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Title:

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Date:

2021-07-01

Citation:

Hu, Y. J., Wang, J., Harwell, J. I. & Wake, M. (2021). Association of in utero antibiotic exposure on childhood ear infection trajectories: Results from a national birth cohort study. *Journal of Paediatrics and Child Health*, 57 (7), pp.1023-1030. <https://doi.org/10.1111/jpc.15371>.

Persistent Link:

<https://hdl.handle.net/11343/298234>

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**Association of in utero antibiotic exposure on childhood ear infection trajectories:
results from a national birth cohort study**

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Acknowledgments

This study uses unit record data from Growing Up in Australia, the Longitudinal Study of Australian Children (LSAC). The study is conducted in partnership between the Department of Social Services, the Australian Institute of Family Studies, and the Australian Bureau of Statistics. The findings and views reported in this paper are solely those of the authors. YJH and JW had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. We thank the LSAC study participants and staff for their contributions and Australian Data Archive for data management.

Competing interests

The authors declare no potential conflicts of interest, including no specific financial interests relevant to the subject of this manuscript.

Ethics approval and consent to participate section

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/jpc.15371](https://doi.org/10.1111/jpc.15371)

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The research methodology and survey content of Growing Up in Australia is reviewed and approved by the Australian Institute of Family Studies Ethics Committee, which is a Human Research Ethics Committee registered with the National Health and Medical Research Council (NHMRC). The Ethics Committee ensures that Growing Up in Australia meets the ethical standards outlined in the National Statement on Ethical Conduct in Research Involving Humans. The LSAC study was approved by the Australian Institute of Family Studies Ethics Committee (AIFS 14-26) in Jan-Feb 2014; the Ethics Committee also provides ethical review and approval for LSAC at every wave.

Consent for publication

Not applicable as this study does not contain data from any individual person

Availability of data and materials

The data that support the findings of this study are available from Australian Data Archive (ADA) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission from Australian Data Archive and corresponding author.

Funding

Research at the Murdoch Children's Research Institute (MCRI) is supported by the Victorian Government's Operational Infrastructure Support Program. The funding bodies did not play any role in the study. JW was supported by the MCRI Lifecourse Postdoctoral Fellowship. MW was supported by the National Health and Medical Research Council (NHMRC) Senior Research Fellowship (1046518) and (Principal Research Fellowship 1160906) in this work.

Authors' contributions

YJH designed and conceptualized the study, JW analysed the data, YJH and JW drafted the initial manuscript. MW was the Health Design Leader for LSAC. MW and JIH provided critical comments and review. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

List of abbreviations

LSAC : The Longitudinal Study of Australian Children

HR: Hazard Ratio

BIC: Bayesian information criterion

SD: Standard deviation

MCRI: Murdoch Children's Research Institute

ADA: Australian Data Archive

Keywords

Utero antibiotic exposure, childhood, ear infection, trajectories, birth cohort

ABSTRACT (246)

Background: Most prescribed medicines during pregnancy are antibiotics, with unknown effects on a foetus and on the infant's acquired microbiome. This study investigates associations between in utero antibiotic exposure and ear infection trajectories over the first decade of life, hypothesising effects on early or persistent, rather than later-developing, ear infections.

Methods: *Design & Participants:* The Longitudinal Study of Australian Children (LSAC) birth cohort recruited a nationally-representative sample of 5107 infants in 2004. *Measures:* Mothers reported antibiotic use in pregnancy when a child was 3-21 months old (wave 1), and ongoing problems with ear infection every 2 years spanning ages 0-1 to 10-11 years (waves 1 to 6). *Analysis:* Latent class models identified ear infection trajectories, and univariable and multivariable multinomial logistic regression determined odds of adverse trajectories by antibiotic exposure.

Results: 4500 (88.1% of original sample) children contributed (mean baseline age 0.7 years; 51.3% boys); 10.4% of mothers reported antibiotic use in pregnancy. Four probability trajectories for ear infection emerged: "consistently low" (86.2%), "moderate to low" (5.6%), "low to moderate" (6.7%) and "consistently high" (1.4%). Antibiotic use in pregnancy was associated with children following "consistently high" (aOR 2.04, 95% CI 1.08 to 3.88, $p=0.03$) and "moderate to low" (aOR 1.78, 95% CI 1.25 to 2.53, $p=0.001$) trajectories.

Conclusions: Antibiotic use in pregnancy is associated with an increased risk of persistent and early childhood ear infections. This highlights the wisdom of cautious antibiotic use during pregnancy, and the need for study of potential mechanisms underlying these associations.

Keywords

In utero antibiotic exposure, childhood, ear infection, trajectories, birth cohort

Highlight

The known: Antibiotic use during pregnancy is common. Middle ear infection is a common early childhood disease. Prenatal antibiotics use can change foetal microbiota.

The new: 10% of pregnant women reported antibiotic use during pregnancy (not including antibiotic use during labour). Children of these mothers were more likely to follow trajectories characterised by early or consistently high rates of ear infections across the first decade of life.

The Implications: This study highlights the wisdom of cautious antibiotic use during pregnancy, and the need for further study on potential mechanisms underlying these associations.

INTRODUCTION

The consumption of antibiotics is increasing worldwide, leading to concern around the increasing prevalence of antibiotic resistance and potential long-term adverse environmental and health effects. One in four women receive at least one antibiotic during pregnancy and the majority of prescribed medicines are antibiotics,¹ which could affect the foetus and newborn in under-appreciated ways that may persist throughout childhood.² For example, antibiotics may perturb maternal bacterial flora from which a newborn infant's microbiome is derived.³ Systematic reviews, animal models and population studies have shown that maternal antibiotics exposure changes the gut microbiome⁴⁻¹⁰ and increases the risk of antimicrobial resistance in neonates.^{11,12} In addition to direct impacts on flora, one of the underlying potential mechanisms is that gut microbiome may influence mucosal innate and adaptive immunity, which may cause systemic immune disorders and increase susceptibility.^{13,14} Antimicrobial exposure in utero has previously been shown to have associations with numerous conditions, including asthma,¹⁵ obesity,¹⁶ attention deficit hyperactivity disorder¹⁷ and others.¹⁰ Some antibiotics, such as aminoglycosides, may also have a direct teratogenic effect on foetal ear development.¹⁸

Middle ear infection (otitis media) is a common early childhood disease. More than 80% of children will experience acute otitis media before 3 years of age, and 40% will have six or more recurrences by the age of 7 years.¹⁹ Otitis media represents the most common reason for childhood physician sick visits and for antibiotic prescription in early childhood.²⁰ The natural history of otitis media is dynamic, including early or late onset, periods of recurrence, persistence, and complete resolution.²¹ The predominant bacteria for otitis media in children globally²² and in Australia²³ are *S. pneumoniae* and *H. influenzae* as identified through bacterial culture. However, otitis media is usually caused by viral infections. A recent Australian study showed that antibiotics are over-prescribed for otitis media for children,²⁴ and a national Australia population study showed that overall antibiotics use in general increased more than 50% from 2001 to 2012.²⁵

If antibiotics during pregnancy were to exert an impact on likelihood of otitis media during childhood, via (for instance) changes to infant microbiome, then we would expect to see this additional risk in infancy most proximal to the antibiotic exposure and either persist or slowly decline through, rather than emerge later in, childhood. This is supported by modelling studies that suggest that, following antibiotic exposure, the gut microbiome may return to stability between 3 months and 5 years later.²⁶ One way to study this hypothesis is to examine longitudinal trajectories²⁷ of propensity to ear infections, requiring collection of both an indicator of antibiotic

use during pregnancy and repeated measurement of ear infection rates at multiple time points in population studies.

The national Longitudinal Study of Australian Children offers this opportunity, with prospective biennial reporting of ongoing ear infections from infancy to age 10-11 years. Therefore, the objective of this study is to analyze the association of parent-reported maternal antibiotic use during pregnancy with risks of different trajectories of middle ear infection spanning the entire first decade of life. We hypothesized that antibiotic consumption in pregnancy would be associated with higher rates of early ear infection that either persist or decline, but not with a tendency to later-onset ear infections.

METHODS

Study design and participants: In 2004, the Longitudinal Study of Australian Children (LSAC) was launched to improve understanding of child development, inform social policy debate, and identify opportunities for intervention and prevention strategies in policy areas concerning children and their families. It used a two-stage random sampling framework stratified by state, urban/rural split and clustered by postcode to recruit two nationally-representative samples of approximately 5000 Australian children each from the Australian Medicare database. Medicare is a core funding mechanism for the Australian universal health care system into which 98% of children are enrolled by their first birthday.²⁸ The two cohorts were the Birth cohort (initially aged 0-1 years) and the Kindergarten cohort (initially aged 4-5 years), both followed every two years with written and interview-administered questionnaires since enrolment covering many areas, including socio-demographic information, child functioning, and characteristics of home, community, relationship, education, health and childcare. This study is ongoing, with subjects now around 16 and 20 years of age in the two cohorts. Details of LSAC's initial study design and recruitment are thoroughly outlined elsewhere.²⁹ This research draws on data from the first 6 "waves" from 2004 to 2014 for the Birth cohort only, with an initial response rate of 57.2% (5107/8921).³⁰ Of these, 73.7% (3764/5107) were retained from wave 1 to wave 6 (the waves relevant to this paper), when the children were aged 10 to 11 years.³¹ The characteristics of participants more likely and reasons to drop out (eg, refused, non-contact, away for entire enumeration period and death of study child)³² are similar to surveys in other countries.³³

Procedures: After obtaining informed consent, trained professional interviewers conducted biennial 90-minute face-to-face interviews in the children's homes with their primary caregivers (usually the biological mother). As well as primary caregivers, other parents/guardians additionally completed written questionnaires, because they may have different perspectives on the child, and also because each parent's health, wellbeing and views on things like family relationships may impact differently on the child.

Measures:

Use of antibiotics in pregnancy: Mothers reported on their use of antibiotics in pregnancy at baseline wave (wave 1) when the child was aged 3 to 21 months in face-to-face interviews. The use of antibiotics in pregnancy was recorded using a categorical question. Mothers were asked "Did you take any medicines/tablets during pregnancy?" and, if they answered yes, "What prescribed

medicines or tablets were taken?- Antibiotics/penicillin (yes/no)?”, with a single yes/no answer applying to all antibiotics.

Ear infection: Parents reported on children’s ongoing ear infections from waves 1 to 6 (ages 0-1 to 10-11 years) at face-to-face interviews. The presence of ear infection was recorded using the same categorical question at each wave, with the responding parent asked “*Does (child of interest) have any of these ongoing conditions - Ear infections (yes/no)?*”³⁴

Potential confounders were age, sex, birth weight and socioeconomic status (wave 1) and passive smoking, all of which have been associated with both antibiotic use and ear infections in the literature.³⁵⁻³⁷ A child’s date of birth, sex and birth weight were taken from LSAC records. Neighbourhood disadvantage was measured using the disadvantage index from the 2001 Socio-Economic Indexes for Areas.³⁸ This is a composite index based on ranking postcodes according to relative disadvantage, using data from the five-yearly Census of Population and Housing administered by the Australian Bureau of Statistics. Contributing items include average household education levels, income levels, employment status and disability for that postcode. The national mean for this index is standardized to 1000 (SD 100), with higher scores reflecting less disadvantage. We created a binary variable of “passive smoking exposure” for children if the parent questionnaire recorded any smokers at home at any LSAC wave from child age 0 to 11 years.

Statistical Analysis: LSAC is an Open Science resource. All data are released by the Australian Data Archive (ADA). Under our ADA licence, we downloaded the LSAC data in Stata format from the ADA website and extracted the relevant variables through Stata. All statistical analyses were performed in Stata 15.0 (StataCorp LLC).

Identification of ear infection trajectories (Aim 1): Trajectory modelling was used to identify groups that have similar patterns of change over time. To examine ear infection trajectories across waves 1 to 6, we conducted group-based trajectory modelling using the ‘traj’ plug-in in Stata.³⁹ Only participants with ear infection data for at least 3 waves were included in the trajectories (**Figure 1**). For trajectory modelling, ear infection data were modelled with binary logit distribution which is designed for the analysis of longitudinal data on a dichotomous outcome variable. In order to extract the most meaningful and distinct trajectories, we considered Bayesian information criterion (BIC) values, average posterior probabilities, the proportion of the sample in each trajectory and visual graphs of trajectories.⁴⁰ We also dropped non-significant (e.g. $p > 0.05$) quadratic or cubic parameters for each trajectory (**Supplementary Tables S1 and S2**).⁴¹ Using

these criteria, we selected and named from visual inspection a four-trajectory solution for child ear infections.

Associations between antibiotic use in pregnancy and ear infection trajectories: We conducted univariable and multivariable multinomial logistic regression analyses for the associations between antibiotic use in pregnancy and ear infection trajectories. For multinomial analysis, we adjusted for age, sex, birth weight, type of delivery (vaginal or caesarean), neighbourhood disadvantage (wave 1) and passive smoking.

RESULTS

Sample characteristics: **Figure 1** presents the study flow from wave 1 of LSAC onward with the number of children at each wave of the Birth cohort of LSAC. Both antibiotic exposures and ear infection trajectories data are available for 4500 children (51.2% boys). **Table 1** summarizes the participant characteristics. The mean age of children included in analyses was 0.7 years (SD 0.2) at wave 1. The mean disadvantage index at wave 1 was 1010 (SD 60), indicating our sample was on average slightly less disadvantaged and more homogeneous than the general Australian population. 10.4% (n=467) had parent-reported antibiotic use in pregnancy.

Ear infection trajectories: Four probability trajectories of parent-reported ear infection emerged (**Figure 2**). The “consistently low” group contained the largest number of children (86.2%, n=3880) and represented a consistently low probability of having ear infections. 5.6% (n=253) of children were in the “moderate to low” group, which represented a decreasing probability of having ear infections from age 3 to 11 years. 6.7% (n=302) of children belonged to the “low to moderate” group, representing the rise in the probability of having ear infections from age 0 and 9 years. The “consistently high” group comprised only a small proportion of children (1.4%, n=65) and was characterized by a consistently high probability of having ear infections.

Association between antibiotic use in pregnancy and ear infection trajectories: The proportion of antibiotic use in pregnancy in each trajectory was: 9.7% in “consistently low”, 11.9% in “low to moderate”, 16.6% in “moderate to low” and 18.5% in “consistently high” (**Table 2**). In univariate analysis, antibiotic use in pregnancy was associated with children following “moderate to low” (OR 1.84, 95% CI 1.31 to 2.62, p=0.001) and “consistently high” (OR 2.10, 95% CI 1.11 to 3.97, p=0.02) trajectories, compared to “consistently low” trajectory. In multivariate analysis, adjusting for age, sex, birth weight, type of delivery, neighbourhood disadvantage and passive smoking, antibiotic use in pregnancy remained strongly associated with children following “moderate to low” (OR 1.78, 95% CI 1.25 to 2.53, p=0.001) and “consistently high” (OR 2.04, 95% CI 1.08 to 3.88, p=0.03) trajectories (**Figure 3**).

DISCUSSION

Principal findings: This study shows that, compared to those not exposed, children exposed to parent-reported antibiotics in utero were around twice as likely to experience high early rates of parent-reported ear infection that either declined or persisted from 0 to 11 years of age. However, they were not more likely to have later-onset ear infections.

While this association does not prove causality, this is important information because parents are the drivers of their child's health care and highly influential in their diagnoses. A few possible causal explanations may be considered. One is that maternal microbiome changes induced through antibiotic use lead to neonatal acquisition of a more disordered, higher risk microbiome.⁹ Our observation that maternal antibiotic use is associated with a moderate frequency of otitis media that decreases with time is consistent with a disordered infant microbiome that is gradually restored. Second, there may be direct anatomic or structural impacts from foetal middle ear antibiotic exposures that might not be reversible and lead to consistently high rates of otitis media. In addition, a genetic factor that predisposes the mother to infections could be inherited by the children, or there is an unmeasured environmental factor that causes both the mother to be at risk for infection and that also increases the child's risk, such as air pollution.⁴² In our study we included only passive smoking in the adjusted model though it had minimum impact.

To the best of our knowledge there is only one other study of 700 children in the Copenhagen Prospective Study that also found maternal antibiotic use in 3rd trimester pregnancy was associated with the risk of otitis media during the first 3 years of life (Hazard Ratio (HR), 1.30 95% CI 1.04 to 1.63).⁴³ In this Danish study, 37% of the mothers received antibiotics during pregnancy which is much higher than our cohort. The Copenhagen Prospective Study utilized clinical and pharmacy records to ascertain antibiotic use whereas we relied on maternal recall, with a relatively low rate reported of 10.4%. LSAC's recall approach may be expected to underestimate antibiotic use in several ways: a) a mother may not understand that a medicine given to them is an antibiotic or may simply forget (recall bias), and b) (unlike the Danish study) the question asked in LSAC did not prompt for antibiotics during labour (of which many mothers may be unaware even if prompted). Given that the baseline enrolment on average occurred when the child was age 0.7 years some respondents may have forgotten or misreported an antibiotic prescription especially earlier in pregnancy. However, questionnaires are still a widely used method for many large cohort studies,⁴⁴ and the likelihood of recall bias was reduced by asking the question in Wave 1, soon after the pregnancy. Future study involving clinical records would increase the reliability and reduce recall bias.

Strengths and limitations: We were able to examine ear infection trajectories by repeated biennial reporting throughout the first 10-11 years of life. The average posterior probability value for each trajectory (**Supplementary Table S2**) was above the recommended value of 0.70,⁴⁵ indicating the model had good assignment accuracy. Our cohort had a large number of participants more than 6 times greater than the Danish cohort. We were also able to follow subjects over a 10-year period to provide a more complete picture of ear infection events and trends at the population level, while the Danish study covered only the first 3 years of life. We thus have a better understanding of patterns of later-developing ear infections.

Our study also has limitations. As in most large population-based studies,⁴² otitis media events were based on parent report. Our parent reports of 'ongoing ear infections' is a less valid source of 'in the moment' information than medical assessment, with one study showing that the diagnostic validity of parent-reported ear infection is limited (sensitivity 17%, positive predictive value 67%) against tympanograms and pneumatic otoscopy.⁴² However, as our study focused on overall decade-long trajectories rather than individual event diagnoses, this repeated biennial report may well give a more complete picture of ear infection over time than would clinical records. Second, differential uptake and attrition may limit generalisability; however, the sample covered a wide social and geographic range and we adjusted for neighbourhood disadvantage. As our sample appeared slightly less disadvantaged and more homogeneous than the general Australian population, these effects may be even more pronounced in a more disadvantaged population where otitis media is more prevalent. Third, the lack of detailed information on which trimester of pregnancy was affected by the exposure may underestimate or overestimate the actual effect. A microbiome effect for example might be exaggerated by a late pregnancy exposure, as was seen in the Copenhagen cohort.⁴³ An anatomic and/or developmental effect might be more pronounced with early foetal exposures; for example, a study by Fan et al highlighted that 1st trimester exposure to a macrolide increased the risk of malformation in children.¹ The timing of pregnancy exposure will be helpful in further investigations of underlying mechanisms behind this observed increased risk. Fourth, a lack of antibiotic prescribing information means we cannot determine if there is a dose-response effect. A recent study has shown that antibiotic exposures had a dose-response effect, with multiple antibiotic prescriptions having an increased association with early childhood infection-related hospitalizations, consistent with the disordered microbiome effect theory.⁴⁶ However, this may not apply to ear infection if antibiotic use affects the ear structure during a narrow window in early foetal development. Fifth, we lack information on potentially confounding cross-generational variables, both behavioural (tendencies for mothers to seek antibiotics for themselves and their child, and for prescribers to provide) and genetic/environmental predisposition to infection. Sixth,

we also acknowledge the maternal infection for which the antibiotic was given rather than antibiotic exposure itself may contribute independently to the association, and our survey questionnaire data do not indicate whether the antibiotics were taken as prescribed or the type and severity of the maternal infection. Early antibiotic use by the infants and children themselves were not analysed in this study. However, antibiotics use for otitis media is increasing.²⁴ This might further exacerbate infant microbiome disruption. In any case, should infants require antibiotic treatment this would support the underlying hypothesis that prenatal exposure increases risk for infections like otitis.

Much larger studies with biological sampling and detailed individual-level data on antibiotic class, duration and diagnoses would further clarify and explain these observations and the underlying mechanisms, causal or otherwise. This population-based study was not designed to answer a causal question but nonetheless emphasizes the wisdom of appropriate and cautious antibiotic use during pregnancy. Previous studies have found that inappropriate antibiotic use may be linked to a prescriber's belief that antibiotics are harmless, especially when they feel pressured to ensure patient satisfaction.⁴⁷⁻⁴⁹ The finding of this study (ie that there may be under-appreciated harms) could perhaps help doctors to limit their prescriptions during pregnancy and reduce antibiotics demanding from parents.

Conclusions: Parent-reported used of prescription antibiotics during pregnancy is associated with an increased risk of persistent or early ear infection in childhood. This emphasizes the importance of appropriate antibiotic use during pregnancy. Further studies with detailed information on antibiotic exposure timing in relation to pregnancy as well as assessments of maternal and infant microbiome will be needed to define causality, mechanisms and resulting burden.

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FIGURES

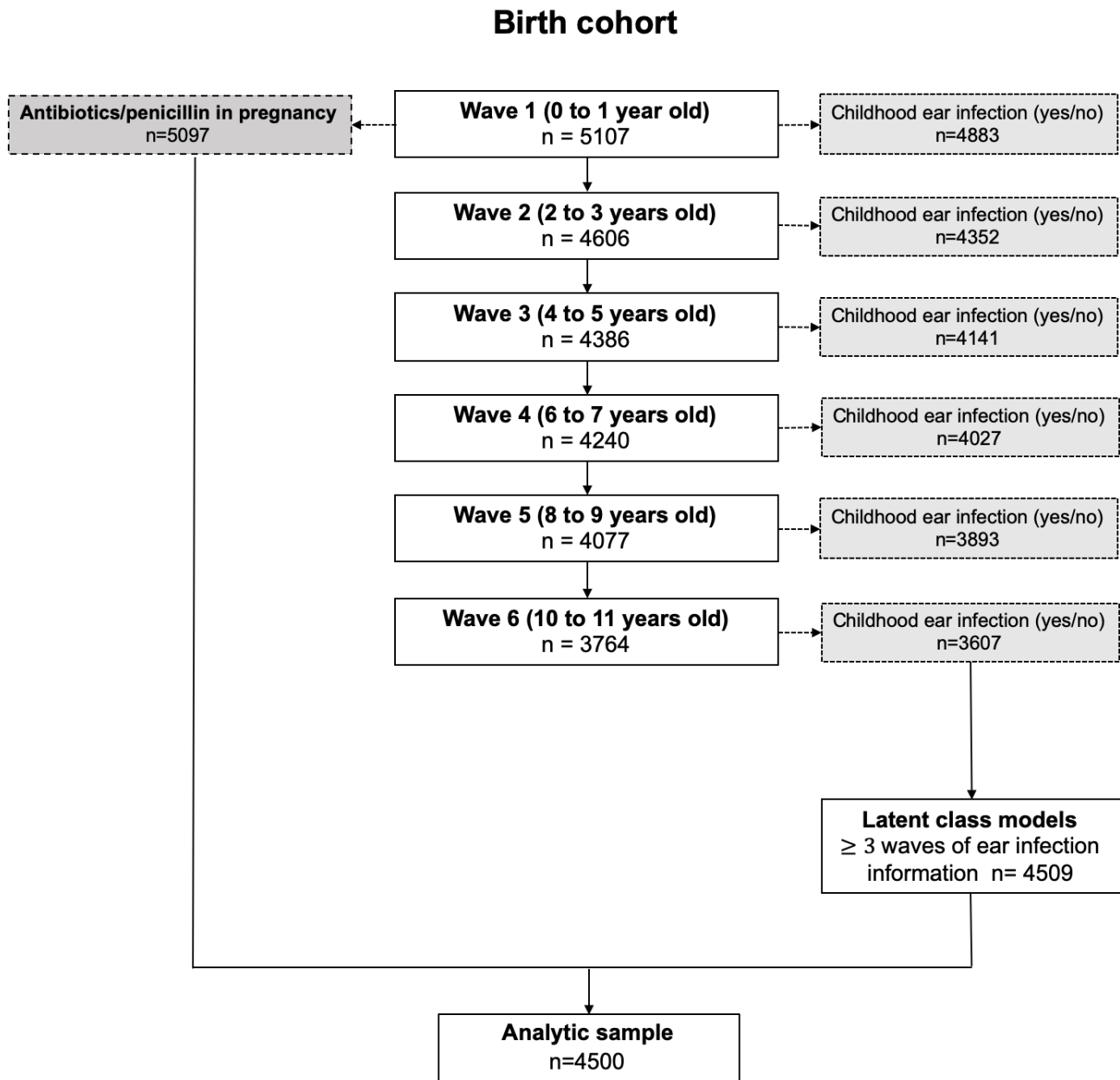


Figure 1. Participant flow chart Birth cohort of LSAC (Longitudinal Study of Australian Children)

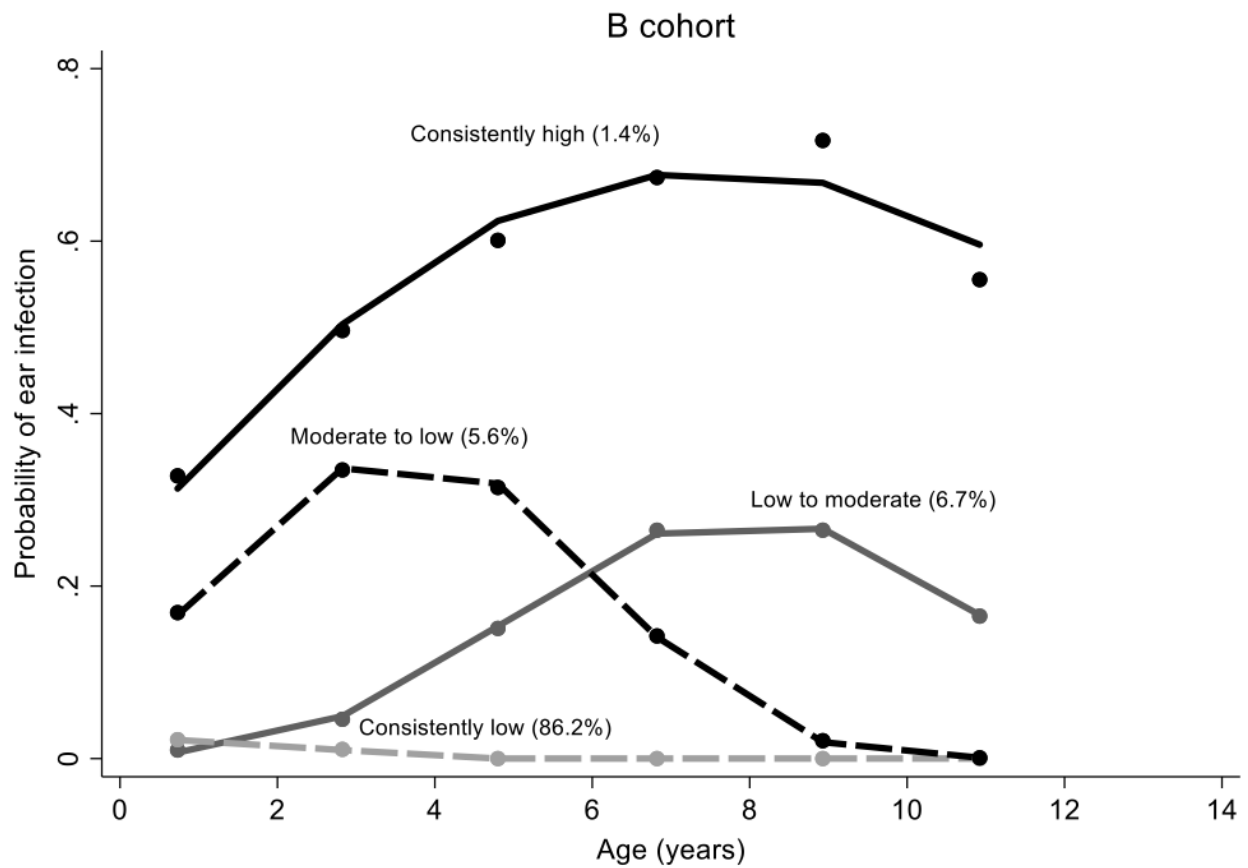


Figure 2. Latent class categories of parent-reported ear infection trajectories from wave 1 to wave 6 in LSAC's Birth cohort

Figure 3. Associations between antibiotic use in pregnancy and ear infection trajectories using multinomial logistic regression. Adjusted for age, sex, neighbourhood disadvantage, birth weight, passive smoking and type of delivery.

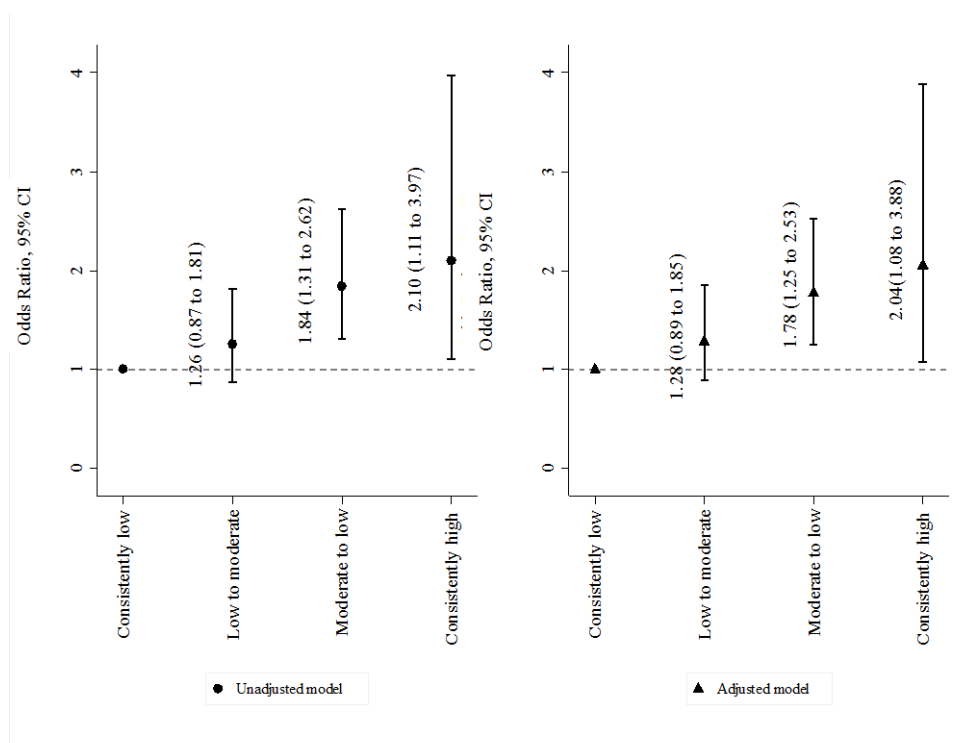


Figure 3. Associations between antibiotics use in pregnancy and ear infection trajectories using multinomial logistic regression.
Adjusted for age, sex, neighbourhood, birth weight, passive smoking and type of delivery.

TABLES

Table 1. Sample characteristics; values are mean (SD) unless specified otherwise

Characteristics		Children n=4500
Age (years)		
	Baseline wave (wave 1)	0.7 (0.2)
	Wave 2	2.8 (0.2)
	Wave 3	4.8 (0.2)
	Wave 4	6.8 (0.3)
	Wave 5	8.9 (0.3)
	Wave 6	10.9 (0.3)
Male sex, %		51.3
Neighbourhood disadvantage at wave 1		1010 (60)
Birthweight (kg)		3.4 (0.6)

Passive smoking, %	22.3
Antibiotics/penicillin in pregnancy, %	10.4
Ear infection trajectories, %	
Consistently low	86.2
Low to moderate	6.7
Moderate to low	5.6
Consistently high	1.4
Type of delivery, %	
Caesarean	39.8
wiVaginal	60.2

Table 2. Associations between antibiotics use in pregnancy and ear infection trajectories using multinomial logistic regression

Ear infection trajectories	Antibiotics in pregnancy, %	OR (95% CI) ^a	p	OR* (95% CI) ^b	p
Consistently low	9.7	reference		reference	
Low to moderate	11.9	1.26 (0.87 to 1.81)	0.22	1.28 (0.89 to 1.85)	0.18
Moderate to low	16.6	1.84 (1.31 to 2.62)	0.001	1.78 (1.25 to 2.53)	0.001
Consistently high	18.5	2.10 (1.11 to 3.97)	0.02	2.04 (1.08 to 3.88)	0.03

^a Unadjusted model

^b Adjusted for age, sex, neighbourhood disadvantage, birth weight and passive smoking.

SUPPLEMENTARY Tables

Table S1. Criteria for selecting the number and shape of trajectories

Table S2. Average posterior probability value for ear infection trajectory groups

Table S1. Criteria for selecting the number and shape of trajectories

Number of latent classes	Trajectory shapes ^a	BIC ^b
B cohort (n=4509)		
2	3 3	-4217.22
2	2 2*	-4211.27
3	3 3 3	-4210.01
3	2 2 2*	-4198.35
4	3 3 3 3	-4208.27
4	3 2 2 2	-4202.57
4	2 2 2 2*	-4196.34
5	3 3 3 3 3 ^c	-4215.49
6	3 3 3 3 3 3 ^c	-4233.03
7	3 3 3 3 3 3 3 ^c	-4282.86

^a Trajectory shapes: 0= intercept; 1=linear; 2=quadratic; 3=cubic.

We examined the significance of all three parameters (linear, quadratic, and cubic) and dropped the ones that were nonsignificant. That is, we started by including linear, quadratic, and cubic parameters for each trajectory. If the cubic parameter was not significant, we dropped it and tested for a quadratic trajectory. If this was not significant, we dropped it and tested for a linear trajectory. We retained the linear parameter even if this was not significant. After each change we compared the results using the BIC criteria.

^b BIC, Bayesian information criterion; the model with the highest (least negative) value of BIC is preferred.

^c One or more of the groups had a very small proportion of the observations.

* All parameters are significant (p<0.05).

Table S2. Average posterior probability value for ear infection trajectory groups

Ear infection trajectory group	Average posterior probability
<i>Kindergarten cohort</i>	
Consistently high	0.80
Moderate to low	0.80
Low to Moderate	0.71
Consistently low	0.90

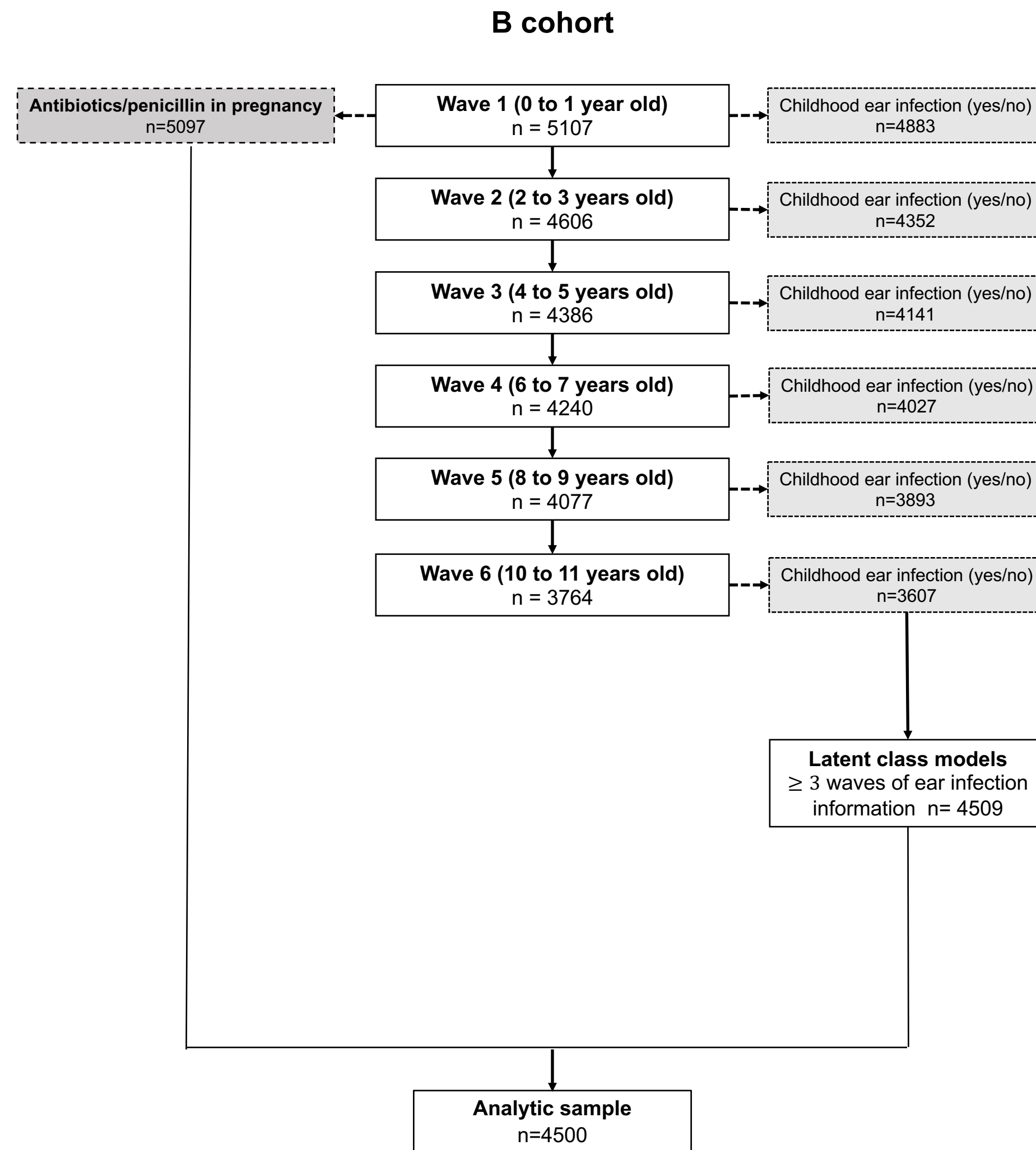


Figure 1. Participants flow chart

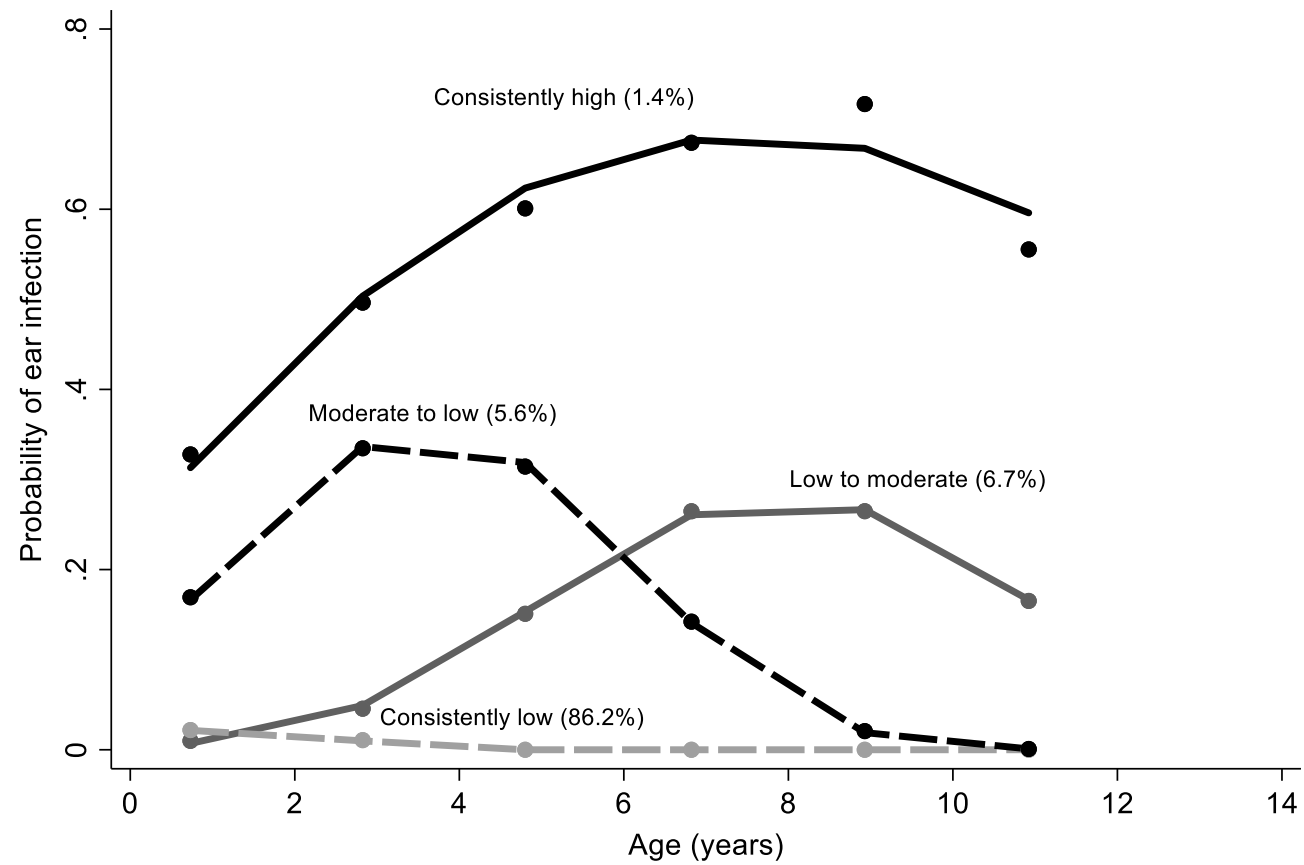


Figure 2. Latent class categories of parent-reported ear infection trajectories from LSAC's wave 1 to wave 6

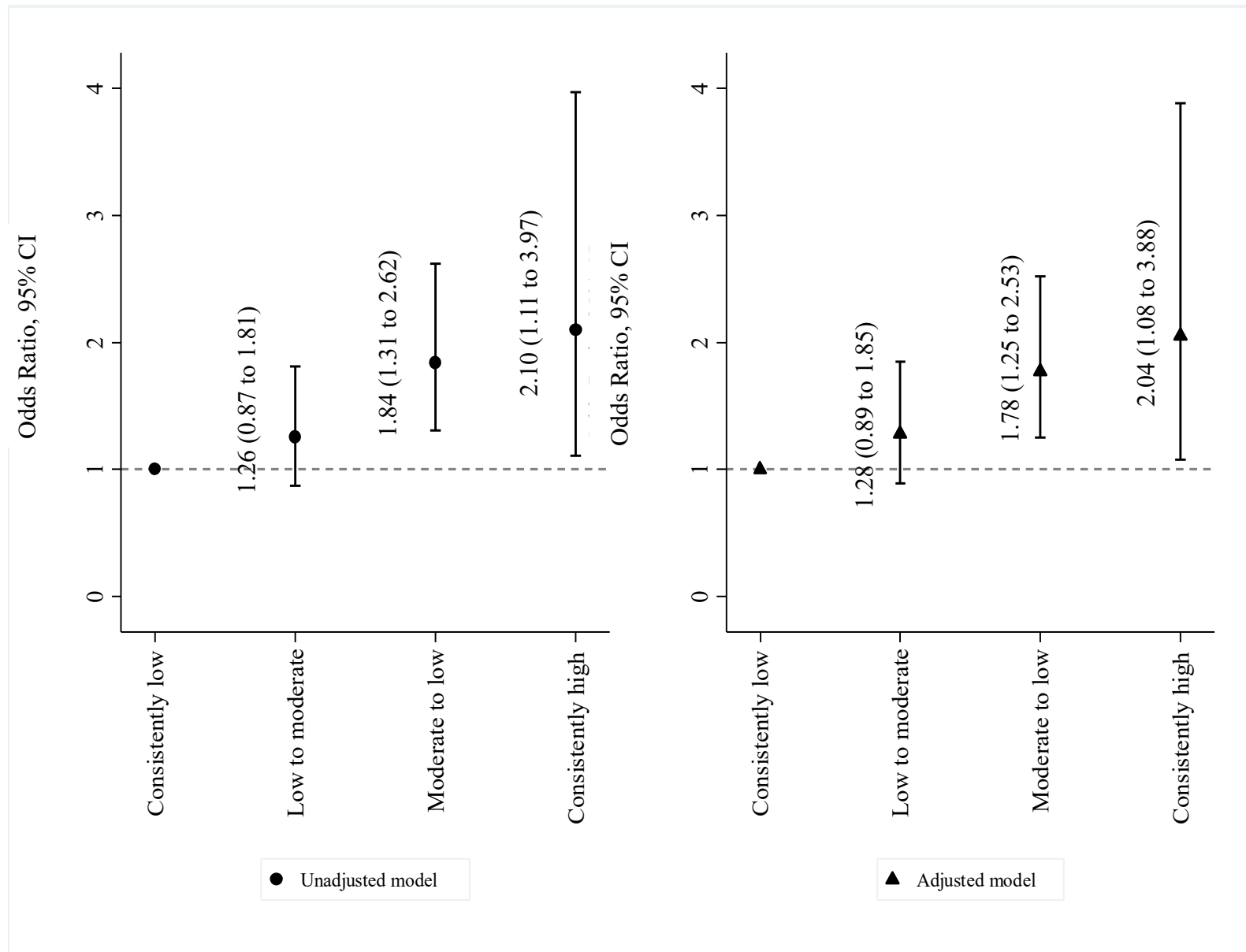


Figure 3. Associations between antibiotics use in pregnancy and ear infection trajectories using multinomial logistic regression.
Adjusted for age, sex, neighbourhood, birth weight, passive smoking and type of delivery.

**Association of in utero antibiotic exposure on childhood ear infection trajectories:
results from a national birth cohort study**

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Acknowledgments

This study uses unit record data from Growing Up in Australia, the Longitudinal Study of Australian Children (LSAC). The study is conducted in partnership between the Department of Social Services, the Australian Institute of Family Studies, and the Australian Bureau of Statistics. The findings and views reported in this paper are solely those of the authors. YJH and JW had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. We thank the LSAC study participants and staff for their contributions and Australian Data Archive for data management.

Competing interests

The authors declare no potential conflicts of interest, including no specific financial interests relevant to the subject of this manuscript.

Ethics approval and consent to participate section

The research methodology and survey content of Growing Up in Australia is reviewed and approved by the Australian Institute of Family Studies Ethics Committee, which is a Human Research Ethics Committee registered with the National Health and Medical Research Council

(NHMRC). The Ethics Committee ensures that Growing Up in Australia meets the ethical standards outlined in the National Statement on Ethical Conduct in Research Involving Humans. The LSAC study was approved by the Australian Institute of Family Studies Ethics Committee (AIFS 14-26) in Jan-Feb 2014; the Ethics Committee also provides ethical review and approval for LSAC at every wave.

Consent for publication

Not applicable as this study does not contain data from any individual person

Availability of data and materials

The data that support the findings of this study are available from Australian Data Archive (ADA) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission from Australian Data Archive and corresponding author.

Funding

Research at the Murdoch Children's Research Institute (MCRI) is supported by the Victorian Government's Operational Infrastructure Support Program. The funding bodies did not play any role in the study. JW was supported by the MCRI Lifecourse Postdoctoral Fellowship. MW was supported by the National Health and Medical Research Council (NHMRC) Senior Research Fellowship (1046518) and (Principal Research Fellowship 1160906) in this work.

Authors' contributions

YJH designed and conceptualized the study, JW analysed the data, YJH and JW drafted the initial manuscript. MW was the Health Design Leader for LSAC. MW and JIH provided critical comments and review. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

List of abbreviations

LSAC : The Longitudinal Study of Australian Children

HR: Hazard Ratio

BIC: Bayesian information criterion

SD: Standard deviation

MCRI: Murdoch Children's Research Institute

ADA: Australian Data Archive

Keywords

Utero antibiotic exposure, childhood, ear infection, trajectories, birth cohort