



# Peripartum Antibiotics Exposure and the Risk of Autoimmune and Autism Disorders in the Offspring

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## Abstract

**Background** As the use of antibiotics during the peripartum period increases, the incidence of autoimmune disorders and autism spectrum disorders (ASDs) is also increasing. In this study, we aim to assess if antibiotic exposure during the peripartum period affects the incidence of autoimmune diseases and ASD in the offspring.

**Methods** We identified children (< 18 years of age) born in Olmsted County from January 1, 2003 through December 31, 2012. Offspring with celiac disease (CD), inflammatory bowel disease (IBD), or ASD diagnoses were matched to two controls on birth date, index date, mother's age at delivery, and sex. Data from the mother's medical records were retrieved to determine peripartum antibiotics use.

**Results** A total of 242 cases and 484 matched controls were included in this study. Median age at the last follow-up was 11.3 years (range: 0.5–14.9), 73% were males in both groups. Odds of CD diagnosis was not statistically different between vaginal delivery with antibiotics compared with vaginal delivery with no antibiotics (odds ratio [OR] = 0.76, 95% confidence interval [CI]: 0.32–1.85), similarly in IBD (OR = 2.41, 95% CI: 0.53–10.98) and ASD (OR = 1.00, 95% CI: 0.55–1.79). Preeclampsia or eclampsia was associated with offspring CD (OR = 3.20, 95% CI: 1.05–9.78). Smoking history and diabetes mellitus were associated with offspring ASD (OR = 1.84, 95% CI: 1.22–2.77 and OR = 2.01, 95% CI: 1.03–3.91, respectively).

**Conclusion** In this cohort, we found no statistically significant association between peripartum antibiotics exposure and the development of CD, IBD, or ASD.

## Keywords

- ▶ antibiotics exposure in pregnancy
- ▶ autism
- ▶ autoimmune disease
- ▶ microbiome

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## Introduction

The use of antibiotics during pregnancy has increased over the last two decades. The risk of devastating complications of group B streptococcus (GBS) perinatal infection like sepsis and meningitis has resulted in the Centers for Disease Control and Prevention (CDC) and American College of Obstetricians and Gynecologists (ACOG) recommending the use of prophylaxis antibiotics in GBS+ mothers.<sup>1</sup> The direct implication of antibiotic exposure on the offspring of those mothers is not well studied. Similarly, the risk of autoimmune diseases in offspring is not clear. Incidence of autoimmune disease is increasing worldwide, approximately 1 of every 31 Americans is affected by at least one autoimmune disease.<sup>2</sup>

A recent study from Olmsted County reported a 2.7-fold increase in the incidence of celiac disease (CD) in children.<sup>2</sup> This increase is not limited to CD but extends to other autoimmune and allergy-related disorders such as asthma, eczema, and inflammatory bowel disease (IBD).<sup>3</sup> Additionally, emerging data are showing an increase in autism spectrum disorders (ASDs) prevalence since 2000.<sup>4</sup> Data set from the CDC suggested a threefold increase in ASD prevalence over the last decade with a current prevalence rate of 18.5% (~1 in 54 children).<sup>4</sup>

The underlying etiology for the observed increment in autoimmune diseases and ASD occurrence is not clear. One hypothesis is that factors which can alter the microbiome during peripartum (last week of gestation and/or during delivery) period, such as antibiotics exposure, infections, and the environment, may play a role. Antibiotics can lead to a perturbation in the neonatal gut microbiome, negatively affecting the development of the immune system. This perturbation may result with increased risk of autoimmune diseases and ASD.<sup>5</sup> Two previous reports concluded that cesarean section (C-section) as a mode of delivery is associated with increased risk of CD.<sup>6</sup> On the contrary, two more recent reports found no significant impact of delivery mode on the risk of CD.<sup>7,8</sup> No reports have addressed the peripartum antibiotics exposure effect on the risk of developing the autoimmune diseases. An interesting association has been reported between gastrointestinal problems in children and ASD with a possible role for gut microbiota in regulating behaviors and ASD subsequently.<sup>9</sup>

Before 2010, there was inconsistent use of antibiotics before or after the C-section delivery. In 2010, the ACOG guidelines recommended administering antibiotics before all C-section deliveries. There is no clear evidence that these recommendations lead to changes in the overall increase in the incidence of autoimmune diseases or ASD.<sup>1</sup>

The current study aims to assess the association of peripartum antibiotics use with CD, IBD, and ASD.

## Materials and Methods

### Study Design

This is a retrospective case-control study. The Mayo Clinic and Olmsted Medical Center institutional review boards

approved the study. Rochester Epidemiology Project (REP) is the source of our data. It involves using three medical records from Mayo Clinic and its affiliated hospitals, Olmsted Medical Center and its affiliated hospital, and the Rochester Family Medicine Clinic.

In our study, we assumed that all C-section cases received peripartum antibiotics and case confirmation was performed in 10%. We compared them to vaginal delivery with antibiotics exposure (Vw) and vaginal delivery without antibiotics exposure (Vw/o) groups. Also, knowing that females have a higher incidence of several autoimmune diseases and males have a higher incidence of ASD (more than 4 to 1),<sup>4,10</sup> we investigated the interaction between sex and the peripartum use of antibiotics on the risk of autoimmune diseases and ASD.

We abstracted information about the peripartum and the delivery from the mother's record including antibiotic usage, steroids administration, and complications or stressful events (i.e., premature rupture of membranes, uterine rupture, placenta excessive bleeding, vasa previa, preeclampsia, and eclampsia), as well as smoking status. We collected information for both the cases and their matched controls (two controls per case) from the children's records including family history of autoimmune diseases, and preterm status (< 37 weeks). Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Mayo Clinic.<sup>11</sup>

### Participants

Olmsted County residents born between January 1, 2003 and December 31, 2012, who had a research authorization to use their medical records were included. Potential cases of CD, IBD, or ASD were identified using the International Classification of Diseases (ICD)-9 and ICD-10 codes (see [Appendix](#) [available online only] for the full set of codes). Two physicians (J.A. and A.B.) reviewed the 285 children who had at least one ICD-9/ICD-10 code for CD, IBD, or ASD. Of these children, 248 were verified manually and confirmed to have the diagnoses based on laboratories, images, pathology, and medical documentation from specialists in these conditions. We excluded 6 children, whom their mothers did not give research authorization leaving us with 242 cases. We identified 71 CD cases (142 controls), 13 IBD cases (26 controls), and 163 ASD cases (326 controls). Five children had more than one of these conditions.

### Matching Characteristics and Statistical Analyses

After identifying cases, controls were identified from the remaining births. Each case was matched to two controls, based on the child's birth date, child's date of last follow-up, child's sex, and mother's age at delivery. Any controls where the mother had not given research authorization were replaced with controls that had research authorization. Just like all other cases, those with multiple conditions were matched to two controls. The amount of balance between the cases and controls on matching characteristics was assessed with the standardized difference as this measure is not affected by sample size like a *p*-value. The difference between

the cases and controls was considered negligible when the standardized difference was less than 0.1.

Univariate conditional logistic regression accounting for the matched pairs was used to assess the association of the CD, IBD, and ASD with the pregnancy and delivery characteristics. Due to the paucity of the IBD cases, we were unable to perform formal comparisons for the other variables. Two-tailed *p*-values less than 0.05 were considered statistically significant. To assess the potential differences of mechanism between the sexes, we tested the interaction of sex and antibiotic exposure in the development of ASD and CD.

## Results

Cases and controls were similar on matching factors, all with standardized differences < 0.1 (–Table 1). Five patients had both diagnoses of CD and ASD. Demographic characteristics are summarized in –Table 2. There were no cases of vasa previa or uterine rupture in either group. Median age at last follow-up was 11.3 years (range: 0.5–14.9), 73% were males in both groups. As would be expected, the ASD group had a higher male percentage compared with CD and IBD (85, 49, and 54%, respectively). Among the included 726 births, 62% had Vw/o, 13% had Vw, and 25% had C-section delivery (–Fig. 1). Median mothers' age at the time of delivery was 29 years (range: 16–50). At the time of delivery 8% of the mothers had diabetes mellitus (DM) and 27% were current or ex-smokers.

### Case Comparisons

In the analyses that follow, we explore whether the risk of CD, IBD, or ASD increases with a variety of exposures. Most of the studied variables are dichotomous (e.g., preterm vs.

full-term). The only exposure with multiple categories is Vw/o, Vw, and C-section with Vw/o being the reference category in this calculation of odds ratios (ORs).

### Celiac Disease

We identified 71 children who were diagnosed with CD. Univariate analysis (–Table 3) showed no significant association of the odds of CD when comparing Vw (*n* = 31) and C-section (*n* = 54) to Vw/o (*n* = 131) (OR = 0.76, 95% confidence interval [CI]: 0.32–1.85 and OR = 0.94, 95% CI: 0.48–1.82, respectively). Preeclampsia/eclampsia (*n* = 13) was significantly associated with developing CD in the offspring (OR = 3.20, 95% CI: 1.05–9.78). Though data was limited, in this sample there was no significant association of the odds of CD when we compared preterm (*n* = 21) to full-term children (OR = 0.40, 95% CI: 0.11–1.48). Mothers' history of DM (*n* = 19) and smoking (*n* = 48) were not significantly associated with CD (OR = 0.55, 95% CI: 0.18–1.73 and OR = 0.88, 95% CI: 0.44–1.78, respectively). The interaction between sex and antibiotics in CD was not significant (*p* = 0.988). In CD, the OR for females were 0.94 (95% CI: 0.39–2.23) and for males the OR was 0.95 (95% CI: 0.42–2.11).

### Inflammatory Bowel Disease

We identified 13 children who were diagnosed with IBD. Among them Vw (*n* = 4), Vw/o (*n* = 6), and C-section (*n* = 3). None of these children were born preterm or were children to diabetic mothers. Twenty-three percent of the mothers were current or ex-smokers. We found no significant association between peripartum antibiotics exposure and IBD (OR = 2.41, 95% CI: 0.53–10.98 and OR = 1.74, 95% CI: 0.33–9.12, respectively) (–Table 4).

**Table 1** Matching characteristics between the identified cases and controls

	Cases ( <i>N</i> = 242)	Controls ( <i>N</i> = 484)	Standardized difference <sup>a</sup>
Child's birth year			
Median	2005	2005	0.001
Range	2003–2011	2003–2011	
Child's age at last follow-up			
Mean (SD)	10.8 (2.8)	10.7 (2.8)	0.018
Median (Q1, Q3)	11.5 (8.9, 13.0)	11.2 (9.0, 12.9)	
Range	1.6–14.8	0.5–14.9	
Mother's age at delivery			
Mean (SD)	30.0 (5.9)	29.9 (5.9)	0.001
Median (Q1, Q3)	29.5 (26.3, 33.5)	29.3 (26.1, 33.8)	
Range	15.6–50.2	15.6–49.0	
Child's sex			
Female	66 (27%)	132 (27%)	0.000
Male	176 (73%)	352 (73%)	

Abbreviations: Q, interquartile; SD, standard deviation.

<sup>a</sup>< 0.1 is considered a negligible difference.

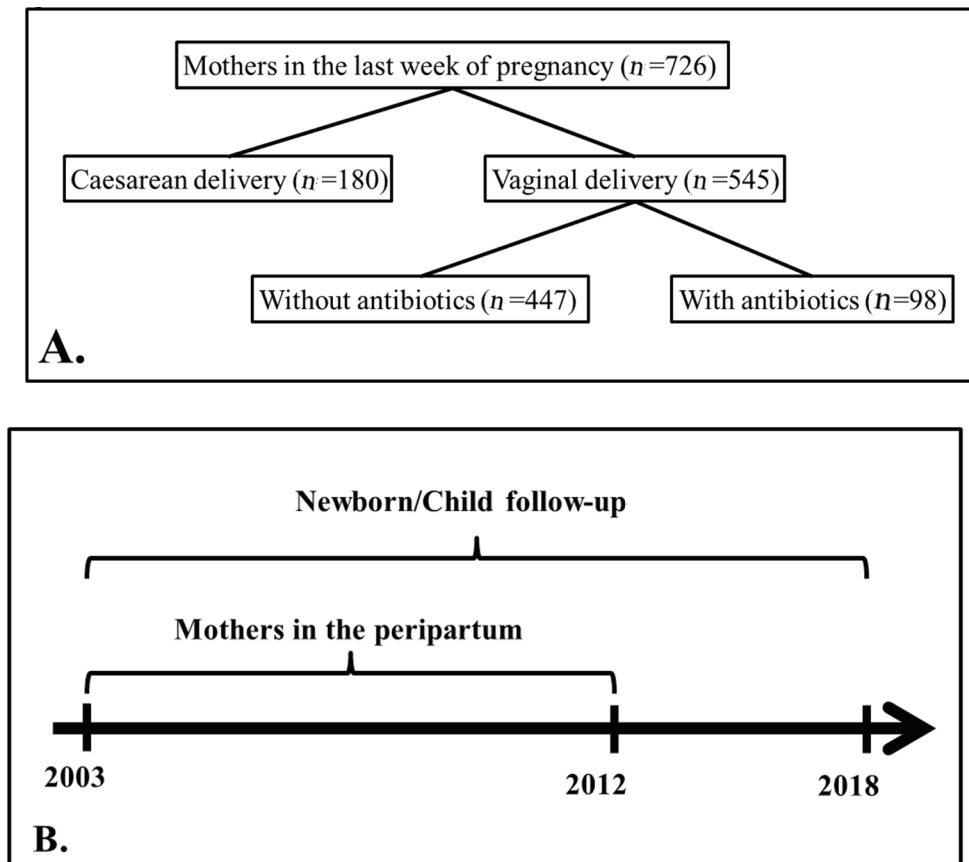
**Table 2** Demographic characteristics of the included population presented as n (%)

	CD (N = 71)	Controls (N = 142)	Total (N = 213)	IBD (N = 13)	Controls (N = 26)	Total (N = 39)	ASD (N = 163)	Controls (N = 326)	Total (N = 489)
Sex, male	34 (49)	68 (49)	102 (49)	7 (54)	14 (54)	21 (54)	139 (85)	278 (85)	417 (85)
Preterm	5 (7)	16 (12)	21 (11)	0 (0)	0 (0)	0 (0)	14 (9)	16 (5)	30 (6)
Family history of IBD	0 (0)	0 (0)	0 (0)	1 (8)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
Family history of CD	1 (1)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Family history of ASD	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (2)	0 (0)	4 (1)
Other family histories <sup>a</sup>	26 (37)	35 (26)	61 (30)	2 (15)	4 (17)	6 (17)	43 (27)	71 (23)	114 (24)
Diabetes mellitus in mother	4 (6)	15 (11)	19 (9)	0 (0)	2 (8)	2 (5)	18 (11)	18 (6)	36 (7)
Mother ever smoked	15 (21)	33 (23)	48 (23)	3 (23)	4 (16)	7 (18)	61 (38)	84 (26)	145 (30)
Steroids administration during pregnancy	3 (4)	6 (4)	9 (4)	1 (8)	1 (4)	2 (5)	14 (9)	14 (4)	28 (6)
PROM	4 (6)	7 (5)	11 (5)	2 (15)	0 (0)	2 (5)	9 (6)	19 (6)	28 (6)
Preeclampsia or eclampsia	8 (11)	5 (4)	13 (6)	1 (8)	1 (4)	2 (5)	9 (6)	15 (5)	24 (5)
Exposure status <sup>b</sup>									
Vw/o	45 (64)	86 (61)	131 (62)	6 (46)	17 (65)	23 (59)	97 (60)	206 (63)	303 (62)
Vw	9 (13)	22 (15)	31 (15)	4 (31)	4 (15)	8 (21)	20 (12)	42 (13)	62 (13)
C-section	16 (23)	34 (24)	54 (24)	3 (23)	5 (19)	8 (21)	46 (28)	78 (24)	124 (25)

Abbreviations: ASD, autism spectrum disorder; CD, celiac disease; C-section, cesarean section; DM, diabetes mellitus; IBD, inflammatory bowel disease; PROM, premature rupture of membranes; Vw/o, vaginal without antibiotics; Vw, vaginal with antibiotics.

<sup>a</sup>Family history of other autoimmune diseases (asthma, type 1 DM, systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis).

<sup>b</sup>per child with the indexed condition. Few children were diagnosed with more than one condition.



**Fig. 1** Study design summary. (A) Flowchart depicts the subgroups of the included mothers per delivery method and per antibiotics exposure for mothers who delivered their babies through the vaginal canal. (The offspring count is matched to the mothers' count per each subgroup.) (B) Overview timeline shows the timeframe of the extracted data of the included mothers who were in the peripartum ranged from 2003 to 2012 and the timeframe of their offspring follow-up ranged from 2003 to 2018 or until they developed one of the conditions of interest.

### Autism Spectrum Disorder

We identified 163 children who were diagnosed with ASD. Neither children in Vw ( $n = 62$ ) nor C-section ( $n = 124$ ) groups had higher odds of ASD than those in the Vw/o group ( $n = 303$ ) (OR = 1.00, 95% CI: 0.55–1.79 and OR = 1.25, 95% CI: 0.81–1.92, respectively) (► [Table 5](#)).

Significant associations were detected between ASD diagnosis in offspring and mothers with DM ( $n = 36$ ) and were current or ex-smokers ( $n = 145$ ) (OR = 2.01, 95% CI: 1.03–3.91 and OR = 1.84, 95% CI: 1.22–2.77, respectively). No significant association was detected between preterm ( $n = 30$ ) or preeclampsia/eclampsia ( $n = 24$ ) and ASD (OR = 2.01, 95% CI: 0.88–4.60 and OR = 1.20, 95% CI: 0.53–2.74, respectively). There was no significant interaction ( $p = 0.512$ ) of sex and antibiotics exposure for the odds of being diagnosed with ASD, the OR for females was 1.59 (95% CI: 0.62–4.06) and 1.12 (95% CI: 0.73–1.74) for males.

### Discussion

Antibiotics exposure during pregnancy is continuously increasing.<sup>1</sup> Since 1980, only 10% out of 640 medications approved by the U.S. Food and Drug Administration have sufficient evidence of safety and effectiveness during pregnancy.<sup>12</sup> Several antibiotics have been proven to cause multiple birth

defects and are associated with different autoimmune diseases in newborns including asthma and obesity.<sup>13</sup> It remains important to treat pregnant women with active infections to prevent any possible fetal harm. However, when it comes to treating mild cases with antibiotics more data about the effect of antibiotics on the offspring is needed. The current study adds to the available important data on the association between peripartum antibiotics exposure and the risk of CD, IBD, and ASD in the offspring. Identifying the role of antibiotics exposure on developing autoimmune diseases like CD and IBD along with ASD will guide the discussion between the treating provider and the pregnant women to reach an informed and shared decision about the antibiotic use.

In this cohort, we found no significant association between the peripartum antibiotic exposure and developing CD, IBD, and ASD which is consistent with two previous studies.<sup>14,15</sup> These older studies used data from questionnaires that put their results at risk of recall bias whereas the strength of our data are that it relied on the electronic medical records to confirm the status of the collected data. Additionally, the two aforementioned reports looked at the antibiotics exposure during the whole period of pregnancy. One of the limitations to this approach is of looking at the antibiotics exposure during the whole period of pregnancy. Early antibiotics exposure may not

**Table 3** Univariate conditional logistic odds ratios for CD

	n (%)	OR (95% CI)	p-Value
Preterm	21 (11)	0.40 (0.11–1.48)	0.17
Diabetes mellitus	19 (9)	0.55 (0.18–1.73)	0.31
Mother ever smoked	48 (23)	0.88 (0.44–1.78)	0.72
Steroids administration during pregnancy	9 (4)	1.00 (0.23–4.35)	1.00
PROM	11 (5)	1.14 (0.33–3.90)	0.83
Preeclampsia or eclampsia	13 (6)	3.20 (1.05–9.78)	0.04
Exposure status			
Vw/o	131 (62)	1 (reference)	
Vw	31 (15)	0.76 (0.32–1.85)	0.55
C-section	54 (24)	0.94 (0.48–1.82)	0.85

Abbreviations: CD, celiac disease; CI, confidence interval; C-section, cesarean section; n, overall total number of events; OR, odds ratio; PROM, premature rupture of membranes; Vw, vaginal with antibiotics; Vw/o, vaginal without antibiotics.

**Table 4** Univariate conditional logistic odds ratios for IBDa

	n (%)	OR (95% CI)	p-Value
Exposure status			
Vw/o	23 (59)	1 (reference)	
Vw	8 (21)	2.41 (0.53–10.98)	0.26
C-section	8 (21)	1.74 (0.33–9.12)	0.51

Abbreviations: CI, confidence interval; C-section, cesarean section; IBD, inflammatory bowel disease; n, overall total number of events; OR, odds ratio; Vw, vaginal with antibiotics; Vw/o, vaginal without antibiotics.

<sup>a</sup>Other variables not calculated due to the small sample size of cases with IBD.

**Table 5** Univariate conditional logistic odds ratios for ASD

	n (%)	OR (95% CI)	p-Value
Preterm	30 (6)	2.01 (0.88–4.60)	0.10
Diabetes mellitus	36 (7)	2.01 (1.03–3.91)	0.04
Mother ever smoked	145 (30)	1.84 (1.22–2.77)	0.003
Steroids administration during pregnancy	28 (6)	2.00 (0.95–4.20)	0.07
PROM	28 (6)	0.95 (0.43–2.09)	0.89
Preeclampsia or eclampsia	24 (5)	1.20 (0.53–2.74)	0.67
Exposure status			
Vw/o	303 (62)	1 (reference)	
Vw	62 (13)	1.00 (0.55–1.79)	0.99
C-section	124 (25)	1.25 (0.81–1.92)	0.31

Abbreviations: ASD, autism spectrum disorder; CI, confidence interval; C-section, cesarean section; n, overall total number of events; OR, odds ratio; PROM, premature rupture of membranes; Vw, vaginal with antibiotic; Vw/o, vaginal without antibiotics.

result in significant lasting effect on the microbiota, as the usual time for bacteria to recover is 1.5 to 6 months which might happen even before the delivery time.<sup>16</sup> In our study, we looked at the exposure during the peripartum period to be able to determine the direct effect of antibiotics on the microbiota<sup>17</sup> and subsequently on the offspring. To our knowledge, this is the first study that investigates the

peripartum exposure and risk of CD, IBD, and ASD development in offspring.

In our study, we found no significant association between C-section delivery and CD which is consistent with previous reports.<sup>6,18</sup> This suggests that newborn exposure to the maternal vaginal flora may play a role in developing the immune system of those children. In a population-based case-control



study, an association was found between elective (not emergency) C-section delivery and CD.<sup>19</sup> This finding suggests that newborn bacterial flora may affect the development of CD. On the other hand, two more recent reports concluded that there is no significant impact of the mode of delivery on the risk of developing CD.<sup>7,8</sup> Our sample on IBD was small but it showed no significant association between IBD and antibiotics exposure or mode of delivery as well. This is consistent with a previous review published in 2014.<sup>20</sup> Our data showed no association between C-section and ASD, while previous systematic review published in 2015 and pooled data from 13 studies showed a moderate positive association between C-section and ASD development (OR = 1.23; 95% CI: 1.07–1.40).<sup>21</sup> Among those studies, only four studies used United States-based populations and the most recent study published in 2009<sup>22</sup> has a smaller number of cases compared with our study which may have affected the conclusion.

Recently, it has been suggested that there is a relative delay in the colonization of the beneficial intestinal bacteria among preterm infants.<sup>23</sup> Based on these findings a population-based case-control study was conducted in 2012 and investigated the risk of CD in preterm infants. The results showed that individuals with preterm birth were less likely to develop CD (OR = 0.87; 95% CI: 0.79–0.95).<sup>19</sup> Our study showed similar findings with OR of 0.40 but was not statistically significant (95% CI: 0.11–1.48); however, our data are limited by the small number of preterm children ( $n = 21$ ) and the missing data.

In our cohort, we found a positive association between preeclampsia/eclampsia and CD in the offspring (OR = 3.20, 95% CI: 1.05–9.78). A recent population-based cohort study found no significant association between severe preeclampsia/eclampsia and CD but their cohort included only 5 children with CD which may have affected the results. The pathophysiology for such an association is not clear, but it is thought that preeclampsia/eclampsia can compromise the blood flow between the placenta and fetus, which may reduce the fetal gut perfusion, which may result in long-term gastrointestinal morbidities.<sup>24</sup>

In our study, we found significant association between maternal smoking status (current or ex-smoker) and the development of ASD in offspring (OR = 1.84; 95% CI: 1.22–2.77). These results are inconsistent with the findings from recent reports that showed no significant association between smoking and ASD.<sup>25,26</sup> Given this inconsistency, we separated the results for current and ex-smokers and found significant association only between ex-smoker mothers and ASD (total  $n = 80$  [17%], OR = 2.25, 95% CI: 1.31–3.85).

### Strengths and Limitations

The current study was established to identify if antibiotic exposure during peripartum is associated with the diseases of interest in their offspring. No other reports addressed the prenatal and intrapartum antibiotics exposure effect on developing CD, IBD, and ASD.

This study took advantage of the population-based medical data available through the REP resources with the ability

to link mothers to their children. This linked medical records system specifically between mothers and their children allowed us access to accurate and detailed clinical and laboratory data over many years, which are not typically available in other databases or research settings. This resource also allowed us to efficiently examine long-term outcomes retrospectively in a well-defined population in a relatively short period, while a prospective study would require years to collect complete data and will be very expensive.

The primary limitation of this study is its retrospective nature. This study relied on the complete and accurate recording of pertinent information in the electronic medical record. Our data provided preliminary information to support the feasibility and importance of studies to identify the causal links between the microbiome and childhood diseases and conditions. Another limitation of our study relates to the average onset of the studied conditions, which varies from younger than 3 years for ASD<sup>27</sup> to around 9 years old to CD<sup>2</sup> and IBD.<sup>28</sup> This could have resulted in missing data of children with less than 5 years' follow-up, especially for CD and IBD conditions. Our sample size was relatively small which reduces our power to detect differences. However, the estimates were small in magnitude and were sometimes in the opposite direction of our expectations although still small. Additionally, the CIs were relatively wide and do not exclude an important association. Therefore, the estimates are imprecise and we cannot be certain in ruling out these associations.

### Conclusion

In this cohort, we found no association between antibiotics exposure during the peripartum period and developing CD, IBD, or ASD.

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