.55)	1.64 (1.54-1.75)	1.71 (1.54-1.91)	<0.001	
≥60 years	74,244	15,152	1.00 (ref)	1.25 (1.17-1.32)	1.42 (1.33-1.51)	1.59 (1.49-1.70)	1.79 (1.62-2.00)	<0.001	
<b>Sex</b>									<0.001
Men	141,223	20,508	1.00 (ref)	1.28 (1.22-1.34)	1.49 (1.42-1.57)	1.72 (1.63-1.82)	1.84 (1.69-2.02)	<0.001	
Women	107,738	21,944	1.00 (ref)	1.26 (1.19-1.32)	1.45 (1.37-1.53)	1.62 (1.53-1.72)	1.77 (1.61-1.95)	<0.001	
<b>Residence</b>									0.061
Capital	41,843	6,888	1.00 (ref)	1.34 (1.23-1.46)	1.62 (1.47-1.77)	1.78 (1.61-1.97)	1.95 (1.66-2.29)	<0.001	
Metropolitan	112,290	18,585	1.00 (ref)	1.27 (1.20-1.34)	1.46 (1.38-1.55)	1.64 (1.54-1.74)	1.74 (1.57-1.92)	<0.001	
Rural	94,828	16,979	1.00 (ref)	1.26 (1.19-1.33)	1.46 (1.38-1.55)	1.70 (1.59-1.80)	1.87 (1.68-2.07)	<0.001	
<b>Body Mass Index</b>									0.161
BMI <18.5	4,988	740	1.00 (ref)	1.20 (0.95-1.52)	1.53 (1.18-1.98)	1.56 (1.17-2.08)	1.67 (1.01-2.77)	<0.001	
18.5≤ BMI <23	89,596	14,423	1.00 (ref)	1.31 (1.24-1.39)	1.55 (1.46-1.65)	1.74 (1.63-1.86)	1.90 (1.69-2.13)	<0.001	
23≤ BMI <25	70,262	11,775	1.00 (ref)	1.29 (1.21-1.38)	1.48 (1.38-1.59)	1.72 (1.60-1.86)	1.90 (1.68-2.15)	<0.001	
25≤ BMI	84,115	15,514	1.00 (ref)	1.23 (1.16-1.31)	1.44 (1.35-1.53)	1.62 (1.52-1.73)	1.74 (1.57-1.94)	<0.001	
<b>Charlson comorbidity index</b>									0.030
0	74,640	8,944	1.00 (ref)	1.22 (1.15-1.29)	1.47 (1.37-1.57)	1.46 (1.34-1.59)	1.50 (1.23-1.83)	<0.001	
1	67,324	11,118	1.00 (ref)	1.23 (1.15-1.31)	1.38 (1.29-1.49)	1.60 (1.48-1.72)	1.59 (1.37-1.83)	<0.001	
≥2	106,997	22,390	1.00	1.28	1.47	1.70	1.91	<0.001	

			(ref)	(1.21-1.36)	(1.38-1.56)	(1.60-1.81)	(1.75-2.08)		
Previous atopic dermatitis									0.024
No	240,200	40,593	1.00 (ref)	1.28 (1.24-1.33)	1.50 (1.44-1.55)	1.70 (1.64-1.77)	1.84 (1.72-1.97)	<0.001	
Yes	8,761	1,859	1.00 (ref)	1.12 (0.92-1.36)	1.28 (1.05-1.57)	1.37 (1.12-1.68)	1.62 (1.22-2.13)	<0.001	
Previous allergic rhinitis									<0.001
No	108,289	12,258	1.00 (ref)	1.38 (1.31-1.46)	1.66 (1.56-1.76)	1.88 (1.75-2.01)	2.06 (1.77-2.41)	<0.001	
Yes	140,672	30,194	1.00 (ref)	1.17 (1.11-1.22)	1.35 (1.28-1.41)	1.54 (1.46-1.62)	1.67 (1.55-1.80)	<0.001	

The aHRs were calculated by Cox proportional hazards regression after adjustments for multivariate variables. Stratified analysis was adjusted for age, sex, residence, body mass index, Charlson comorbidity index, the number of healthcare visits, previous atopic dermatitis, and previous allergic rhinitis.

aHR indicates adjusted hazard ratio; CI, confidence interval; and ref, reference.

**Supplementary Table 4. Risk for asthma according to cumulative days of antibiotics prescribed stratified with sex.**

	Cumulative days of antibiotics prescribed for 5 years before the index date											
	Men						Women					
	None	1-14 days	15-30 days	31-90 days	≥91 days	<i>P</i> for trend	None	1-14 days	15-30 days	31-90 days	≥91 days	<i>P</i> for trend
Number of participants, n	24,674	65,154	29,737	18,834	2,824		13,776	46,914	26,757	18,418	1,873	
Events, n	2,173	8,469	5,098	4,075	693		1,802	8,494	6,069	4,983	596	
Person-years	292,588	753,904	333,344	203,770	29,390		161,668	534,665	296,399	195,749	18,781	
aHR (95% CI)												
Model 1 <sup>a</sup>	1.00 (ref)	1.28 (1.22-1.34)	1.49 (1.42-1.57)	1.72 (1.63-1.82)	1.84 (1.69-2.02)	<0.001	1.00 (ref)	1.26 (1.19-1.32)	1.45 (1.37-1.53)	1.62 (1.54-1.72)	1.77 (1.61-1.95)	<0.001
Model 2 <sup>b</sup>		1.00 (ref)	1.18 (1.14-1.22)	1.36 (1.31-1.41)	1.47 (1.35-1.59)	<0.001		1.00 (ref)	1.16 (1.12-1.20)	1.30 (1.26-1.35)	1.44 (1.32-1.57)	<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 (intra-abdominal infections, urinary tract infections, intestinal infectious diseases, skin, soft tissue, bone, and joint infections, and others).

<sup>a</sup>Antibiotics non-user group was set as a reference group.

<sup>b</sup>Antibiotics 1-14 days user group was set as a reference group.

n indicates number of people; aHR, adjusted hazard ratio; CI, confidence interval; and ref, reference.

**Supplementary Table 5. Risk by follow-up period of asthma incidence according to cumulative days 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	
<b>Asthma incidence for &lt;2 years</b>						
Number of participants, n	897	3,698	2,442	2,187	366	
Events, n	580	2,826	2,008	1,843	303	
Person-years	909	3,670	2,418	2,169	362	
aHR (95% CI)						
Model 1 <sup>a</sup>	1.00 (ref)	1.09 (0.99-1.19)	1.15 (1.04-1.26)	1.19 (1.08-1.32)	1.18 (1.02-1.36)	<0.001
Model 2 <sup>b</sup>		1.00 (ref)	1.06 (1.00-1.12)	1.10 (1.04-1.17)	1.09 (0.96-1.24)	0.003
<b>Asthma incidence for ≥2 years</b>						
Number of participants, n	37,553	108,370	54,052	35,065	4,331	
Events, n	3,395	14,137	9,159	7,215	986	
Person-years	453,346	1,284,898	627,326	397,350	47,810	
aHR (95% CI)						
Model 1 <sup>a</sup>	1.00 (ref)	1.26 (1.21-1.31)	1.46 (1.40-1.52)	1.62 (1.55-1.69)	1.70 (1.58-1.84)	<0.001
Model 2 <sup>b</sup>		1.00 (ref)	1.16 (1.13-1.20)	1.30 (1.26-1.34)	1.37 (1.28-1.47)	<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).

<sup>a</sup>Antibiotics non-user group was set as a reference group.

<sup>b</sup>Antibiotics 1-14 days user group was set as a reference group.

n indicates number of people; aHR, adjusted hazard ratio; CI, confidence interval; and ref, reference.



**Supplementary Table 6. Risk of according to a single specific class of antibiotics compared to antibiotics non-user group.**

Exposure variable	Total	Events	Person-years	aHR (95% CI)
<b>Tetracyclines</b>				
Antibiotic non-user	38,450	3,975	454,255	1.00 (ref)
Only-user	1,319	170	15,409	1.15 (0.98-1.34)
<b>Macrolides</b>				
Antibiotic non-user	38,450	3,975	454,255	1.00 (ref)
Only-user	7,186	948	83,490	1.14 (1.07-1.23)
<b>Fluoroquinolones</b>				
Antibiotic non-user	38,450	3,975	454,255	1.00 (ref)
Only-user	11,542	1,669	131,878	1.16 (1.10-1.23)
<b>Penicillins (including ampicillin and amoxicillin)</b>				
Antibiotic non-user	38,450	3,975	454,255	1.00 (ref)
Only-user	25,557	3,566	296,238	1.20 (1.15-1.26)
<b>Sulfonamides</b>				
Antibiotic non-user	38,450	3,975	454,255	1.00 (ref)
Only-user	489	63	5,683	1.02 (0.79-1.30)
<b>Lincosamides</b>				
Antibiotic non-user	38,450	3,975	454,255	1.00 (ref)
Only-user	148	14	1,765	0.83 (0.49-1.40)
<b>Cephalosporins</b>				
Antibiotic non-user	38,450	3,975	454,255	1.00 (ref)
Only-user	18,457	2,593	212,682	1.18 (1.12-1.24)

Model 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.

aHR, adjusted Hazard Ratio; CI, Confidence Intervals; ref, reference.