Antibiotic exposure during pregnancy and childhood asthma: a national birth cohort study investigating timing of exposure and mode of delivery

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ABSTRACT

Objective To investigate whether antibiotic exposure during pregnancy was associated with childhood asthma and if this relationship was conditional on timing of exposure and mode of delivery.

Design A cohort study using multivariable logistic regression models adjusting for a priori defined confounders. Pregnant women were recruited from 1996 to 2002.

Setting The Danish National Birth Cohort.

Patients Of the 96 832 children in the cohort, 32 651 children were included in the study population.

Main outcome measure Parent-reported childhood asthma at 11 years.

Results A total of 5522 (17%) children were born to mothers exposed to antibiotics during pregnancy. In adjusted analyses, children born to exposed mothers had higher odds of asthma (OR 1.14, 95% CI 1.05 to 1.24). There was no association with antibiotic exposure in the first trimester (OR 1.02, 95% CI 0.83 to 1.26), but higher odds were observed for antibiotic exposure in the second to third trimester (OR 1.17, 95% CI 1.06 to 1.28), compared with unexposed children. The overall association between antibiotics during pregnancy and childhood asthma was only observed in vaginally born children (OR 1.17, 95% CI 1.07 to 1.28) but not in caesarean section born children (planned caesarean section: OR 0.95, 95% CI 0.66 to 1.37; caesarean emergency: OR 0.96, 95% CI 0.73 to 1.28). In exposed vaginally born children, the odds for childhood asthma requiring treatment during the preceding year were 34% higher (OR 1.34, 95% CI 1.21 to 1.49), compared with unexposed vaginally born children.

Conclusions Antibiotic exposure in mid-to-late pregnancy is associated with higher odds of childhood asthma in vaginally born children. Mode of delivery may modify the association.

What is already known on this topic?

- Antibiotic use during pregnancy has been suggested to increase the risk of asthma in the offspring, but findings remain inconsistent.
- Previous studies differ significantly in research design, sample size, diagnostic methods, timing of exposure in pregnancy and follow-up period.

What this study adds?

- Antibiotic exposure in second to third trimester of pregnancy is associated with higher odds of asthma in vaginally born children but not those born by caesarean section.
- No evidence of association is observed for antibiotic exposure in the first trimester of pregnancy.
- Mode of delivery appears to modify the association between antibiotic exposure during pregnancy and childhood asthma.

INTRODUCTION

In Denmark, as elsewhere, antibiotic use in pregnancy is increasing.[1 2] A large Danish study estimated that 37% of all infants born in 2010 were exposed to systemic antibiotic use during pregnancy.[1] While maternal antibiotics during pregnancy treat and prevent infections in both mother and fetus,[3–5] potential adverse effects are of considerable concern. Studies have reported associations with adverse outcomes in the offspring later in life,[5–11] including asthma.[12–14]

These outcomes have been suggested to be mediated in part by the effects of antibiotics on the maternal microbiome, which largely determines the initial composition of the infant microbiome.[15] This initial infant microbiome contributes to immune development and is increasingly recognised as a predictor of disease risk in the offspring,[16] but the specific mechanisms underlying prenatal antibiotics and long-term effects on immune-related child health outcomes remains uncertain. Mode of delivery may also determine subsequent immune ontogeny in the offspring, as caesarean section born infants acquire their initial microbiome from maternal skin and the immediate environment, rather than the enteric maternally derived microbiome transferred to vaginally born infants.[17 18]

The putative association between antibiotic exposure in pregnancy and childhood asthma has been supported by most[12 14 19–23] but not all studies.[13 24–27] The inconsistency in findings may reflect differences in sample size, study design, identified confounders, exposure/outcome definitions, timing of exposure and follow-up period. We investigated whether antibiotic exposure during pregnancy was associated with childhood asthma and whether this was conditional on timing of

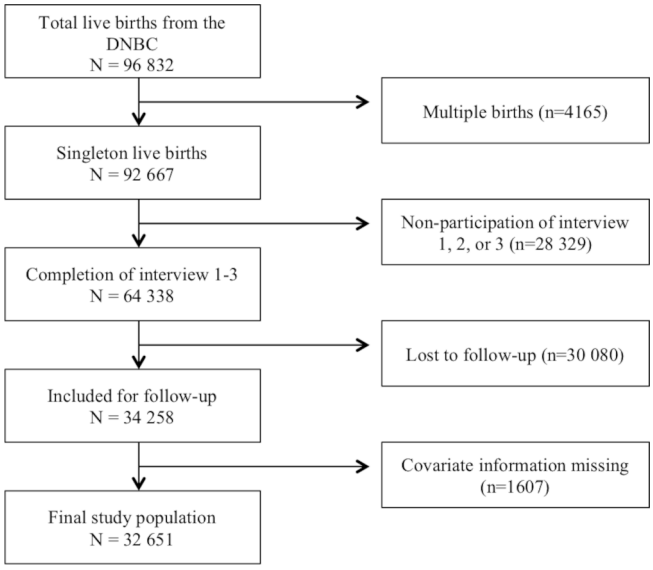

Figure 1 Flow chart of the study population. DNBC, Danish National Birth Cohort.

exposure and mode of delivery. We used detailed data on a large population-based cohort to address some of the previous methodological shortcomings.[28]

METHODS

Study design and data source

Participants were from the Danish National Birth Cohort (DNBC), a longitudinal birth cohort established in 1996 to explore health impacts of prenatal and early life exposures.[29] Pregnant women were recruited to the DNBC by their general practitioner (GP) at the first antenatal visit at gestational week 6–10. Approximately 60% of all Danish GPs participated in the recruitment between 1996 and 2002, and approximately 30% of all Danish pregnant women were included at the time.[30]

Information about maternal characteristics, prenatal exposures and child health was obtained by telephone and online questionnaires. Telephone interviews were performed at three time points: twice during pregnancy (16 and 30 weeks' gestation) and once postnatally with retrospective pregnancy information (6 months postpartum). Follow-up information at 11 years was obtained through online questionnaires completed by mothers.[29]

Study population

The sample population was 96 832 live births from the DNBC. We excluded multiple births (n=4165) and pregnancies where mothers did not complete all baseline interviews (n=64 338). A total of 34 258 (37% of singleton live births) mothers completed the follow-up questionnaire. The final study population included 32 651 singleton children with complete data on covariates (figure 1).

Antibiotic exposure during pregnancy

Information on antibiotic exposure during pregnancy was obtained at second and third interview covering before and after 30 weeks' gestation, respectively ('Have you taken any medication against infection or inflammation during pregnancy? E.g. penicillin, sulfa drug, other antibiotics or medicine against fungus?'). Antifungal medication was coded separately. Information on specific gestational week of antibiotic exposure was recorded. Pregnant women were classified as exposed if they indicated taking antibiotics at any time during pregnancy. To investigate potential impact of timing of exposure and to account for potential latency in antibiotic induced changes to the maternal microbiome, antibiotic use was analysed as early pregnancy (during first trimester), mid-to-late pregnancy (during second to third trimester) and by specific trimester. Pregnant women reporting antibiotics in more than one exposure period in pregnancy were excluded. Pregnant women were classified as unexposed if they had not reported any antibiotics during pregnancy.

Childhood asthma

Information on childhood asthma was obtained from a questionnaire completed by mothers when the child was 11 years old ('Has your child ever had asthma?'). Child's age at the most recent asthma exacerbation and whether they received antiasthma medication in the preceding year was recorded. In sensitivity analyses, two supplementary asthma definitions were included. To differentiate asthma from other respiratory diseases in early childhood with similar symptoms, asthma was defined as 'latest asthma attack at age 5 years or later', and to investigate severity, asthma was defined as 'asthma medication received in the past year'.

Covariates

Potential confounders were identified a priori with data from the DNBC: maternal smoking in pregnancy (yes or no); prepregnancy maternal body mass index (BMI; <18.5, 18.5–24.9, 25–30 and >30 kg/m^2); maternal history of asthma (yes or no); paternal history of asthma (yes or no); parity (0, 1 and >1); and socio-occupational status (high, middle and low).[31] Additional information on sex (male or female), maternal age at delivery (<20, 20–24, 25–29, 30–34 and >34 years), gestational age (<34, 34–36, 37–42 and >42 completed weeks gestation) and mode of delivery (vaginal, planned caesarean section and emergency caesarean section) was obtained from the Danish Medical Birth Registry.[32]

Statistical analyses

Descriptive analyses identified characteristics of the study population. Pearson's χ^2 test compared exposed and unexposed children. Multivariable logistic regression models estimated associations between antibiotic exposure during pregnancy and childhood asthma, including timing of exposure. To assess the impact of gestational age and mode of delivery on the overall association, the main analyses were run in three models with and without further adjustments for gestational age and/or mode of delivery. Stratified analyses and effect modifier analyses evaluated possible effect modification by mode of delivery. Sensitivity analyses explored the effect of different asthma definitions. All associations were estimated using Stata V.13.1.

Ethics statements

Written informed consent was obtained from all DNBC participants prior to data collection. Children born into the cohort participated on their mother's consent until age 18 years. Participants could withdraw their data from the cohort at any time (currently <20 mothers and children).[29]

RESULTS

Of the 32 651 studied children, 5522 (17%) were born to mothers who reported antibiotic use during pregnancy (table 1).

Table 1 Characteristics of the study population

		Antibiotic exposure during pregnancy		
	Total	Unexposed	Exposed	P value*
	n (%)	n (%)	n (%)	
All mothers	32 651 (100.0)	27 129 (83.1)	5522 (16.9)	
Sex of child				
Female	16 389 (50.2)	13 634 (50.3)	2755 (49.9)	0.621
Male	16 262 (49.8)	13 495 (49.7)	2767 (50.1)	
Maternal age at birth				
≤19	71 (0.2)	58 (0.2)	13 (0.2)	0.619
20–24	2184 (6.7)	1834 (6.8)	350 (6.3)	
25–29	12 535 (38.4)	10 441 (38.5)	2094 (37.9)	
30–34	12 652 (38.8)	10 490 (38.7)	2162 (39.2)	
≥35	5209 (16.0)	4306 (15.9)	903 (16.4)	
Maternal smoking in pregnancy				
No	25 485 (78.1)	21 250 (78.3)	4235 (76.7)	0.007
Yes	7166 (22.0)	5879 (21.7)	1287 (23.3)	
Maternal BMI before pregnancy				
Underweight (<18.5)	1357 (4.2)	1113 (4.1)	244 (4.4)	<0.001
Normal (18.5–24.9)	23 126 (70.8)	19 363 (71.4)	3763 (68.2)	
Overweight (25-30)	5961 (18.3)	4918 (18.1)	1043 (18.9)	
Obese (>30)	2207 (6.8)	1735 (6.4)	472 (8.6)	
Maternal asthma history				
No	29 984 (91.8)	24 999 (92.2)	4985 (90.3)	<0.001
Yes	2667 (8.2)	2130 (7.9)	537 (9.7)	
Paternal asthma history				
No	30 073 (92.1)	24 999 (92.2)	5074 (91.9)	0.511
Yes	2578 (7.9)	2130 (7.9)	448 (8.1)	
Socio-occupational status†				
High	23 490 (71.9)	19 460 (71.7)	4030 (73.0)	0.020
Middle	8311 (25.5)	6979 (25.7)	1332 (24.1)	
Low	850 (2.6)	690 (2.5)	160 (2.9)	
Parity				
0	15 337 (47.0)	12 961 (47.8)	2376 (43.0)	<0.001
1	12 020 (36.8)	9777 (36.0)	2243 (40.6)	
≥2	5294 (16.2)	4391 (16.2)	903 (16.4)	
Gestational age				
Early preterm birth (<34 weeks)	114 (0.4)	112 (0.4)	29 (0.5)	0.015
Late preterm birth (34–36 weeks)	924 (2.8)	734 (2.7)	190 (3.4)	
Normal birth (37–42 weeks)	31 460 (96.4)	26 177 (96.5)	5283 (95.7)	
Postterm birth (>42 weeks)	126 (0.4)	106 (0.4)	20 (0.4)	
Mode of delivery				
Vaginally born	28 083 (86.0)	23 400 (86.3)	4683 (84.8)	0.018
Planned caesarean section born	1819 (5.6)	1485 (5.5)	334 (6.1)	
Emergency caesarean section born	2749 (8.4)	2244 (8.3)	505 (9.2)	
Childhood asthma				
No	28 413 (87.0)	23 695 (87.3)	4718 (85.4)	<0.001
Yes	4238 (13.0)	3434 (12.7)	804 (14.6)	

*P value calculated using χ^2 test.
†'High'=persons with higher education (4 years beyond high school) or in management; 'middle'=skilled workers and persons with middle-range training; 'low'=unskilled workers and the unemployed.
BMI, body mass index.

Compared with unexposed mothers, mothers exposed to antibiotics during pregnancy reported more maternal asthma, smoking during pregnancy, overweight/obesity, were less likely to be primigravidae, but were similar age. During follow-up, 4238 (13%) children had reported asthma. Of these, 804 (15%) had mothers who were exposed to antibiotics during pregnancy. A total of 4568 (14%) children were delivered by caesarean section.

Overall, antibiotic exposure during pregnancy was associated with higher odds of childhood asthma after adjusting for confounders (model 1: OR 1.14, 95% CI 1.05 to 1.24) (table 2). Results were similar with additional adjustment for gestational

Table 2 Crude and adjusted ORs for childhood asthma according to antibiotic exposure during pregnancy

	Total	Unadjusted OR	Model 1*	Model 2†	Model 3‡
	n (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Antibiotic exposure					
No exposure	27 129 (83.1)	1 (reference)	1 (reference)		
Any exposure	5522 (16.9)	1.18 (1.08 to 1.28)	1.14 (1.05 to 1.24)	1.13 (1.04 to 1.23)	1.13 (1.04 to 1.23)
1. Trimester	853 (2.6)	1.05 (0.86 to 1.29)	1.02 (0.83 to 1.26)	1.02 (0.83 to 1.25)	1.02 (0.83 to 1.25)
2. Trimester	1972 (6.0)	1.14 (1.00 to 1.30)	1.12 (0.98 to 1.28)	1.11 (0.97 to 1.27)	1.11 (0.97 to 1.27)
3. Trimester	2035 (6.2)	1.14 (1.00 to 1.30)	1.12 (0.98 to 1.28)	1.11 (0.98 to 1.27)	1.11 (0.98 to 1.27)
2–3. Trimester	4526 (13.9)	1.20 (1.10 to 1.31)	1.17 (1.06 to 1.28)	1.16 (1.06 to 1.27)	1.16 (1.06 to 1.27)

*Adjusted for sex, maternal age, maternal smoking, maternal BMI, maternal asthma, paternal asthma, socio-occupational status and parity.
†Additionally adjusted for gestational age.
‡Additionally adjusted for gestational age and mode of delivery.
BMI, body mass index.

age and mode of delivery (model 3: OR 1.13, 95% CI 1.04 to 1.23). The overall absolute risk difference was 1.9% and number needed to harm (NNH) was 53. The higher odds of childhood asthma were only observed for antibiotic exposure in second to third trimester (OR 1.17, 95% CI 1.06 to 1.28), compared with no exposure. This association persisted in the trimester-specific analysis although with wider CIs (second trimester: OR 1.12, 95% CI 0.98 to 1.28; third trimester: OR 1.12, 95% CI 0.98 to 1.28). No association was observed for exposure in the first trimester (OR 1.02, 95% CI 0.83 to 1.26).

The higher odds of asthma after antibiotic exposure was observed in vaginally born children (OR 1.17, 95% CI 1.07 to 1.28) but not in those born by caesarean section (planned: OR 0.95, 95% CI 0.66 to 1.37; emergency: OR 0.96, 95% CI 0.73 to 1.28) (table 3). Among vaginal births, the absolute risk difference was 2.2% and NNH was 45. There was a weak modifying effect on a multiplicative scale with the joint effect of antibiotic exposure and caesarean section differing from the product of the independent effects (OR 1.09, 95% CI 0.89 to 1.33) (table 4). The odds of asthma following antibiotics in the first trimester were not evident in vaginally born children nor in caesarean section-born children (OR 1.05, 95% CI 0.84 to 1.31; and OR 0.89, 95% CI 0.52 to 1.52, respectively). For antibiotics in second to third trimester, the odds of asthma were evident in vaginally born children (OR 1.22, 95% CI 1.10 to 1.34), but not in caesarean section born children (OR 0.91, 95% CI 0.71 to 1.16).

Higher odds of childhood asthma were observed regardless of asthma definition (figure 2). The corresponding odds when defining asthma by use of asthma medication in the preceding year were OR 1.30 (95% CI 1.18 to 1.43) and by most recent exacerbation ≥5 years were OR 1.21 (95% CI 1.07 to 1.35). Stratified by mode of delivery, significantly higher odds of asthma requiring medication within the preceding year were observed in vaginally born children (OR 1.34, 95% CI 1.21 to 1.49) but essentially unchanged in caesarean section born children (OR 1.06, 95% CI 0.82 to 1.36). Higher odds of asthma attack at age ≥5 years were evident in vaginally born children (OR 1.22, 95% CI 1.08 to 1.38) but not in caesarean section born children (OR 1.11, 95% CI 0.83 to 1.49).

DISCUSSION

Antibiotic exposure in mid-to-late pregnancy was consistently associated with childhood asthma in vaginally born children and the association appeared to be modified by mode of delivery. The highest odds were observed in exposed vaginally born children with asthma that required treatment during the preceding year.

Antibiotic exposure closer to delivery (mid-to-late pregnancy), but not in first trimester, was associated with childhood asthma. Exposure in late first trimester may, however, have similar effects to that of early second trimester. We previously reported a similar relationship between timing of antibiotics in pregnancy and risk of infection in offspring, with a more evident association when exposure was closer to delivery.[16] In other studies, a trimester-specific association has also been suggested, with more significant impact of antibiotics on asthma later in pregnancy.[12 13 23] In a recent meta-analysis of prenatal antibiotic use in each trimester, a positive association was proposed in all trimesters.[27] Our findings suggest that the relationship between antibiotics in pregnancy and childhood asthma may be causal, although confounding by indication remains a possibility.

Our results are in keeping with the hypothesis that effects of antibiotics impact the maternally derived microbiome in vaginally born children and that this may increase the odds of childhood asthma. However, this observational study did not address underlying mechanisms, and this interpretation, while plausible, remains speculative. The effect modifier analysis suggested a modest modifying effect by mode of delivery. The observed

Table 3 Associations between antibiotics during pregnancy and childhood asthma in all, vaginally born and caesarean section born children

			Caesarean section born	
	All children	Vaginally born	Planned	Emergency
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Antibiotic exposure				
No exposure	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Any exposure	1.14 (1.05 to 1.24)	1.17 (1.07 to 1.28)	0.95 (0.66 to 1.37)	0.96 (0.73 to 1.28)

ORs were adjusted for sex, maternal age, maternal smoking, maternal BMI, maternal asthma, paternal asthma, socio-occupational status and parity.
BMI, body mass index.

Table 4 Effect modifier analysis of antibiotic exposure during pregnancy and mode of delivery on childhood asthma

	Antibiotic exposure during pregnancy		P value for effect modification*
	No exposure	Any exposure	
	OR (95% CI)	OR (95% CI)	
Mode of delivery			0.115
Vaginally born	1 (reference)	1.17 (1.07 to 1.28)	
Caesarean section born	1.12 (1.01 to 1.25)	1.09 (0.89 to 1.33)	

ORs were adjusted for sex, maternal age, maternal smoking, maternal BMI, maternal asthma, paternal asthma, socio-occupational status and parity.
*Measure of effect modification on multiplicative scale
BMI, body mass index.

association only in vaginally, but not caesarean section, born children may also be attributed in part to a relative small number of exposed women delivering by caesarean section in our study population. Future prospective studies should address specific underlying mechanisms, particularly the role of the microbiome in immune ontogeny.

Most,[14 19–23] but not all,[13 24 25 27] previous studies of antibiotics in pregnancy and childhood asthma report similar results. Discrepancies may reflect methodological heterogeneity, with variations in follow-up period, study design, sample size and exposure and outcome definitions, particularly in asthma definitions.[28] Mulder *et al*[13] reported no association between the overall use of antibiotics in pregnancy and preschool asthma, performing a prescription-based case–sibling analysis. Örtqvist *et al*[24] performed both a case–sibling analysis and a cohort analysis with no association in the case–sibling analysis, suggesting that associations in the cohort study may reflect confounding by shared familial factors. We attempted to account for shared inherited and environmental factors by adjusting for parental asthma and maternal smoking, but we cannot exclude residual unmeasured confounding, such as paternal/household smoking that we were not able to adjust for.

Several studies have investigated asthma in children <5 years.[2 12 21 22 24] Among young children, diagnosis of asthma is challenging, and similar symptoms from viral-induced wheeze[33] increase the risk of misclassification. Despite these limitations, Lapin *et al*[12] reported a higher risk of doctor-diagnosed asthma

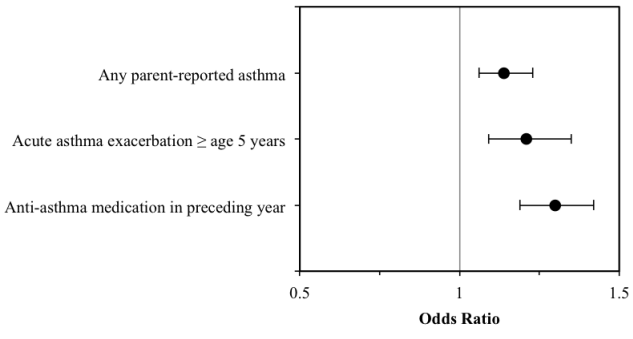

Figure 2 Adjusted ORs for associations between antibiotic exposure during pregnancy and childhood asthma using different asthma definitions. Data points are ORs with 95% CIs adjusted for sex of child, maternal age at delivery, maternal smoking in pregnancy, maternal BMI, maternal asthma, paternal asthma, socio-occupational status and parity. Reference is no exposure of antibiotics during pregnancy. BMI, body mass index.

in children ≤3 years of age following prenatal antibiotic exposure. In our study, the sensitivity analysis using alternative definitions to differentiate asthma from early life respiratory infections did not affect the overall findings, and the estimated association was unlikely to reflect misclassification.

We did not adjust for early life antibiotic exposure because childhood antibiotics lie on the causal pathway rather than acting as a confounder. Viral respiratory infections are common in childhood, are often treated (inappropriately) with antibiotics[34] and are associated with subsequent asthma.[35] Adjusting for antibiotics in early life may underestimate the true effect. For analogous reasons, we did not adjust for breast feeding.

We recognise that maternal infections in pregnancy—rather than or in addition to antibiotics—could affect the association. Studies, including a meta-analysis, indicate that maternal infections in pregnancy increases the risk of childhood asthma[36 37] but acknowledge the inherent difficulties in differentiating infections from their treatment.

Strengths and limitations

The DNBC enables a large study population with extensive covariate data on child and mother. Unlike most studies, our cohort had a relatively long follow-up, but increased evidence of association in those with more severe asthma (recent medication or exacerbation) gives confidence to the diagnosis of asthma at 11 years. Using interviews to assess antibiotic exposure use may be a more robust measure than prescription-based information, as many pregnant women have poor drug compliance, even after purchasing medication.[7] A DNBC study estimated low compliance with prescription drugs dispensed during pregnancy, especially those for local or short-term treatments, such as antibiotics.[38]

We relied solely on maternal reporting for exposure and outcome data. Pregnant women may not recall accurately if and when they took antibiotics; an inherent limitation is the quality of exposure data in the trimester-specific analyses. We attempted to reduce this limitation using repeated standardised questionnaires. Women undergoing caesarean section are given prophylactic antibiotics perinatally, but during most of the study period, the Danish national guidelines were to administer antibiotics after cord clamping[39] and therefore would not affect the infant microbiome. Similarly, maternal recall of asthma may be inconsistent, although the diagnosis of childhood asthma at 11 years is usually unequivocal, so misclassification with viral-induced wheeze is less likely than at younger ages.

A total of 30 080 children were excluded because of loss to follow-up. In a separate analysis, characteristics of mothers who were lost to follow-up were fairly similar to mothers in the study population, although mothers lost to follow-up reported higher antibiotic intake, more smoking, were more overweight/obese, younger and more socially disadvantaged (table 5). These differences were relatively small and key covariates were included in the analyses, but generalisability of findings may be limited. In trimester-specific analyses, the generalisability is affected by the exclusion of women reporting antibiotics in more exposure periods.

We were unable to investigate a dose–response relationship of pregnancy antibiotics and childhood asthma as granular data on antibiotic doses were not available from maternal report. Further studies should examine possible dose–response and aim to reproduce our findings in different settings.

CONCLUSIONS

Antibiotic exposure in mid-to-late pregnancy was associated with childhood asthma by 11 years of age in vaginally but not

Table 5 Characteristics of loss to follow-up at 11 years of age

	Total	Status of loss to follow-up		
	Completed baseline	Lost to follow-up	Completed follow-up	P value*
	n (%)	n (%)	n (%)	
Total	64 338 (100.0)	30 080 (46.8)	34 258 (53.3)	
Antibiotic exposure				
No	52 430 (81.5)	24 132 (80.2)	28 298 (82.6)	<0.001
Yes	11 536 (17.9)	5745 (19.1)	5791 (16.9)	
Missing	372 (0.6)	203 (0.7)	169 (0.5)	
Sex of child				
Female	31 501 (49.0)	14 283 (47.5)	17 218 (50.3)	<0.001
Male	32 837 (51.0)	15 797 (52.5)	17 040 (49.7)	
Maternal age at birth				
≤19	276 (0.4)	196 (0.7)	80 (0.2)	<0.001
20–24	5390 (8.4)	3085 (10.3)	2305 (6.7)	
25–29	24 911 (38.7)	11 832 (39.3)	13 079 (38.2)	
30–34	23 989 (37.3)	10 698 (35.6)	13 291 (38.8)	
≥35	772 (15.2)	4269 (14.2)	5503 (16.1)	
Maternal smoking				
No	47 266 (73.5)	20 807 (69.2)	26 459 (77.2)	<0.001
Yes	16 516 (25.7)	8988 (29.9)	7528 (22.0)	
Missing	556 (0.9)	285 (1.0)	271 (0.8)	
Maternal BMI				
Underweight	2723 (4.2)	1311 (4.4)	1412 (4.1)	<0.001
Normal	42 701 (66.4)	18 807 (62.5)	23 894 (69.8)	
Overweight	12 510 (19.4)	6334 (21.1)	6176 (18.0)	
Obese	5378 (8.4)	3103 (10.3)	2275 (6.6)	
Missing	1026 (1.6)	525 (1.8)	501 (1.5)	
Maternal asthma history				
No	58 530 (91.0)	27 120 (90.2)	31 410 (91.7)	<0.001
Yes	5745 (8.9)	2929 (9.7)	2816 (8.2)	
Missing	63 (0.1)	31 (0.1)	32 (0.1)	
Paternal asthma history				
No	58 731 (91.3)	27 376 (91.0)	31 355 (91.5)	0.006
Yes	5189 (8.1)	2481 (8.3)	2708 (7.9)	
Missing	418 (0.7)	223 (0.7)	195 (0.6)	
Socio-occupational status†				
High	43 008 (66.9)	18 488 (61.5)	24 520 (71.6)	<0.001
Middle	18 757 (29.2)	10 003 (33.3)	8754 (25.6)	
Low	2351 (3.7)	1452 (4.8)	899 (2.6)	
Missing	222 (0.4)	137 (0.5)	85 (0.3)	
Parity				
0	29 857 (46.4)	13 712 (45.6)	16 145 (47.1)	<0.001
1	23 791 (37.0)	11 216 (37.3)	12 575 (36.7)	
≥2	10 653 (16.6)	5130 (17.1)	5523 (16.1)	
Missing	37 (0.1)	22 (0.1)	15 (0.1)	
Gestational age				
Early preterm birth (<34 weeks)	493 (0.8)	256 (0.9)	237 (0.7)	1.112
Late preterm birth (34–36 weeks)	1954 (3.0)	935 (3.1)	1019 (3.0)	
Normal birth (37–42 weeks)	61 447 (95.5)	28 687 (96.4)	32 760 (95.6)	
Postterm birth (>42 weeks)	251 (0.4)	119 (0.4)	132 (0.4)	
Missing	193 (0.3)	83 (0.3)	110 (0.3)	
Mode of delivery				
Vaginally born	54 690 (85.0)	25 308 (84.1)	29 382 (85.8)	<0.001
Planned caesarean section born	3783 (5.9)	1859 (6.2)	1924 (5.6)	
Emergency caesarean section born	5865 (9.1)	2913 (9.7)	2952 (8.6)	

*P value calculated using χ^2 test.
†'High'=persons with higher education (4 years beyond high school) or in management; 'middle'=skilled workers and persons with middle-range training; 'low'=unskilled workers and the unemployed.
BMI, body mass index.

caesarean section born children. Further studies should address the mechanisms underlying this epidemiological observation to identify possible interventions. The profligate use of antibiotics in pregnancy should be balanced against the increasing evidence on adverse long-term health outcomes in the offspring, as well as broader concerns regarding antimicrobial resistance.

Contributors CSU, LHP and BHB designed the study. CSU performed the analyses of the data. All authors contributed to the writing of the paper. BHB supervised the project.

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Data availability statement No data are available. The data from the study are not publicly available due to considerations for privacy and anonymity of the participants. The data were retrieved from the DNBC and were used under licence for the current study. All requests for data from the DNBC must include a research protocol to be submitted to the Danish Data Protection Agency (Datatilsynet).

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