

# Impact of previous antibiotic use on clinical outcomes in asthma

# Contents

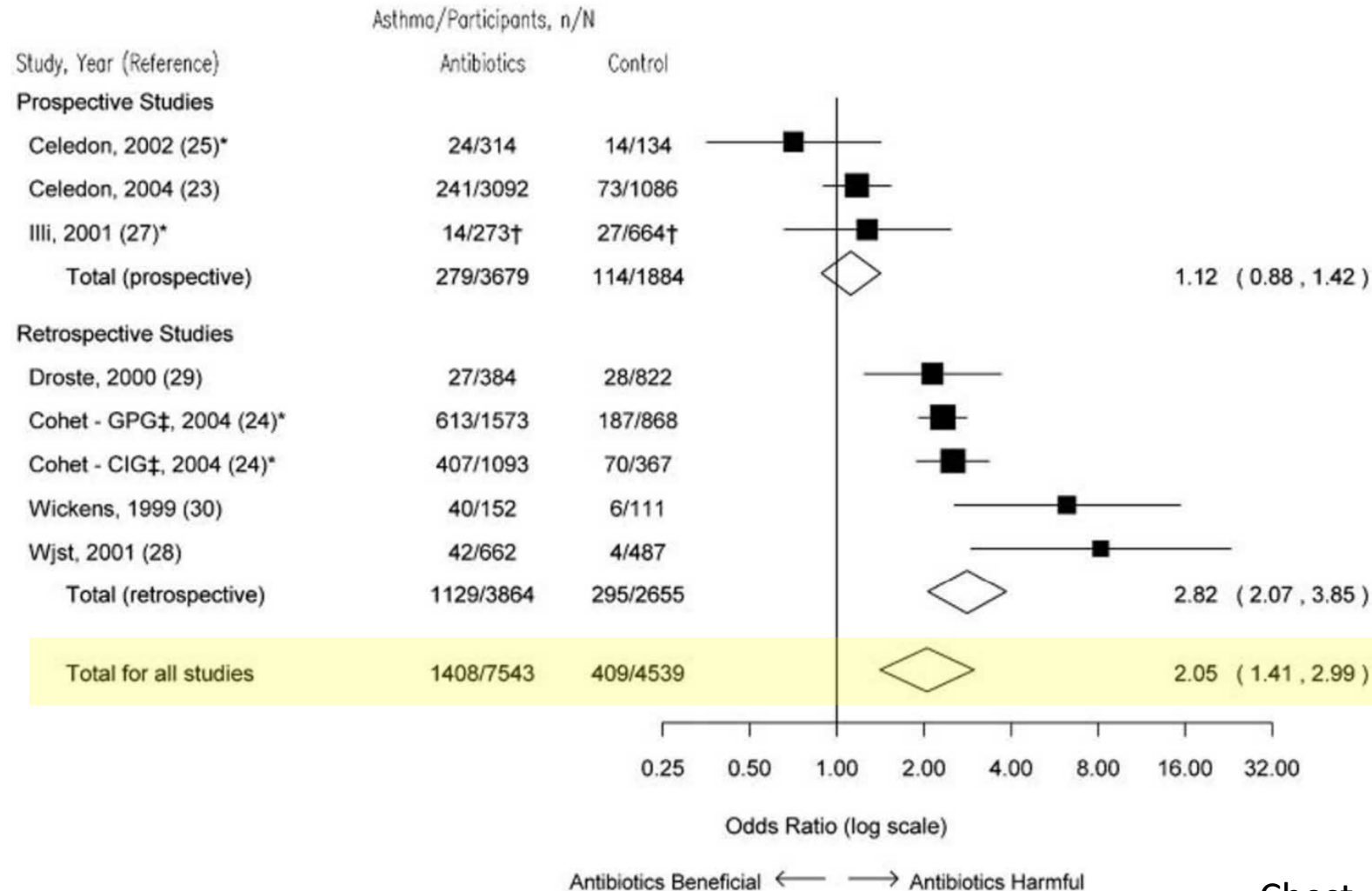
- **Exposure to antibiotics and asthma in children**
- **Exposure to antibiotics and asthma in adults**
- **Mechanism linking antibiotics exposure to asthma**
- **Exposure to antibiotics and asthma outcomes**

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# Does Antibiotic Exposure During Infancy Lead to Asthma?

- Meta-analysis: Antibiotics in the first year

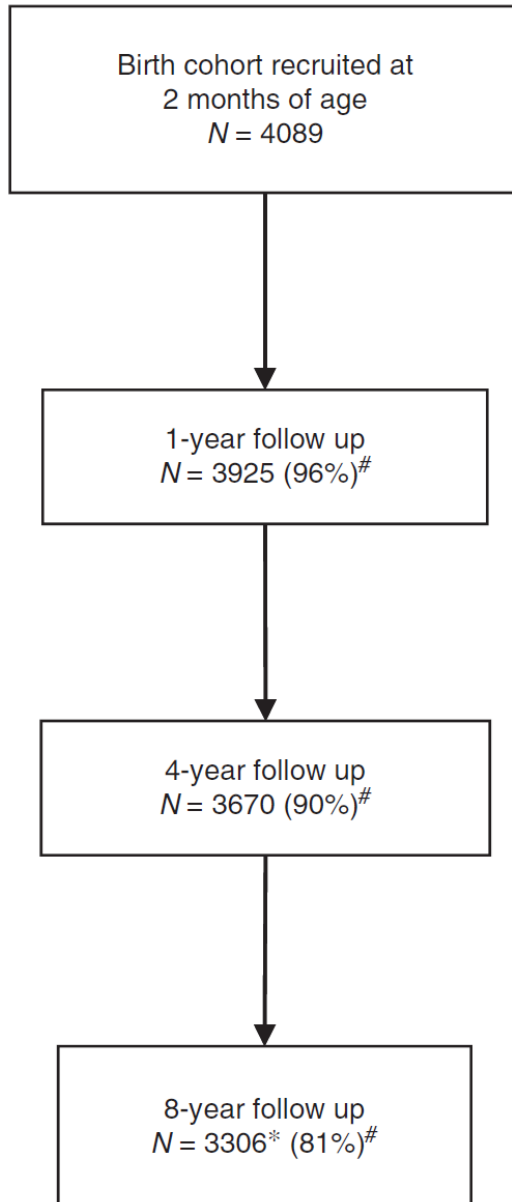


# Antibiotics for 1 year and asthma after 1 year

		n	Percent	HR: Crude	95% CI	HR: Adj	95% CI
Infections (n = 21,129)							
Gastrointestinal	Never	13,714	64.9	1.34	1.25-1.45	1.00	0.92-1.08
	Ever	7,415	35.1				
Respiratory	Never	9,725	46.0	1.66	1.54-1.79	1.26	1.16-1.36
	Ever	11,404	54.0				
Conjunctivitis	Never	13,951	66.0	1.23	1.13-1.32	0.97	0.90-1.05
	Ever	7,178	34.0				
Otitis media	Never	16,709	79.1	1.45	1.33-1.57	1.13	1.04-1.23
	Ever	4,420	20.9				
Candida	Never	17,306	81.9	1.24	1.13-1.36	0.99	0.90-1.08
	Ever	3,823	18.1				
Bacterial	Never	20,339	96.3	1.49	1.27-1.76	1.18	1.00-1.40
	Ever	790	3.7				
Viral	Never	20,133	95.3	0.98	0.83-1.16	0.82	0.69-0.97
	Ever	996	4.7				
Antibiotics (n = 21,129)							
Penicillin	Never	18,701	88.5	1.22	1.09-1.35	0.99	0.89-1.10
	Ever	2,428	11.5				
Amoxycillin	Never	10,144	48.0	1.64	1.52-1.76	1.25	1.16-1.36
	Ever	10,985	52.0				
Macrolides	Never	16,656	78.8	1.76	1.63-1.90	1.41	1.30-1.53
	Ever	4,473	21.2				
Cephalosporins	Never	19,795	93.7	1.88	1.67-2.12	1.44	1.28-1.63
	Ever	1,334	6.3				
Augmentin	Never	20,603	97.5	1.76	1.47-2.11	1.43	1.19-1.72
	Ever	526	2.5				
Total no. of prescriptions of antibiotics							
0		7,632	36.1	—	—	—	—
1		5,539	26.2	1.45	1.31-1.61	1.26	1.13-1.40
2		3,446	16.3	1.86	1.66-2.08	1.46	1.30-1.65
3		2,043	9.7	2.41	2.13-2.72	1.76	1.56-2.01
4		1,179	5.6	2.66	2.31-3.07	1.82	1.56-2.13
>4		1,290	6.1	3.13	2.75-3.57	1.99	1.72-2.31

- UK General Practice Research DB
- Asthma defined based on **ICD-8 codes**
  - After the first year of life
- Antibiotics based on **prescription**
  - in the first year of life

# Antibiotics for 1 year and asthma at 4, 8 year



- Population-based birth cohort in Stockholm, Sweden, 1994-1996
- Diagnoses of asthma at 4 and 8 years of age were derived from the **follow-up questionnaires**
- Antibiotic use was evaluated **through questionnaire**.

	Antibiotic use during the first year							
	No (n = 1886)			Yes (n = 1420)			Crude OR (95% CI)	Adjusted OR (95% CI)
	n	%	OR	n	%			
Wheeze	228	12	1.0	254	18	1.6 (1.3–1.9)	1.4 (1.2–1.8)	
Asthma	103	5	1.0	125	9	1.7 (1.3–2.2)	1.5 (1.1–2.0)	
Allergic rhinitis	193	10	1.0	176	13	1.2 (1.0–1.5)	1.2 (0.9–1.5)	
Eczema	345	18	1.0	318	22	1.3 (1.1–1.5)	1.3 (1.1–1.5)	
Food hypersensitivity	173	10	1.0	181	14	1.4 (1.2–1.8)	1.4 (1.1–1.7)	
Any sensitization*	335	24	1.0	244	24	1.0 (0.8–1.2)	0.9 (0.7–1.1)	

# Antibiotics for 1 year and asthma at 4, 8 year

**Confounding effect of respiratory infection** on the relationship between antibiotic use during the first year of life and development of allergic diseases

Multivariable analysis (adjusted OR)

At 4 years of age

During first year of life	Wheeze	Asthma
Antibiotic use	1.2 (1.1–1.5)	1.4 (1.1–1.7)
Pneumonia	1.0 (0.6–1.7)	1.5 (0.8–2.8)
Bronchitis	1.9 (1.4–2.6)	1.7 (1.1–2.7)
Otitis	1.1 (0.8–1.4)	0.9 (0.6–1.3)

At 8 years of age

During first year of life	Wheeze	Asthma
Antibiotic use	1.1 (0.9–1.4)	1.2 (0.9–1.5)
Pneumonia	0.8 (0.4–1.6)	1.1 (0.5–2.3)
Bronchitis	1.6 (1.1–2.4)	1.5 (0.9–2.4)
Otitis	1.1 (0.8–1.5)	0.8 (0.5–1.2)

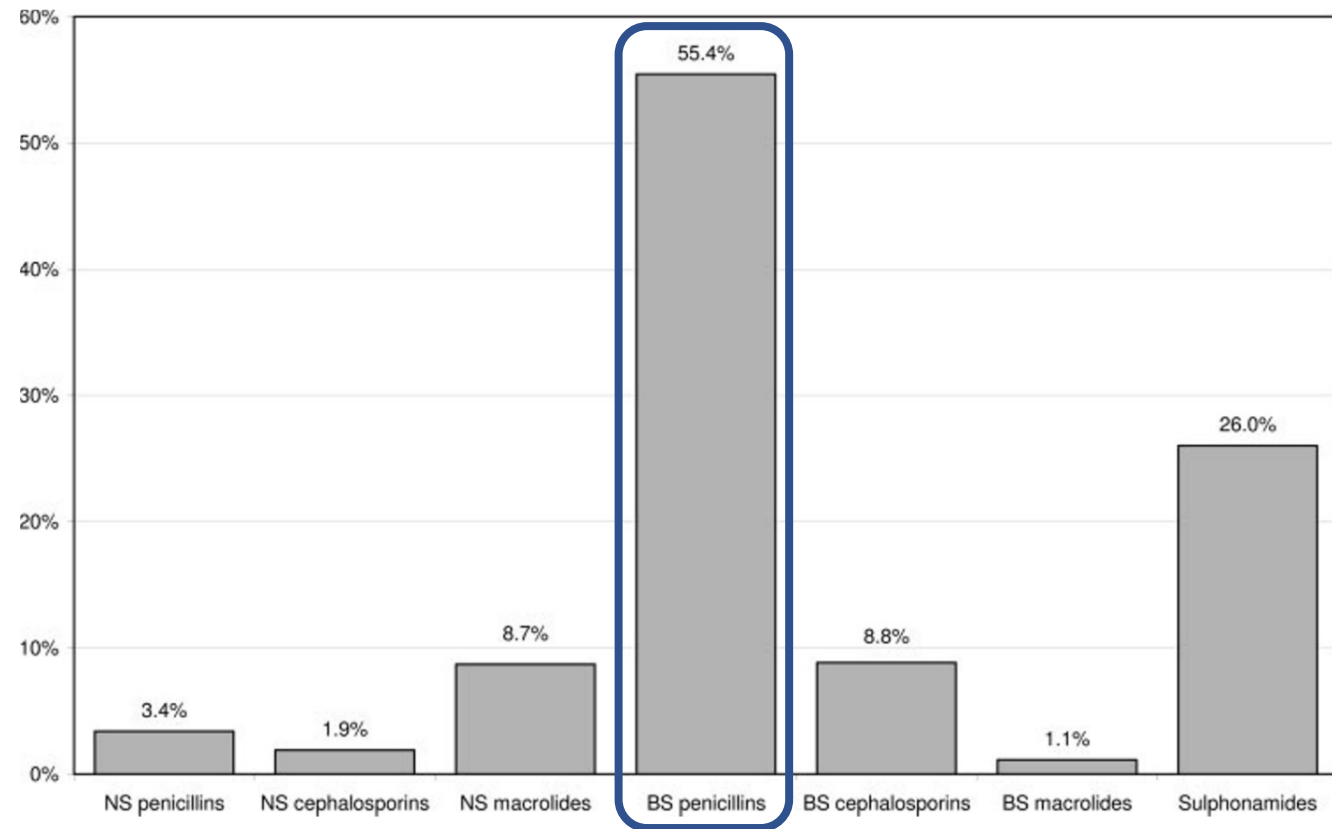
# Antibiotics for 1 year and asthma at 4, 8 year

## Multivariable analysis (adjusted OR)

	One course of antibiotics		Two or more courses of antibiotics		<i>p</i> for trend	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
<i>4 years of age</i>						
Wheeze	1.2 (0.9–1.5)	1.0 (0.8–1.3)	2.2 (1.8–2.8)	1.6 (1.1–2.2)	<0.001	<0.01
Asthma	1.2 (0.9–1.7)	1.1 (0.7–1.6)	2.4 (1.7–3.2)	1.9 (1.2–3.0)	<0.001	<0.01
<i>8 years of age</i>						
Wheeze	1.3 (0.9–1.7)	1.1 (0.8–1.5)	1.8 (1.4–2.4)	1.3 (0.9–1.9)	<0.001	0.16
Asthma	1.1 (0.8–1.6)	1.1 (0.7–1.6)	1.7 (1.2–2.3)	1.5 (0.9–2.4)	<0.01	0.11

# Antibiotics for 1 year and asthma at 7 year

- Canada, Registered with the Manitoba Health Services Insurance Plan (n=13,116)
- Asthma defined if any criteria met:
  - at least two physician visits for asthma
  - one asthma hospitalization
  - two prescriptions for any asthma drug
- Exposure to antibiotics based on **prescription**
  - in the first year of life



**Broad-spectrum penicillin**

**Narrow spectrum:** Penicillin, cloxacillin, cephalixin, cefadroxil, and erythromycin

**Broad spectrum:** Others

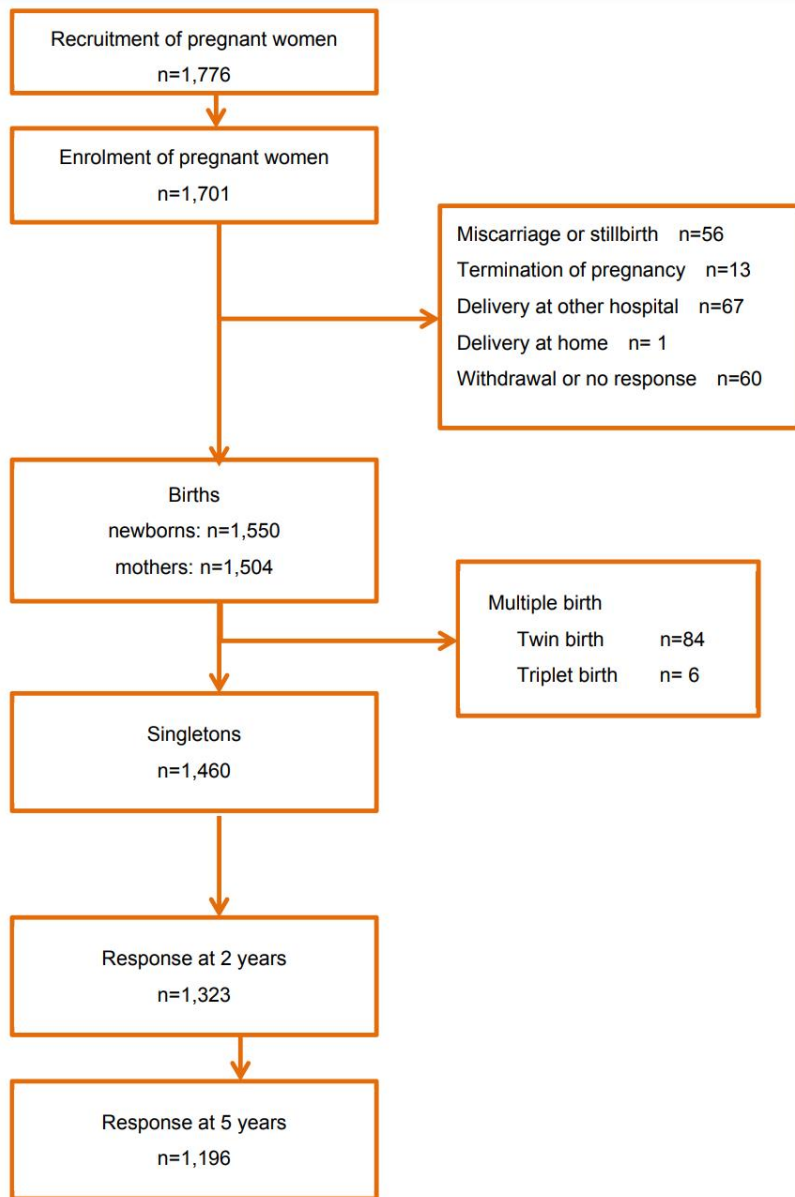
# Antibiotics for 1 year and asthma at 7 year

## Adjusted OR for asthma

Variables (Reference Group)	All Children (n = 13,116)
Courses of antibiotics (none)	
1–2	1.21 (1.01–1.46)
3–4	1.30 (1.04–1.63)
> 4	1.46 (1.14–1.88)
Each lower respiratory tract infection†	1.06 (1.02–1.09)
Each non-respiratory tract infection‡	1.15 (1.12–1.19)
Maternal history of asthma	2.21 (1.73–2.81)
No. of health-care visits during first year	1.01 (1.00–1.02)
No. of siblings	0.82 (0.76–0.87)
<del>Urban location</del> → Rural location	1.65 (1.40–1.94)
Male gender	1.75 (1.50–2.04)

Characteristics	Children, No.	Time to First Antibiotic		BS Cephalosporins	
		Days	p Value	%	p Value
Rural residence	728	119	0.06	47.0	0.0001
Urban residence	773	126		32.1	
No maternal asthma	1,381	123	NS	39.8	NS
Maternal asthma	120	122		33.3	
No dog in birth year	208	134	NS	37.5	NS
Dog in birth year	72	124		33.3	

# Antibiotics for 2 year and asthma at 5 year



- Japan, Tokyo Children’s Health, Illness and Development Study, n=1,196
- **Objective:** to elucidate the relation between postnatal antibiotic exposures within the first 2 years of life and allergic diseases in children at 5 years of age

## Outcomes of children at 5 y old

Wheeze current

A positive answer from the caregiver to the question (child at 5 y old), “Has your child ever had wheezing or whistling in the past 12 months?”

Asthma current

A positive answer from the caregiver to the question (child at 5 y old), “Has your child ever been diagnosed by a doctor as having asthma in the past 12 months?”

Exposure to antibiotics

History of antibiotic use

A positive answer from caregivers to the question (child at 2 y old), “Has your child ever taken antibiotics?”

Types of antibiotics use

A positive answer from caregivers to the question (child at 2 y old), “What types of antibiotics has your child taken?,” which was classified into 4 groups (penicillin, cephem, macrolide, and others).

**Using  
Questionnaire**

# Antibiotics for 2 year and asthma at 5 year

	Crude OR	95% CI		P value	Adjusted OR <sup>a</sup>	95% CI		P value	Power <sup>b</sup>
		Lower	Upper			Lower	Upper		
Current wheeze									
All antibiotics	1.36	0.95	1.94	.089	1.24	0.86	1.78	.255	
Penicillin	1.11	0.60	2.09	.736	1.16	0.61	2.18	.653	
Cephem	1.44	0.96	2.16	.075	1.39	0.92	2.09	.122	
Macrolide	1.20	0.78	1.85	.410	1.04	0.66	1.64	.856	
Current asthma									
All antibiotics	1.78	1.15	2.75	.009	1.72	1.10	2.70	.017	0.75
Penicillin	1.88	0.58	2.53	.602	1.21	0.58	2.56	.612	
Cephem	2.02	1.28	3.20	.003	1.97	1.23	3.16	.005	0.84
Macrolide	2.59	0.97	2.60	.064	1.46	0.88	2.44	.145	

# Antibiotics and time to asthma development

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- Sweden, The Prescribed Drug Register cohort, n=211,192, Born from 1 July 2005 to 30 June 2009
- **Objective:** to estimate the associations between prescribed antibiotics and asthma medication in the Swedish population
- **Definition of asthma**
  - ✓ **Any asthma medication**, except oral b2-agonists, dispensed **at least twice**
- **Definition of antibiotic use**
  - ✓ **ATC codes** (Amoxillin, penicillin, cephalosporin, sulphonamide, macrolide and 'other antibiotics')
  - ✓ Between birth and 31 July 2009

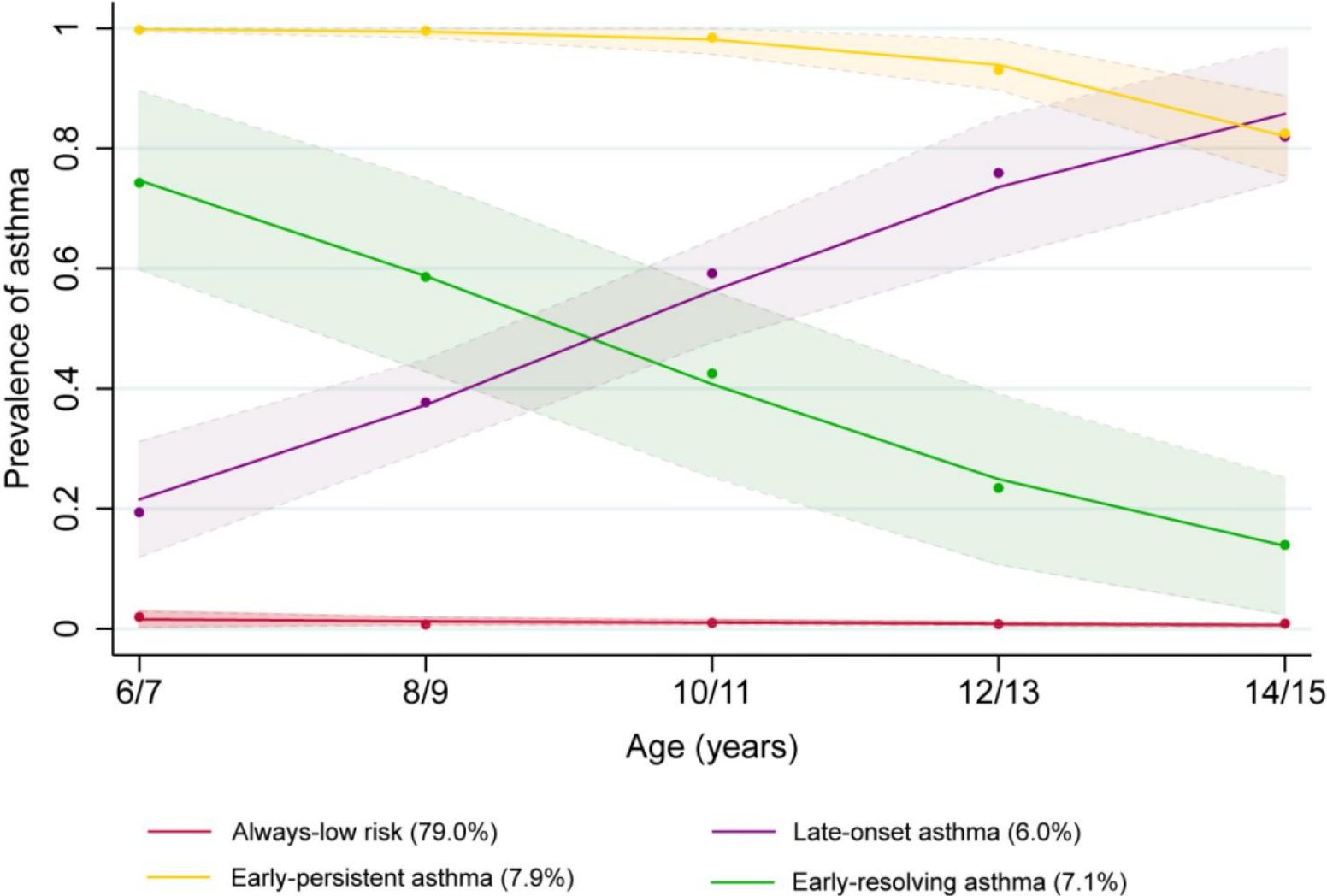
# Antibiotics and time to asthma development

		Age at first asthma medication (years)		
		<1 HR (95% CI)	1 HR (95% CI)	≥2 HR (95% CI)
Spectrum				
All	Narrow	1.60 (1.35–1.91)	1.28 (1.09–1.50)	0.96 (0.65–1.41)
	Broad	2.04 (1.71–2.42)	1.83 (1.56–2.15)	1.38 (0.94–2.04)
Male	Narrow	1.55 (1.30–1.85)	1.25 (1.06–1.48)	0.92 (0.62–1.38)
	Broad	1.91 (1.60–2.28)	1.78 (1.51–2.10)	1.29 (0.86–1.93)
Female	Narrow	1.69 (1.41–2.03)	1.32 (1.12–1.57)	1.04 (0.69–1.57)
	Broad	2.29 (1.89–2.76)	1.92 (1.62–2.28)	1.56 (1.04–2.35)
No. of prescriptions				
All	1–2	1.72 (1.45–2.05)	1.37 (1.16–1.61)	0.85 (0.53–1.36)
	3–5	2.25 (1.86–2.72)	2.03 (1.72–2.40)	1.26 (0.78–2.02)
	≥6	2.36 (1.76–3.16)	2.50 (2.09–3.01)	1.77 (1.10–2.86)
Male	1–2	1.65 (1.38–1.97)	1.34 (1.13–1.58)	0.79 (0.49–1.28)
	3–5	2.07 (1.70–2.53)	1.98 (1.66–2.35)	1.19 (0.73–1.93)
	≥6	2.21 (1.59–3.07)	2.34 (1.92–2.85)	1.56 (0.95–2.56)
Female	1–2	1.85 (1.54–2.22)	1.42 (1.19–1.68)	0.92 (0.57–1.51)
	3–5	2.61 (2.08–3.27)	2.14 (1.79–2.57)	1.37 (0.83–2.24)
	≥6	2.62 (1.61–4.25)	2.86 (2.31–3.55)	2.13 (1.29–3.51)

**Narrow spectrum:** Penicillin, cloxacillin, cephalexin, cefadroxil, and erythromycin

**Broad spectrum:** Others

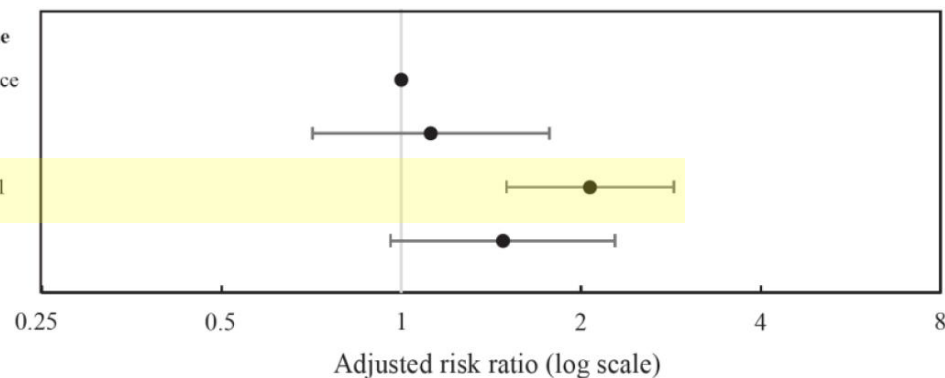
# Antibiotics and childhood asthma trajectories



# Antibiotics and childhood asthma trajectories

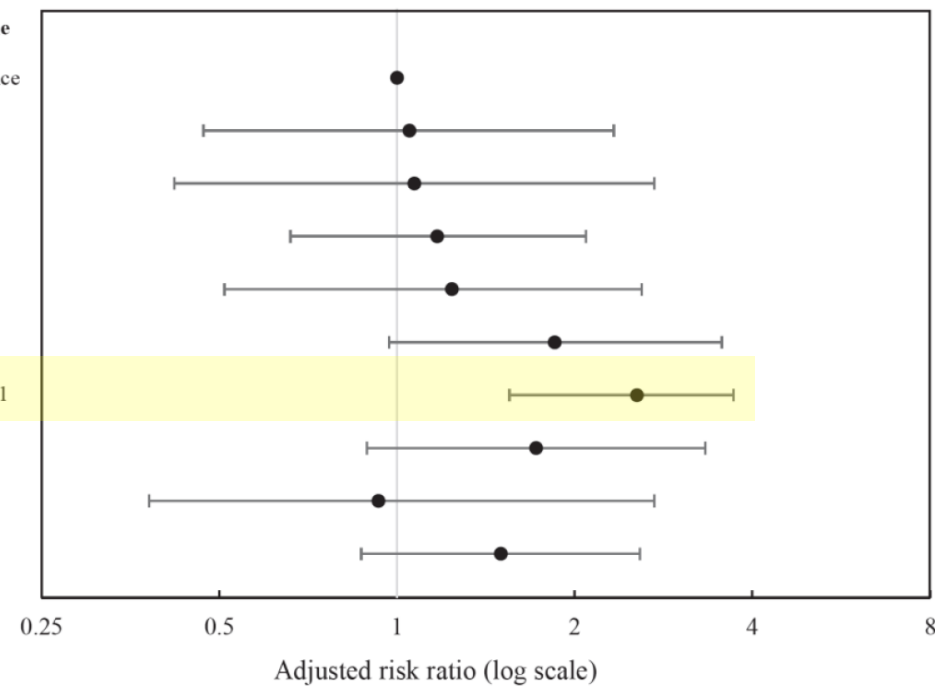
## Early-life antibiotic exposure to all children <sup>a</sup>

	n	Adjusted risk ratio (95% CI)	p-value
Always-low risk	3508	1	Reference
Early-resolving asthma	213	1.12 (0.71–1.77)	0.63
Early-persistent asthma	384	2.07 (1.50–2.86)	< 0.001
Late-onset asthma	213	1.48 (0.96–2.28)	0.08



## Early-life antibiotic exposure <sup>a</sup>

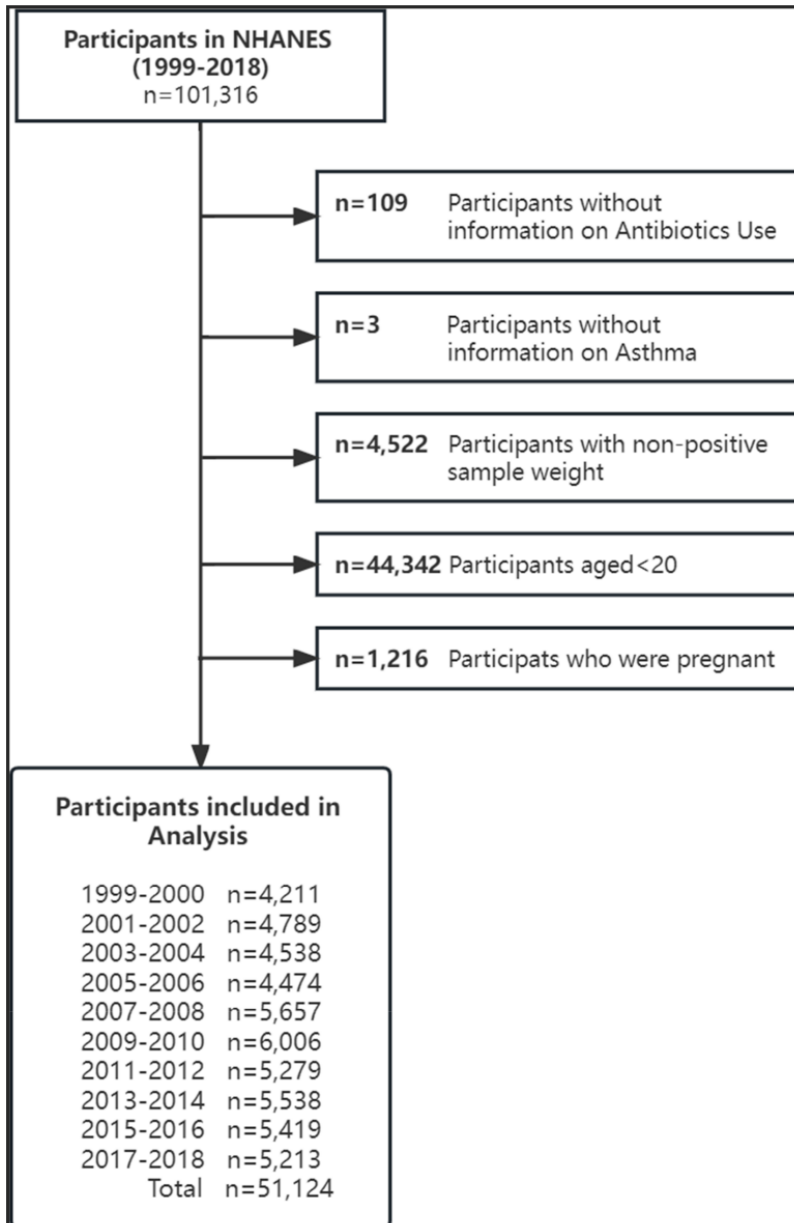
	Number of courses	n	Adjusted risk ratio (95% CI)	p-value
Always-low risk		3401	1	Reference
Early-resolving asthma	1	10	1.05 (0.47–2.33)	0.91
	2	10	1.07 (0.42–2.73)	0.89
	≥ 3	37	1.17 (0.66–2.09)	0.59
Early-persistent asthma	1	21	1.24 (0.66–2.32)	0.50
	2	17	1.85 (0.97–3.55)	0.06
	≥ 3	79	2.55 (1.75–3.72)	< 0.001
Late-onset asthma	1	16	1.72 (0.89–3.33)	0.11
	2	6	0.93 (0.33–2.64)	0.90
	≥ 3	32	1.50 (0.87–2.58)	0.15



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- Exposure to antibiotics and asthma in children
- **Exposure to antibiotics and asthma in adults**
- Mechanism linking antibiotics exposure to asthma
- Exposure to antibiotics and asthma outcomes

# Exposure to antibiotics and asthma in adults



- NHANES in US, 1999-2018, n=51,124, **>20 years old**
- **Objective:** to assess the relationship between antibiotic exposure and asthma in adults
- **Definition of antibiotic use**
  - ✓ In-home interview: any prescription antibiotics during the **preceding 30 days**
- **Definition of asthma**
  - ✓ Through self-administered questionnaires
    - “Has a doctor or other health professional ever told you that you have asthma?”
    - “In the past 12 months have you had wheezing or whistling in your chest?”
    - “During the past 12 months, have you had an episode of asthma or an asthma attack?”

# Adjusted odds ratio for the prevalent asthma

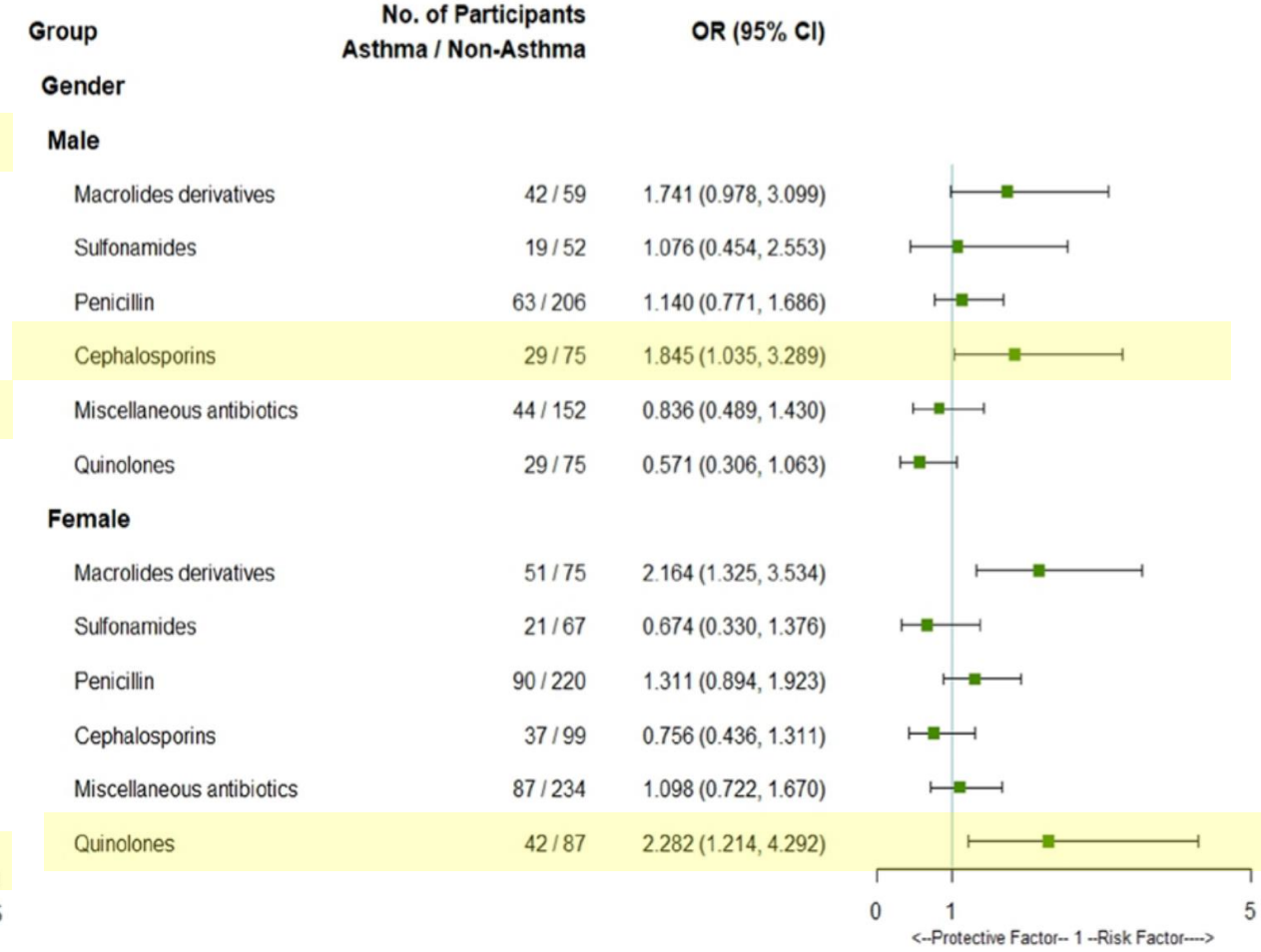
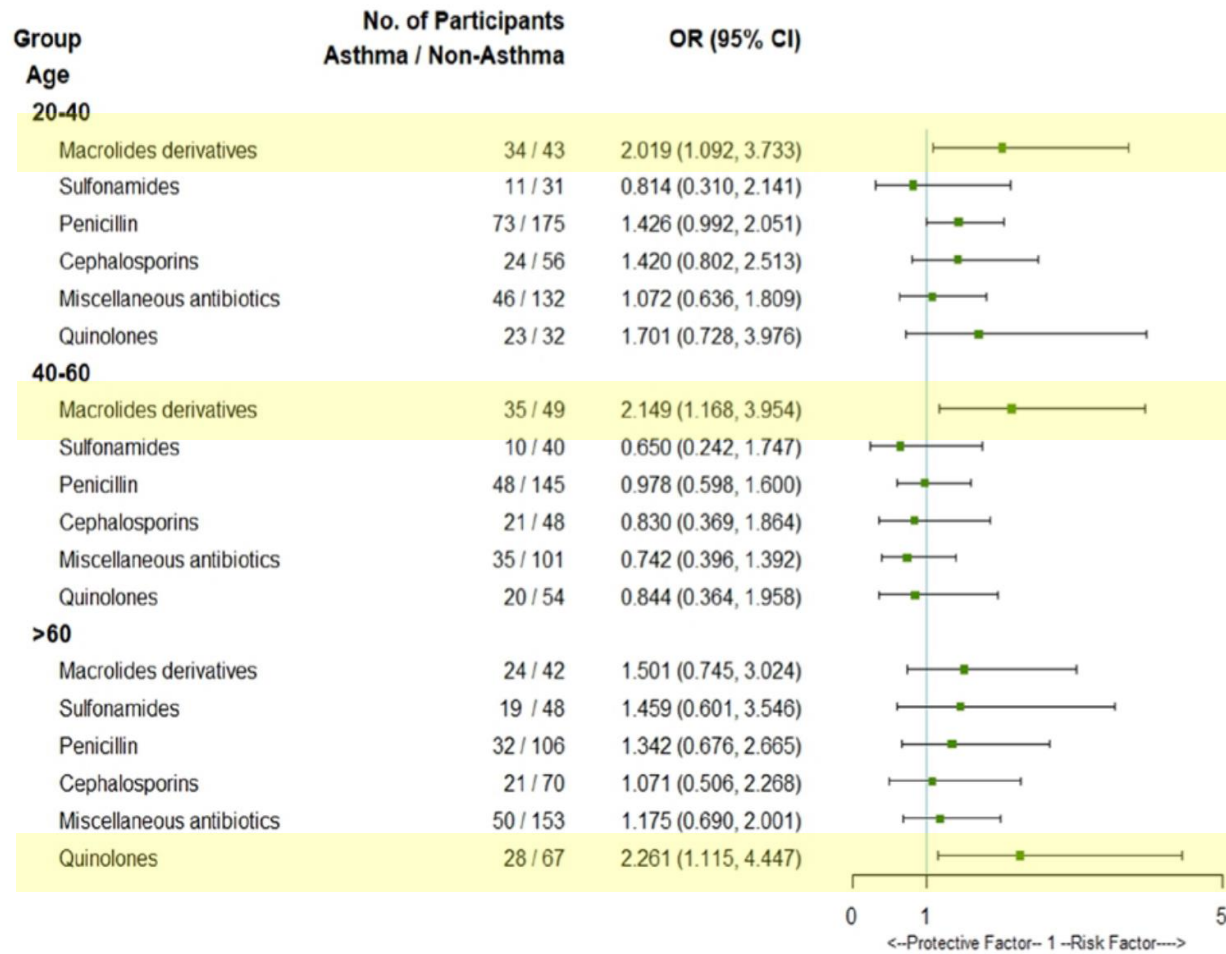
	Model 1				Model 2				Model 3			
	OR	<i>p</i>	95%CI		OR	<i>p</i>	95%CI		OR	<i>p</i>	95%CI	
			Lower	Upper			Lower	Upper			Lower	Upper
Not used antibiotics	ref	/	/	/	ref	/	/	/	ref	/	/	/
Macrolides derivatives	2.557	0.001	1.811	3.612	2.593	<0.001	1.831	3.671	1.983	0.008	1.341	2.930
Sulfonamides	1.112	0.180	0.690	1.790	1.032	0.184	0.607	1.755	0.862	0.219	0.482	1.544
Penicillin	1.547	0.691	1.190	2.011	1.423	0.919	1.085	1.864	1.235	0.738	0.934	1.634
Cephalosporins	1.339	0.553	0.937	1.915	1.257	0.506	0.863	1.830	1.092	0.679	0.717	1.663
Miscellaneous antibiotics	1.230	0.169	0.926	1.632	1.099	0.080	0.807	1.498	0.986	0.282	0.683	1.423
Quinolones	2.053	0.077	1.344	3.137	2.038	0.051	1.317	3.155	1.369	0.458	0.844	2.220

Model 1 was not adjusted;

Model 2 adjusted for age, sex, ethnicity, educational level, socioeconomic status, health insurance status, and BMI;

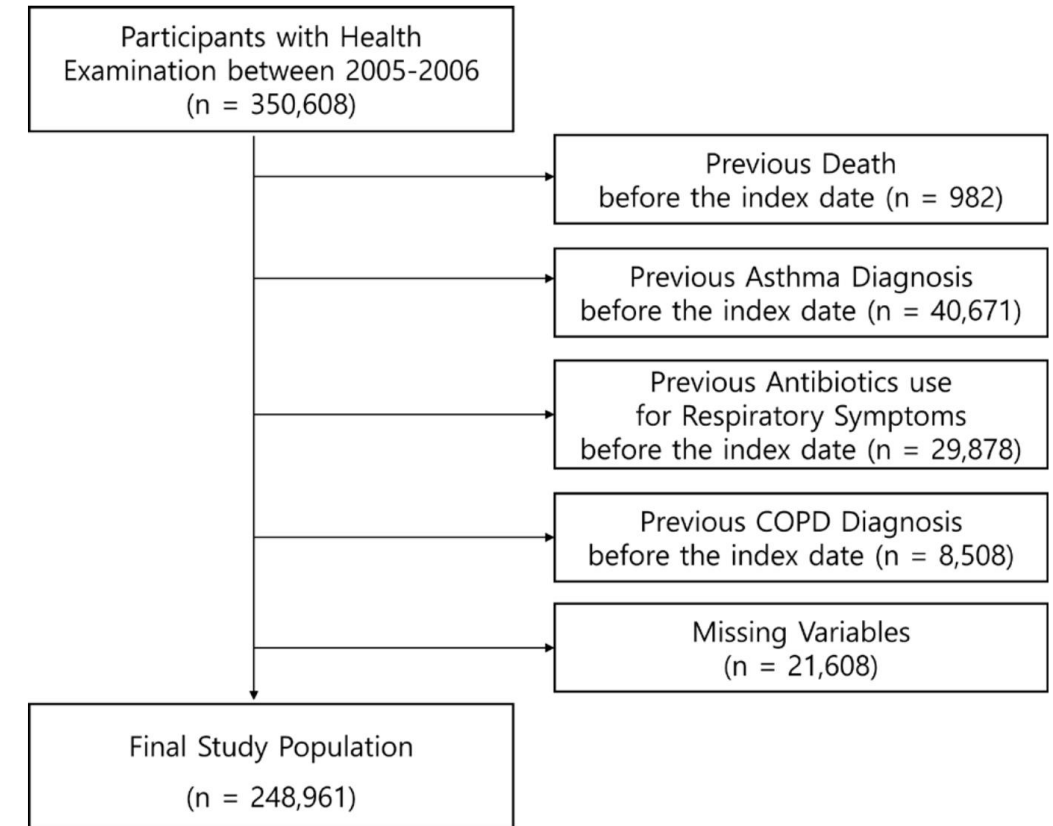
Model 3 further adjusted for smoking status, history of diseases (including infection, bronchitis and emphysema), and family history of asthma

# Subgroup analysis – Age/Sex



# Exposure to antibiotics and asthma in adults

- KNHANES in Korea, 2005-2006, n=248,961, **>40 years old**
- **Objective:** to evaluate the risk of incident asthma according to antibiotics exposure
- **Definition of antibiotic use**
  - ✓ The cumulative antibiotic prescription days for 5 years (2002-2006)
- **Definition of asthma**
  - ✓ **ICD-10 codes (J45, J46)** from 2007 to 2019
  - ✓ **AND prescribed asthma medication** (Oral  $\beta$ 2-agonists, LABA, ICS, LTRA)



# Cumulative days of antibiotics

**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

Model 1 was adjusted for variables in baseline characteristics;

Model 2 was adjusted for the variables in model 1 plus infectious diseases

# Number of antibiotic classes

**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

Model 1 was adjusted for variables in baseline characteristics;

Model 2 was adjusted for the variables in model 1 plus infectious diseases

# Single specific class of antibiotics

Exposure variable	Total	Events	Person-years	aHR (95% CI)
Tetracyclines				
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)
Macrolides				
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)
Fluoroquinolones				
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)
Penicillins (including ampicillin and amoxicillin)				
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)
Sulfonamides				
Antibiotic non-user	38,450	3,975	454,255	1.00 (ref)
Only-user	489	63	5,683	1.02 (0.79-1.30)
Lincosamides				
Antibiotic non-user	38,450	3,975	454,255	1.00 (ref)
Only-user	148	14	1,765	0.83 (0.49-1.40)
Cephalosporins				
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)

Adjusted for variables in baseline characteristics

BMJ Open Respir Res. 2023 Oct;10(1):e001643.

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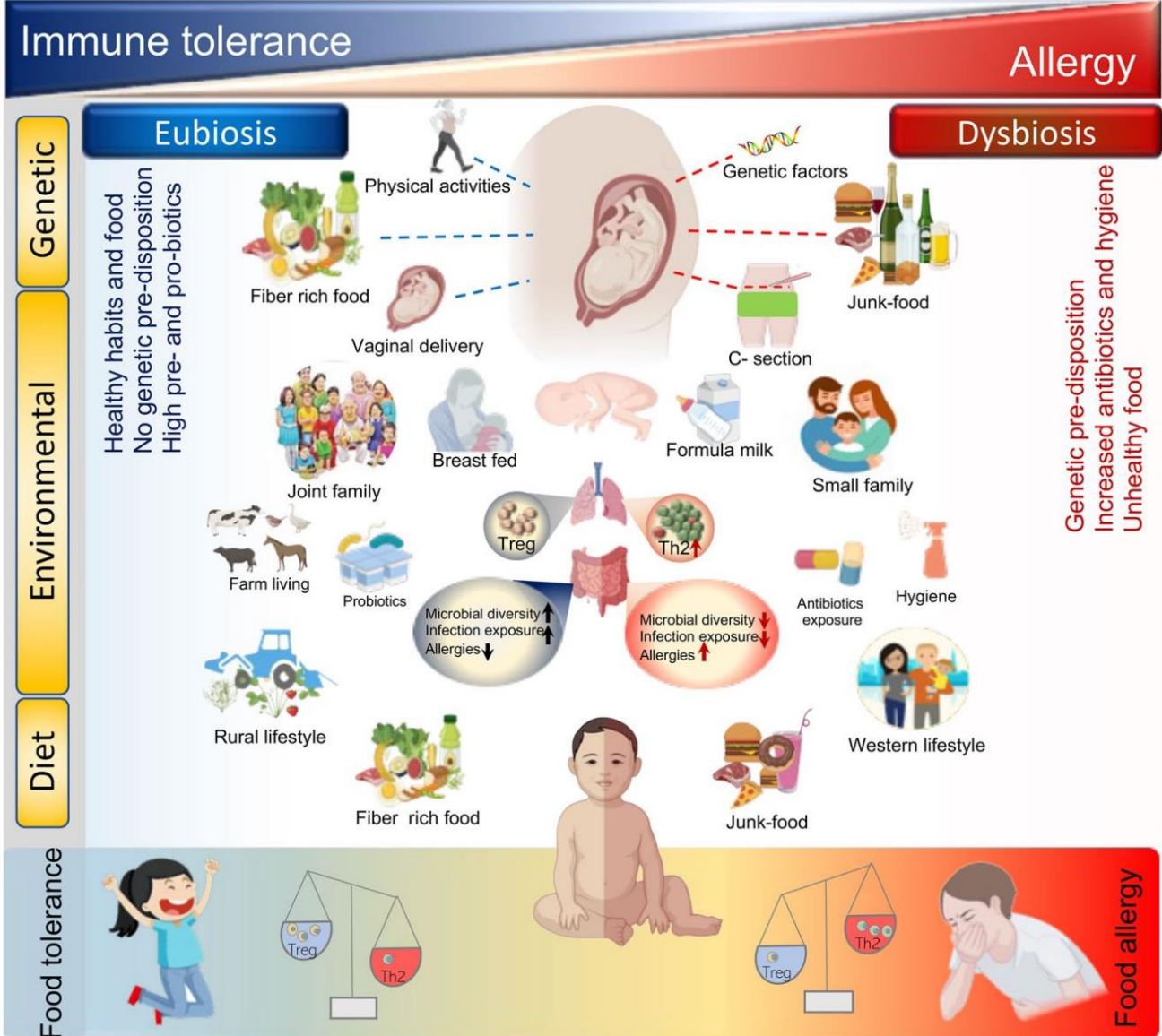
- Exposure to antibiotics and asthma in children
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# Link between antibiotics and asthma

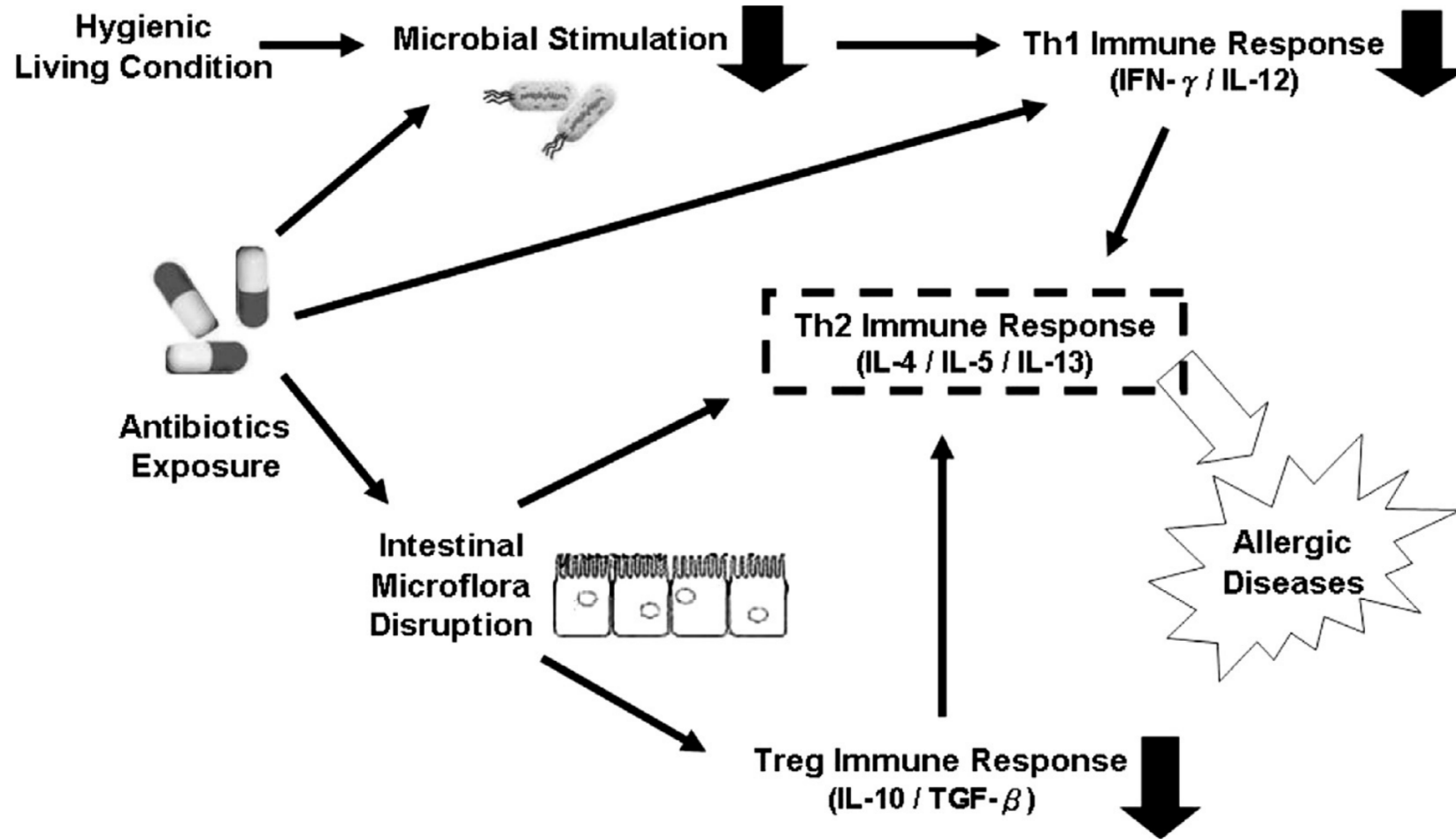
## Potential biological mechanisms

: Antibiotics may lead the immune system towards an allergic inflammation pathway

Clin Exp Allergy. 2015 Jan;45(1):6-8.



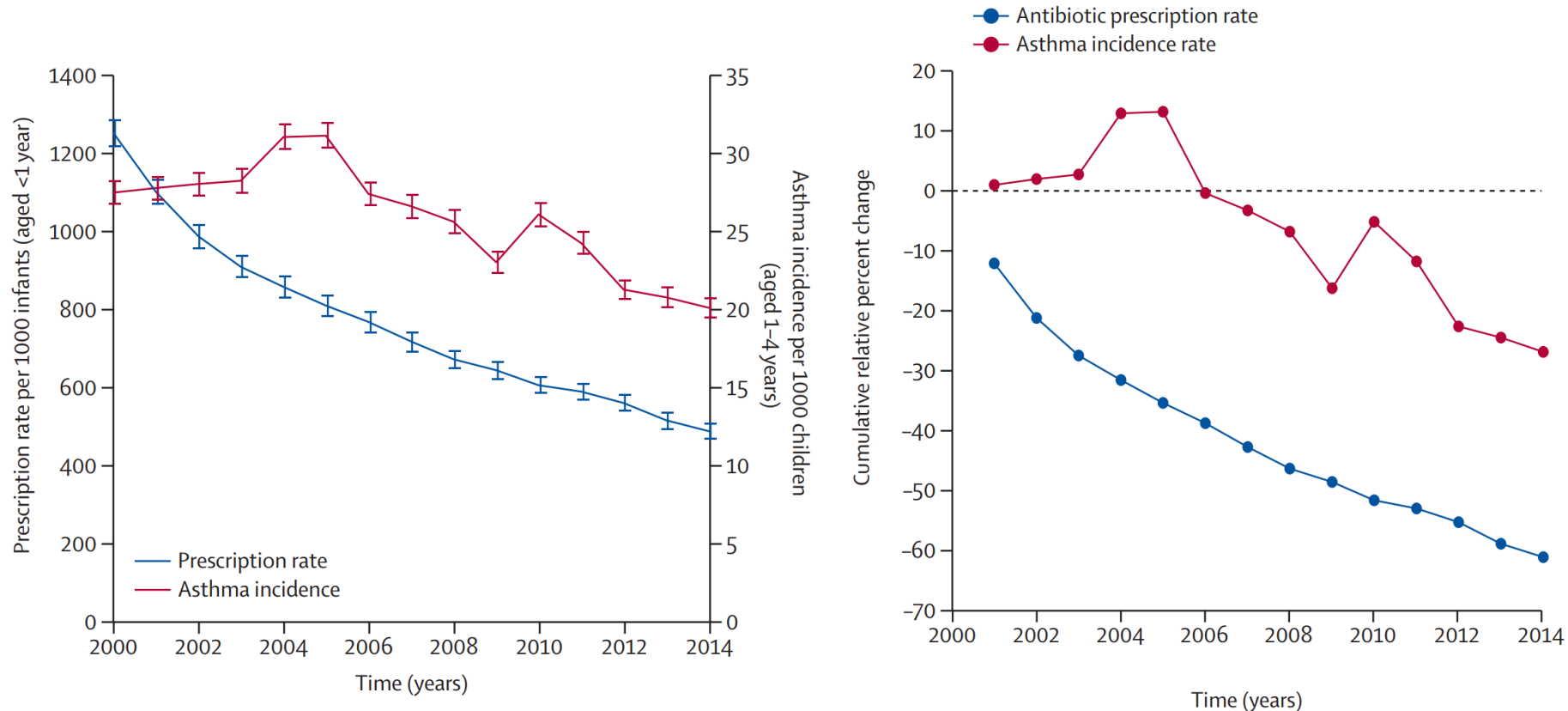
# Antibiotics and allergic immune response



# Antibiotic prescription & asthma incidence

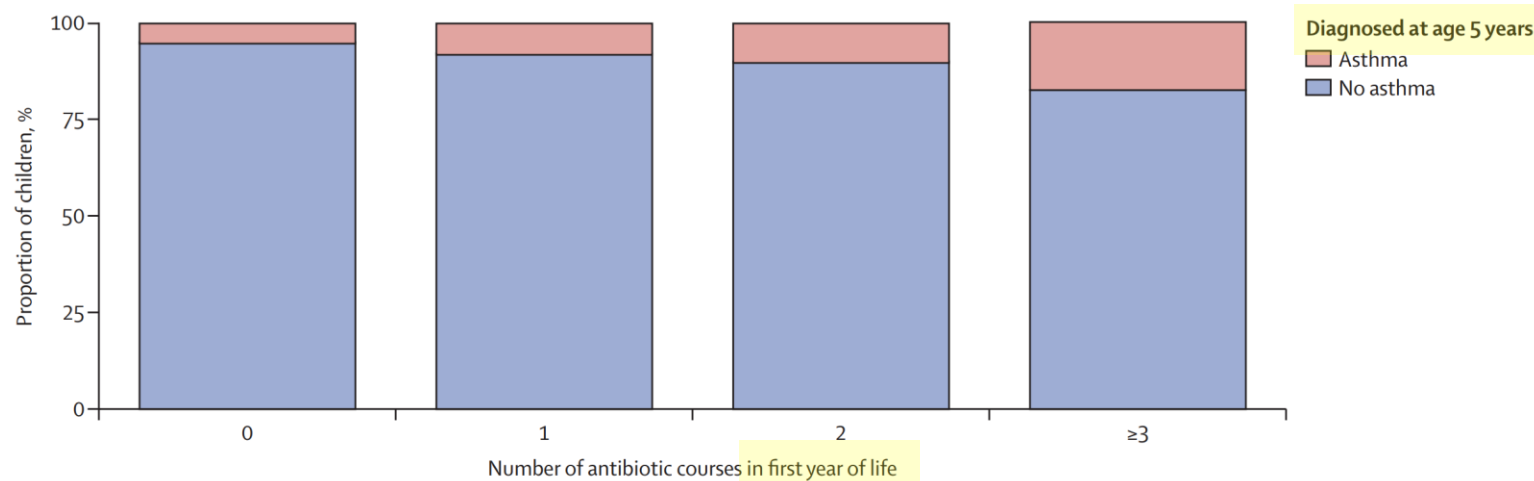
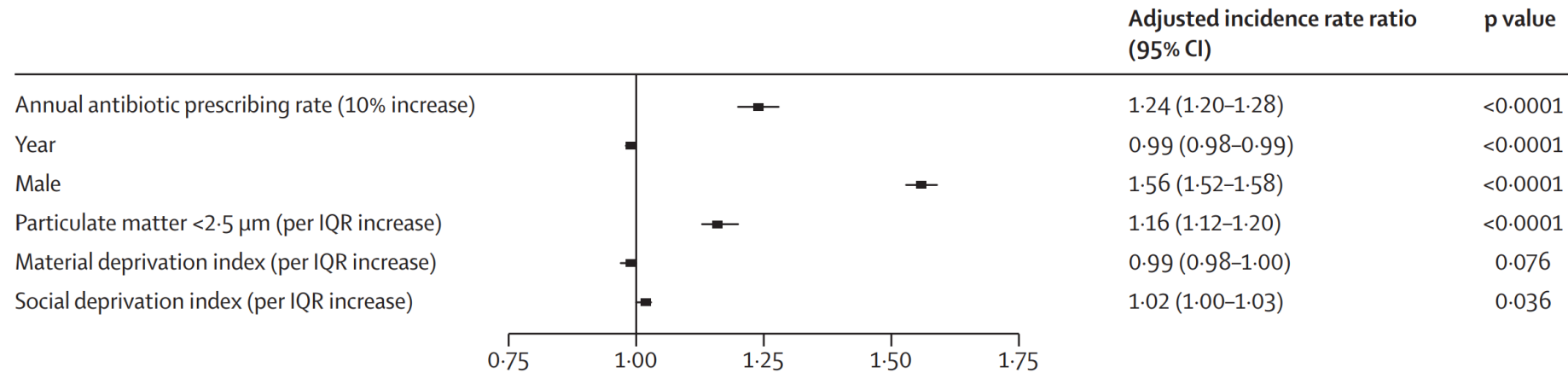
**Prospective CHILD birth cohort** (population 4.7 million), British Columbia, Canada

✓ The rate of asthma incidence & Antibiotic prescription were decreasing.



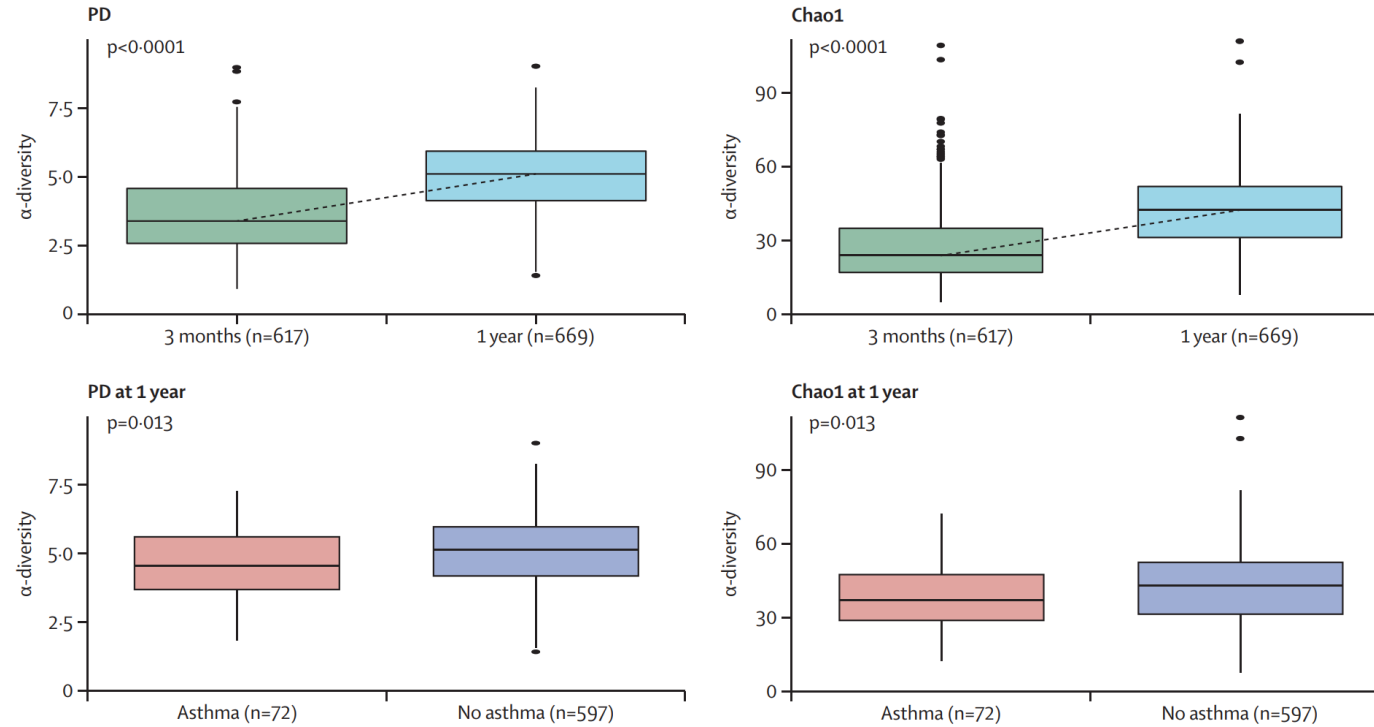
# Antibiotic prescription & asthma incidence

- Antibiotic prescription rate / antibiotic courses were related with asthma incidence.



# Asthma & gut microbiome diversity

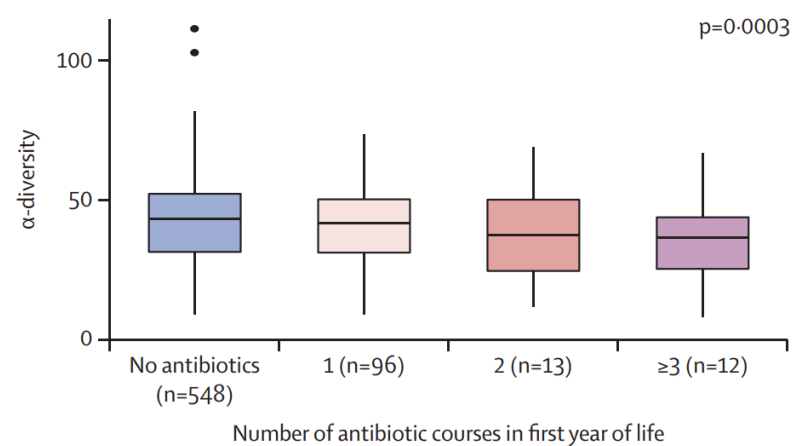
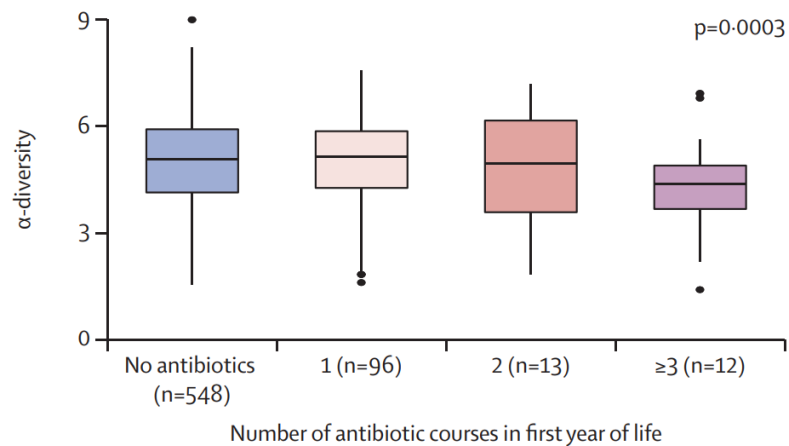
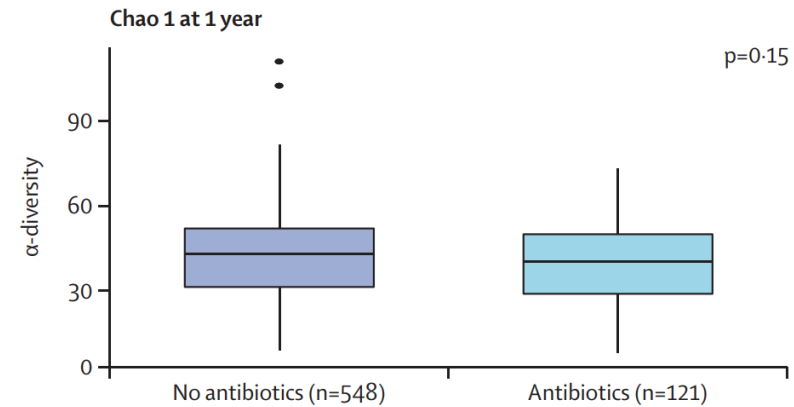
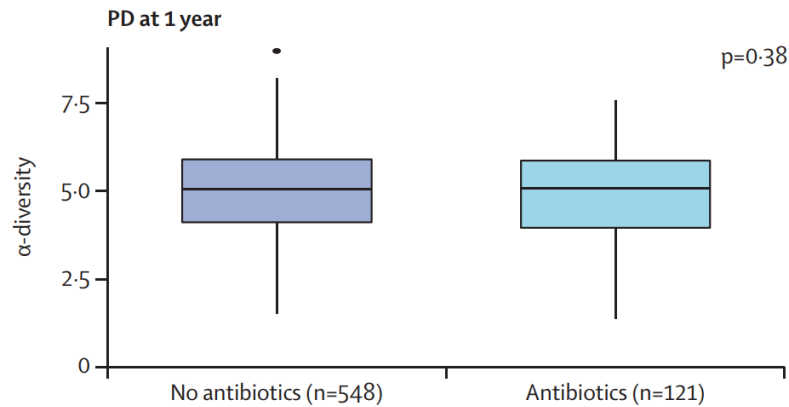
- Decreased gut  $\alpha$ -diversity in infants who developed asthma



	Asthma	No asthma	Adjusted odds ratio	p value
Participants*	63	507	..	..
Chao1 at 1 year (IQR)				
Median (range)	1.8 (0.6 to 3.5)	2.1 (0.4 to 5.3)	0.68 (0.46 to 0.99)	0.046

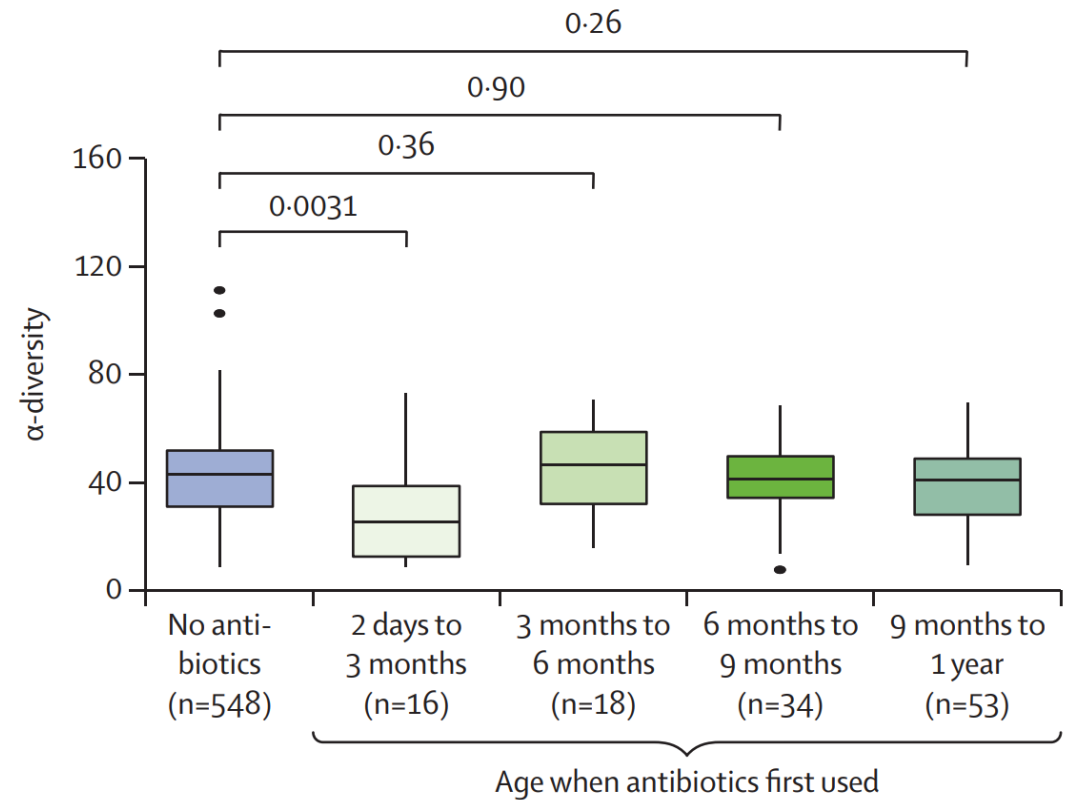
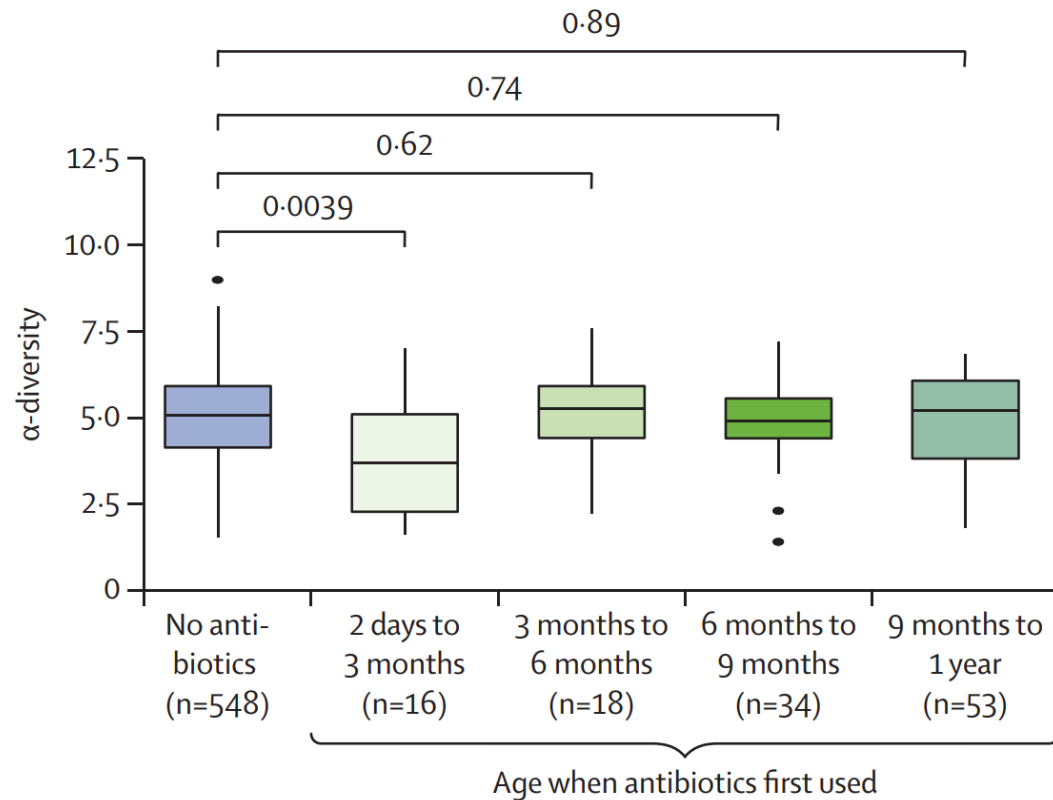
# Antibiotic prescription & gut microbiome diversity

- Decreased gut  $\alpha$ -diversity in infants who were exposed to antibiotics in the first year of life

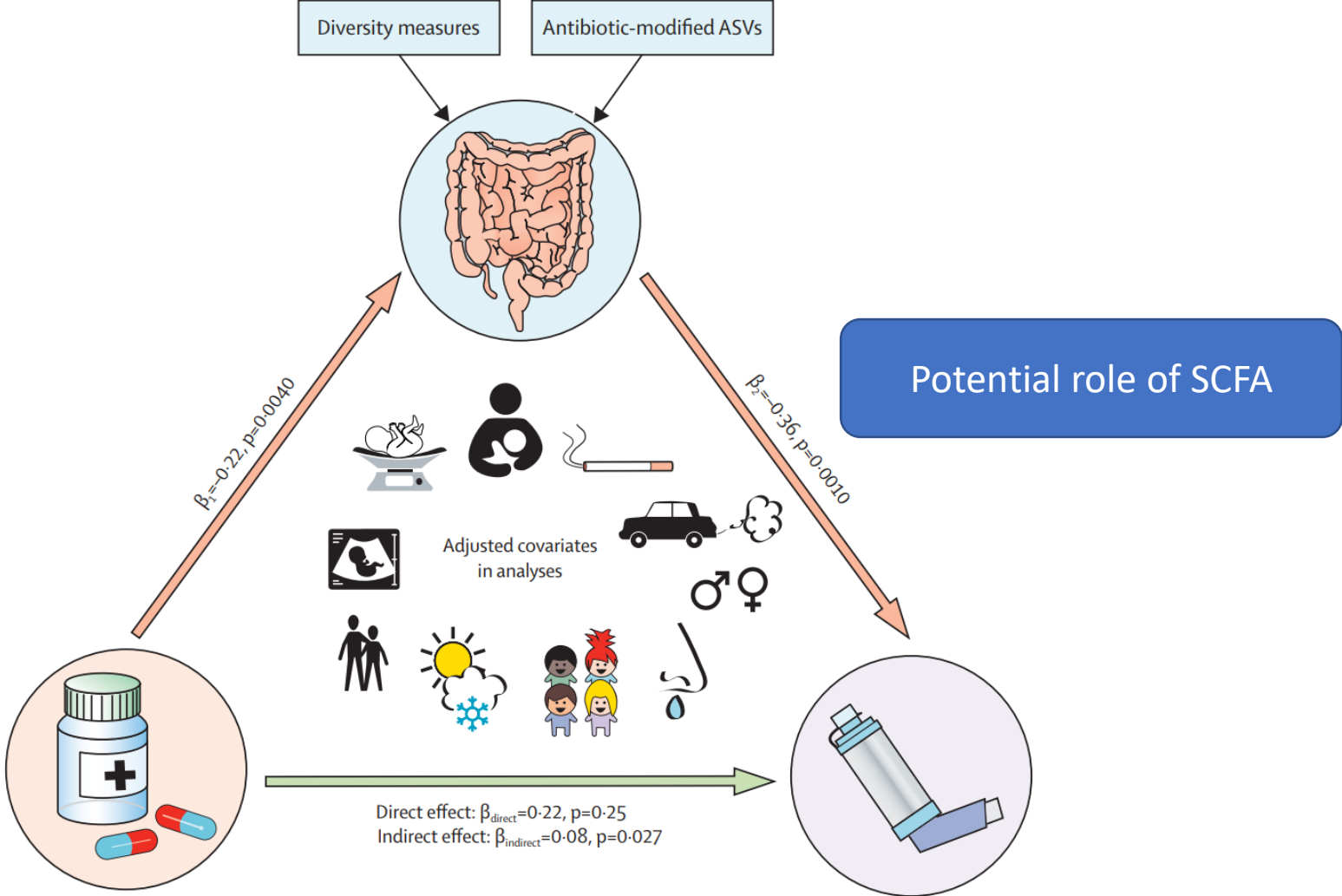


# Antibiotic prescription & gut microbiome diversity

- The stool of infants who received antibiotics before 3 months of age had significantly reduced  $\alpha$ -diversity at age 1 year



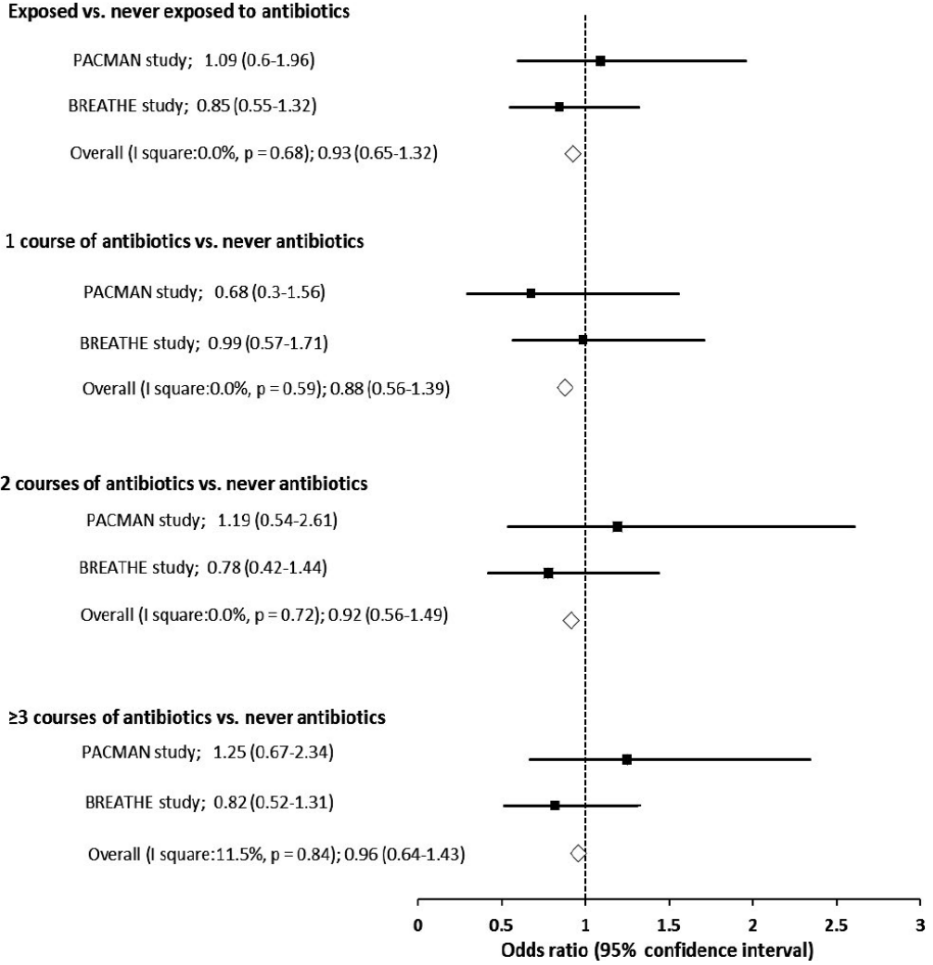
# Link between antibiotic exposure and asthma



# Contents

- Exposure to antibiotics and asthma in children
- Exposure to antibiotics and asthma in adults
- Mechanism linking antibiotics exposure to asthma
- **Exposure to antibiotics and asthma outcomes**

# Early life exposure and asthma exacerbations



Asthma exacerbations

	Crude OR (95% CI)	Adjusted OR (95% CI) <sup>a</sup>
<b>PACMAN</b>		
Ever exposed vs never exposed to antibiotic, n=668		
Ever exposed, n=523	1.16 (0.65-2.08)	1.09 (0.60-1.96)
Never exposed, n=145	Reference	
Frequency of antibiotic use <sup>b</sup> , n=668		
1 antibiotic, n=131	0.74 (0.33-1.66)	0.68 (0.30-1.56)
2 antibiotics, n=102	1.39 (0.65-2.96)	1.19 (0.54-2.61)
≥3 antibiotics, n=290	1.29 (0.70-2.39)	1.25 (0.67-2.34)
Cumulative duration of antibiotic use, n=667		
≤10 d n=121	0.81 (0.36-1.81)	0.67 (0.28-1.58)
11-30 d n=225	1.01 (0.52-1.96)	0.95 (0.48-1.87)
≥30 d n=176	1.66 (0.86-3.18)	1.61 (0.83-3.13)

Asthma exacerbations

# Objective

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- ✓ Currently, the impact of antibiotic exposure on clinical outcomes in asthma patients remains poorly understood.
- ✓ Therefore, this study aims to investigate **the effects of previous antibiotic exposure on acute exacerbations, mortality, and medical costs** in patients with asthma.

# Inclusion criteria

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- Health Insurance Review and Assessment (HIRA) Service claim database
- Duration: 2020.1.1 ~ 2022.12.31
- Eligible criteria: asthma patients
  - 1) **Group:** exposure vs. no exposure to antibiotics (1 year, 2020.1.1~2020.12.31)
  - 2) **Clinical outcomes** (2 years, 2021.1.1~2022.12.31)
- **Definition of asthma**
  - 1) **Age  $\geq$  15 years**
  - 2) **ICD-10 codes for asthma as the primary or secondary diagnosis**
  - 3)  **$\geq$  1 drug for asthma at least twice per year**
    - ✓ SAMA, SABA, SAMA+SABA,
    - ✓ ICS, LABA, LAMA, ICS+LABA, ICS+LABA+LAMA
    - ✓ Theophylline, leukotriene antagonist, systemic corticosteroids, systemic beta agonist

# Antibiotics for respiratory infection

Class	Specific drugs
<b>Macrolide</b>	Azithromycin, Clarithromycin, Erythromycin, Roxithromycin
<b>Quinolone</b>	Levofloxacin, Moxifloxacin, Gemifloxacin
<b>B-lactam antibiotics</b>	Amoxicillin, Amoxicillin/Clavulanate, Ampicillin, Ampicillin/Sulbactam, Cefditoren, Cefepime, Cefixime, Cefoperazone/Sulbactam, Cefotaxime, Cefpodoxime, Ceftazidime, Ceftriaxone, Piperacillin/Sulbactam, Piperacillin/Tazobactam

- **Definition of exposure to antibiotics**
  - ✓ One or more antibiotics for previous 1 year
  - ✓ Cumulative duration of antibiotics ≥ 4 weeks

# Baseline characteristics

	Exposure to antibiotics group	No exposure to antibiotics group	P-value
<b>N (%)</b>	138,586 (25.2%)	410,839 (74.8%)	
<b>Age, years</b>			
<b>Mean (<math>\pm</math>SD)</b>	61.63 $\pm$ 17.55	60.12 $\pm$ 18.13	<0.001
$\geq$ 65, n (%)	69,922(50.5)	192,160(46.8)	<0.001
<b>Sex, male, n (%)</b>	64,176(46.3)	195,298(47.5)	<0.001
<b>Allergic disease</b>			
Sinusitis, n (%)	33,745(24.4)	62,389(15.2)	<0.001
Rhinitis, n (%)	121,696(87.8)	345,851(84.2)	<0.001
<b>History of pneumonia</b>			
Outpatient clinic visit or hospitalization, n (%)	11829(8.5)	3278(0.8)	<0.001
Hospitalization, n (%)	6,697(4.8)	1,238(0.3)	<0.001
Length of stay in hospital, median (IQR)	13(8,22)	8(5,13)	<0.001
<b>History of bronchiectasis, n (%)</b>	11,772(8.5)	20,228(4.9)	<0.001
<b>Charlson comorbidity index, mean (<math>\pm</math>SD)</b>	3.41 $\pm$ 2.26	2.98 $\pm$ 2.05	<0.001

# Asthma treatment according to antibiotics exposure

	Exposure to antibiotics group	No exposure to antibiotics group	P-value
<b>N (%)</b>	138,586	410,839	
<b>Medications</b>			
Oral beta-agonist	40,017(28.9)	97,247(23.7)	<0.001
Methylxanthines	58,582(42.3)	156,505(38.1)	<0.001
LTRA	82,664(59.7)	221,490(53.9)	<0.001
<b>Inhalers</b>			
SABA only	13,178(9.5)	39,676(9.7)	0.105
ICS only	5,016(3.6)	13,558(3.3)	<0.001
ICS/LABA	79,445(57.3)	284,596(69.3)	<0.001
ICS/LABA + LAMA	9,323(6.7)	19,604(4.8)	<0.001
<b>Systemic steroids</b>			
Use of oral corticosteroid, n (%)	102,385(73.9)	203,156(49.5)	<0.001
Cumulative dose (OCS) <sup>a</sup> , mean (SD), mg	499.38±1103.61	324.72±833.74	<0.001

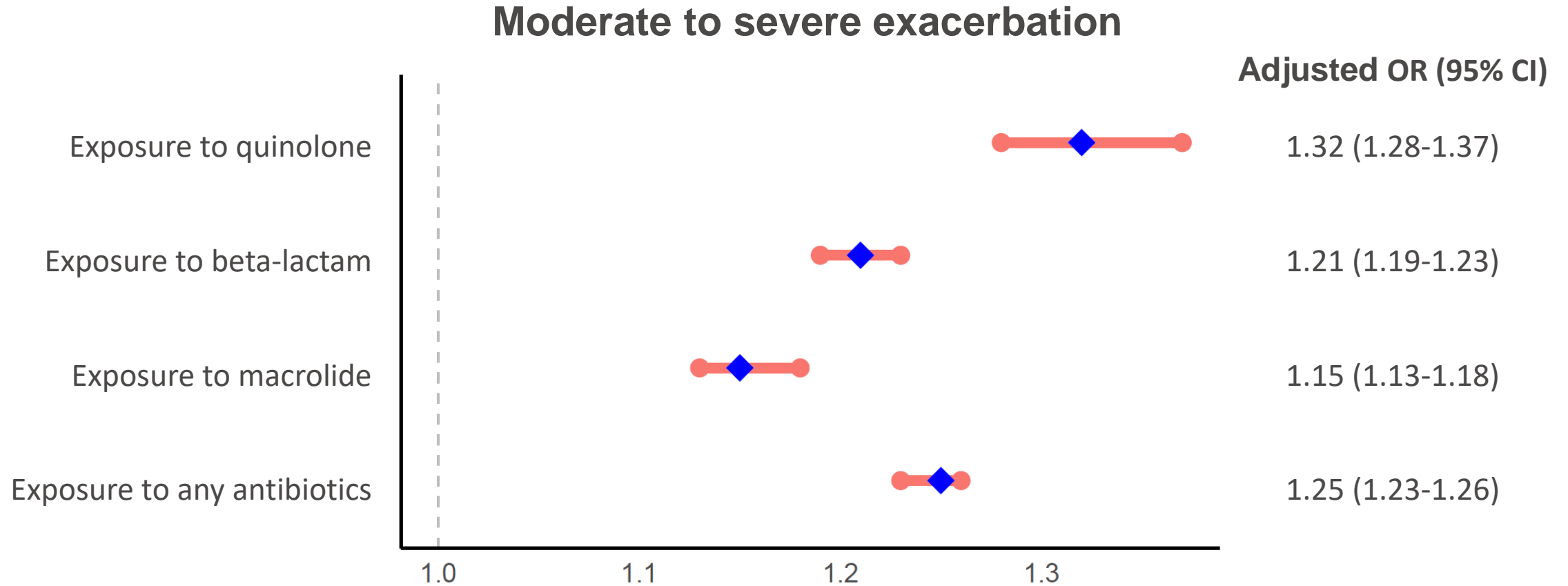
# Clinical outcomes according to antibiotics exposure

	Exposure to antibiotics group	No exposure to antibiotics group	P-value
<b>N (%)</b>	138,586	410,839	
<b>Exacerbation</b>			
Moderate, n (%)	36995(26.7)	93434(22.7)	<0.001
Severe, n (%)	11396(8.2)	20917(5.1)	<0.001
Moderate-to-severe, n (%)	43194(31.2)	105842(25.8)	<0.001
<b>Death, n (%)</b>	5757(4.2)	7658(1.9)	<0.001
<b>Medical cost, Korean Won, median [IQR]</b>			
Outpatient	2,595,915(1,397,015-4,585,550)	1,917,255(989,790-3,452,810)	<0.001
Inpatient	4,836,845(1,910,560-14,208,420)	3,553,920(1,452,220-9,947,750)	<0.001
Medication cost	4,427,605(1,921,230-10,976,140)	2,783,260(1,209,460-6,727,830)	<0.001

## Definition of the severity of exacerbation

- **Moderate:** 1) OPD visit & 2) additional treatment (antibiotics or systemic steroid)
- **Severe:** 1) ER visit or Hospitalization & 2) additional treatment (antibiotics or systemic steroid)

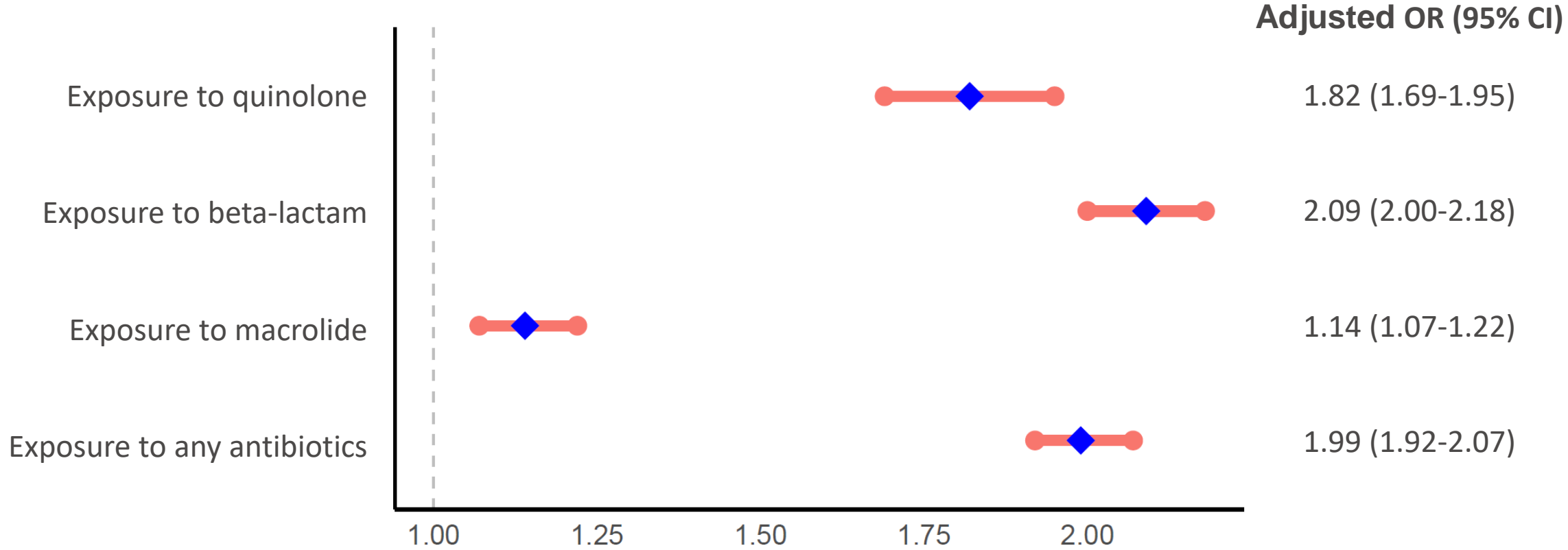
# Multivariable analysis for moderate to severe AE



Covariables included age, sex, history of pneumonia, rhinitis, sinusitis, bronchiectasis, CCI, inhaled therapy (SABA, ICS, ICS/LABA, ICS/LABA + LAMA)

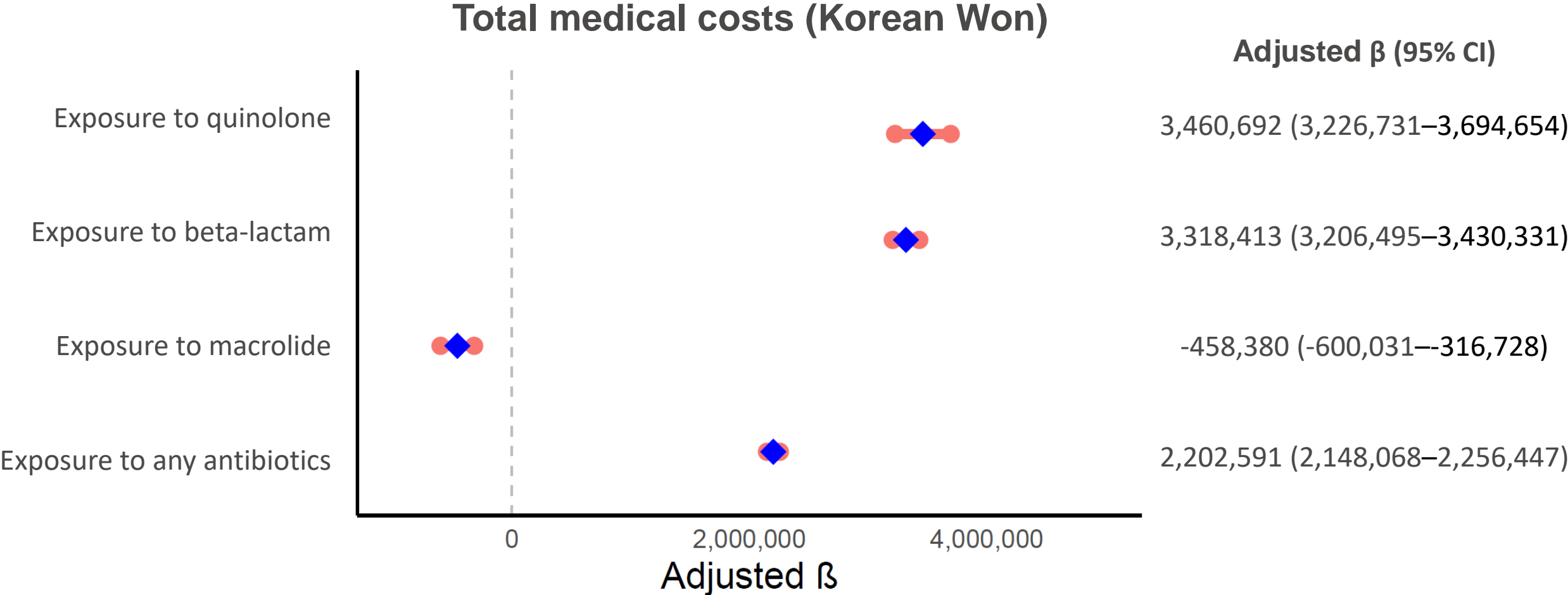
# Multivariable analysis for all-cause mortality

## All-cause mortality



Covariables included age, sex, history of pneumonia, rhinitis, sinusitis, bronchiectasis, CCI, inhaled therapy (SABA, ICS, ICS/LABA, ICS/LABA + LAMA)

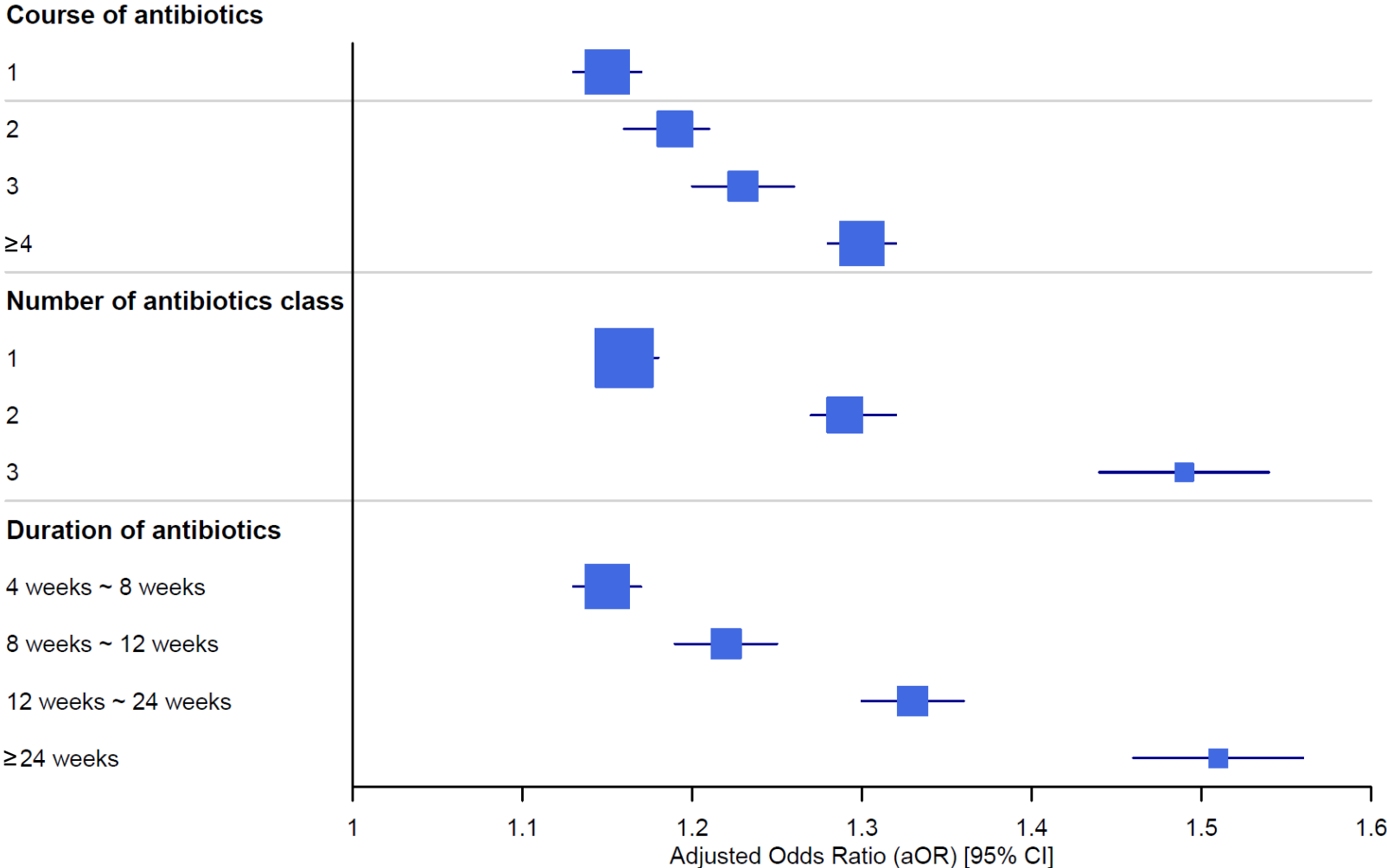
# Multivariable analysis for total medical costs



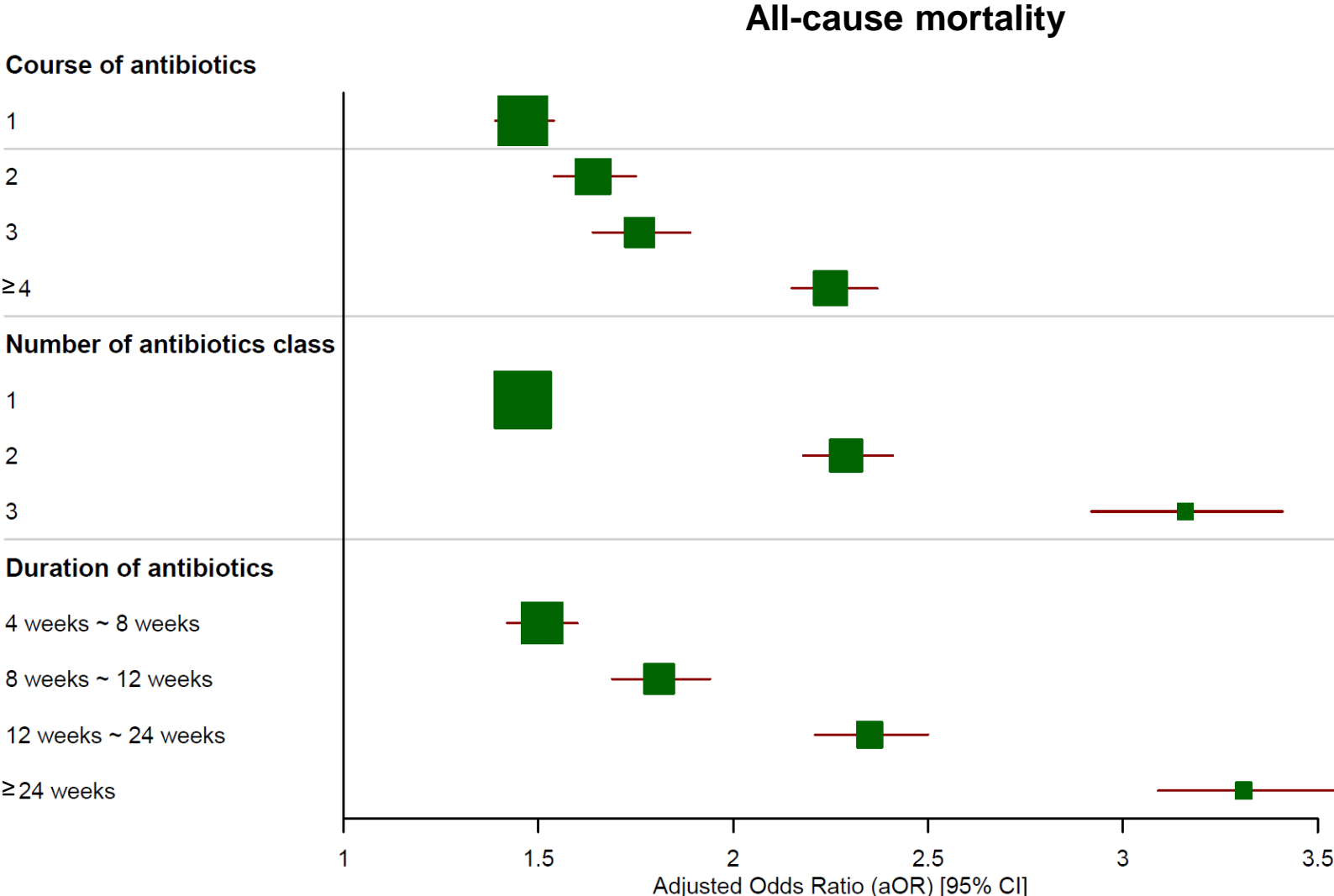
Covariables included age, sex, history of pneumonia, rhinitis, sinusitis, bronchiectasis, CCI, inhaled therapy (SABA, ICS, ICS/LABA, ICS/LABA + LAMA)

# Impact of intensity of antibiotic exposure

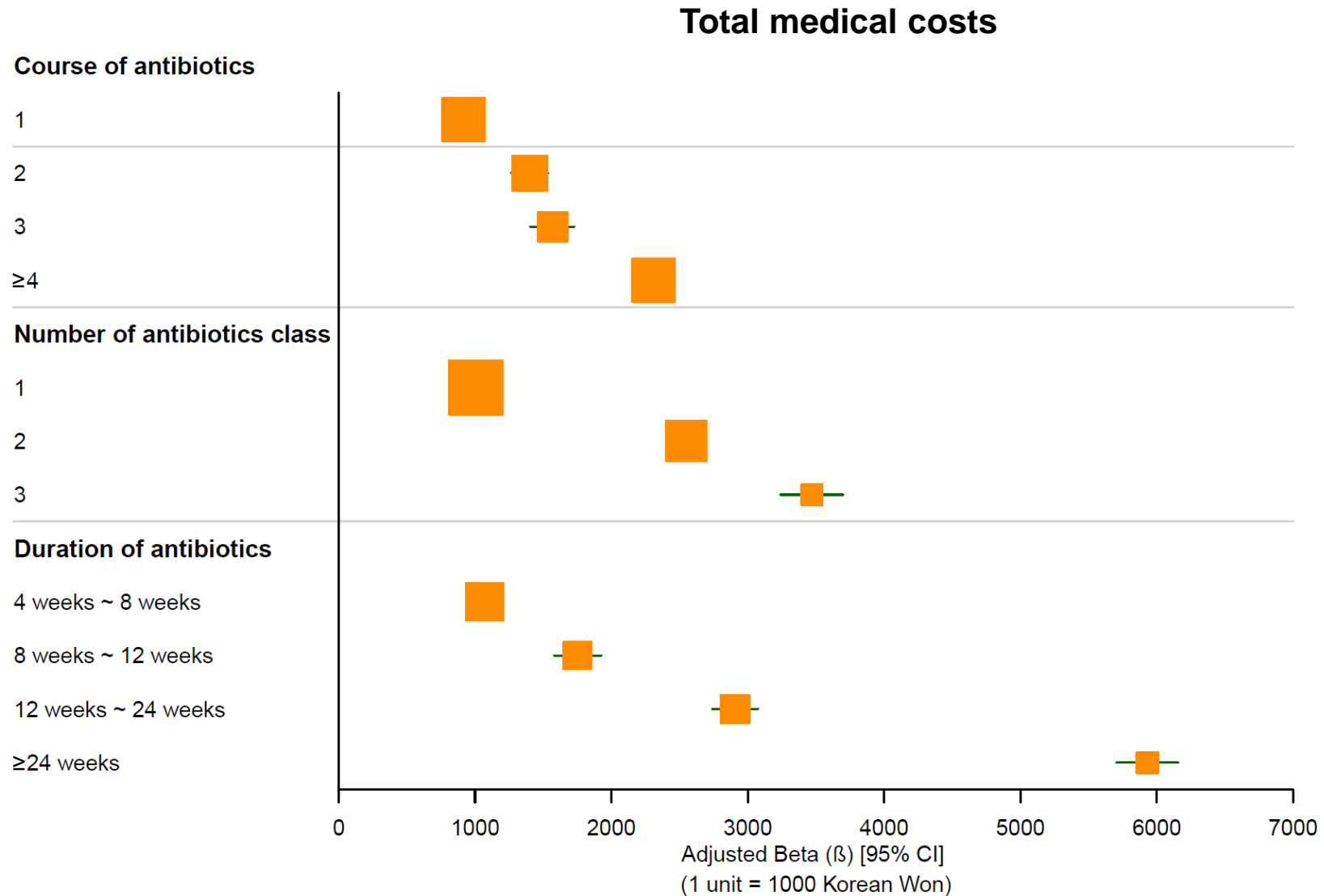
## Moderate to severe exacerbation



# Impact of intensity of antibiotic exposure



# Impact of intensity of antibiotic exposure



# Summary

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- **Exposure to antibiotics and asthma in children**

- ✓ Antibiotic exposure within 1 year of birth is related with asthma
- ✓ Early exposure / Beta-lactam, macrolide / Broad spectrum, more courses, higher number of antibiotics

- **Exposure to antibiotics and asthma in adults**

- ✓ More exposure to antibiotics is related with diagnosis of asthma
- ✓ Macrolide, fluoroquinolone, penicillin class / Cumulative days / Number of antibiotic classes

# Summary

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- **Mechanism linking antibiotics exposure to asthma**

- ✓ Antibiotics may lead the immune system towards an allergic inflammatory (T2) pathway
- ✓ Antibiotics → Change in gut microbiome (dysbiosis) → Change in SCFA → Allergic inflammation → Asthma

- **Exposure to antibiotics and asthma outcomes**

- ✓ Exposure to antibiotics is related with worse outcomes (AE, mortality, cost) in asthma
- ✓ Worse outcomes in those with fluoroquinolone or beta-lactam antibiotics than macrolide
- ✓ Worse outcomes in those with more courses, higher numbers, and longer duration of antibiotics

**Thank you for your attention**



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