

Association of in Utero Antibiotic Exposure With Childhood Ear Infection Trajectories: A National Birth Cohort Study

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Abstract

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 2.06, 95% CI 1.09 to 3.91, $p=0.03$) 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.

Highlights

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 Some antibiotics, such as aminoglycosides, may have a direct teratogenic effect on foetal ear development.⁴

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.⁵ Otitis media represents the most common reason for childhood physician sick visits and for antibiotic prescription in early childhood.⁶ The natural history of otitis media is dynamic, including early or late onset, periods of recurrence, persistence, and complete resolution.⁷ 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 either persist or slowly decline through, rather than emerge later in, childhood. One way to study this hypothesis is to examine longitudinal trajectories⁸ 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 maternal antibiotic use during pregnancy with risks of different trajectories of middle ear infection across the 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) 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.⁹ The two cohorts were the Birth cohort (initially aged 0-1 years) and the Kindergarten cohort (initially aged 4-5 years), both followed biennially since enrolment. Details of LSAC's initial study design and recruitment are thoroughly outlined elsewhere.¹⁰ 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). 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.¹¹

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). Primary caregivers as well as other parents/guardians additionally completed written questionnaires.

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.

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. The responding mother was asked "*What prescribed medicines or tablets were taken?- Antibiotics/penicillin (yes/no)?*"

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)?*"¹²

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.¹³⁻¹⁵ 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.¹⁶ 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: 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.¹⁷ 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.¹⁸ We also dropped non-significant (e.g. $p > 0.05$) quadratic or cubic parameters for each trajectory (**Supplementary Tables S1 and S2**).¹⁹ 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, 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.

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

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, 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 2.06, 95% CI 1.09 to 3.91, $p=0.03$) trajectories (**Figure 3**).

Discussion

Principal findings: This study shows that, compared to those not exposed, children exposed to prescription antibiotics in utero were around twice as likely to experience high early rates of 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, and further prospective studies are warranted, 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.²⁰ 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.²¹ 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).²² 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 mother may not understand that a medicine given to them is an antibiotic, they may simply forget (recall bias), and (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 an antibiotic prescription especially earlier in pregnancy.

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 0.70,²³ 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,²¹ 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.²¹ 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.²² 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 detailed antibiotic prescribing information makes it difficult to 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.²⁴ 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.

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.²⁵ This study suggests there may be under-appreciated harms, which could help to influence prescriber behaviour.

Conclusion

Parent-reported use 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.

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

Declarations

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.

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.

Competing interests

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

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Authors' contributions

Dr. Hu designed and conceptualized the study, Dr. Wang analysed the data, Dr. Hu and Dr Wang drafted the initial manuscript. Prof Wake was the Health Design Leader for LSAC. Prof Wake and Dr. Harwell provided critical comments and review. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Figures

B cohort

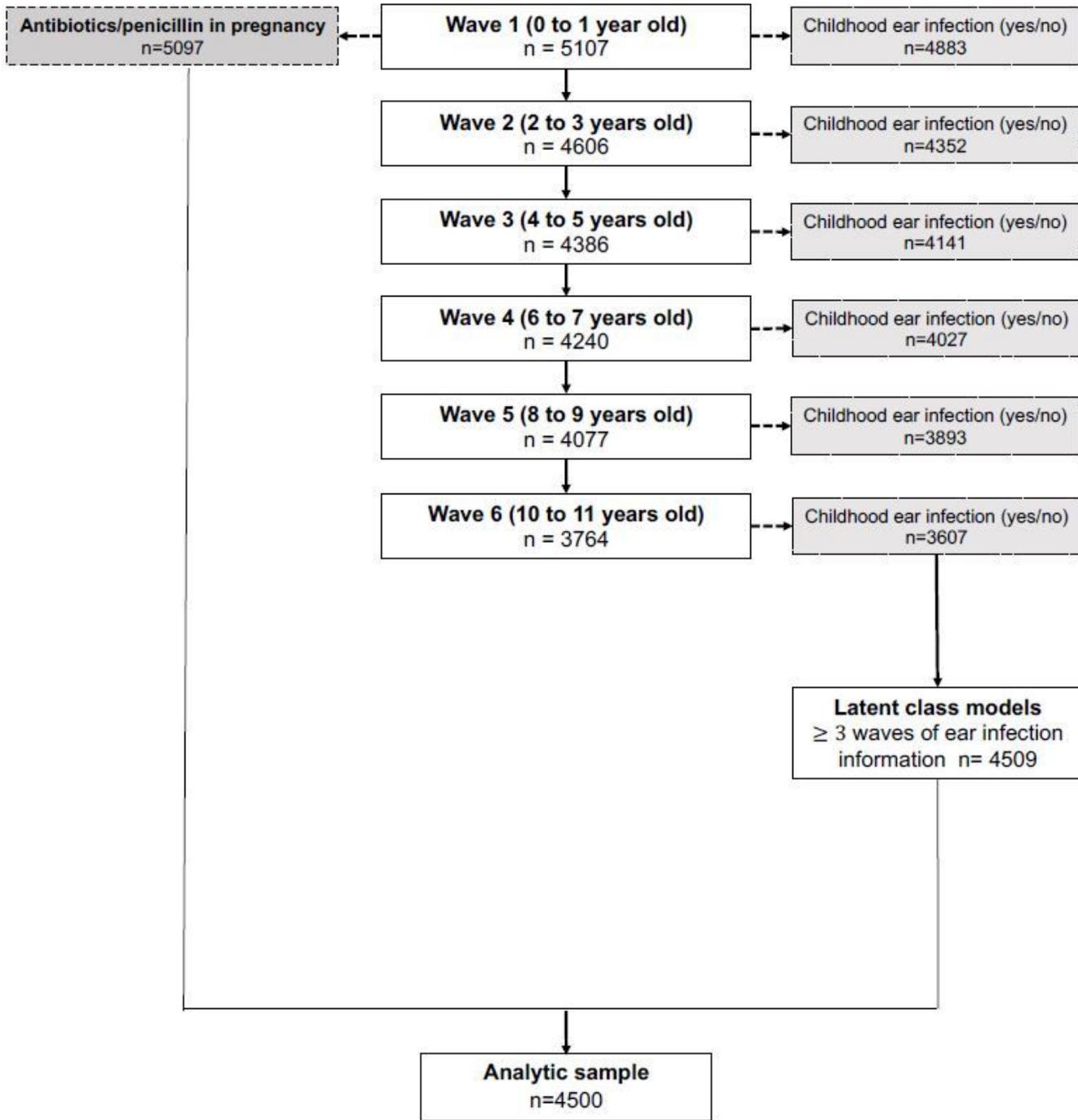


Figure 1

Participants flow chart.

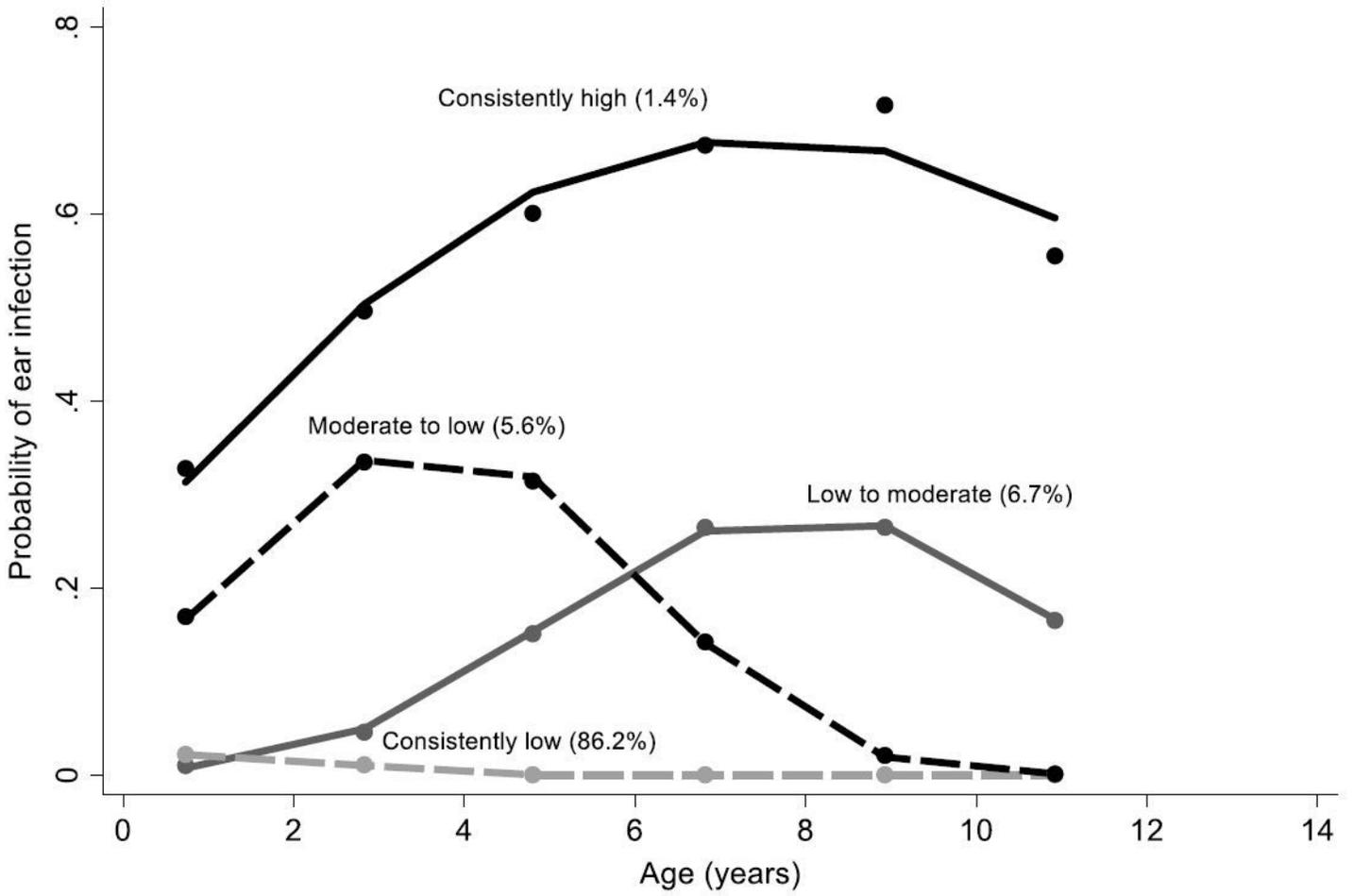


Figure 2

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

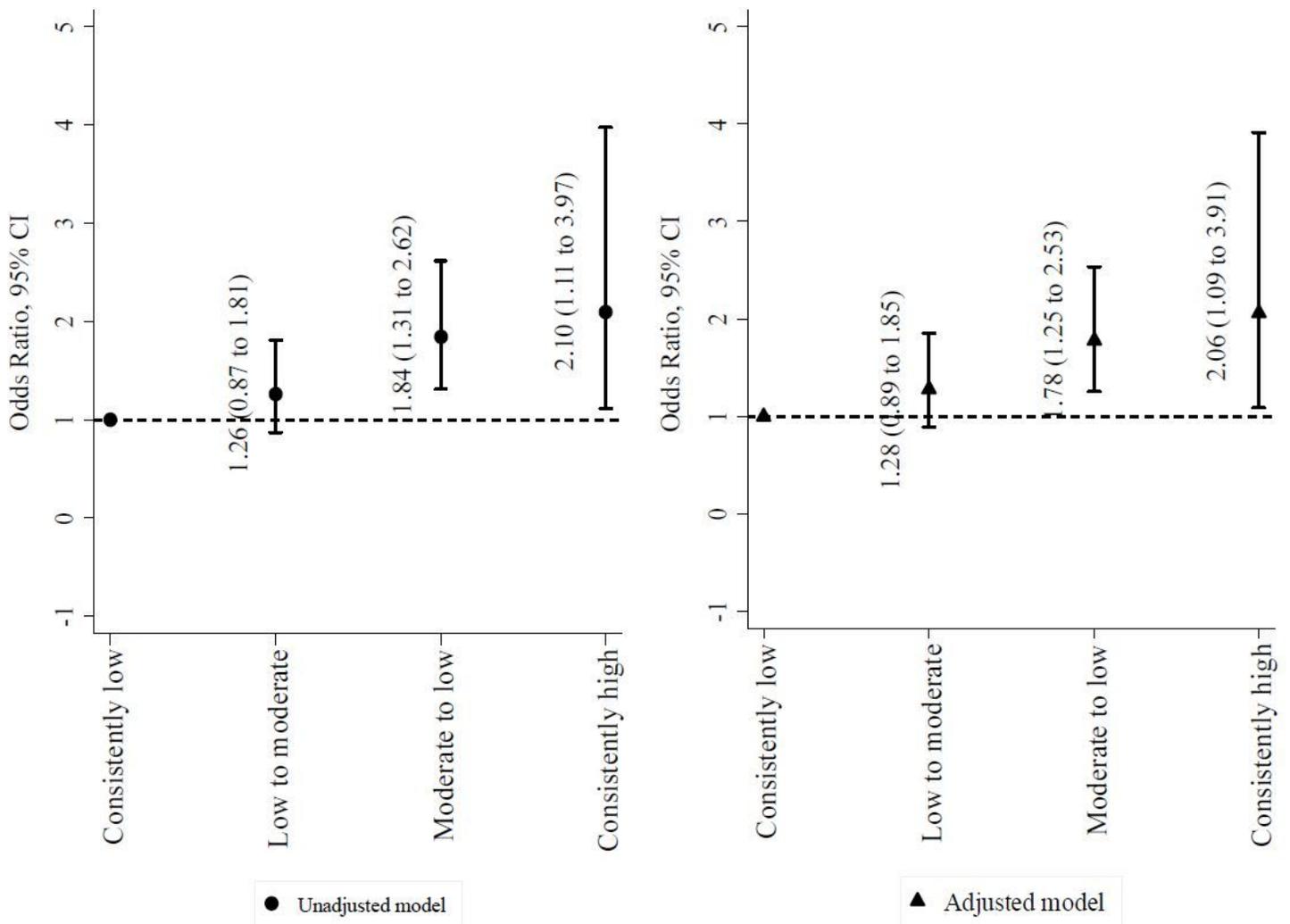


Figure 3

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

Supplementary Files

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