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https://youtu.be/eL-4zGyXuy0

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Preventing Childhood Asthma and Allergy:

The Neglected Impacts of Antibiotic Stewardship and Human Milk Exposure in Infants

Public Health Ontario Grand Rounds

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CIHR IRSC Canadian Institutes of Health Research Instituts de recherche en santé du Canada

Pacific Public Health FOUNDATION

BC Centre for Disease Control
Provincial Health Services Authority

Provincial Health Services Authority

UBC

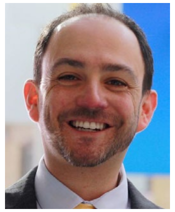
We acknowledge that we live and work on the traditional unceded territory of the xʷməθkʷəy̓əm (Musqueam), Sḵwx̱wú7mesh Úxwumixw (Squamish), səl̓ilw̓ətaʔɬ (Tsleil-Waututh) and kʷikʷəƛ̓əm (Kwikwetlem) Nations.

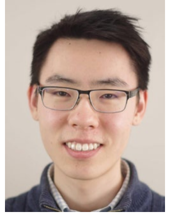
Objectives

- To understand recent changes in childhood asthma epidemiology, possible explanations and correlation with changing antibiotic use in infancy
- To overview current evidence linking perturbation of the developing infant gut microbiota and subsequent experience of atopic disease.
- To summarize studies to date and provide detailed description of published findings from the Canadian Healthy Infant Longitudinal Development Study
- To draw inference about effects at scale in population from a cohort study of 600,000 Canadian children from BC and Manitoba.
- To discuss current implications, knowledge gaps and future research.

Team effort


Hannah Lishman


Nathan Nickel


Max Xie


Lisa Flaten

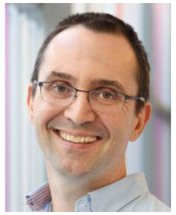

Hind Sbihi


Abdullah Mamun


Caren Rose


Ashley Roberts


Meghan Azad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CHILD COHORT STUDY

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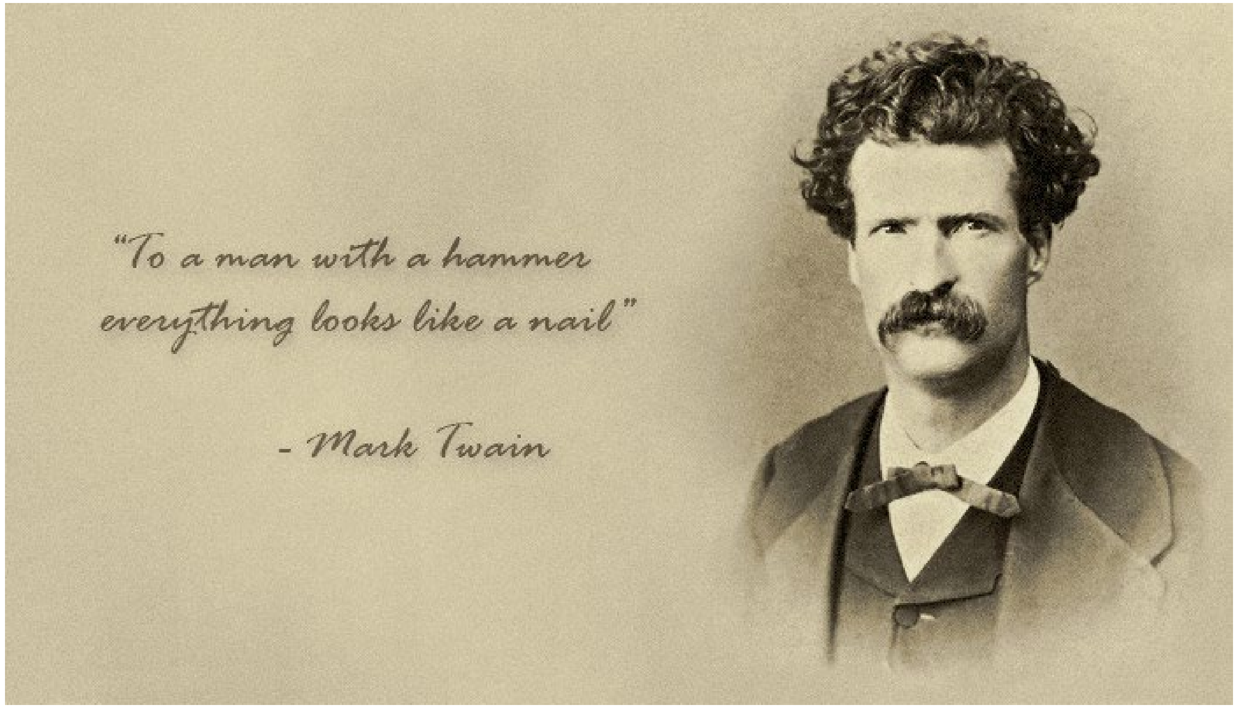
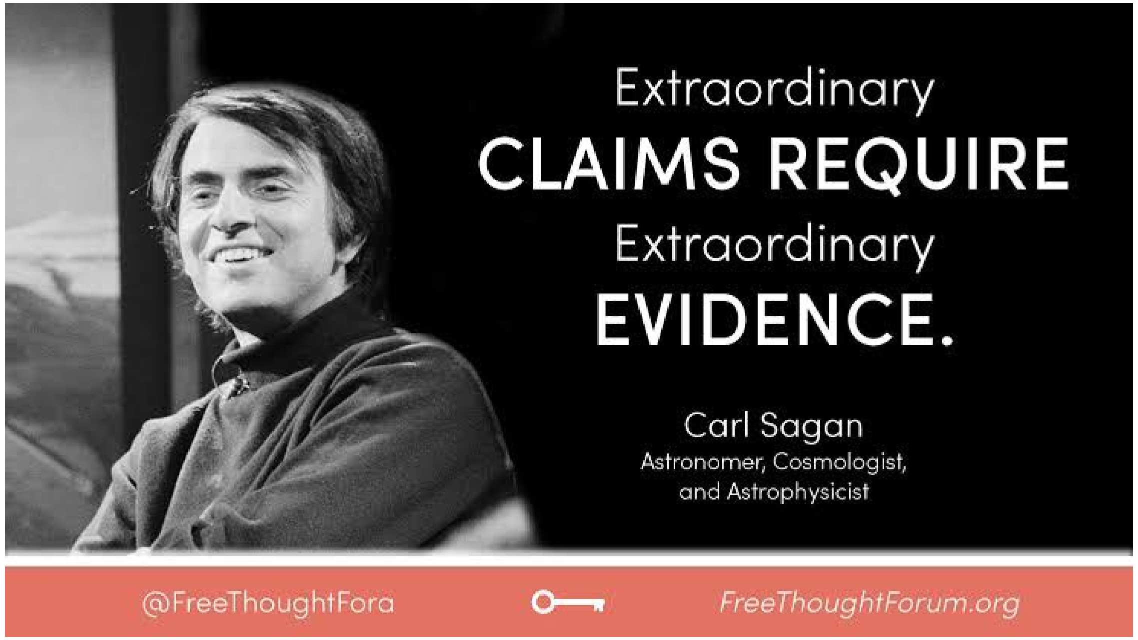
Thesis: Developing Gut Microbiota and Atopy

- Prenatal period and early infancy is a key period for development of the immune system.
- Influenced by genetics, host biology and environment
- <u>Gut microbiota are a key element of that environment</u> and may be changed by diet, environment and medical interventions, especially antibiotics
- Microbiota interact with and train the developing immune system.
- Perturbation of that development by antibiotics may predispose to abnormal immune system development and higher risk of atopy
- This may explain population level trends we are seeing today

Donald K, Finlay BB. Early-life interactions between the microbiota and immune system: impact on immune system development and atopic disease.
Nat Rev Immunol. 2023 Nov;23(11):735-748. doi: 10.1038/s41577-023-00874-w. Epub 2023 May 3. PMID: 37138015.





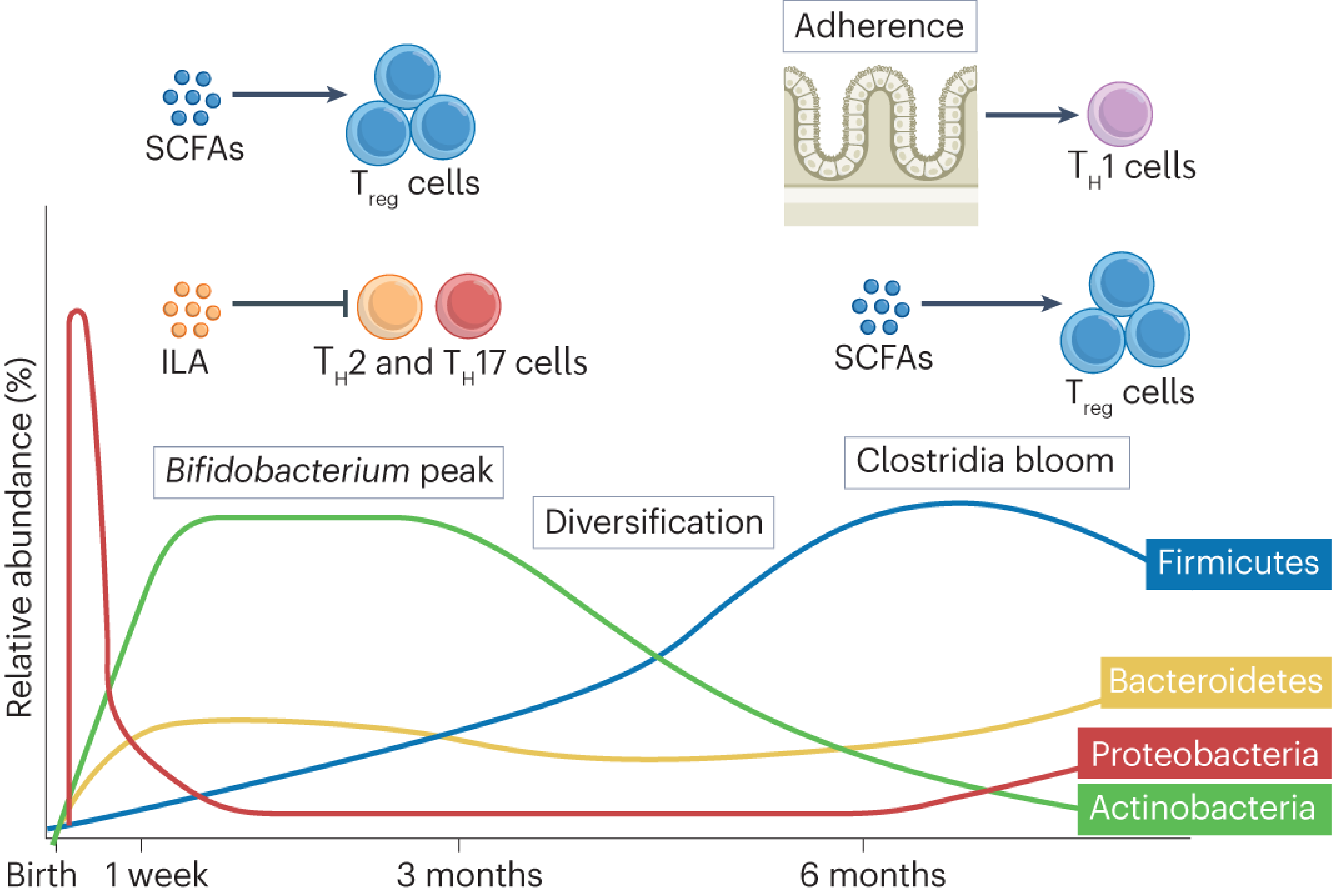
- Population Studies
- Prospective Cohort Studies
- Studies of the gut microbiota and atopic outcomes
- Experimental Studies

Before Starting

- Antibiotics are often needed to save lives
- Breastfeeding, chest-feeding, lactating, nursing, human milk feeding – not everyone can manage
- We need to support people unconditionally and avoid stigma

Terms provided by the Academy of Breastfeeding Medicine Position Statement and Guideline: Infant Feeding and Lactation-Related Language and Gender

Image provided by Breastfeeding Committee of Canada



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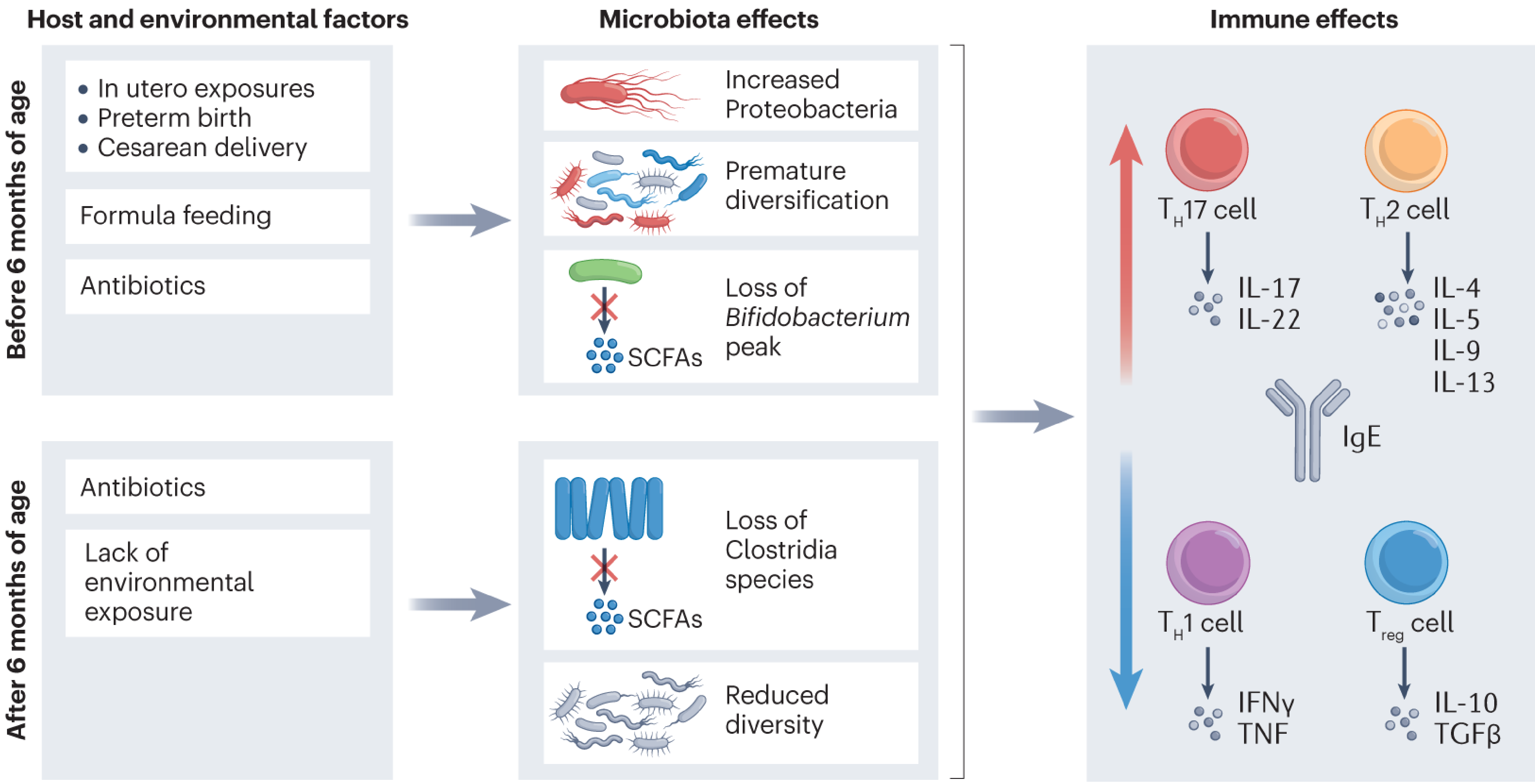
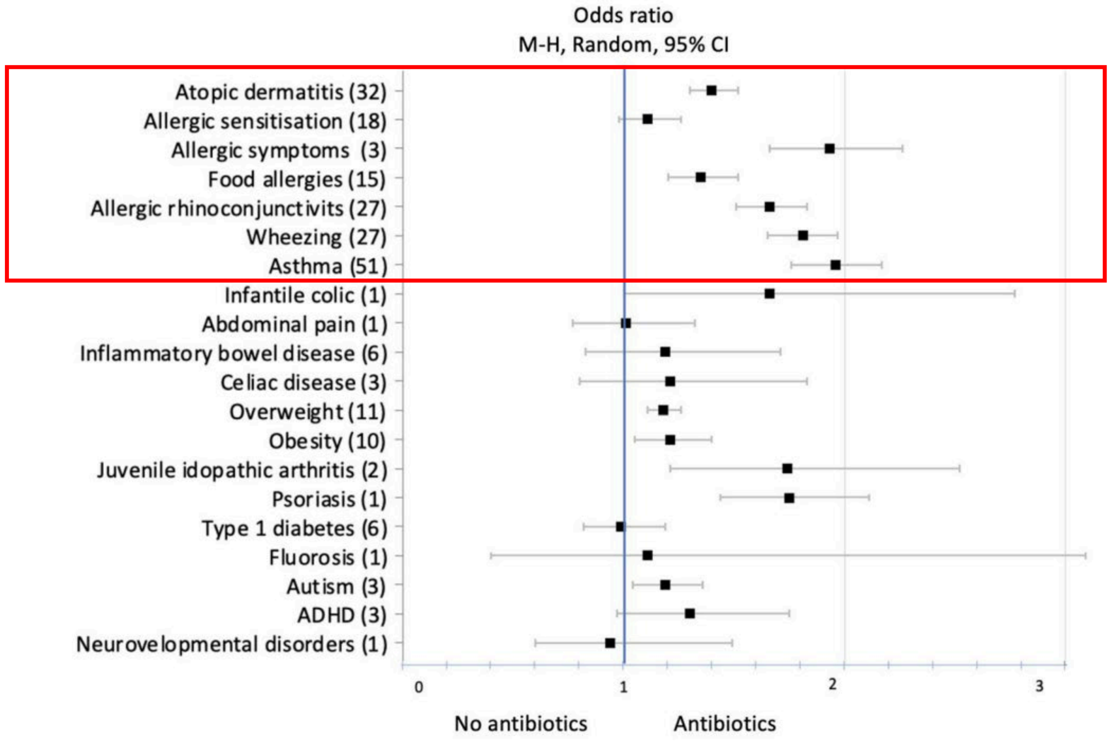


Donald K, Finlay BB. Early-life interactions between the microbiota and immune system: impact on immune system development and atopic disease. Nat Rev Immunol. 2023 Nov;23(11):735-748. doi: 10.1038/s41577-023-00874-w. Epub 2023 May 3. PMID: 37138015.

Systematic Review on Antibiotic Exposure



CI – confidence interval H-M – Mantel-Haenszel

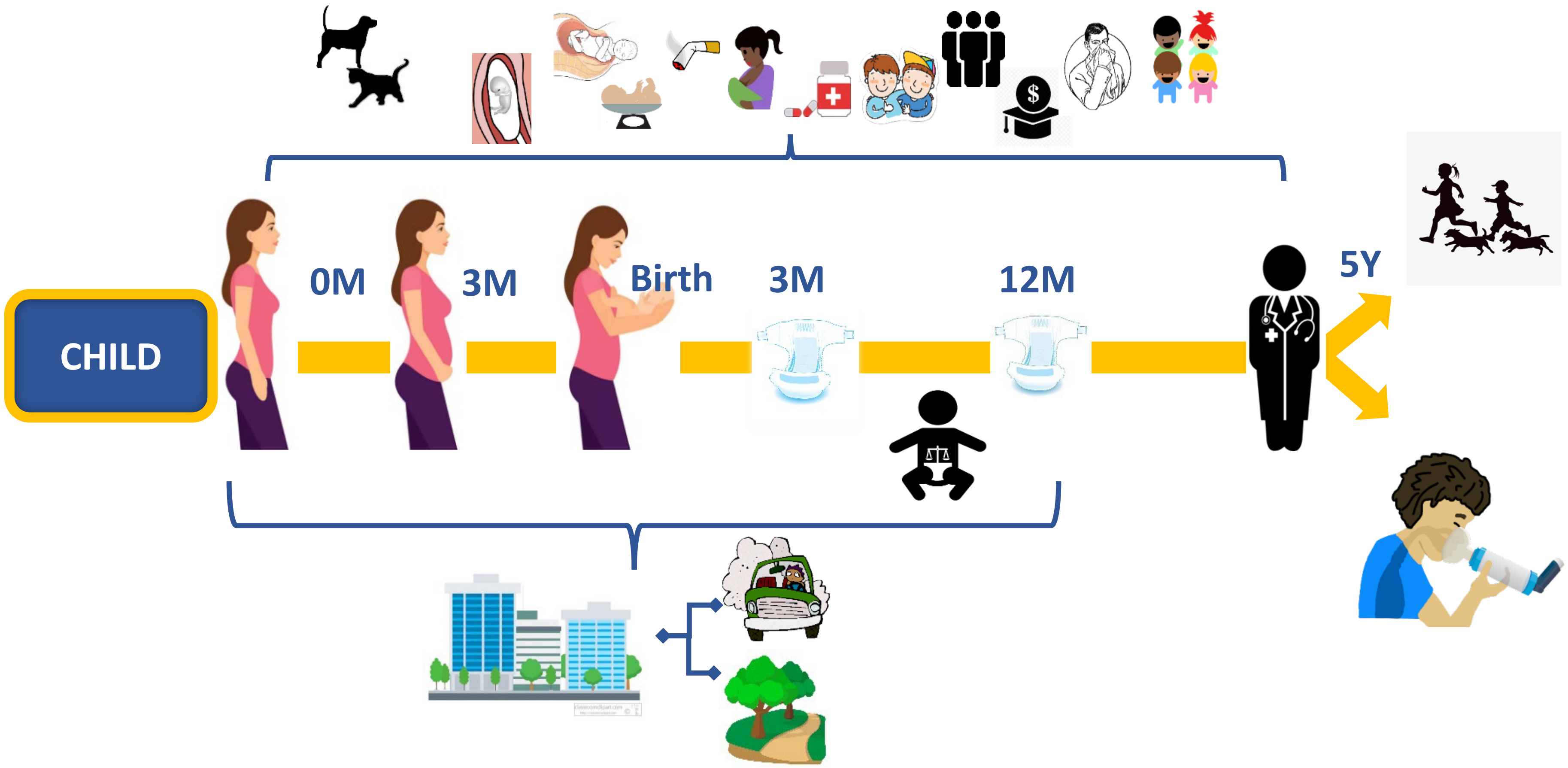
Figure 1. Comparison of incidence of adverse health outcomes in children exposed and not exposed to antibiotics.

Duong QA, Pittet LF, Curtis N, Zimmermann P. Antibiotic exposure and adverse long-term health outcomes in children: A systematic review and meta-analysis. J Infect. 2022 Sep;85(3):213-300. doi: 10.1016/j.jinf.2022.01.005. Epub 2022 Jan 10. Erratum in: J Infect. 2022 Nov 3;: PMID: 35021114.

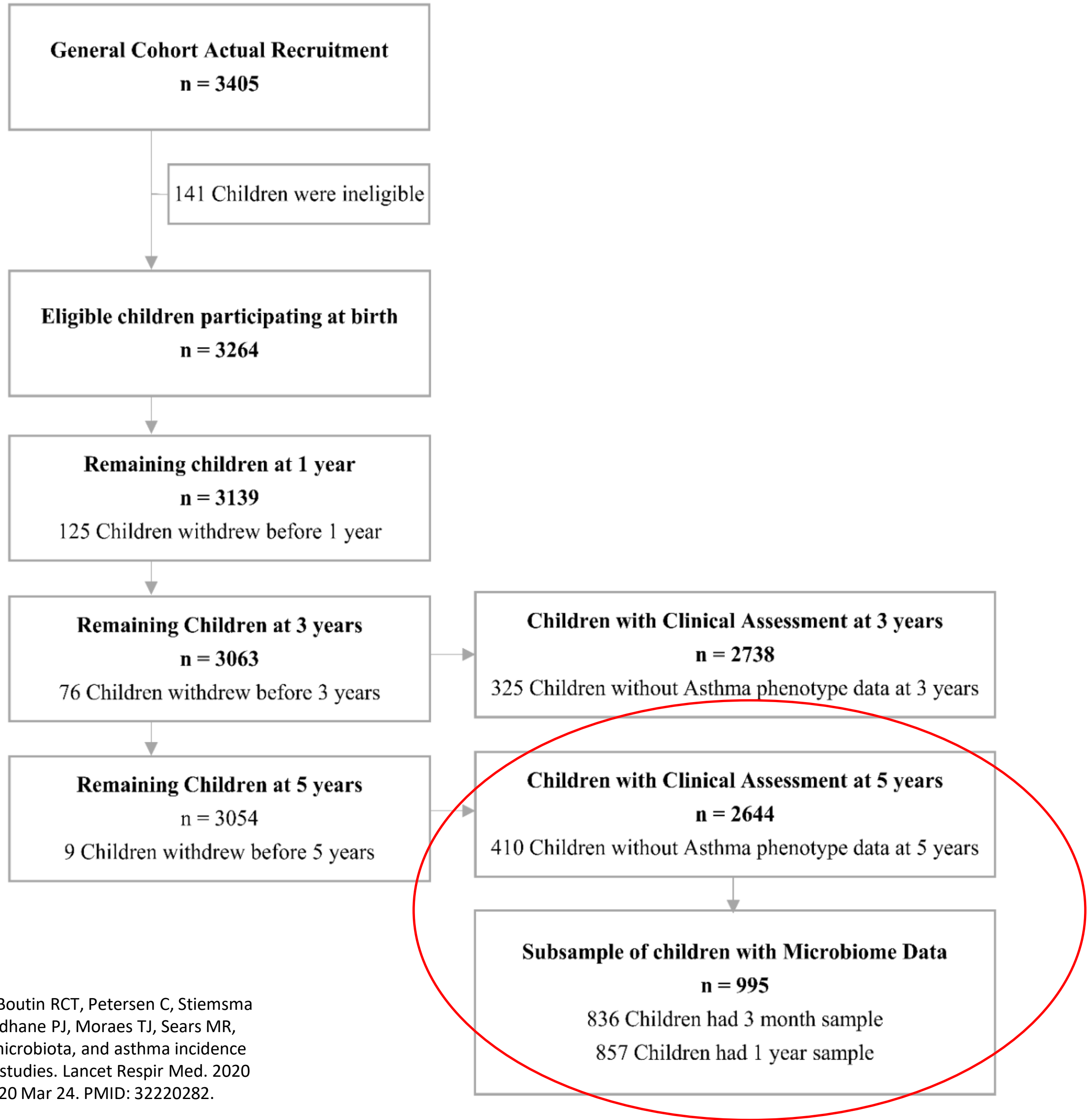
- Meta-analysis of 51 studies
- 2x odds of developing asthma in children exposed to antibiotics
- Significantly higher odds of developing other allergic diseases
- Exposure in first 3 months is most important

HANDLE ANTIMICROBIALS WITH CARE

Canadian Healthy Infant Longitudinal Development Study (CHILD): Study design



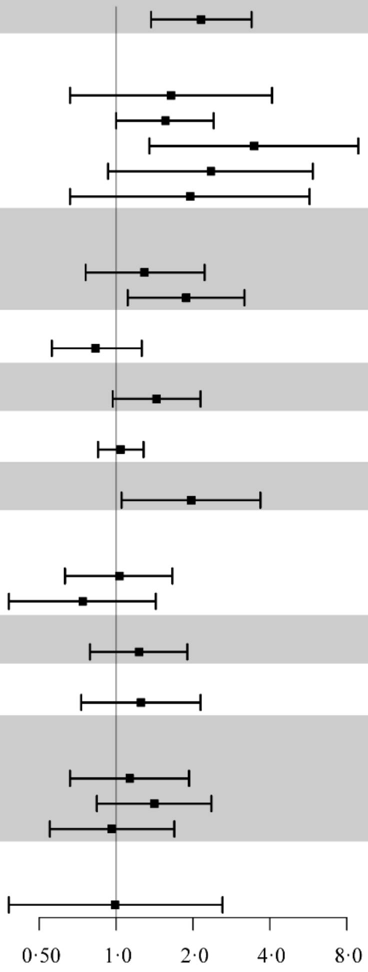
CHILD: Study sample and Microbiota subsample



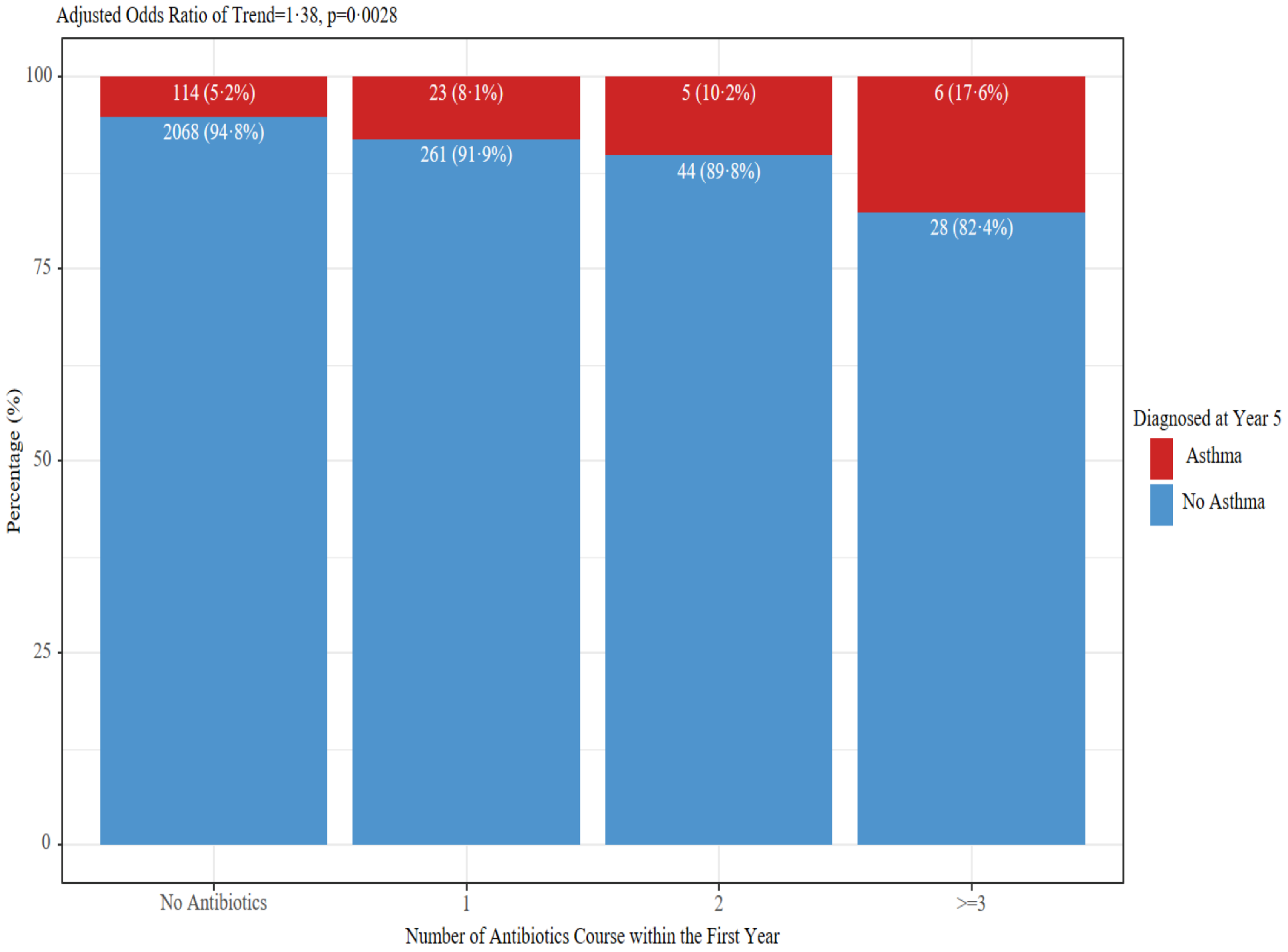
Patrick DM, Sbihi H, Dai DLY, Al Mamun A, Rasali D, Rose C, Marra F, Boutin RCT, Petersen C, Stiemsma LT, Winsor GL, Brinkman FSL, Kozyrskyj AL, Azad MB, Becker AB, Mandhane PJ, Moraes TJ, Sears MR, Subbarao P, Finlay BB, Turvey SE. Decreasing antibiotic use, the gut microbiota, and asthma incidence in children: evidence from population-based and prospective cohort studies. Lancet Respir Med. 2020 Nov;8(11):1094-1105. doi: 10.1016/S2213-2600(20)30052-7. Epub 2020 Mar 24. PMID: 32220282.

After adjusting for covariates, the adjusted OR for outpatient antibiotic exposure before age 1 year was 2·54 (95%CI: 1·7-3·8, p<0·001). To address the risk of confounding by indication, we excluded 95 children who received antibiotics for respiratory symptoms.

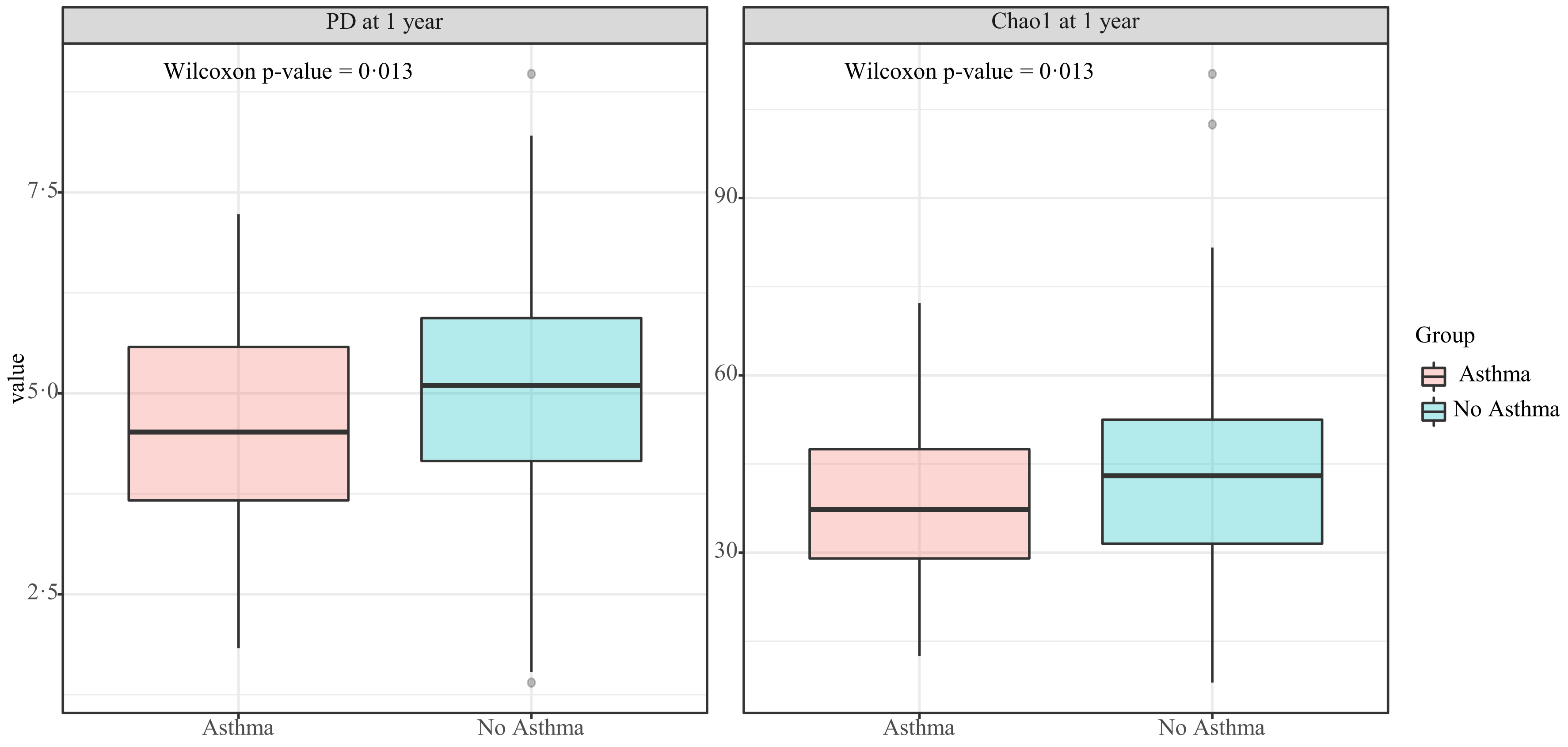
Subgroup	Patients	Asthma	No Asthma	Adjusted Odds Ratio	P Value
No. patients	1947	118	1829		
Antibiotics use by age 1 year	289 (14·8%)	29 (24·6%)	260 (14·2%)	2·15 (1·37, 3·39)	0·00093*
Ethnicity of child					
Caucasian White	1262 (64·8%)	60 (50·8%)	1202 (65·7%)	Ref	
East Asian	71 (3·6%)	6 (5·1%)	65 (3·6%)	1·64 (0·66, 4·08)	0·29
Multiracial	467 (24%)	36 (30·5%)	431 (23·6%)	1·56 (1, 2·41)	0·048*
South Asian	40 (2·1%)	6 (5·1%)	34 (1·9%)	3·47 (1·35, 8·88)	0·0095*
South East Asian	53 (2·7%)	6 (5·1%)	47 (2·6%)	2·35 (0·93, 5·89)	0·069·
Other	54 (2·8%)	4 (3·4%)	50 (2·7%)	1·95 (0·66, 5·72)	0·23
Mode of Delivery					
Vaginal	1482 (76·1%)	77 (65·3%)	1405 (76·8%)	Ref	
C−Section with labor	243 (12·5%)	20 (16·9%)	223 (12·2%)	1·29 (0·76, 2·22)	0·35
C−Section without labor	222 (11·4%)	21 (17·8%)	201 (11%)	1·88 (1·11, 3·18)	0·018*
Having Older Sibling	917 (47·1%)	51 (43·2%)	866 (47·3%)	0·83 (0·56, 1·26)	0·39
Male	1037 (53·3%)	74 (62·7%)	963 (52·7%)	1·44 (0·97, 2·14)	0·069·
Birth Weight Z Score					
Median (Range)	−0·1 (−3·1, 4·3)	−0·1 (−2, 2·5)	−0·1 (−3·1, 4·3)	1·04 (0·85, 1·28)	0·67
Parental Atopy	1581 (81·2%)	106 (89·8%)	1475 (80·6%)	1·97 (1·05, 3·67)	0·034*
Breastfeeding status at 6 months					
None	409 (21%)	26 (22%)	383 (20·9%)	Ref	
Partial	1179 (60·6%)	75 (63·6%)	1104 (60·4%)	1·03 (0·63, 1·66)	0·92
Exclusive	359 (18·4%)	17 (14·4%)	342 (18·7%)	0·74 (0·38, 1·43)	0·37
Tobacco smoke exposure to age 1 year	500 (25·7%)	34 (28·8%)	466 (25·5%)	1·23 (0·79, 1·9)	0·36
NO_2 (ppb) in year 1 (interquartile change)					
Median (Range)	1·1 (0·1, 3·4)	1·2 (0·3, 3·4)	1·1 (0·1, 3·4)	1·25 (0·73, 2·14)	0·42
Season of Birth					
Spring	543 (27·9%)	29 (24·6%)	514 (28·1%)	Ref	
Summer	488 (25·1%)	29 (24·6%)	459 (25·1%)	1·13 (0·66, 1·93)	0·66
Fall	445 (22·9%)	35 (29·7%)	410 (22·4%)	1·41 (0·84, 2·36)	0·2
Winter	471 (24·2%)	25 (21·2%)	446 (24·4%)	0·96 (0·55, 1·69)	0·89
Urban vs Rural living					
Urban	1834 (94·2%)	113 (95·8%)	1721 (94·1%)	Ref	
Rural	113 (5·8%)	5 (4·2%)	108 (5·9%)	0·99 (0·38, 2·61)	0·99



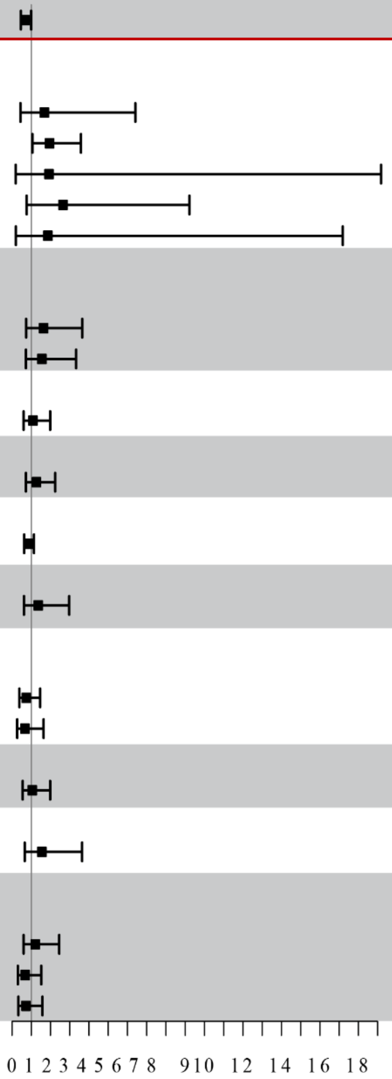
Dose-Response Is Evident



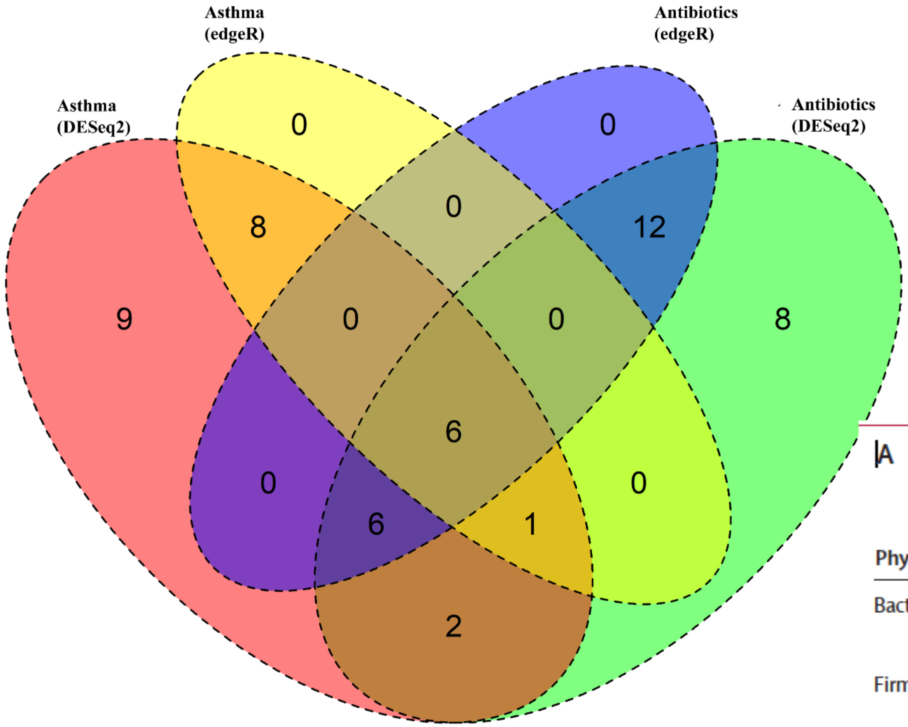
Gut Microbiome: Asthma

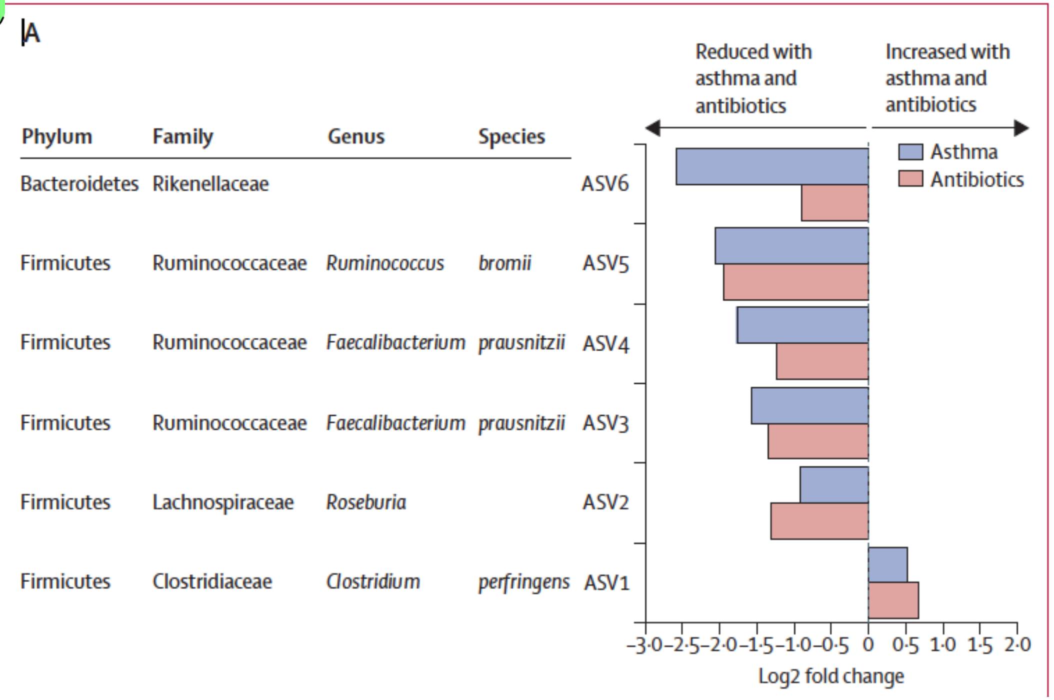


Subgroup	Children	Asthma	No Asthma	Adjusted Odds Ratio	P-Value
No . patients	570	63	507		
Chao1 at 1 year (IQR change)					
Median (Range)	2 (0·4, 5·3)	1·8 (0·6, 3·5)	2·1 (0·4, 5·3)	0·68 (0·46, 0·99)	0·046*
Ethnicity of Child					
Caucasian White	376 (66%)	31 (49·2%)	345 (68%)	Ref	
East Asian	21 (3·7%)	3 (4·8%)	18 (3·6%)	1·68 (0·44, 6·41)	0·45
Multiracial	141 (24·7%)	23 (36·5%)	118 (23·3%)	1·95 (1·06, 3·58)	0·032*
South Asian	6 (1·1%)	1 (1·6%)	5 (1%)	1·92 (0·19, 19·18)	0·58
South East Asian	18 (3·2%)	4 (6·3%)	14 (2·8%)	2·65 (0·76, 9·22)	0·13
Other	8 (1·4%)	1 (1·6%)	7 (1·4%)	1·86 (0·2, 17·19)	0·58
Mode of Delivery					
Vaginal	432 (75·8%)	42 (66·7%)	390 (76·9%)	Ref	
C−Section with labor	63 (11·1%)	10 (15·9%)	53 (10·5%)	1·64 (0·73, 3·65)	0·23
C−Section without labor	75 (13·2%)	11 (17·5%)	64 (12·6%)	1·55 (0·72, 3·33)	0·27
Ha ving Older Sibling					
	271 (47·5%)	29 (46%)	242 (47·7%)	1·09 (0·6, 1·98)	0·78
Male					
	325 (57%)	40 (63·5%)	285 (56·2%)	1·27 (0·72, 2·24)	0·41
Birth Weight Z Score					
Median (Range)	0 (−2·5, 3·7)	−0·2 (−2, 1·7)	0 (−2·5, 3·7)	0·85 (0·63, 1·14)	0·28
Parental Atopy					
	458 (80·4%)	54 (85·7%)	404 (79·7%)	1·36 (0·62, 2·97)	0·45
Breastfeeding status at 6 months					
None	116 (20·4%)	16 (25·4%)	100 (19·7%)	Ref	
Partial	351 (61·6%)	37 (58·7%)	314 (61·9%)	0·74 (0·38, 1·46)	0·39
Exclusive	103 (18·1%)	10 (15·9%)	93 (18·3%)	0·67 (0·27, 1·64)	0·38
Tobacco smoke exposure to age 1 year					
	138 (24·2%)	16 (25·4%)	122 (24·1%)	1·05 (0·55, 1·98)	0·89
NO_2 (ppb) in year 1 (IQR change)					
Median (Range)	1·1 (0·1, 3·1)	1·2 (0·3, 3·1)	1·1 (0·1, 3·1)	1·55 (0·66, 3·64)	0·32
Season of Birth					
Spring	153 (26·8%)	18 (28·6%)	135 (26·6%)	Ref	
Summer	148 (26%)	20 (31·7%)	128 (25·2%)	1·21 (0·6, 2·45)	0·59
Fall	133 (23·3%)	12 (19%)	121 (23·9%)	0·68 (0·3, 1·52)	0·34
Winter	136 (23·9%)	13 (20·6%)	123 (24·3%)	0·72 (0·33, 1·58)	0·42

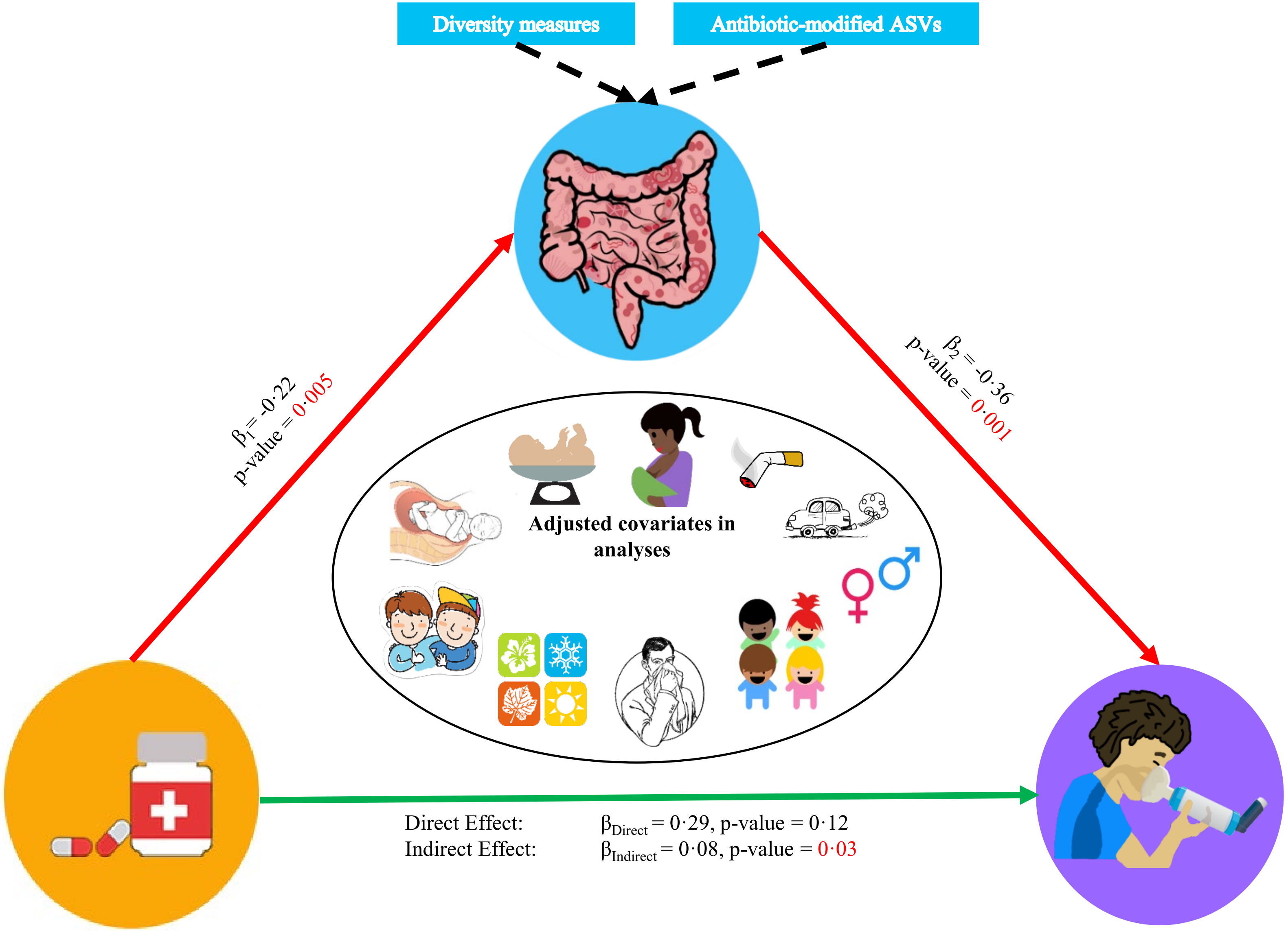


Taxa Identification





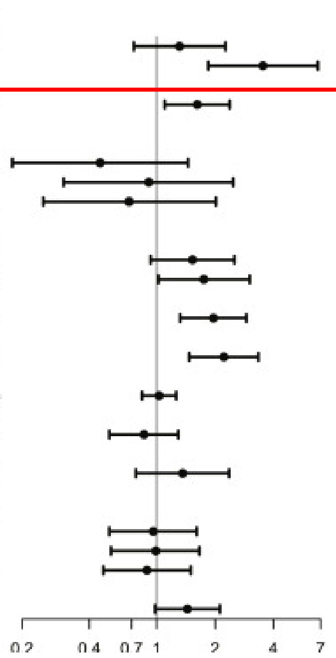
Structural Equation Modeling



Human milk exposure mitigates against Antibiotic-associated Asthma Risk

Human milk = effect modifier, acts to restore a disturbed gut microbiome in infancy, greatly reduces risk of atopic outcomes in infants at risk

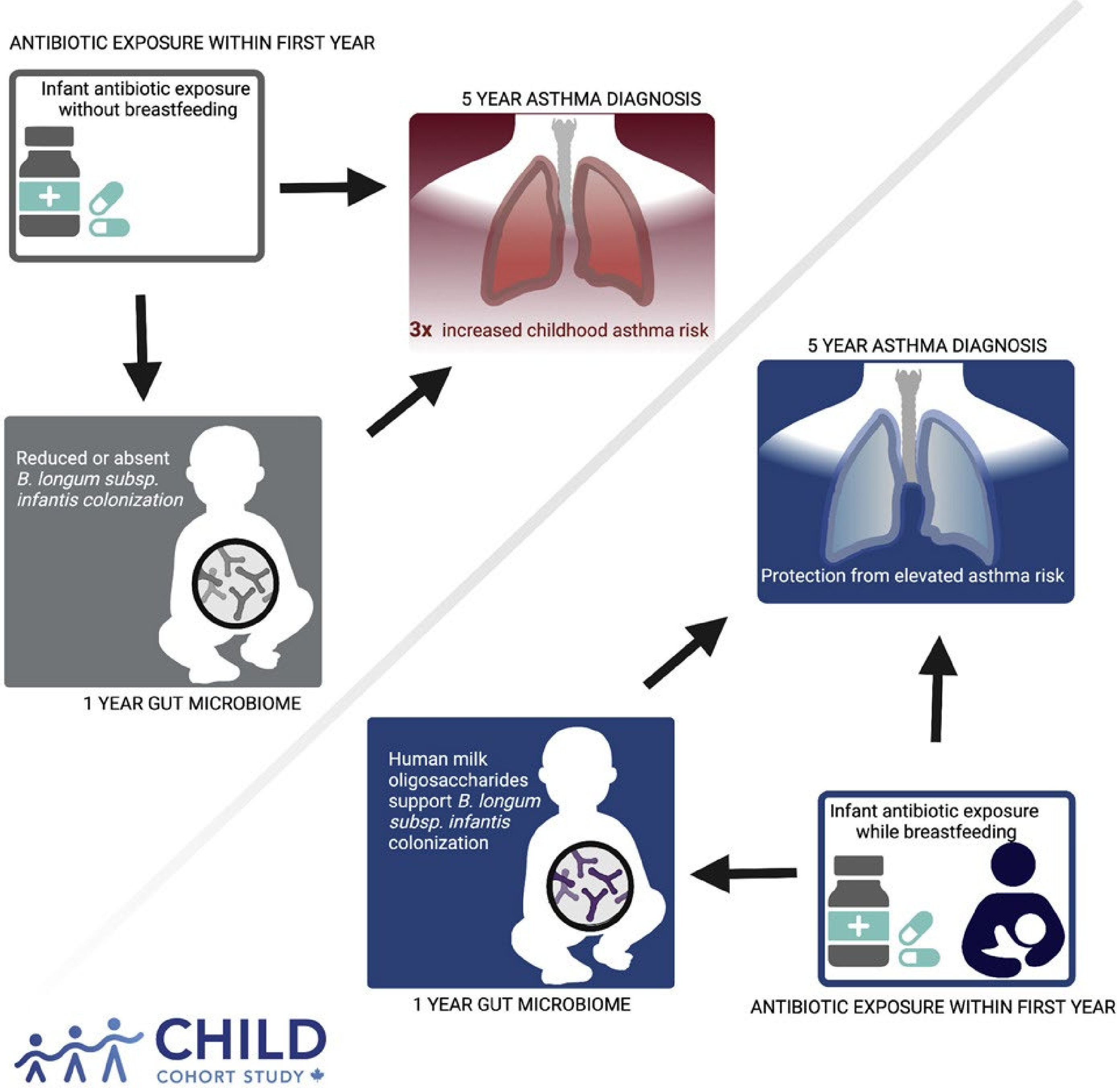
Variables	No Asthma	Asthma	Adjusted Odds Ratio	P Value
No. participants	1948	121	---	---
Antibiotics use by age 1 year				
No Antibiotics	1632 (83.8%)	89 (73.6%)	Ref	---
Antibiotics exposure with breastfeeding	226 (11.6%)	18 (14.9%)	1.31 (0.76, 2.26)	0.33
Antibiotics exposure without breastfeeding	90 (4.6%)	14 (11.6%)	3.53 (1.84, 6.78)	<0.001
Non−Caucasian	665 (34.1%)	55 (45.5%)	1.62 (1.1, 2.38)	0.014
Duration of Breastfeeding				
No Breastfeeding	55 (2.8%)	5 (4.1%)	Ref	---
Breastfeeding up to 6 months	488 (25.1%)	24 (19.8%)	0.51 (0.18, 1.45)	0.21
Breastfeeding up to 12 months	687 (35.3%)	51 (42.1%)	0.91 (0.33, 2.48)	0.85
Breastfeeding beyond 12 months	718 (36.9%)	41 (33.9%)	0.72 (0.26, 2.02)	0.53
Mode of Delivery				
Vaginal	1477 (75.8%)	78 (64.5%)	Ref	---
C−Section with labor	255 (13.1%)	24 (19.8%)	1.53 (0.93, 2.52)	0.097
C−Section without labor	216 (11.1%)	19 (15.7%)	1.75 (1.02, 3.02)	0.043
Mother Asthma	447 (22.9%)	45 (37.2%)	1.96 (1.32, 2.90)	<0.001
Father Asthma	354 (18.2%)	39 (32.2%)	2.22 (1.47, 3.34)	<0.001
Birth weight Z score				
Median (Range)	−0.1 (−3.1, 4.3)	−0.1 (−2, 2.5)	1.03 (0.84, 1.26)	0.8
Having older sibling	828 (42.5%)	47 (38.8%)	0.86 (0.57, 1.29)	0.47
NO² (parts per billion) in year 1, per IQR increase				
Median (Range)	1 (0.1, 3.5)	1.1 (0.2, 3.4)	1.36 (0.78, 2.36)	0.28
Season of Birth				
Spring	543 (27.9%)	35 (28.9%)	Ref	---
Summer	475 (24.4%)	29 (24%)	0.96 (0.57, 1.61)	0.87
Fall	442 (22.7%)	29 (24%)	0.99 (0.58, 1.66)	0.96
Winter	488 (25.1%)	28 (23.1%)	0.89 (0.53, 1.50)	0.65
Male	1028 (52.8%)	75 (62%)	1.44 (0.98, 2.12)	0.066



Effect of breastfeeding on antibiotic-associated asthma risk

- Full metagenomic sequence gives better resolution on species at play and on metabolic pathways
- Compared to infants who received antibiotics without breastfeeding, the presence of breastfeeding during antibiotic exposure actually increases species richness closer to non-antibiotic exposed levels
- 8/9 impacted species "rescued" by breastfeeding
- *B. longum subspecies infantis* enrichment during antibiotic exposure restores the microbiome and reduces asthma risk
- *B. infantis* colonization is enriched by human milk oligosaccharides

Dai DLY, Petersen C, Hoskinson C, Del Bel KL, Becker AB, Moraes TJ, Mandhane PJ, Finlay BB, Simons E, Kozyrskyj AL, Patrick DM, Subbarao P, Bode L, Azad MB, Turvey SE. Breastfeeding enrichment of B. longum subsp. infantis mitigates the effect of antibiotics on the microbiota and childhood asthma risk. Med. 2023 Feb 10;4(2):92-112.e5. doi: 10.1016/j.medj.2022.12.002. Epub 2023 Jan 4. PMID: 36603585.


ANTIBIOTIC EXPOSURE WITHIN FIRST YEAR
Infant antibiotic exposure without breastfeeding
5 YEAR ASTHMA DIAGNOSIS
3x increased childhood asthma risk
Reduced or absent *B. longum subsp. infantis colonization*
1 YEAR GUT MICROBIOME
5 YEAR ASTHMA DIAGNOSIS
Protection from elevated asthma risk
Human milk oligosaccharides support *B. longum subsp. infantis* colonization
Infant antibiotic exposure while breastfeeding
1 YEAR GUT MICROBIOME
ANTIBIOTIC EXPOSURE WITHIN FIRST YEAR
CHILD
COHORT STUDY

Article | Open access | Published: 29 August 2023

Delayed gut microbiota maturation in the first year of life is a hallmark of pediatric allergic disease

Courtney Hoskinson, Darlene L. Y. Dai, Kate L. Del Bel, Allan B. Becker, Theo J. Moraes, Piushkumar J. Mandhane, B. Brett Finlay, Elinor Simons, Anita L. Kozyrskyj, Meghan B. Azad, Padmaja Subbarao, Charisse Petersen & Stuart E. Turvey

Nature Communications **14**, Article number: 4785 (2023) | Cite this article

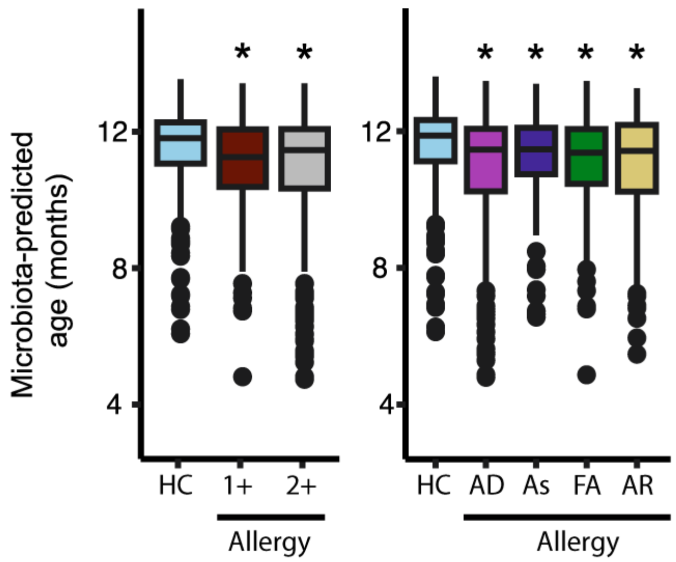
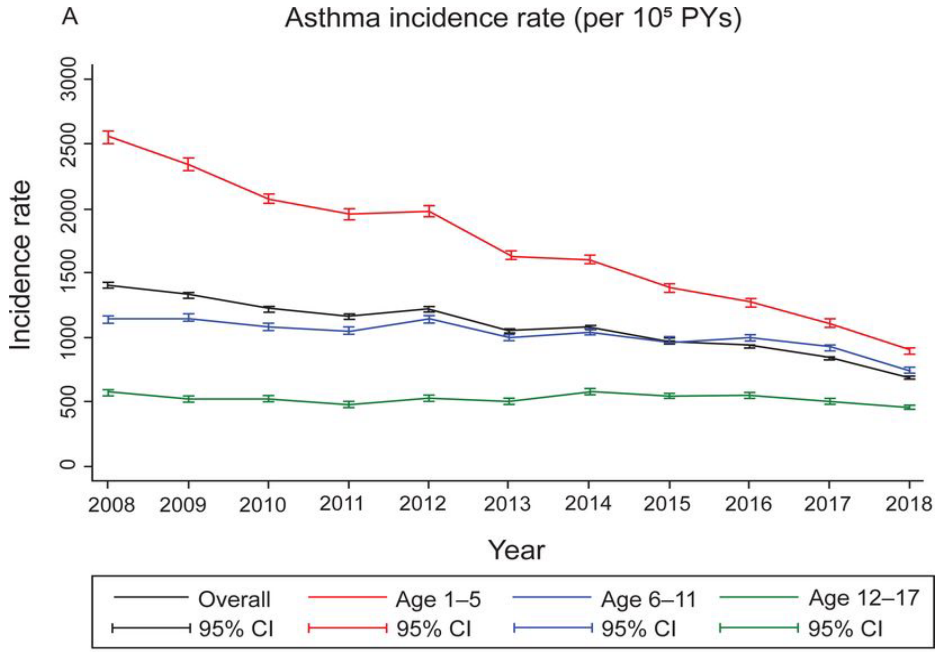


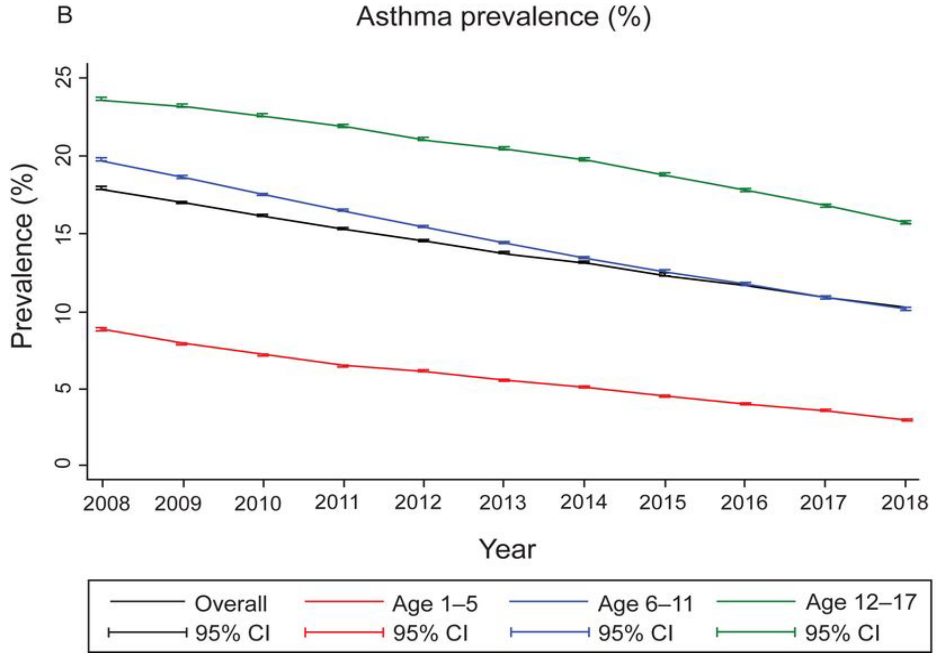
Fig 1 Predicted age of 1-year samples for clinical diagnoses at 5 years

What’s Happening in England?

The fall in incidence among 1-5 year-olds, translates to 10,000 fewer asthma cases in their birth cohort of 600,000 each year.

Canadian Chronic Disease Surveillance System data track the same way.





Kallis C, Maslova E, Morgan AD, Sinha I, Roberts G, van der Valk RJP, Quint JK, Tran TN.
Recent trends in asthma diagnosis, preschool wheeze diagnosis and asthma exacerbations in English children and adolescents: a SABINA Jr study.
Thorax. 2023 Dec;78(12):1175-1180. doi: 10.1136/thorax-2022-219757.

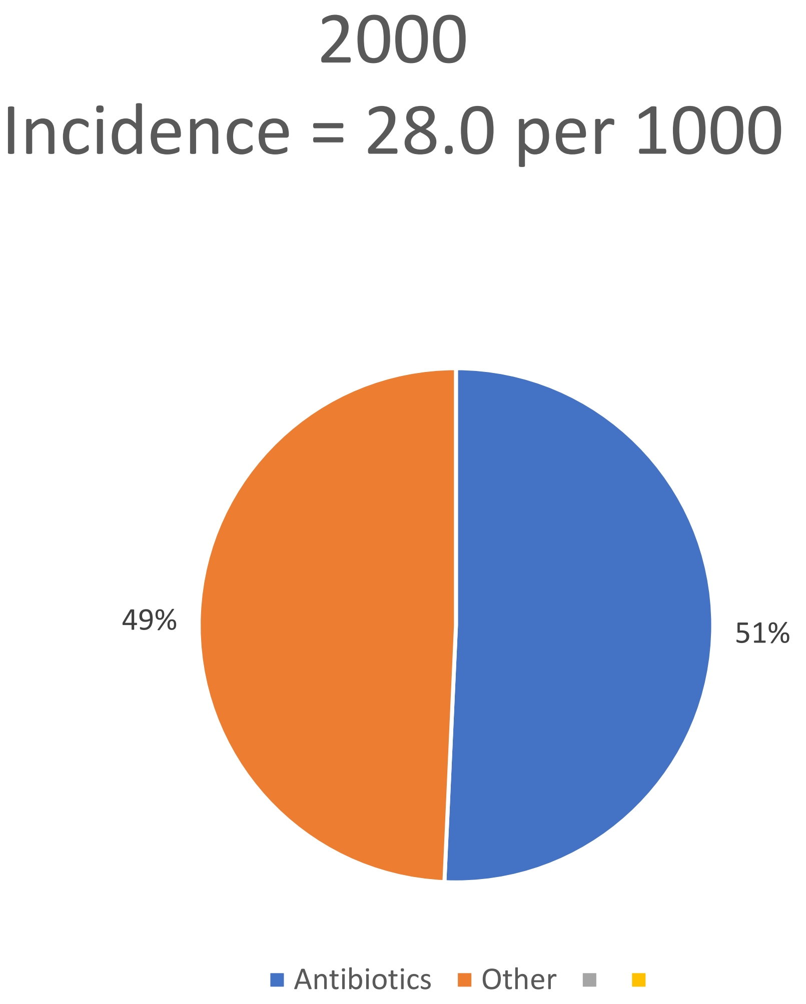
Population Attributable Risk

The potential reduction in incidence that would be observed if a specific exposure were eliminated from the population

It can be calculated if you know the proportion of your population exposed and the relative risk

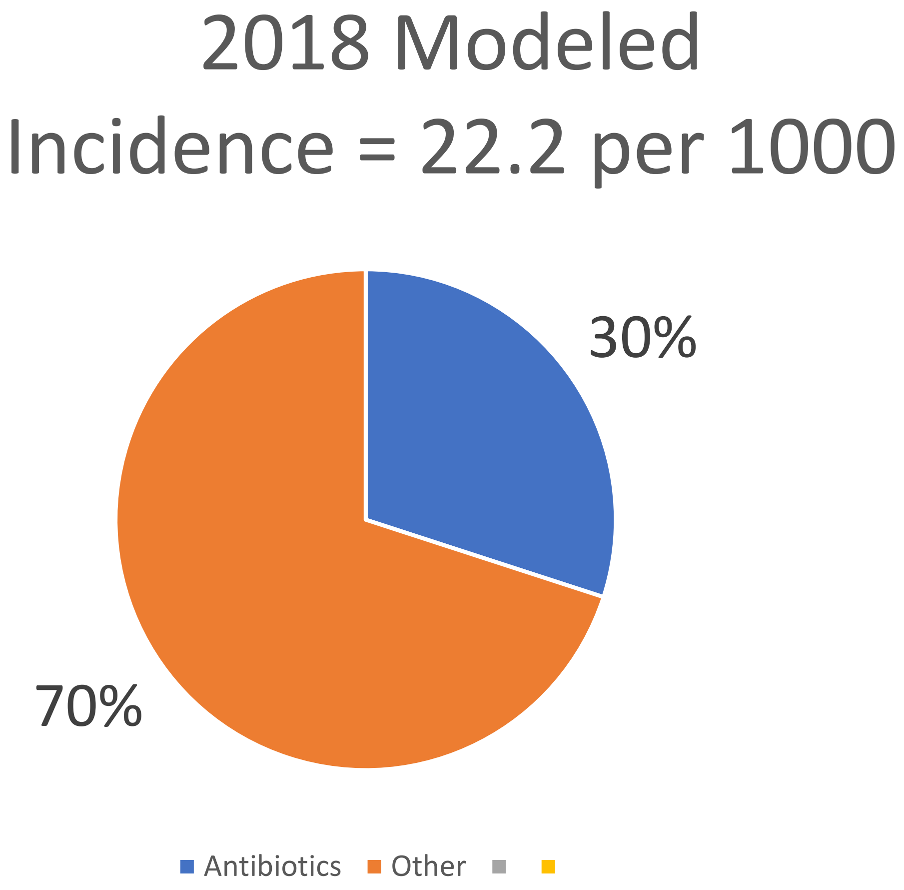
How might the combination of decreased exposure AND falling relative risk (because of increased breast-feeding uptake) affect asthma incidence?

Childhood Asthma Incidence British Columbia Estimates for Infant Antibiotic Risk-Attributable Burden



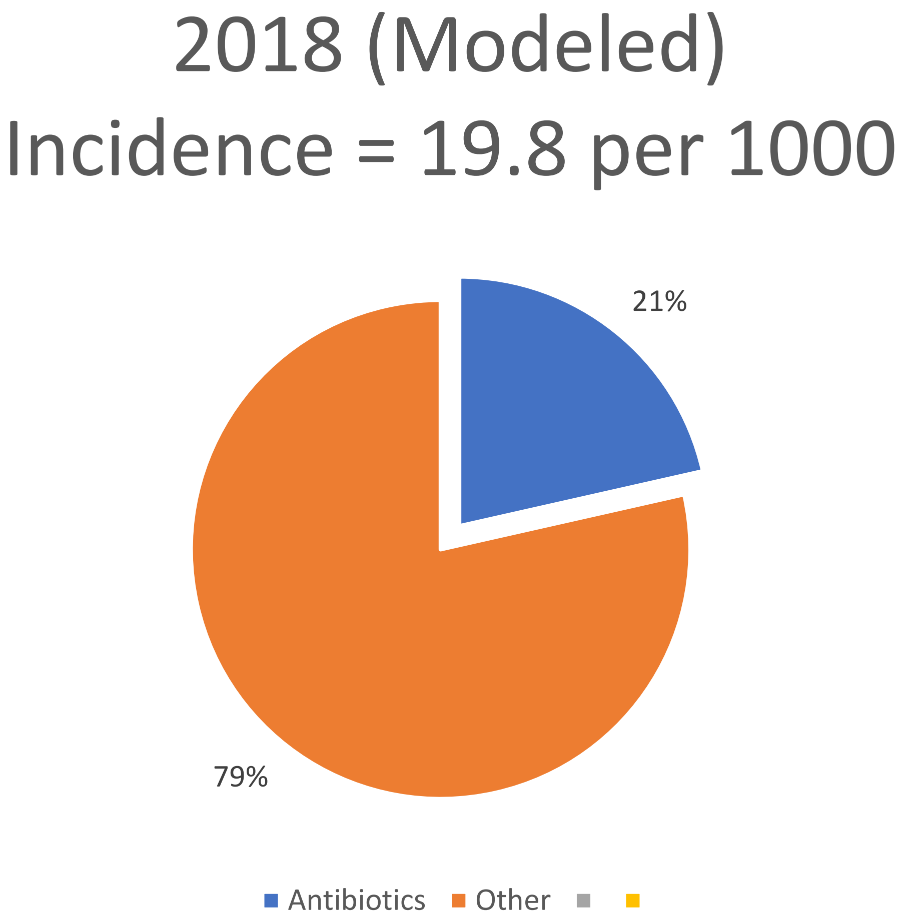
- P(exposed antibiotics) = 67%
- P(breastfed to 6 months) = 45%
- Blended RR = 2.53

Counter-factual Model: No increase in BF 2000-2018 Estimates for Infant Antibiotic Risk-Attributable Burden



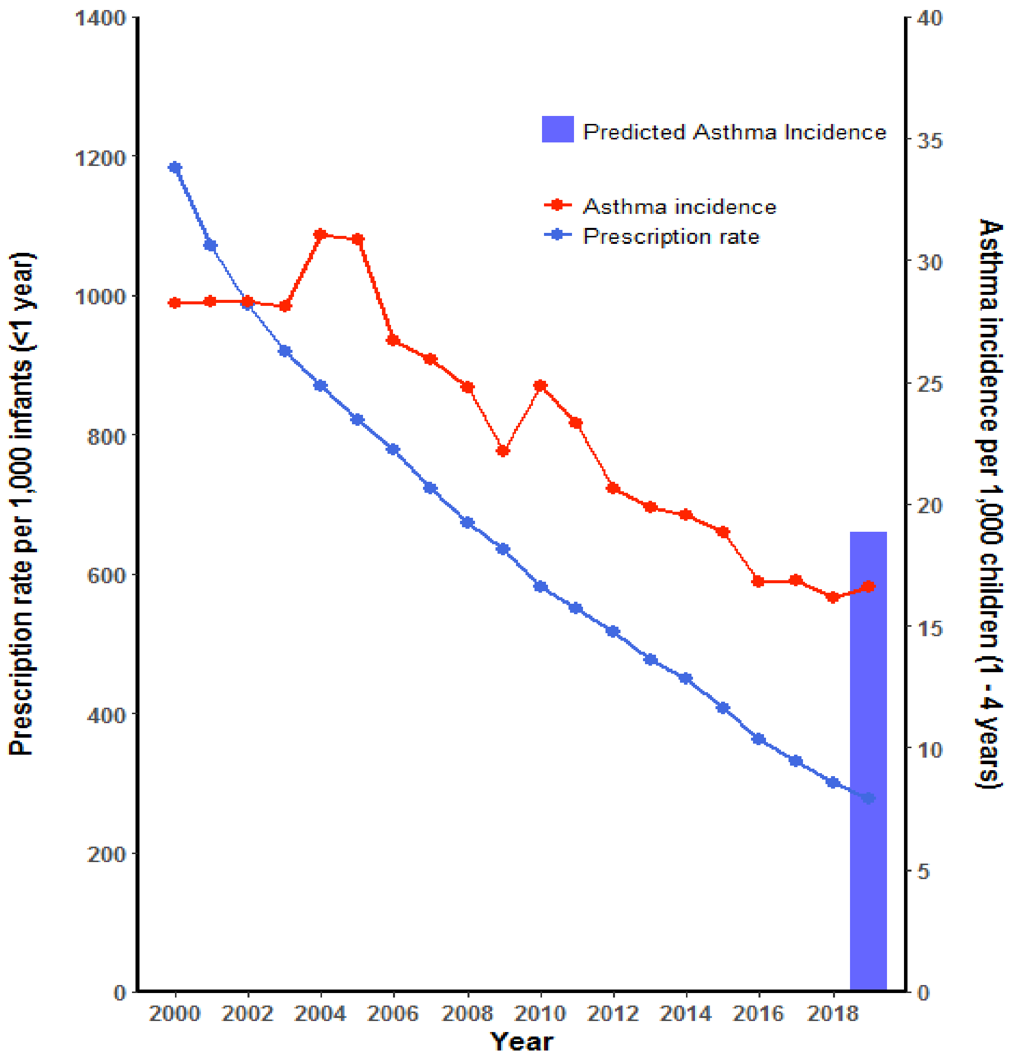
- P(exposed antibiotics) ↓ 28%
- P(breastfed to 6 months) = 45%
- Blended RR = 2.53

Counter-factual: No increase in Breastfeeding from 2000
Estimates for Infant Antibiotic Risk Attributable Burden



- P(exposed antibiotics) ↓28%
- P(breastfed to 6 months) ↑ 70%
- Blended RR ↓ 1.98

The ecological picture in British Columbia, Canada



At Population Level

- The effect size measured in cohort studies from declining antibiotic use and increasing breastfeeding are on a scale to explain dramatic observed reductions in incidence of asthma in children and resulting fall in prevalence.

Ecological Studies

- Correlation of asthma with declining infant antibiotic use
- Prediction of incidence in small geographic areas
- Strength of association between antibiotic exposure and asthma risk may be diminishing over time, explained by increases in breast feeding
- But... Confounding: *Reduction in other risk factors*
- Confounding by Indication: *What if respiratory infections that drive antibiotic use themselves cause asthma*?
- Reverse causation: *What if a declining asthma is resulting in fewer antibiotics being prescribed*?
- Need to study at <u>individual</u> level in **large populations**

Study design

Aim: Quantify the risk of developing asthma and atopic conditions by age 5 in infants who received antibiotics before their 1^{st} birthday compared with those who did not.

<u>Design:</u> retrospective cohort study recruiting all infants born in BC and Manitoba from 2001-2011, following up to age 7 and parental ”look-back” 5 years before each birth (1996-2018)

<u>Exposure:</u> antibiotic exposure by 1^{st} birthday

<u>Outcome:</u> asthma, eczema or hay fever by 5^{th} birthday

<u>Method:</u> multivariable logistic regression, clustering standard errors on mother’s ID

<u>Missingness:</u> variables over 6% missing not included in final models, considered separately using multiple imputation assuming MAR

Open access Protocol

BMJ Open

Investigating the effect of early life antibiotic use on asthma and allergy risk in over 600 000 Canadian children: a protocol for a retrospective cohort study in British Columbia and Manitoba

Hannah Lishman ,[1,2] Nathan C Nickel,[3,4,5] Hind Sbihi,[1,2] Max Xie,[2] Abdullah Mamun,[2] Bei Yuan Zhang,[6] Caren Rose,[1,2] Patricia Janssen,[1] Ashley Roberts,[7,8] Meghan B Azad ,[3,5,9] Stuart Turvey,[7,8] David M Patrick[1,2]

Lishman H, Nickel NC, Sbihi H, et al. Investigating the effect of early life antibiotic use on asthma and allergy risk in over 600 000 Canadian children: a protocol for a retrospective cohort study in British Columbia and Manitoba. BMJ Open 2023;13:e067271. doi:10.1136/ bmjopen-2022-067271

Ethics and Data Disclaimers

UBC Ethics Approval H19-03255. All BC data are provided by Population Data BC. Further information on the datasets used for this project is at: https://my.popdata.bc.ca/project_listings/20-141. All inferences, opinions, and conclusions drawn in this material are those of the authors, and do not reflect the opinions or policies of the Data Stewards.

Nitrogen dioxide data, PM2.5 metrics, NDVI metrics were indexed to DMTI Spatial Inc. postal codes, were provided by CANUE (Canadian Urban Environmental Health Research Consortium).

The authors acknowledge the Manitoba Centre for Health Policy for use of data contained in the Manitoba Population Research Data Repository under project #2021-042 (HIPC #2021/2022-27). The results and conclusions are those of the authors and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, or other data providers is intended or should be inferred. Data used in this study are from the Manitoba Population Research Data Repository housed at the Manitoba Centre for Health Policy, University of Manitoba and were derived from data provided by Manitoba Health, Healthy Child, Vital Statistics and CANUE.

populationdata BC

Manitoba Centre for Health Policy

Data sources

BC		MB	
Dataset	**Data provided by**	**Dataset**	**Data provided by**
BC Perinatal Data Registry (BCPDR)	Perinatal Services BC	BabyFirst/Families First Screening	Healthy Child Manitoba
Medical Services Plan (MSP)	BC Ministry of Health (MoH)	Medical Claims	Manitoba Health
Discharge Abstracts Database (DAD)	BC MoH	Hospital Discharge Abstract Database (H-DAD)	Manitoba Health
Pharmanet	BC MoH	Drug Program Information Network (DPIN)	Manitoba Health
Central Demographics File	Population Data BC	Manitoba Health Insurance Registry	Manitoba Health
Vital Statistics (Births)	BC MoH		
Vital Statistics (Deaths)	BC MoH	Vital Statistics Mortality	Manitoba Vital Statistics Agency
BCCDC Childhood Immunisations	BC Centre for Disease Control	Manitoba Immunization Monitoring System (MIMS)	Manitoba Health
CANUE	Canadian Urban Environmental Health Research Consortium	CANUE	Canadian Urban Environmental Health Research Consortium
CHILD breastfeeding data	Canadian Healthy Infant Longitudinal Development Study	CHILD breastfeeding data	Canadian Healthy Infant Longitudinal Development Study
		Manitoba Infant Feeding Database	Manitoba Interdisciplinary Lactation Centre (MILC)

Covariates

- maternal age, maternal BMI, prenatal smoking/alcohol/drug use, prenatal and intrapartum antibiotic use, diabetes, parental history of atopy

- mode of delivery, sex, gestational age, season of birth, # of siblings, 1st birthday immunisations, # of RTI visits, likelihood of human milk exposure

- urban/rural residence, material deprivation, greenness, area-level air quality indicators (nitrogen dioxide [NO2] and fine particulate matter [PM2.5])

Limitations

- Outcomes are based on clinical diagnostic codes - eczema and hay fever are likely an underestimate

- Potential for misclassification of asthma, possibly explaining reduced associations compared with prospective cohorts in BC

- Do not have data for all variables in our theoretical framework, potential for residual confounding

- Only capturing community antibiotic prescribing (but this is the vast majority)

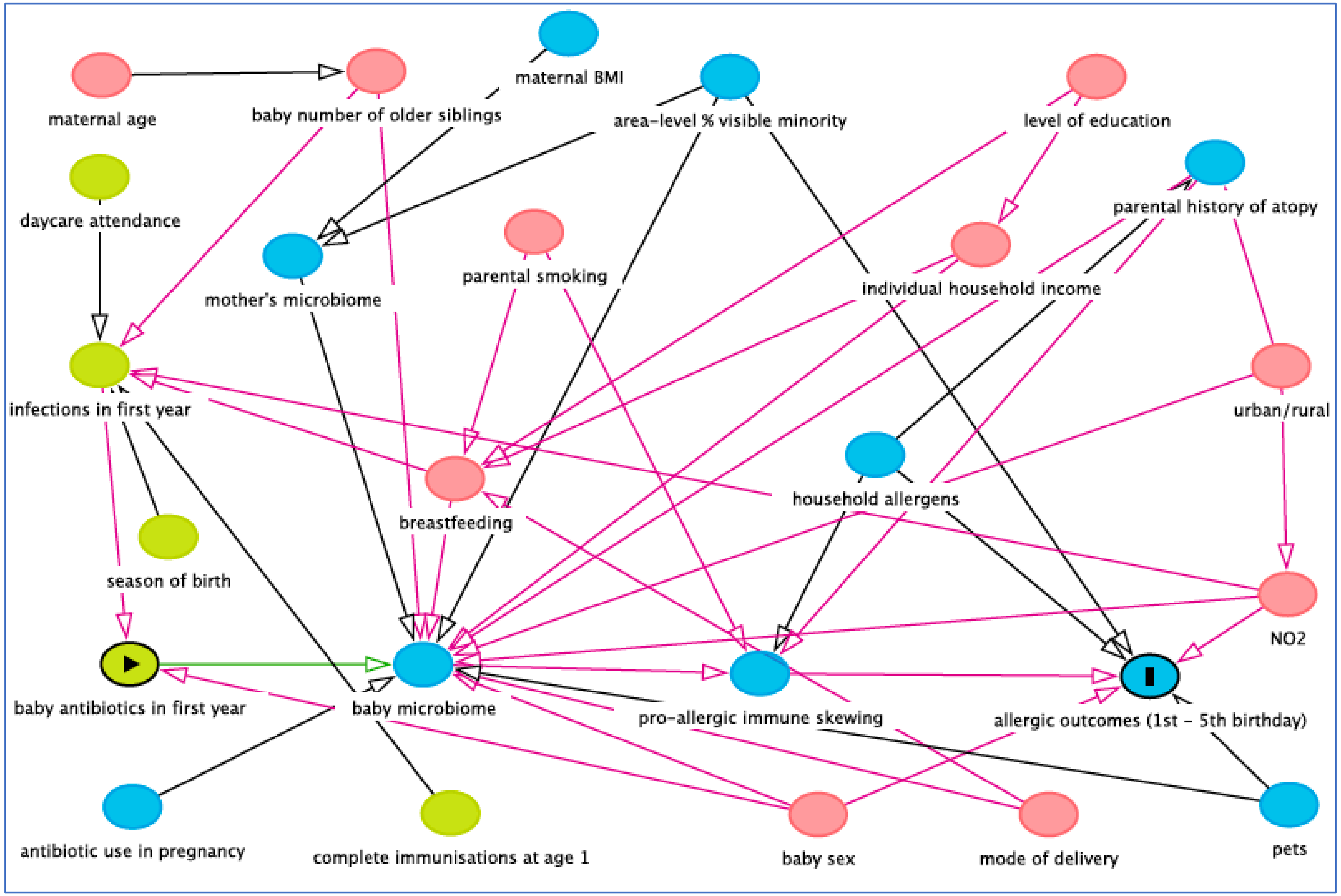


Fig 1 Directed acyclic graph characterizing relationship between antibiotics in infancy and atopic outcomes in childhood

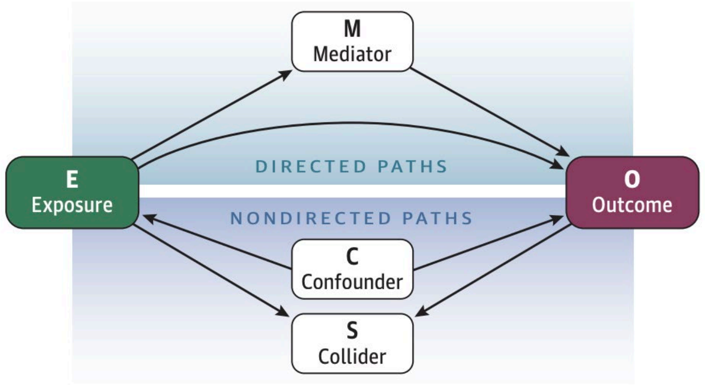


Fig 2 Example of Directed and Nondirected Paths[1]

- A way of describing the mechanistic pathway
- Helped us establish if any biasing pathways were open when building our models
- Helped to identify confounders vs. colliders

[1]Lipsky AM, Greenland S. Causal Directed Acyclic Graphs. *JAMA.* 2022;327(11):1083–1084. doi:10.1001/jama.2022.1816

Exclusion criteria

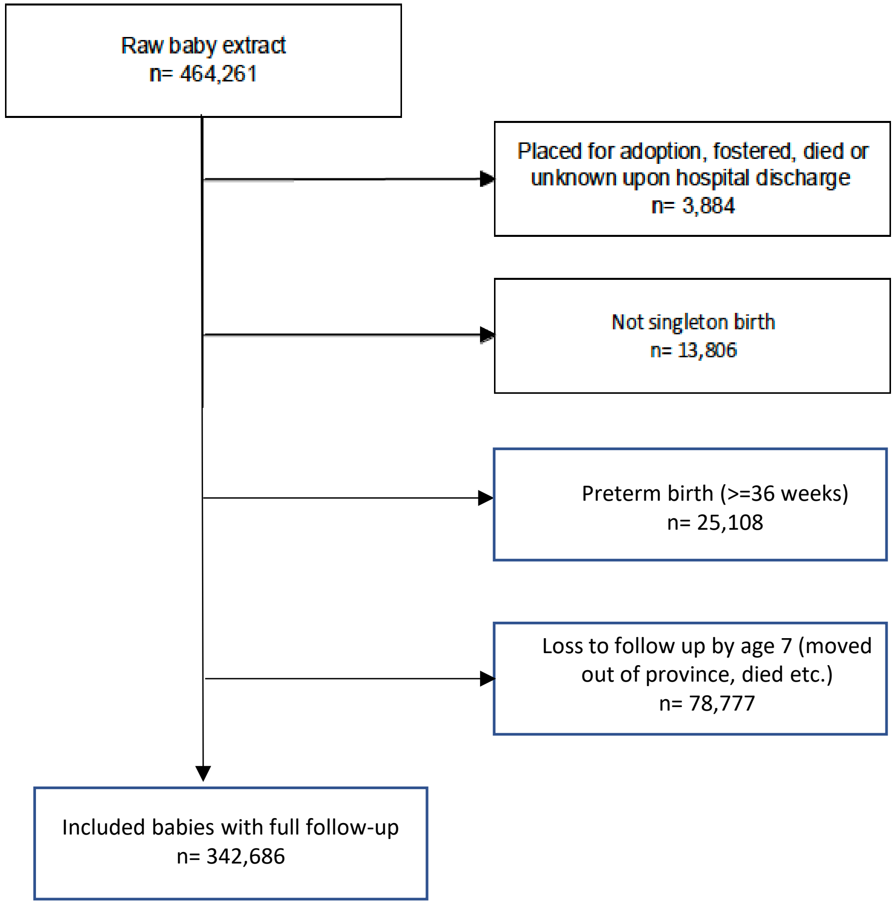


Figure 1. Flowchart of exclusion criteria for BC cohort study

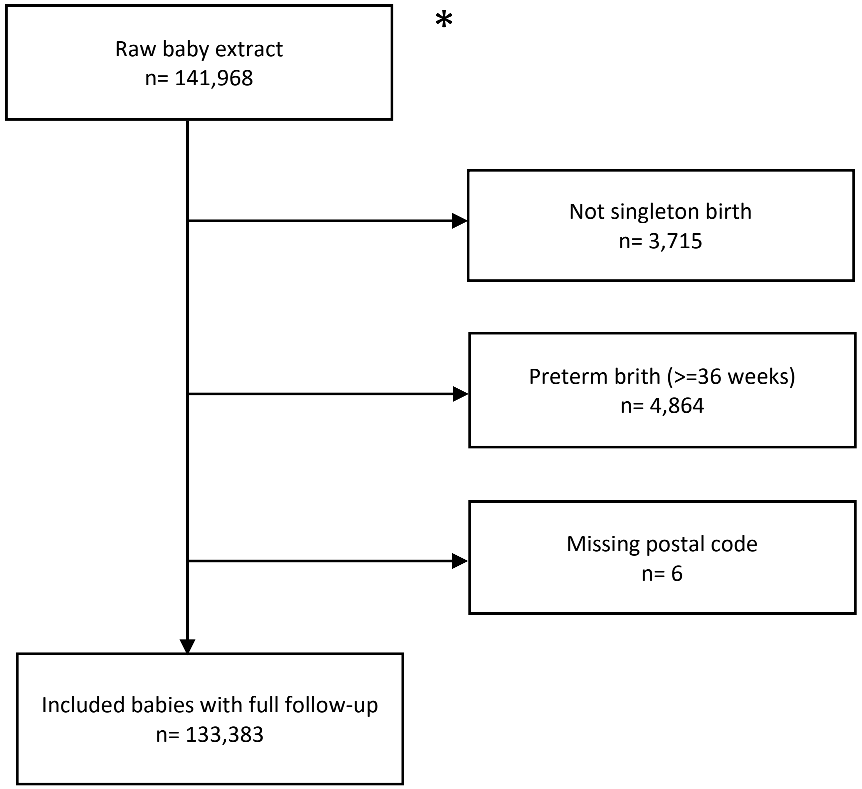


Figure 2. Flowchart of exclusion criteria for MB cohort study

* Raw MB extract included only infants with full follow up to age 7

Descriptive results (BC)

- 36% of infants received antibiotics
- 9.4%, 0.63%, 0.91% diagnosed with asthma, eczema and hay fever, respectively

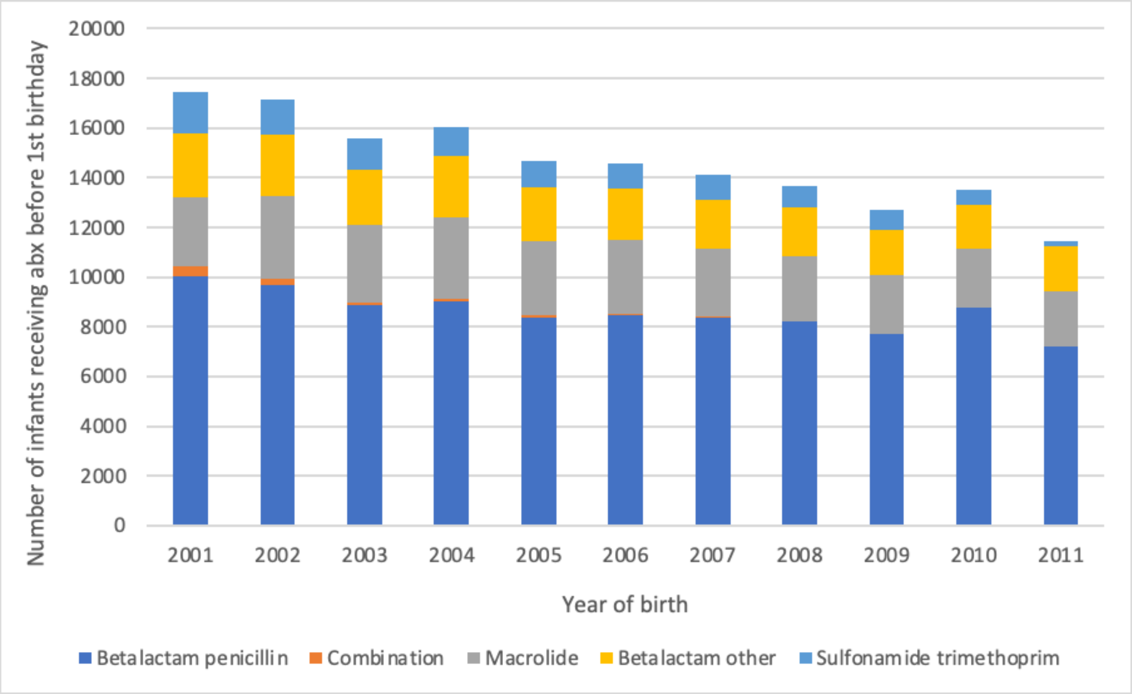


Figure 1. Number of infants receiving antibiotics in their 1st year by year of birth and antibiotic class in BC

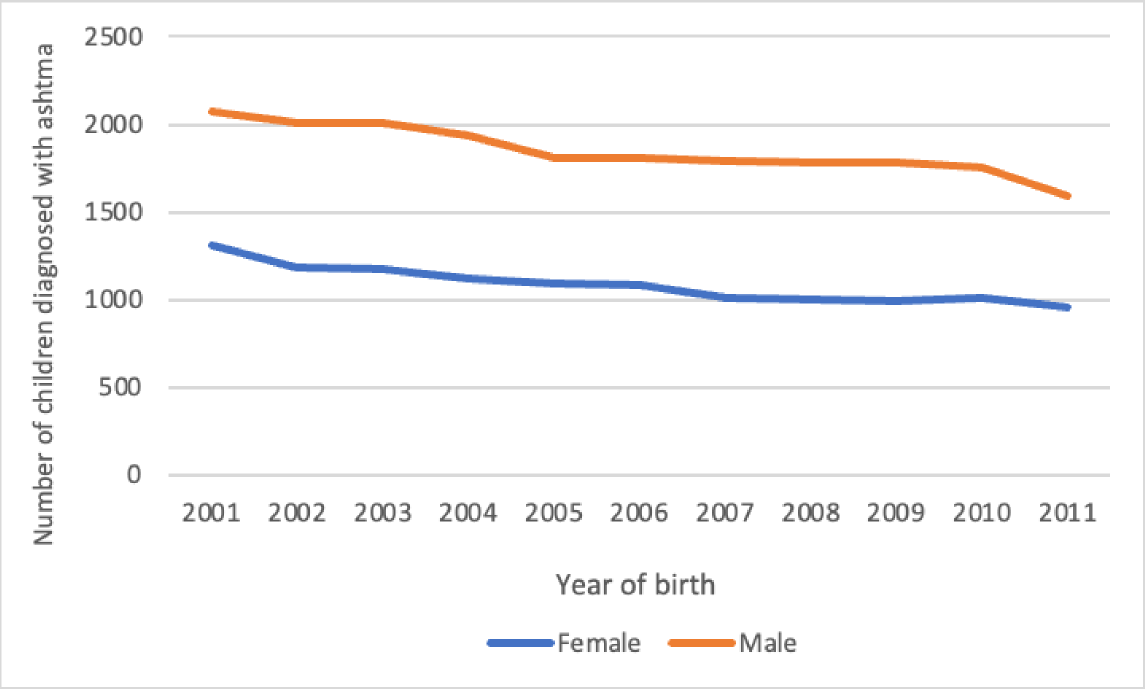


Figure 2. Number of children diagnosed with asthma between 1st and 5th birthdays by sex and year of birth in BC

Descriptive results (MB)

- 43% of infants received antibiotics in MB

- 10.6%, 5.2% diagnosed with asthma and hay fever, respectively

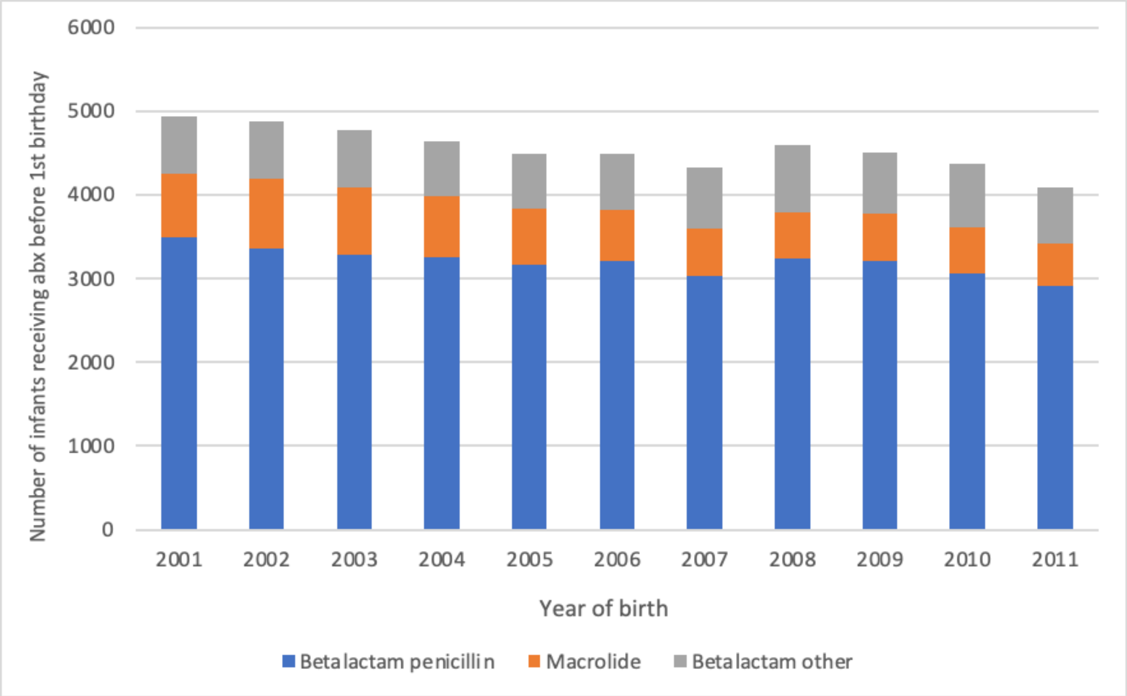


Figure 1. Number of infants receiving antibiotics in their 1st year by year of birth and antibiotic class in MB

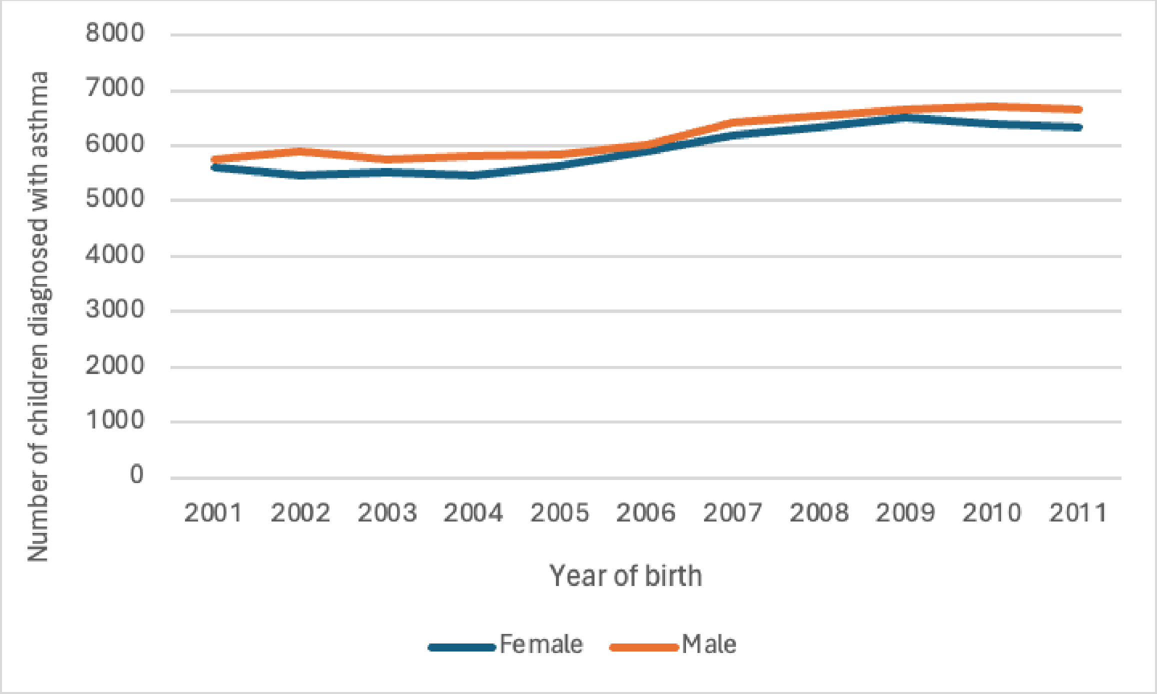


Figure 2. Number of infants diagnosed with asthma before 5 by sex and year of birth in MB

Adjusted models (BC)

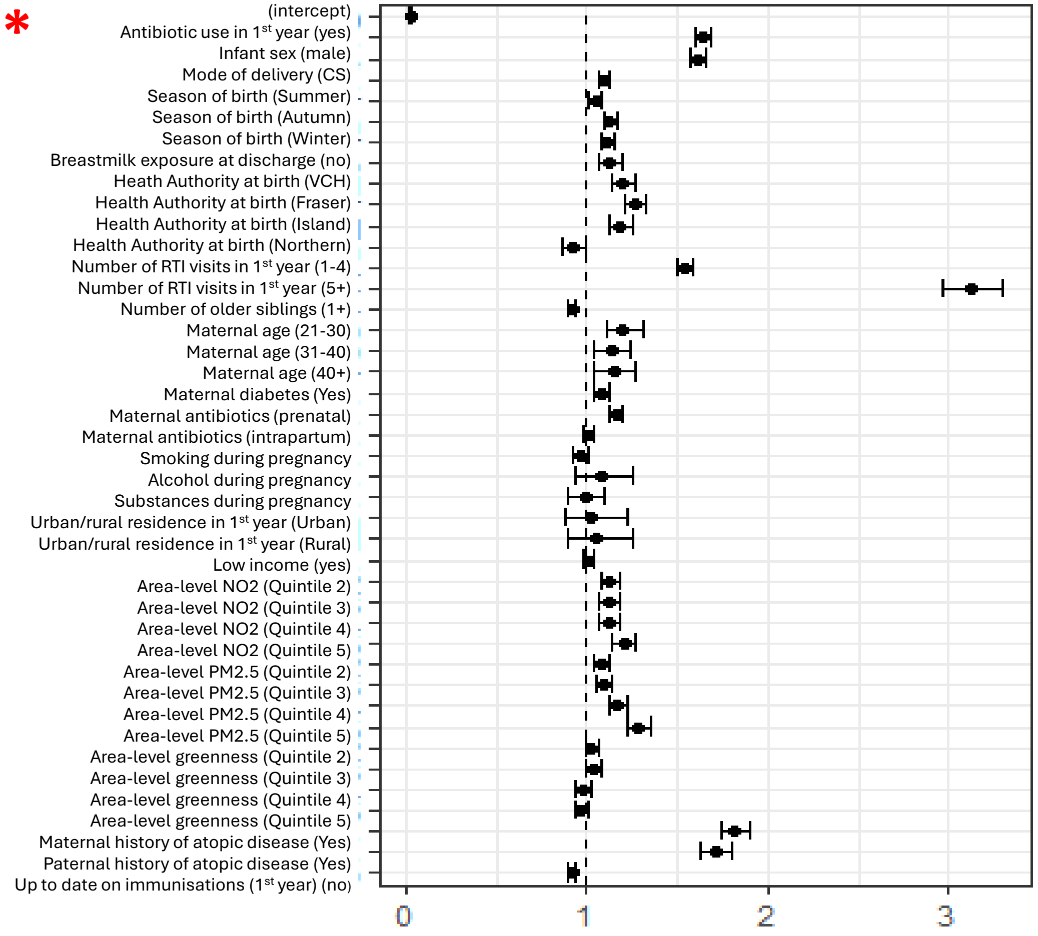


Fig 1. Adjusted logistic regression - antibiotic use before the 1st birthday and development of asthma between the 1st and 5th birthdays.

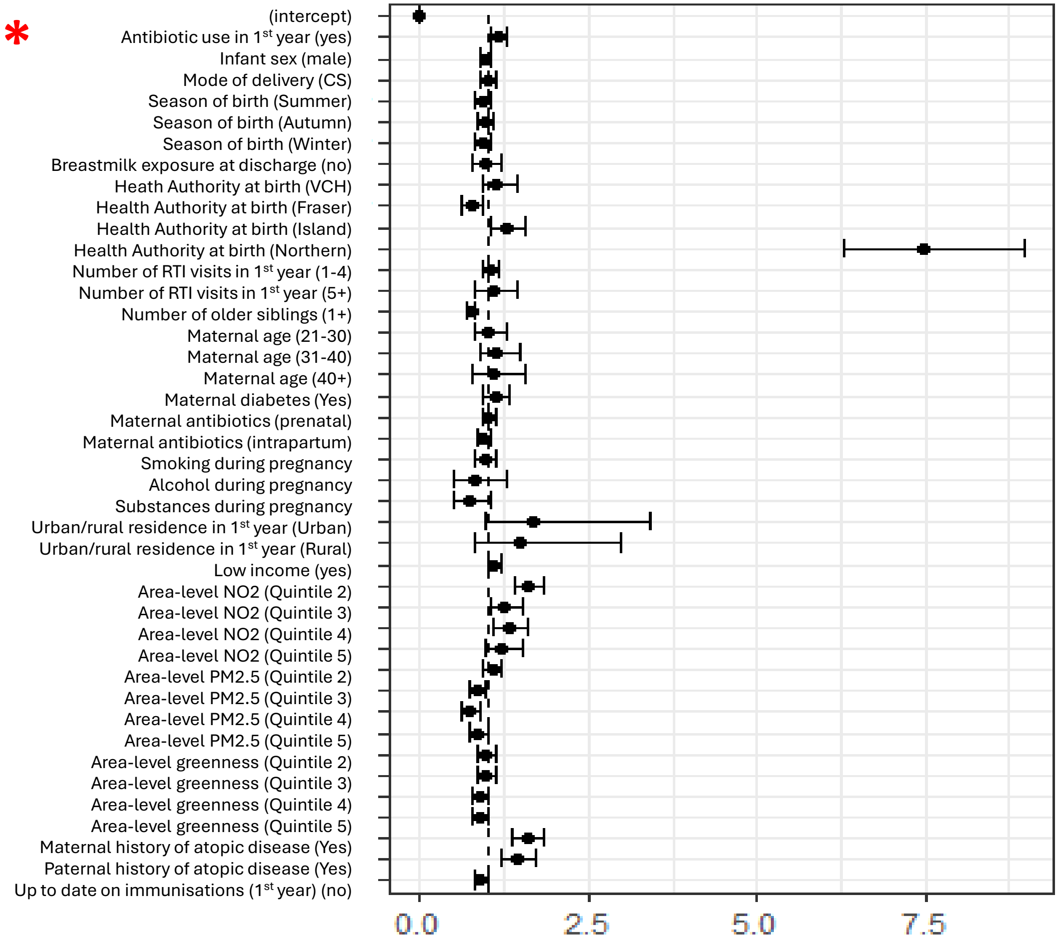


Fig 2. Adjusted logistic regression - antibiotic use before the 1st birthday and development of eczema between the 1st and 5th birthdays.

Adj OR **1.64** (95%CI 1.60-1.68, p<0.001)

Adj OR **1.17** (95%CI 1.06-1.29, p<0.01)

Adjusted models (BC) - cont'd

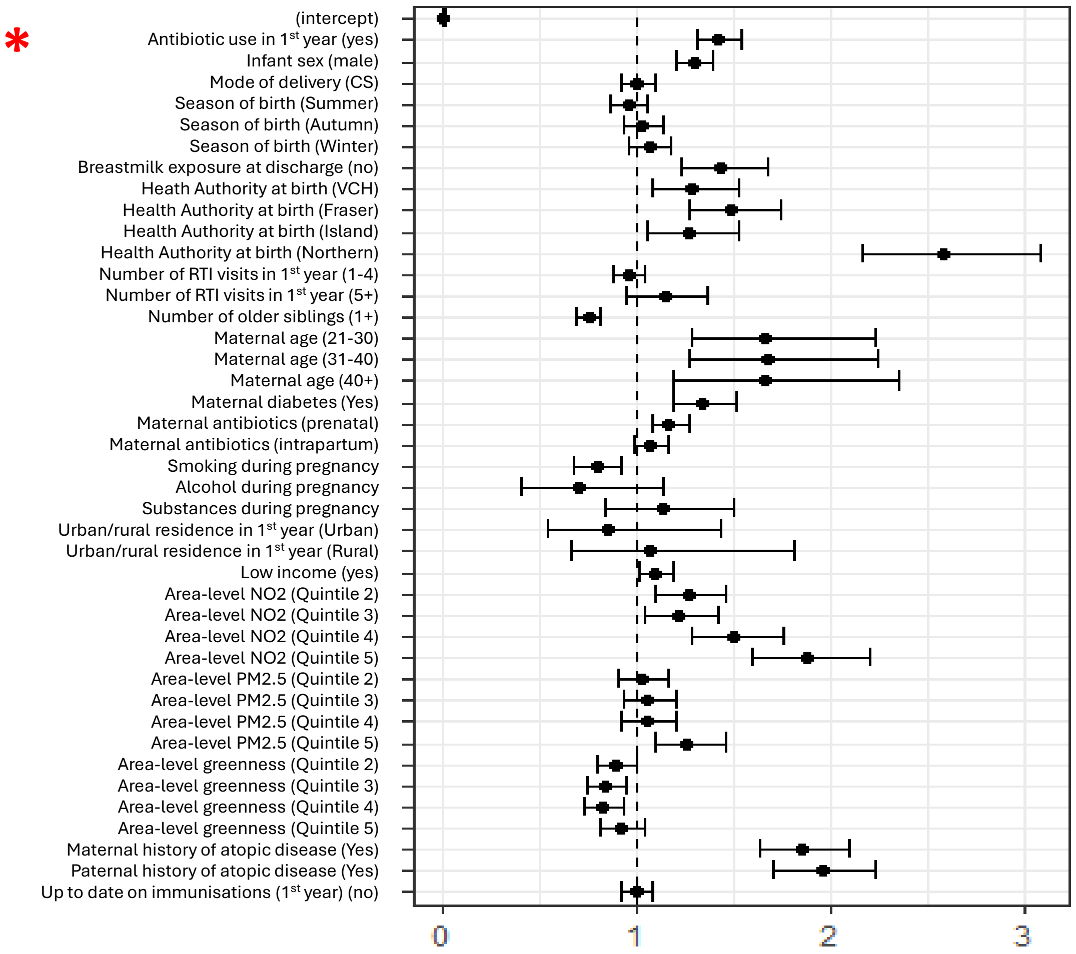


Fig 3. Adjusted logistic regression - antibiotic use before the 1st birthday and development of hay fever between the 1st and 5th birthdays.

Adj OR **1.42** (95%CI 1.31-1.54, $p<0.001$)

Adjusted models (MB)

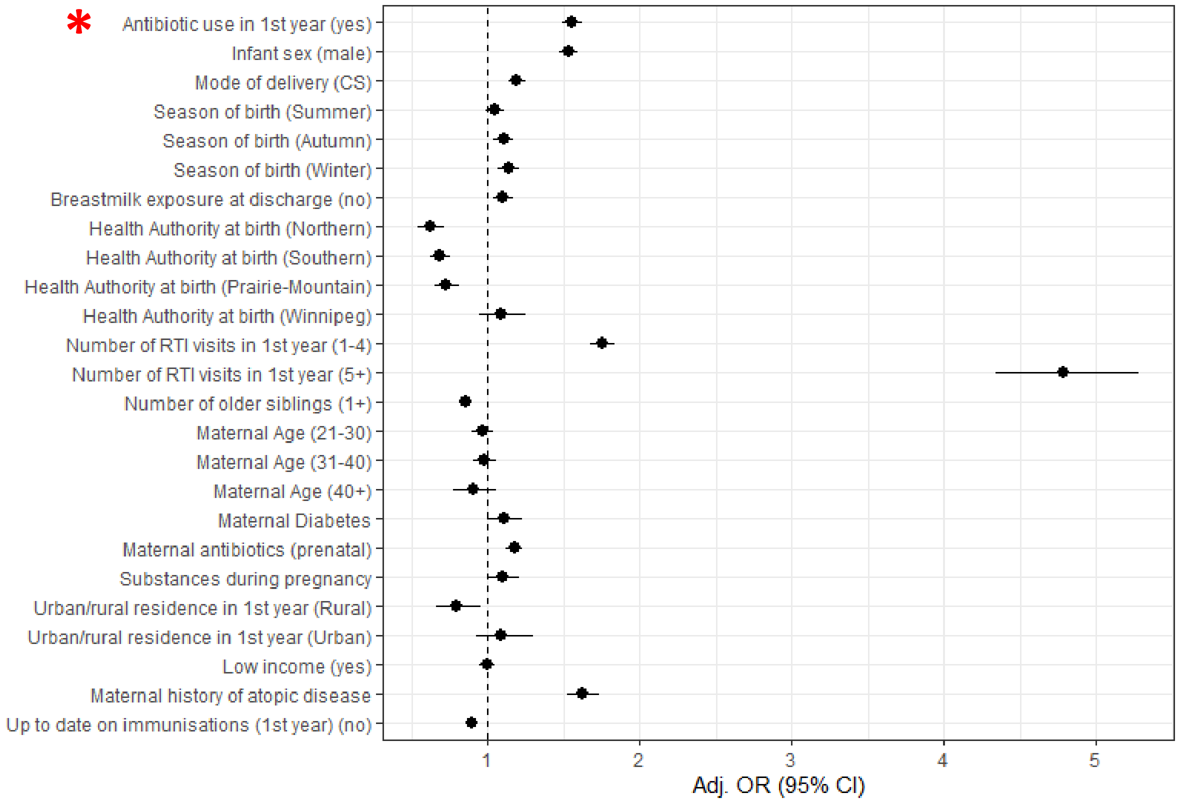


Fig 1. Adjusted logistic regression - antibiotic use before the 1st birthday and development of asthma between the 1st and 5th birthdays.

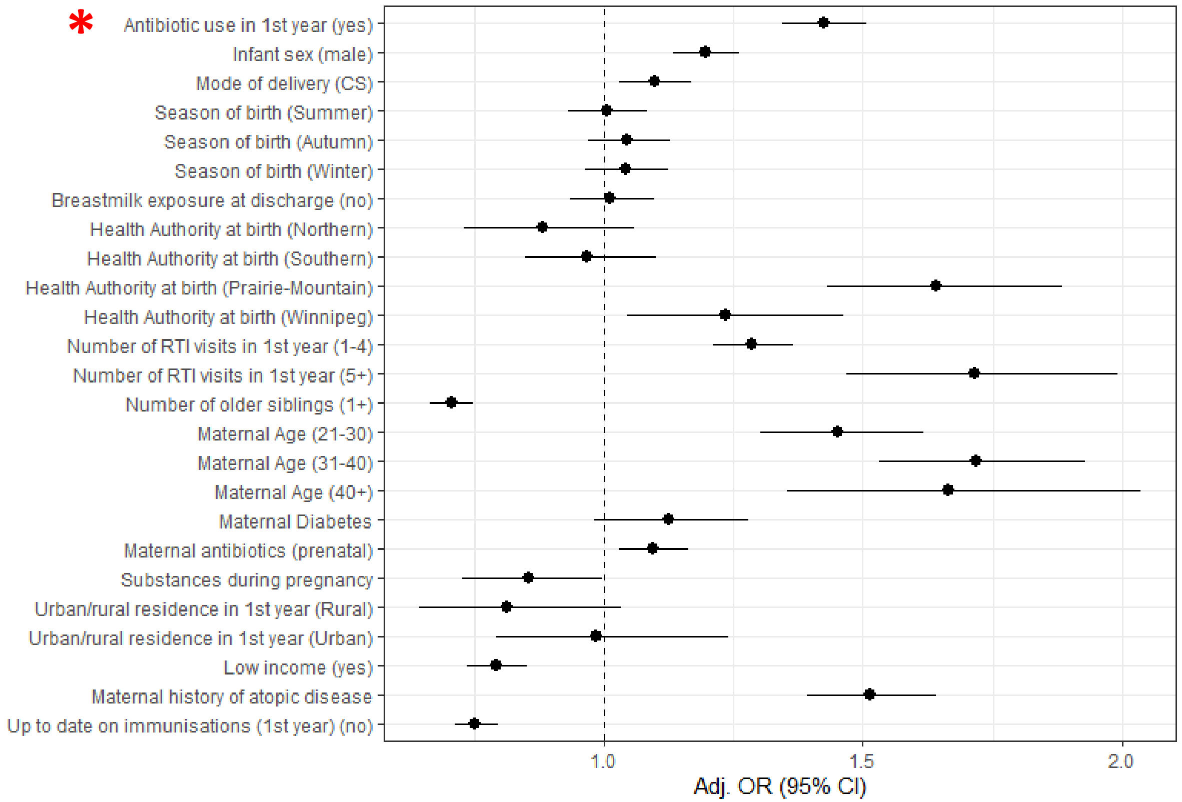
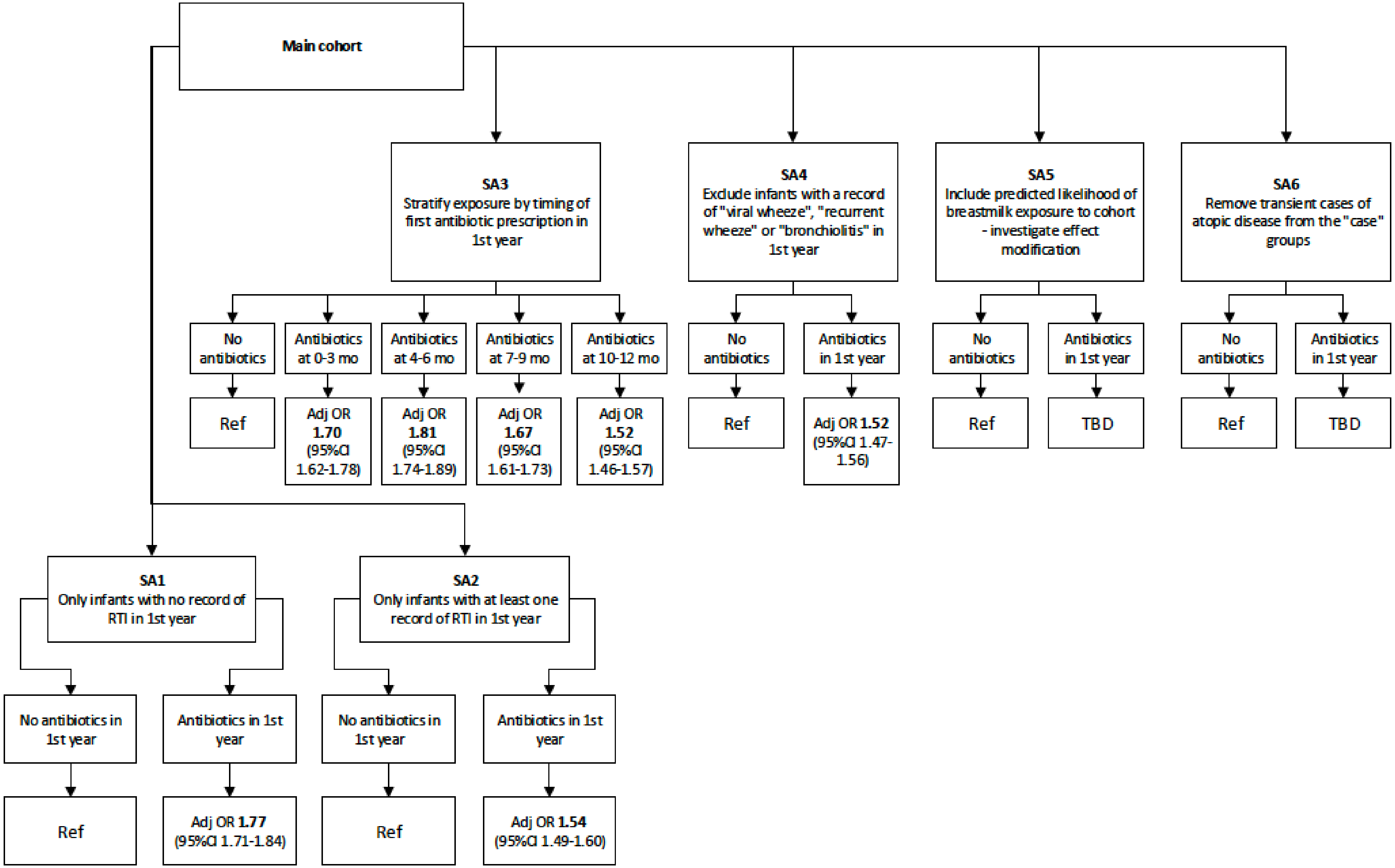


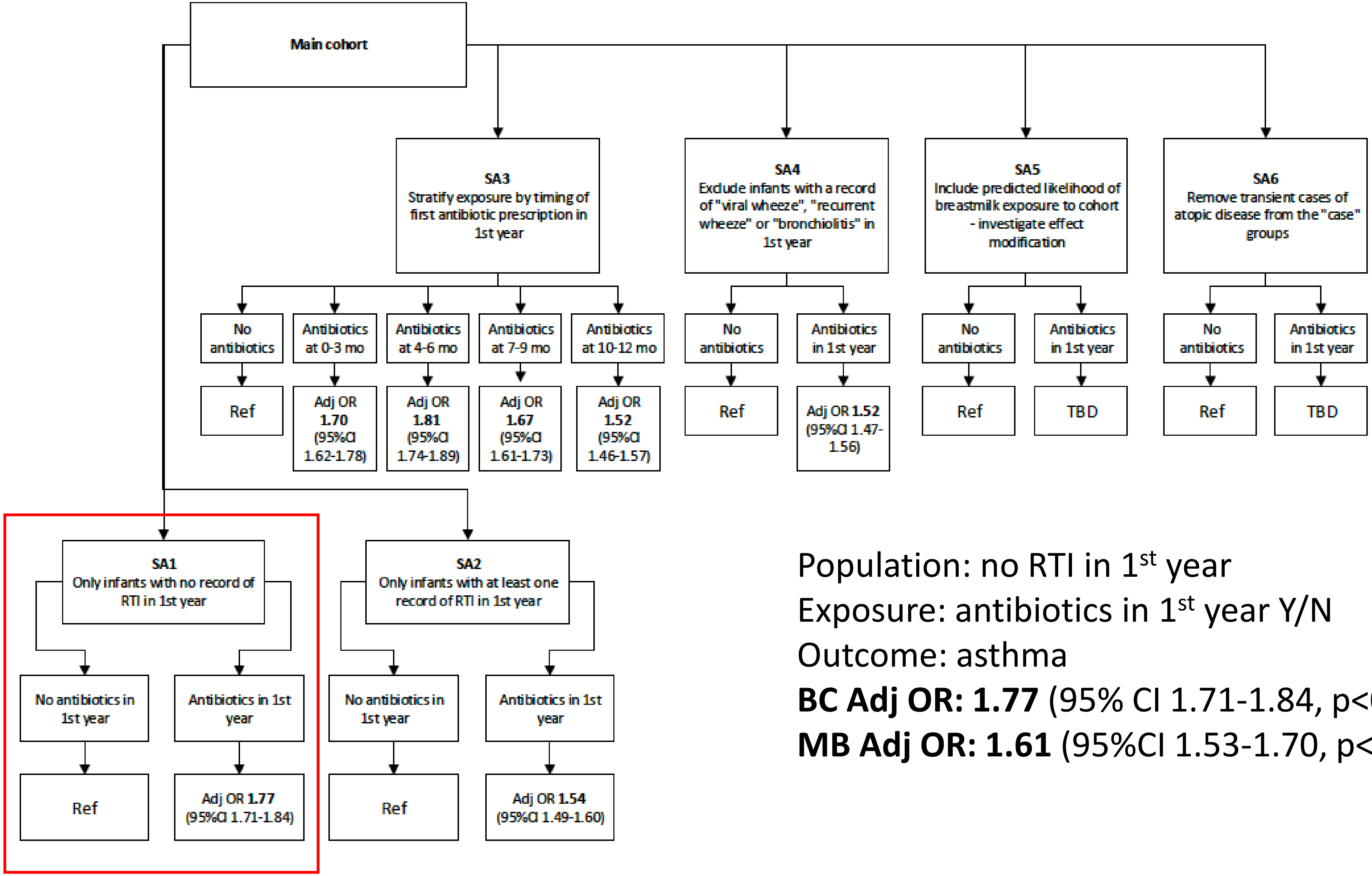
Fig 2. Adjusted logistic regression - antibiotic use before the 1st birthday and development of hay fever between the 1st and 5th birthdays.

Adj OR **1.55** (95%CI 1.49-1.62, p<0.001)

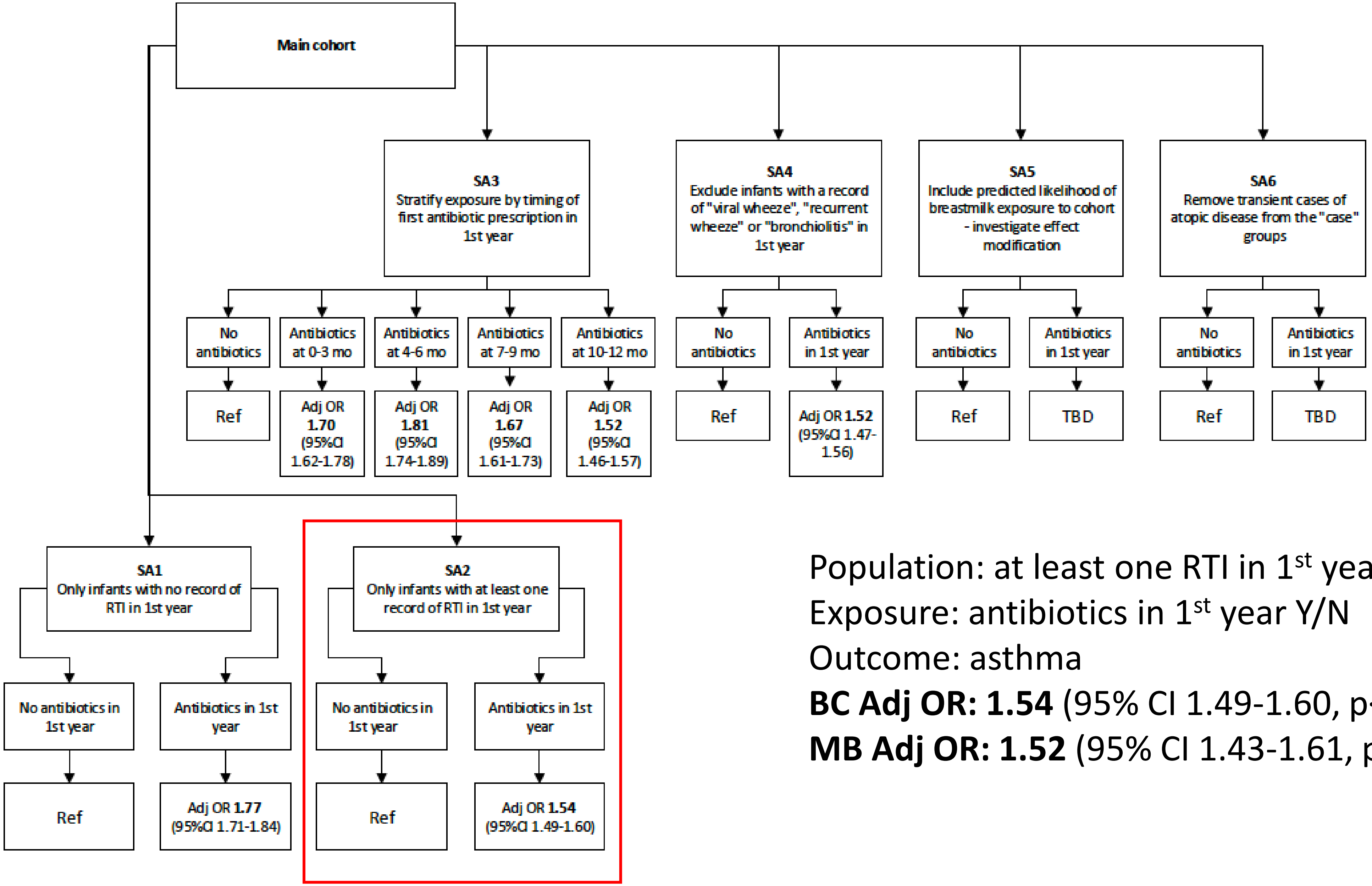
Adj OR **1.42** (95%CI 1.34-1.51, p<0.001)

Sensitivity analyses


Main cohort
SA3
Stratify exposure by timing of first antibiotic prescription in 1st year
SA4
Exclude infants with a record of "viral wheeze", "recurrent wheeze" or "bronchiolitis" in 1st year
SA5
Include predicted likelihood of breastmilk exposure to cohort - investigate effect modification
SA6
Remove transient cases of atopic disease from the "case" groups
No antibiotics
Antibiotics at 0-3 mo
Antibiotics at 4-6 mo
Antibiotics at 7-9 mo
Antibiotics at 10-12 mo
No antibiotics
Antibiotics in 1st year
No antibiotics
Antibiotics in 1st year
No antibiotics
Antibiotics in 1st year
Ref
Adj OR 1.70 (95%CI 1.62-1.78)
Adj OR 1.81 (95%CI 1.74-1.89)
Adj OR 1.67 (95%CI 1.61-1.73)
Adj OR 1.52 (95%CI 1.46-1.57)
Ref
Adj OR 1.52 (95%CI 1.47-1.56)
Ref
TBD
Ref
TBD
SA1
Only infants with no record of RTI in 1st year
SA2
Only infants with at least one record of RTI in 1st year
No antibiotics in 1st year
Antibiotics in 1st year
No antibiotics in 1st year
Antibiotics in 1st year
Ref
Adj OR 1.77 (95%CI 1.71-1.84)
Ref
Adj OR 1.54 (95%CI 1.49-1.60)



Population: no RTI in 1st year
Exposure: antibiotics in 1st year Y/N
Outcome: asthma
BC Adj OR: 1.77 (95% CI 1.71-1.84, p<0.001)
MB Adj OR: 1.61 (95%CI 1.53-1.70, p<0.001)



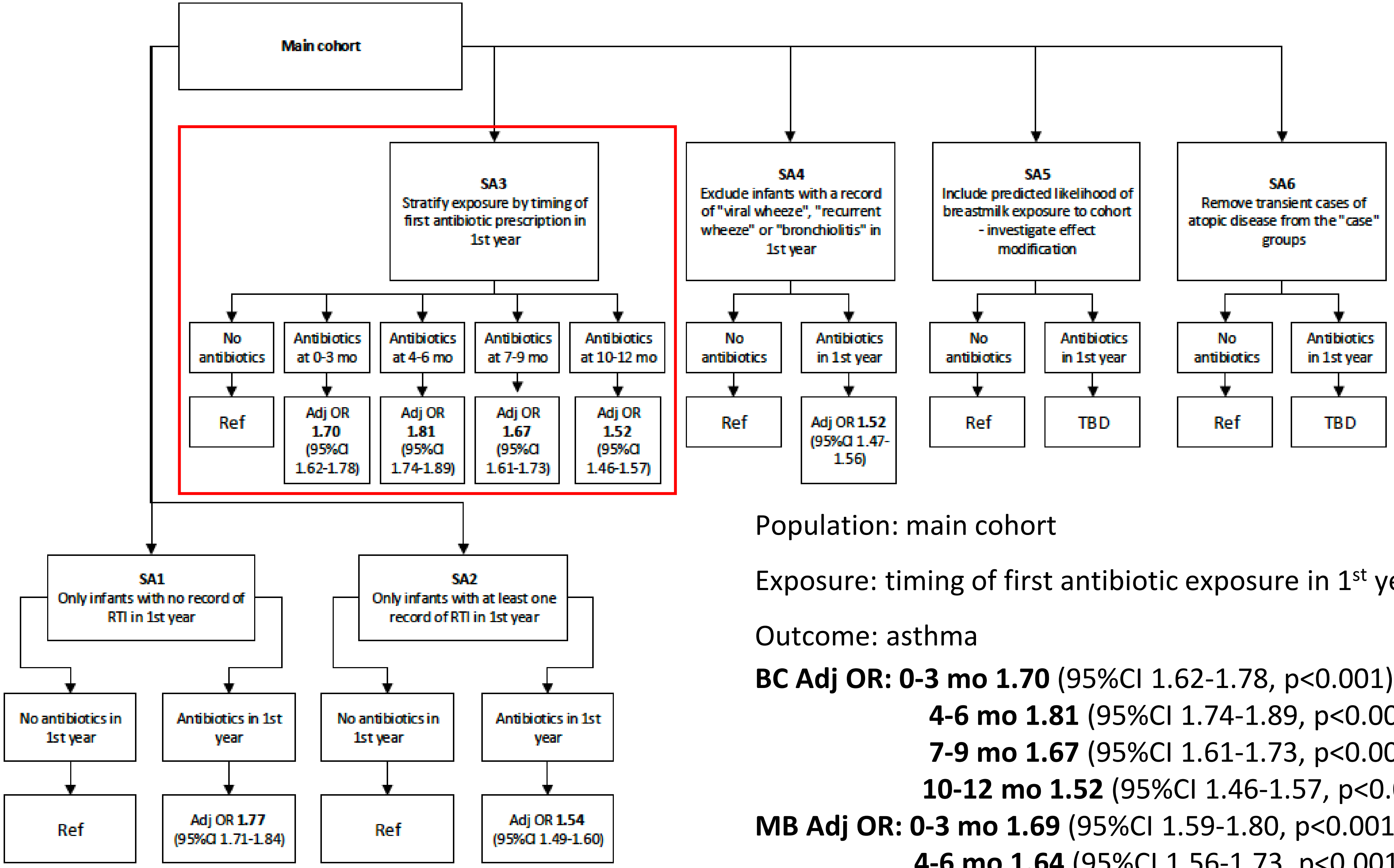
Population: at least one RTI in 1st year

Exposure: antibiotics in 1st year Y/N

Outcome: asthma

BC Adj OR: 1.54 (95% CI 1.49-1.60, p<0.001)

MB Adj OR: 1.52 (95% CI 1.43-1.61, p<0.001)



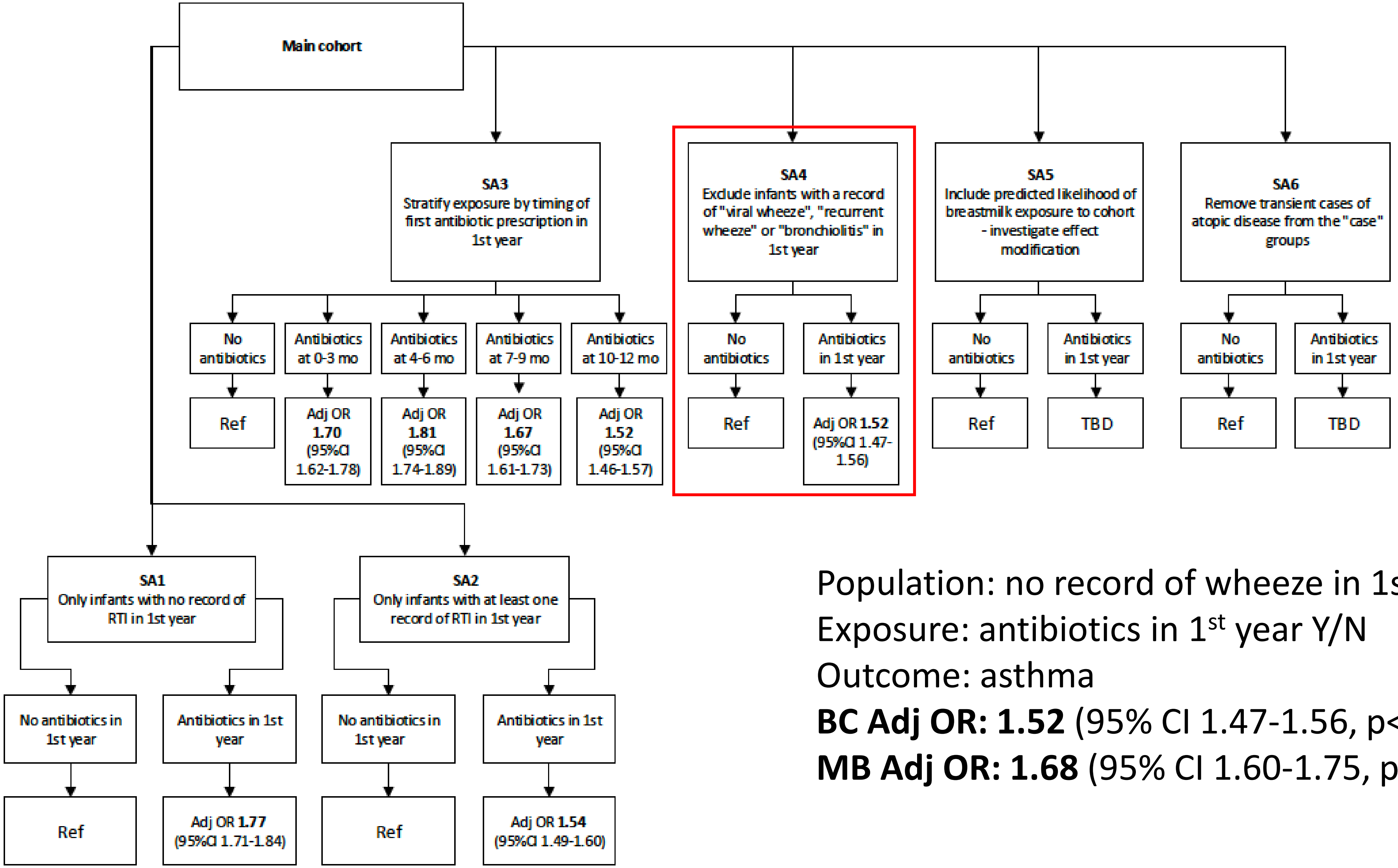
Population: main cohort

Exposure: timing of first antibiotic exposure in 1st year

Outcome: asthma

BC Adj OR: 0-3 mo 1.70 (95%CI 1.62-1.78, p<0.001)
4-6 mo 1.81 (95%CI 1.74-1.89, p<0.001)
7-9 mo 1.67 (95%CI 1.61-1.73, p<0.001)
10-12 mo 1.52 (95%CI 1.46-1.57, p<0.001)

MB Adj OR: 0-3 mo 1.69 (95%CI 1.59-1.80, p<0.001)
4-6 mo 1.64 (95%CI 1.56-1.73, p<0.001)
7-9 mo 1.41 (95%CI 1.34-1.49, p<0.001)
10-12 mo 1.44 (95%CI 1.60-1.75, p<0.001)



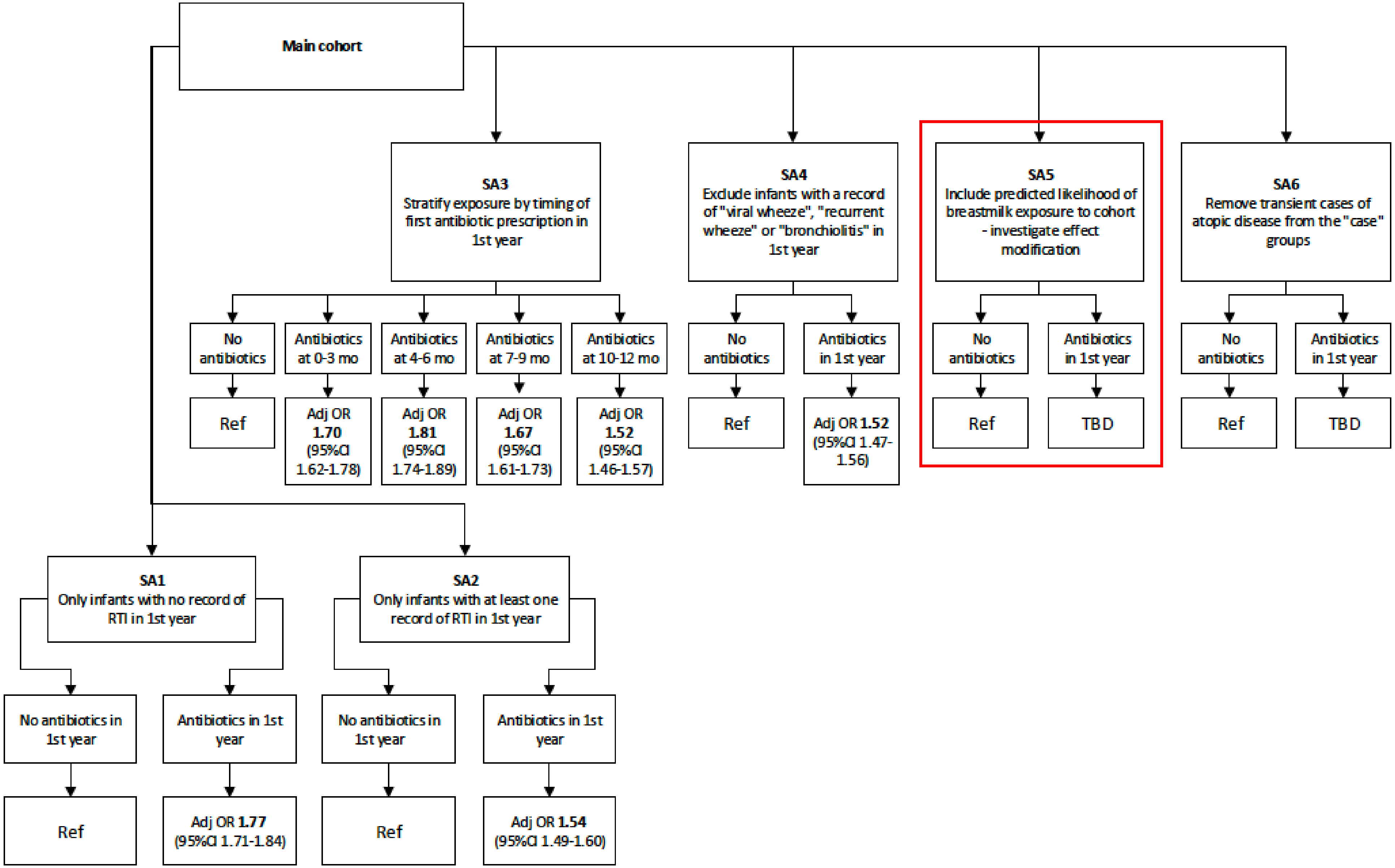
Population: no record of wheeze in 1st year

Exposure: antibiotics in 1st year Y/N

Outcome: asthma

BC Adj OR: 1.52 (95% CI 1.47-1.56, p<0.001)

MB Adj OR: 1.68 (95% CI 1.60-1.75, p<0.001)



Main cohort
SA3
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No antibiotics
Antibiotics at 0-3 mo
Antibiotics at 4-6 mo
Antibiotics at 7-9 mo
Antibiotics at 10-12 mo
Ref
Adj OR **1.70** (95%CI 1.62-1.78)
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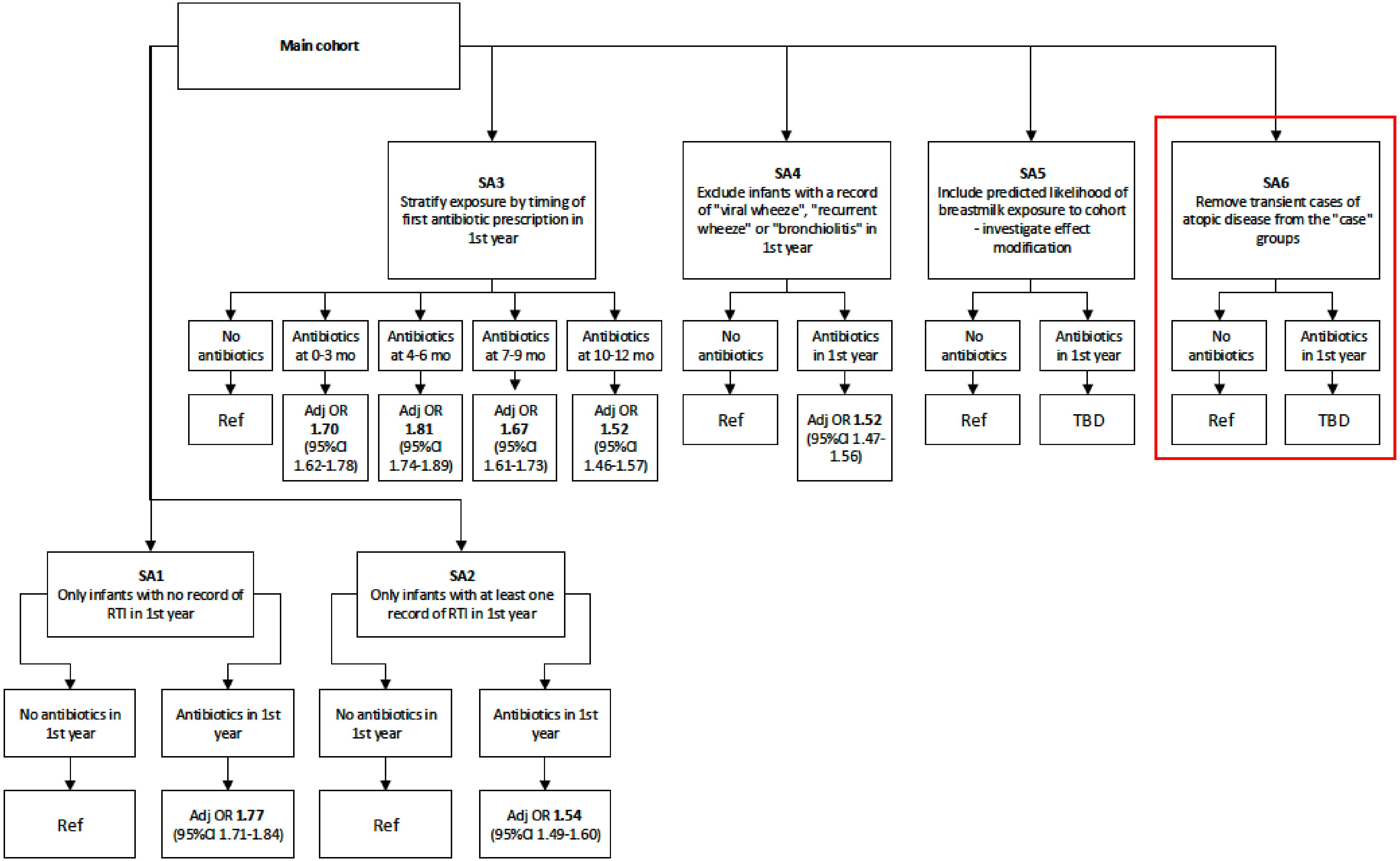
Adj OR **1.67** (95%CI 1.61-1.73)
Adj OR **1.52** (95%CI 1.46-1.57)
SA4
Exclude infants with a record of "viral wheeze", "recurrent wheeze" or "bronchiolitis" in 1st year
No antibiotics
Antibiotics in 1st year
Ref
Adj OR **1.52** (95%CI 1.47-1.56)
SA5
Include predicted likelihood of breastmilk exposure to cohort - investigate effect modification
No antibiotics
Antibiotics in 1st year
Ref
TBD
SA6
Remove transient cases of atopic disease from the "case" groups
No antibiotics
Antibiotics in 1st year
Ref
TBD
SA1
Only infants with no record of RTI in 1st year
No antibiotics in 1st year
Antibiotics in 1st year
Ref
Adj OR **1.77** (95%CI 1.71-1.84)
SA2
Only infants with at least one record of RTI in 1st year
No antibiotics in 1st year
Antibiotics in 1st year
Ref
Adj OR **1.54** (95%CI 1.49-1.60)



Main cohort
SA3
Stratify exposure by timing of first antibiotic prescription in 1st year
SA4
Exclude infants with a record of "viral wheeze", "recurrent wheeze" or "bronchiolitis" in 1st year
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Antibiotics in 1st year
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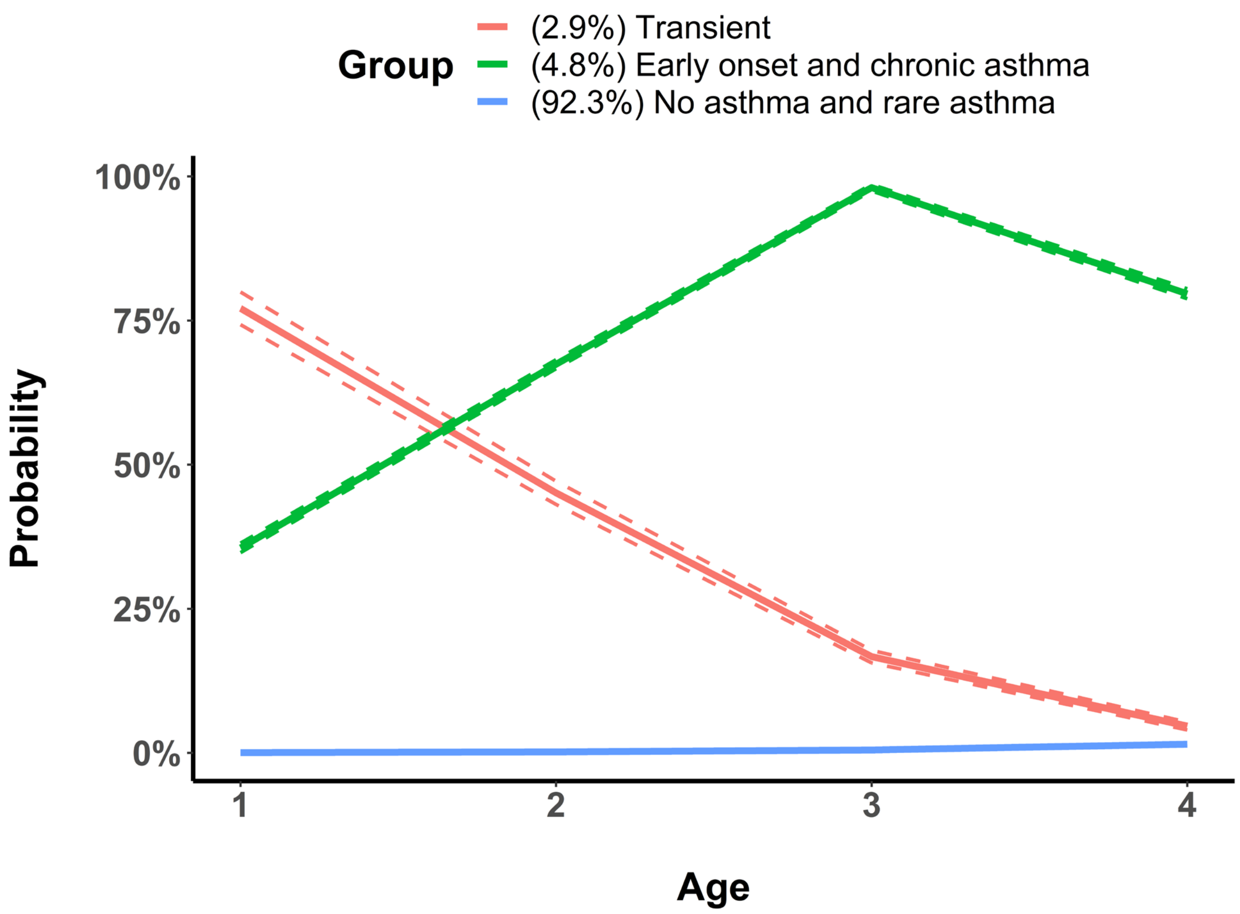
Ref
Adj OR 1.54 (95%CI 1.49-1.60)

Asthma trajectories



Summary

- 64%, 17% and 42% higher adjusted odds of asthma, eczema and hay fever in antibiotic-exposed infants in BC

- 55% and 42% higher adjusted odds of asthma and hay fever in antibiotic-exposed infants in MB

- Association with asthma is robust in children only receiving antibiotics for non-respiratory infections

- Children receiving their first antibiotic earlier in infancy had higher odds of developing asthma

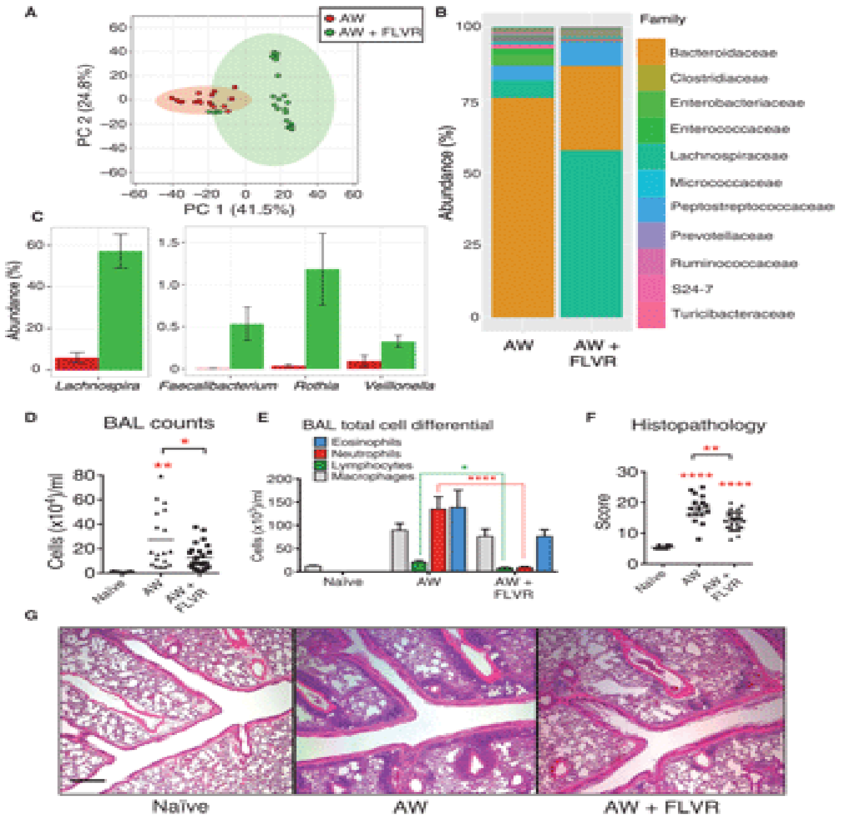
Associations with all atopic outcomes supports hypothesis that mechanistic pathway is immune-regulated and influenced by gut microbial dysbiosis early in life

Can We Settle the Question of Confounding By Indication?

- Declining asthma trend over 20 years seen in absence of major declines in viral respiratory infection
- Cohort analyses have stratified by or excluded those who got antibiotics for respiratory infections, and still find a robust association
- Structural Equation Modeling in CHILD Cohort – The impact through microbiota is more likely than through infection
- Experimental studies in the mouse model show mitigation of asthma risk by returning protective flora – no RTI interference
- ViroScan Serological Study at 1 year underway to measure cumulative viral exposure

Mouse Models of Asthma

- Protective value of key taxa experimentally verified in a mouse model of asthma



Marie-Claire Arrieta et al., Sci Transl Med 2015;7:307ra152

A significant fraction of the decline in asthma incidence observed over the last two decades may be an unexpected dividend of prudent antibiotic use and higher exposure to human breast milk.

Next Steps

- Antibiotic Class specific effects
- Exploration in other populations (CPRD Aurum UK)
- Following work on CORAL Ireland and that of other Cohorts
- Knowledge Translation – Stewardship and breast feeding were good ideas even before this evidence – <u>who</u> needs to know?
- Intervention trials of Pre/Pro/Synbiotics for Kids who need antibiotics?
- Consider implications and relevance for LMICs

Your Summary Haiku

Reduce asthma risk
Avoid antibiotics
Foster breast feeding