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Maternal depressive symptoms linked to reduced fecal Immunoglobulin A concentrations in infants

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ABSTRACT

Secretory Immunoglobulin A (sIgA) plays a critical role to infant gut mucosal immunity. Delayed IgA production is associated with greater risk of allergic disease. Murine models of stressful events during pregnancy and infancy show alterations in gut immunity and microbial composition in offspring, but little is known about the stress-microbiome-immunity pathways in humans. We investigated differences in infant fecal sIgA concentrations according to the presence of maternal depressive symptoms during and after pregnancy. A subsample of 403 term infants from the Canadian Healthy Infant Longitudinal Development (CHILD) cohort were studied. Their mothers completed the Center of Epidemiologic Studies Depression Scale when enrolled prenatally and again postpartum. Quantified by Immundiagnostik sIgA ELISA kit, sIgA from infant stool was compared across maternal depressive symptom categories using Mann-Whitney U-tests and logistic regression models that controlled for various covariates. Twelve percent of women reported clinically significant depressive symptoms only prenatally, 8.7% had only postpartum symptoms and 9.2% had symptoms both pre and postnatally. Infants born to mothers with pre and postnatal symptoms had significantly lower median sIgA concentrations than those in the reference group (4.4 mg/g feces vs. 6.3 mg/g feces; $p = 0.033$). The odds for sIgA concentrations in the lowest quartile was threefold higher (95% CI: 1.25–7.55) when mothers had pre and postnatal symptoms, after controlling for breastfeeding status, infant age, antibiotics exposure and other covariates. Postnatal symptoms were not associated with fecal sIgA, independently of breastfeeding status. Infants born to mothers with depressive symptoms appear to have lower fecal sIgA concentrations, predisposing them to higher risk for allergic disease.

1. Introduction

Critical to gut mucosal immunity in early life and a marker of immune maturation in infants (Brandtzaeg, 2013), secretory Immunoglobulin A (sIgA) is provided solely through breastmilk and not via the placenta to protect the infant from infection during

Abbreviations: sIgA, secretory Immunoglobulin A; DS, depressive symptoms; CES-D, Center of Epidemiologic Studies Depression scale; ELISA, enzyme-linked immunosorbent assay; SSRI, selective serotonin reuptake inhibitor; CHILD, Canadian Healthy Infant Longitudinal Development study.

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the first few weeks of life until the infant gut begins to produce endogenous sIgA (Battersby and Gibbons, 2013; Walker, 2013). Protective immunity fully develops in the infant within the first year of life, although it can vary between individuals (Gleeson and Cripps, 2004). This immunoglobulin prevents pathogen penetration of the gut mucosa, but also allows for oral tolerance to environmental antigens (Brandtzaeg, 2013). Respiratory and gastrointestinal infections and allergic disorders are more common in persons with IgA-deficiency, pointing to the importance of sIgA in preventing these conditions (Yel, 2010). In addition, sIgA also plays a key role in the establishment of the newborn's gut microbiota composition. Delayed immune maturation and IgA production in infants is associated with increased risk of IgE-related allergic diseases, potentially related to altered infant microbial composition (Kukkonen et al., 2010; Sandin et al., 2011).

A common condition, depression affects approximately 7–12% of women during pregnancy and 7–19% of women after giving birth (Gaynes et al., 2005; Gavin et al., 2005; Bennett et al., 2004; Evans et al., 2012). The majority of women do not seek mental health care for their symptoms of sadness and anxiety, loss of enjoyment and interest, and changes in appetite and sleeping patterns (McGarry et al., 2009; Byatt et al., 2016; Vigod et al., 2016). Many of these symptoms affect the environment in which the infant develops and have the capacity to cause developmental delay in language and cognition (Grace et al., 2003); they can also increase susceptibility to chronic disease. Accumulating epidemiological evidence support links between pre and postnatal maternal distress and the development of asthma and allergy (Klinnert et al., 2001; Kozyrskyj et al., 2008; Guxens et al., 2014; Andersson et al., 2016; van de Loo et al., 2016; Lee et al., 2016), which has been attributed to maternal behaviours such as smoking or reduced breastfeeding, or other factors which affect the infant's immune system, stress biology or risk for allergic diseases (Van Lieshout and Macqueen, 2012; Dreger et al., 2010; Lodge and Dharmage, 2016; Cook-Mills, 2015).

Indeed, distress in the mother can reduce breastfeeding (Bascom and Napolitano, 2015), the main source of sIgA (Bridgman et al., 2016; Walker, 2010), promote smoking which lowers breast milk IgA levels (Bachour et al., 2012) and increase exposure to selective serotonin reuptake inhibitors (SSRIs), a primary treatment for depression, all of which have immunomodulatory effects on the fetus or infant (Vigod et al., 2016; Nguyen et al., 2009; Ho et al., 2015). It can also induce stress in the infant through reduced quality of mother-infant interactions, such as responding appropriately to infant cues or playing with the infant (McLearn et al., 2006). Mother-infant interaction is emerging as a predictor of asthma and atopic diseases (Mantymaa et al., 2003; Yatsenko et al., 2016; Letourneau et al., 2017). Animal models of stressful events during pregnancy and infancy show changes to the maternal vaginal microbiome and to the intestinal microbial composition of offspring (Jasarevic et al., 2015; Galley and Bailey, 2014; Jasarevic et al., 2014). A first report in humans found infants born to mothers with greater stress during pregnancy more likely have gut dysbiosis (Zijlmans et al., 2015), perturbations in gut microbial composition (van Best et al., 2015). Specifically, infants exposed to high maternal stress during gestation had reduced abundance of lactic acid bacteria up to 3.5 months after birth compared with those exposed to low stress levels in utero (Zijlmans et al., 2015). Lactic acid bacteria are considered stimulatory in gut IgA production (Kim et al., 2016). The sole study on intestinal sIgA and stress which was in mice, indicated that chronic restraint stress lowered sIgA concentrations in the small intestine compared to the control group (Jarillo-Luna et al., 2007). Few studies have addressed the stress-microbiome-immunity connections in humans.

Using data from the Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort, the purpose of this study was to determine the association between maternal pre and postnatal depressive symptoms (DS) and infant fecal sIgA concentrations. Our study tested for covariates not previously tested, such as breastfeeding and antidepressant use. We hypothesized that infants born to mothers with both pre and postnatal DS would have lower fecal sIgA concentrations, and that some of the covariates may explain this association.

2. Materials and methods

2.1. Study population

Pregnant women aged 18 and older were recruited from 2009 to 2012 into the CHILD birth cohort (www.childstudy.ca) of over 3000 families currently being followed. Written informed consent was obtained at enrollment. This study was approved by the University of Alberta, University of British Columbia, University of Manitoba, and McMaster University Human Research Ethics Boards. Infants were clinically assessed at birth and at three months. Subbarao et al. (2015) documented the inclusion and exclusion criteria and methodology for this cohort study. Children born with major congenital abnormalities or respiratory distress syndrome, born in a multiple birth, resulting from in vitro fertilization or born before 35 weeks gestation were excluded. A subsample of 403 full-term infants of the CHILD cohort from three study sites, Edmonton, Vancouver and Winnipeg, was investigated in this quantitative study based on fecal sample availability.

2.2. Variables

2.2.1. Depressive symptoms (DS)

Maternal self-reported symptoms of depression were collected at recruitment (mean 27 weeks) and 36 weeks gestation, and at 6 months and 12 months of child age. Pre and postnatal DS were determined using the 20-item Center for Epidemiologic Studies Depression (CES-D) Scale (Radloff, 1977). Mothers reported the frequency of experiencing various depression behaviours, cognitions and affect during the past one week using scores ranging from zero (none of the time) to three (most or all the time; five to seven days). The scores were summed, and sums of 16 and greater are accepted as clinically significant levels of DS.

2.2.2. Fecal sIgA

Fecal secretory IgA was measured in stool samples that were collected during the CHILD 3-month home visits; some visits were delayed beyond 3–4 months. Moraes et al. (2015) documented the detailed stool collection procedure for CHILD. Stool samples (5–10 g) were collected from a freshly soiled diaper using a sterile spatula, divided into aliquots and stored at −80 °C. Freezing of stool has been reported to not have a major impact on the quantification of sIgA (Forrest, 1992).

The sIgA ELISA (enzyme-linked immunosorbent assay) kit from Immundiagnostik was used to measure the amounts of sIgA in mg per gram of feces. After thawing the stool samples, sIgA was extracted with IDK Extract extraction buffer. The stool samples were diluted 1:125 in wash buffer. The diluted patient samples, controls, and 100 µl standards were put into a microtiter plate and washed and incubated at room temperature. After the wells were aspirated and washed, the microtiter plate was tapped on absorbent paper. 100 µl of conjugate was added, and then the samples were incubated at room temperature and shaken on a horizontal mixer. After the final washing step and adding TMB substrate, the samples were incubated in the dark for 10–20 min.

Absorption was determined with an ELISA reader at 450 nm against 620 nm as a reference. The results of the microplate reader were multiplied by the dilution factor of 12,500. Standards with known concentrations provided in the kit were used to create standard curves to determine concentrations.

2.2.3. Potential covariates

Potential covariates were selected from data obtained from the CHILD general cohort questionnaires administered at the prenatal period, at birth and during 3-month visits.

Depression history was collected from mother reports of having depression before pregnancy. Maternal asthma or allergy status was based on self-reports during pregnancy. Information on mothers taking selective serotonin reuptake inhibitors (SSRIs) was obtained from maternal medication questionnaires. Delivery mode information recorded in delivery records or neonatal health charts was categorized as: emergency caesarean, scheduled caesarean and vaginal delivery. Antibiotic exposure determined whether the infant was exposed to antibiotics at any time from birth to 3 months of age (caesarean section, antibiotics during vaginal delivery, antibiotics used before the 3-month visit). Gravida indicated whether the mothers were primigravida or not. Small-for-gestational-age (SGA) was defined as born with birthweight below 10th percentile for corresponding gestational age and gender based on Canadian birthweight for gestational age charts. Breastfeeding status at stool collection indicated whether the infant was exclusively breastfed, partially breastfed or not breastfed. Number of children and pets at home living with the infant before the 3-month visit was extracted from home environment questionnaires. Prenatal smoke exposure was considered positive when the mother smoked during pregnancy or another household member smoked, and postnatal smoke exposure was positive when a member in the household smoked. Infant allergic eczema was determined based on parental reports if there was rash in more than one area except diaper rash (face, inside elbow, ankle, back of knee, wrist/hand, scalp, other) or if there was a diagnosis of atopic dermatitis.

2.3. Statistical analyses

Statistical analyses were conducted using SPSS version 24.0, and figures were created from GraphPad Prism 6. Based on CES-D scores, mothers were classified into one of 4 groups: mothers with scores above the CES-D cut-off only at 27 or 36 weeks gestation were grouped in the Prenatal group, mothers with scores above the cut-off only at 6 or 12 months (N = 2 for infants with 12-month data only) of child age were grouped into the Postnatal group, mothers with higher scores in both pre and postnatal periods were grouped into the Both group, and mothers with scores below the cut-off at both time points were placed in the reference group. The DS groups were mutually exclusive. Due to the skewness of the sIgA data, we compared median concentrations of sIgA in each of the DS groups to the reference group. Mann-Whitney U-tests with sequential Bonferroni correction for three pairs of interest were used to detect median differences in sIgA concentrations. Mann-Whitney tests between the Both and reference categories were compared to an alpha of 0.05 a priori, while Prenatal and Postnatal comparisons to reference were compared to sequentially adjusted critical p-values (prenatal having the most adjustment). Logistic regression modelling was conducted to find DS group associations with the lowest quartile sIgA (<3.23 mg/g feces) vs. the other three quartiles, adjusting for confounding factors that were selected on the 10% rule (Bliss et al., 2012), where if the addition of the covariate caused a percent change in the odds ratio greater than 10%, the covariate was kept in the model.

3. Results

Twelve percent of women in our sample had clinically significant DS only in the prenatal period, 8.7% had elevated symptoms postpartum only and 9.2% had clinically significant symptoms both pre and postnatally (Table 1 and S1). A greater percentage of women with existing depression or being treated with SSRIs, compared to women without this history, reported DS symptoms during pregnancy or postnatally as well (Table 1). The mean of stool collection time was 3.8 months, while the range was 2–8 months. Significantly lower median fecal sIgA concentrations or higher percentages of sIgA values in the lowest quartile were observed in infants partially or not breastfed and among infants living with household pets. In the reference group, 4% of women took SSRIs at any time during the pre and postnatal period, while 18.8% in the Prenatal group, 3.2% in the Postnatal group and 16.7% in the Both group took SSRIs (Table 1). Our subsample was representative of all infants in the three CHILD sites, with only breastfeeding status rates being significantly lower among study infants (Table S1). The increase in sample size of non-breastfed infants gives us sufficient sample size to adjust models for this confounding factor.

Median sIgA concentrations were significantly lower in the infants of the Both group (4.4 mg/g feces, IQR = 2.4–8.0) compared to the reference group (6.3 mg/g feces, IQR = 3.6–12.4, p = 0.033; Fig. 1). Infants in the Prenatal group had median sIgA concentrations of 5.19 (IQR = 2.02–9.78) mg/g feces, and those in the Postnatal group had a median of 5.69 (IQR = 2.62–8.56) mg/g feces; however, these groups did not have significantly lower concentrations than the reference group. The percentage of infants having sIgA concentrations in the lowest quartile (<3.23 mg/g feces) was 20% in the reference group, which was lower than the percentages found in any of the DS groups (35–37%; Fig. 1).

3.1. Median infant fecal sIgA by maternal depressive symptoms, stratified comparisons

Following stratification by breastfeeding status at stool collection, significantly lower sIgA concentrations were seen in not breastfed infants of mothers with both pre and postnatal DS compared to the reference group (p = 0.033; Fig. 2). Median sIgA concentrations did not differ by DS group in partially breastfed infants, but appeared to be lower across the DS groups of exclusively breastfed infants; borderline statistical significance was noted for the Prenatal group. Exclusively breastfed infants had a larger interquartile range in values than infants partially breastfed or not breastfed (Table S2). As shown in Figs. 3 and 4, there were many instances when significantly lower sIgA concentrations were revealed in the Both group following stratification by other covariates. This was observed for infants exposed to antibiotics (p = 0.027), born to a mother with no depression history (p = 0.021) and born to a mother who had asthma or another allergic condition (p = 0.032). Fig. 4 shows significantly lower infant sIgA concentrations in the Postnatal group compared to the reference group when the mother had asthma or allergy during pregnancy (p = 0.041).

3.2. Lowest quartile sIgA by maternal depressive symptoms, crude and adjusted associations

The crude odds ratio (OR) for lowest fecal sIgA quartile was 2.12 (95% CI: 1.02–4.42; Fig. 5) for the Both DS group, indicating that infant exposure to maternal DS during the pre- and postnatal periods elevated the likelihood of low fecal sIgA concentrations by 2-fold when compared to infants of mothers with few DS symptoms. In the same crude model, the OR for the Prenatal DS group was 2.08

Table 1
Infant fecal sIgA concentrations and percentage distribution of potential covariates in relation to maternal depressive symptoms and low sIgA (n = 403).

	Reference (3.9% SSRI use)	Prenatal only (18.8% SSRI use)	Postnatal only (3.2% SSRI use)	Both (16.7% SSRI use)		Fecal sIgA concentrations		Lowest quartile sIgA	
	N (%)	N (%)	N (%)	N (%)	p-value*	median (IQR)	p-value**	N (%)	p-value***
Infant sex									
Male	159 (71)	25 (11.2)	20 (8.9)	20 (8.9)	0.89	6.1 (3.3–12.0)	0.58	54 (24)	0.67
Female	121 (68.4)	24 (13.6)	15 (8.5)	17 (9.6)		5.6 (3.1–10.4)		46 (25.8)	
Pre-pregnancy depression history									
Yes	40 (50.6)	18 (22.8)	10 (12.7)	11 (13.9)	**<0.001**	6.2 (3.3–11.4)	**0.04**	25 (31.6)	0.13
No	236 (74.9)	29 (9.2)	25 (7.9)	25 (7.9)		5.1 (2.3–9.3)		74 (23.4)	
Maternal asthma/allergy during pregnancy									
Yes	175 (69.2)	33 (13)	18 (7.1)	27 (10.7)	0.19	6.0 (3.3–11.0)	0.61	61 (24.1)	0.59
No	101 (71.1)	15 (10.6)	17 (12)	9 (6.3)		5.7 (3.0–11.1)		38 (26.6)	
Delivery mode									
Vaginal	198 (70.2)	30 (10.6)	30 (10.6)	24 (8.5)	0.10[a]	6.1 (3.2–11.2)	0.50	70 (24.6)	0.56
Scheduled caesarean	47 (69.1)	8 (17)	4 (8.5)	3 (6.4)		5.6 (3.5–10.9)		19 (27.9)	
Emergency caesarean	32 (68.1)	11 (16.2)	1 (1.5)	9 (13.2)		5.4 (3.0–10.5)		9 (19.1)	
Antibiotics exposure up to 3 months									
Yes	155 (70.5)	31 (14.1)	16 (7.3)	18 (8.2)	0.28	5.6 (3.1–11.2)	0.28	58 (26.2)	0.43
No	120 (70.6)	15 (8.8)	18 (10.6)	17 (10)		6.1 (3.3–12.0)		39 (22.8)	
Gravida									
Primigravida	112 (73.7)	19 (12.5)	12 (7.9)	9 (5.9)	0.32	5.1 (2.9–10.0)	0.08	43 (28.3)	0.18
Multigravida	165 (67.3)	30 (12.2)	23 (9.4)	27 (11)		6.4 (3.5–12.1)		55 (22.3)	
Small for gestational age									
Yes	20 (74.1)	4 (14.8)	2 (7.4)	1 (3.7)	0.83[a]	7.5 (4.5–16.0)	0.06	3 (11.1)	0.11[a]
No	256 (69.6)	45 (12.2)	33 (9)	34 (9.2)		5.7 (3.1–10.8)		95 (25.7)	
Prenatal SSRI use									
Yes	5 (27.8)	8 (44.4)	0 (0)	5 (27.8)	**<0.001**[a]	3.6 (2.5–7.0)	0.12	6 (33)	0.42
No	269 (71.9)	40 (10.7)	34 (9.1)	31 (8.3)		6.0 (3.2–11.4)		93 (24.8)	
Postnatal SSRI use									
Yes	10 (43.5)	8 (34.8)	1 (4.3)	4 (17.4)	**<0.01**[a]	4.6 (3.3–7.4)	0.18	6 (26.1)	0.89
No	266 (71.9)	40 (10.8)	31 (8.4)	33 (8.9)		6.0 (3.2–11.5)		92 (24.8)	
Prenatal smoke exposure									
Yes	10 (62.5)	3 (18.8)	2 (12.5)	1 (6.3)	0.15[a]	5.1 (1.8–12.3)	0.39	6 (37.5)	0.24
No	203 (72)	32 (11.3)	26 (9.2)	21 (7.4)		6.0 (3.2–11.1)		69 (24.4)	
Postnatal smoke exposure									
Yes	31 (67.4)	7 (15.2)	2 (4.3)	6 (13)	0.12[a]	4.9 (2.8–9.6)	0.25	14 (30.4)	0.37
No	184 (72.2)	29 (11.4)	25 (9.8)	17 (6.7)		6.1 (3.2–11.5)		62 (24.4)	
Pets at home									
Yes	127 (68.6)	22 (11.9)	13 (7)	23 (12.4)	0.20	5.3 (2.7–10.4)	**0.03**	55 (29.7)	**0.05**
No	151 (70.9)	27 (12.7)	21 (9.9)	14 (6.6)		6.4 (3.7–12.0)		45 (21)	
Children at home									
Yes	135 (71.4)	20 (10.6)	17 (9)	17 (9)	0.79	6.5 (3.6–11.9)	0.11	43 (22.6)	0.34
No	144 (68.9)	29 (13.9)	17 (8.1)	19 (9.1)		5.3 (3.1–10.7)		56 (26.8)	
Breastfeeding status at stool collection									
None	64 (64)	15 (15)	11 (11)	10 (10)	0.30	3.4 (2.0–5.9)	**<0.001**	47 (47)	**<0.001**
Partial	108 (72)	13 (8.7)	16 (10.7)	13 (8.7)		5.5 (3.2–10.0)		39 (26)	
Exclusive	99 (75.6)	15 (11.5)	6 (4.6)	11 (8.4)		10.1 (5.6–16.2)		11 (8.4)	
Infant allergic eczema									
Yes	28 (65.1)	4 (9.3)	4 (9.3)	7 (16.3)	0.36[a]	5.9 (3.4–11.2)	0.84	9 (20.9)	0.55
No	251 (71.1)	44 (12.5)	28 (7.9)	30 (8.5)		5.8 (3.1–11.0)		89 (25.1)	

The bolded p-values were there to emphasize statistical significance with an alpha of 0.05.
* Percent distribution of potential covariates in relation to maternal depressive symptoms. (χ^2)
** Mann-Whitney tests for median differences.
*** Percent distribution of covariates in relation to lowest quartile sIgA concentrations. (χ^2)
[a] Fischer's Exact Test.

(95% CI: 1.08–4.01) and for the Postnatal DS group, it was 2.31 (95% CI: 1.10–4.87).

The final logistic regression model was obtained after the purposeful selection of confounding and clinically significant variables (see Table S3). In this model, the likelihood of having low fecal sIgA concentrations was 3.07 for infants in the Both group, with multiple adjustment for infant age at stool sample collection, breastfeeding status, antibiotics exposure, presence of household pets, maternal gravida status, maternal asthma or allergy during pregnancy and prenatal SSRI use (95% CI: 1.25–7.55; Fig. 5).

There was a 2.44 (95% CI: 1.07–5.57) greater odds of having lowest quartile sIgA when mothers were in the Prenatal group in the same model. However, the infant fecal sIgA association with maternal postnatal DS was lost in the final model, which includes the breastfeeding status variable. Thirty infants had their stool collected at greater than six months; sensitivity analyses indicated that including these infants did not greatly affect our results (Table S4). These infants were included in our final model and we adjusted for infant age at sampling time in this model.

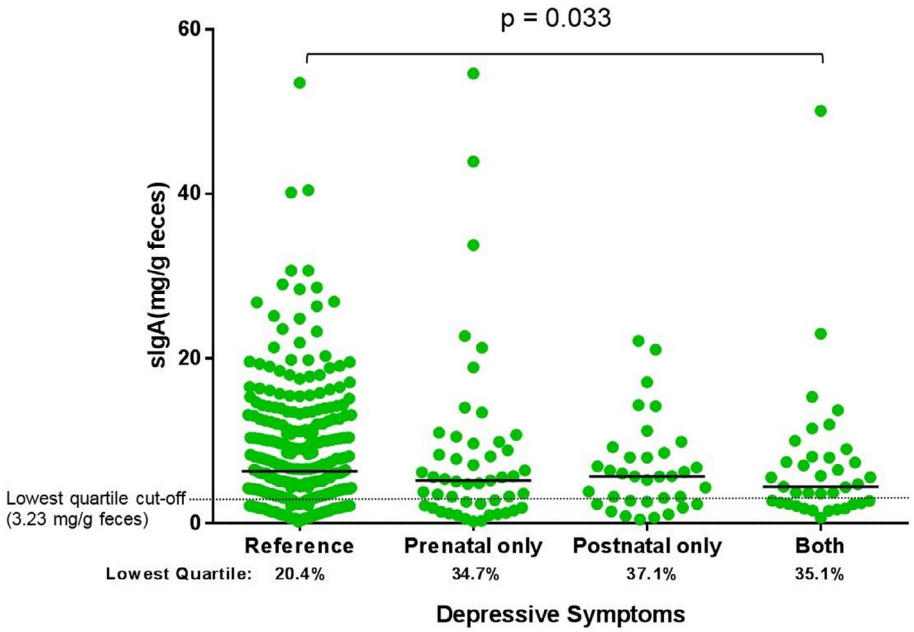

Fig. 1. Infant fecal sIgA concentrations depending on depressive symptoms (DS) status of the mother. Secretory IgA concentrations were significantly lower in the Both group compared to the reference group. Lowest quartile cut-off for sIgA used in logistic regression models was at 3.23 mg/g feces. Percentages of those below the lowest quartile cut-off in the reference group was 20.4%, and for the DS groups, they were 34.7%, 37.1% and 35.1% respectively.

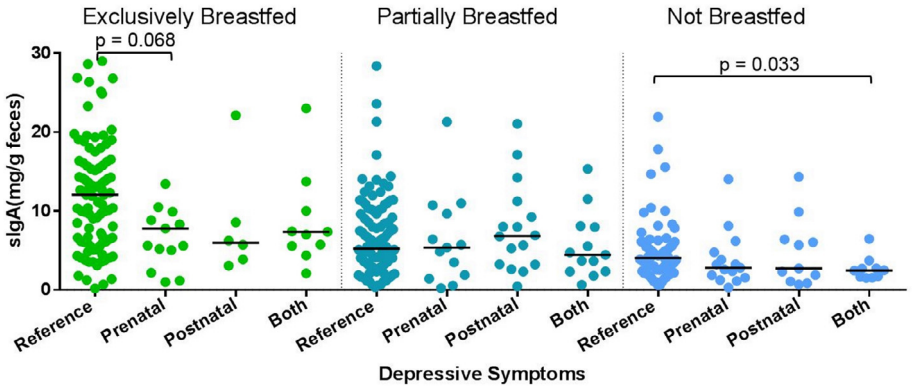

Fig. 2. Secretory IgA concentrations according to breastfeeding status at stool collection time for the reference and maternal depressive symptoms (DS) groups. Exclusively breastfed infants (green) showed borderline significantly lower sIgA concentrations in infants of the Prenatal group compared to the reference group while infants not breastfed (blue) had significantly lower sIgA when in the Both group compared to the reference group. No significant differences were seen in the partially breastfed infants (teal) among DS groups. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

In a subsample of 403 infants from a prospective birth cohort, exposure to clinically significant levels of maternal depressive symptoms throughout the pre and postnatal period, was associated with reduced infant fecal sIgA concentrations in the first few months of life. We found a statistically significant 3-fold higher likelihood of having sIgA concentrations in the lowest quartile for these infants after multiple adjustment for various covariates (95% CI: 1.25–7.55). This significant association is consistent with the sole study which found that repeated restraint stress, applied directly to offspring mice and not dams during pregnancy, lowered total intestinal IgA in mice (Jarillo-Luna et al., 2007). Maternal prenatal stress affects the maternal gut and vaginal microbiome, both of which influence initial microbial colonization of the infant gut (Beijers et al., 2014). Although these animal models of stress are not directly applicable to depression in humans, stress is a common risk factor for maternal depression (Vigod et al., 2016; Norhayati et al., 2015), and both stress and depression, along with anxiety, are presentations of psychological distress. A first report on humans has shown prenatal maternal distress to be associated with gut dysbiosis in infants and the development of gastrointestinal symptoms (eg. diarrhea and gastroenteritis) and allergic symptoms in the first three months of the infant's life (Zijlmans et al., 2015), but whether maternal distress also affects human infant gut immunity has not been previously investigated.

Our results show that maternal depressive symptoms are associated with lowered infant fecal sIgA, a vital component in the first-line defense of the immature immune system and the development of gut microbiota in early life. Infants are exposed to a myriad of pathogenic and commensal microbes after birth, and the reason as to why some newborns are not able to survive this transition is still unknown. Evidence of the important role of sIgA in this transition comes from murine models, which show lasting alterations

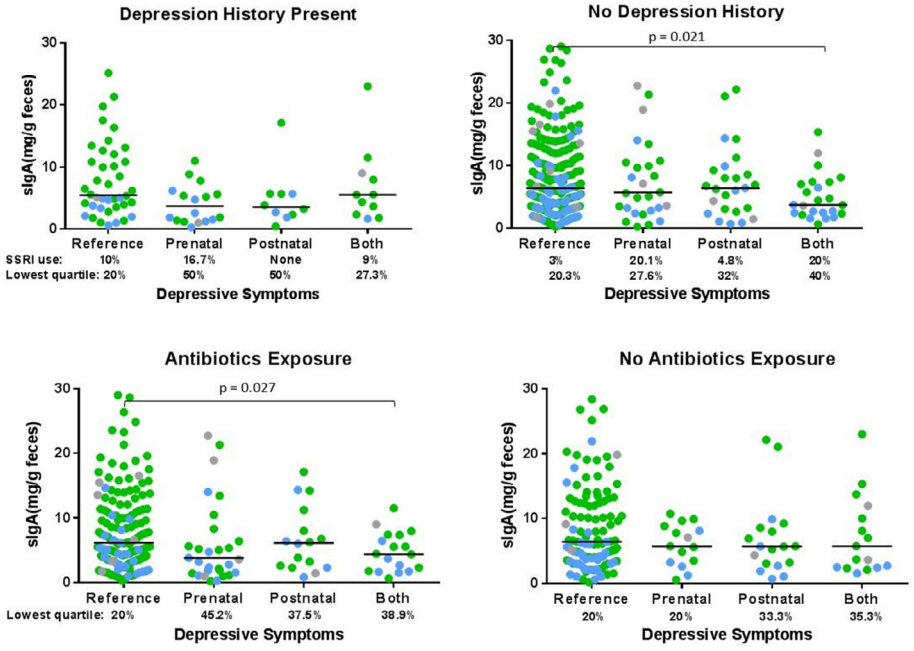

Fig. 3. Secretory IgA concentrations among depressive symptoms groups after stratification for maternal depression history and antibiotics exposure up to three months of infant age. Breastfed (both exclusively and partially) infants are in green and infants not breastfed are in blue (missing breastfeeding status is in gray). 2–10 points were omitted from each graph to enable better visualization of levels in the lower range.

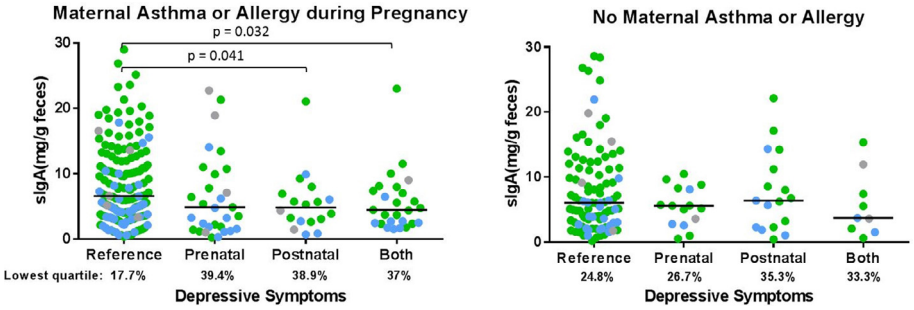

Fig. 4. Infant sIgA concentrations based on maternal depressive symptoms groups after stratification for the presence of maternal asthma or allergy during pregnancy. Green data points indicate breastfed infants at stool collection, and blue indicates infants not breastfed (missing breastfeeding status is in gray). 2–10 points were omitted from each graph to enable better visualization of levels in the lower range. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

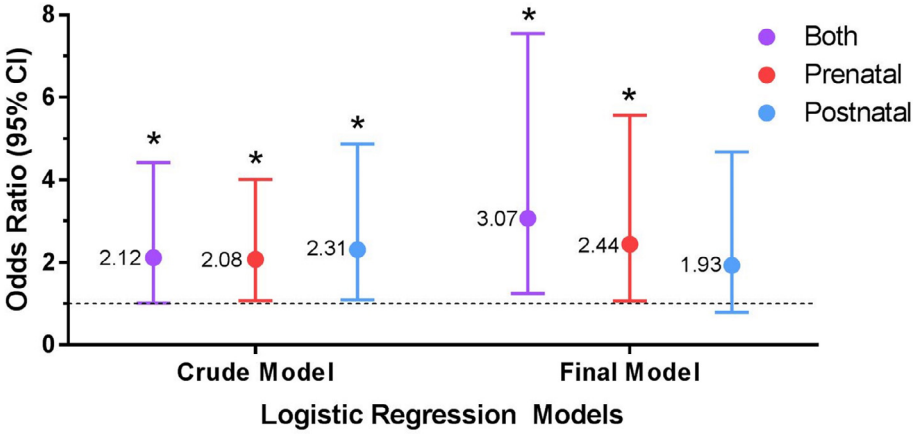

Fig. 5. Crude and final model odds ratios (OR) of infant sIgA concentrations in the lowest quartile for exposure to clinically significant levels of maternal depressive symptoms. Significant OR indicated with an asterisk. Final model controlled for infant age at stool collection, breastfeeding status at stool collection, antibiotics exposure, maternal asthma or allergy during pregnancy, pets, gravida and prenatal SSRI use. Single adjustment models are shown in the Supplementary Table S3.

to gut microbial composition and compromised gut epithelial barrier function in pups born to sIgA-deficient dams (Rogier et al., 2014). In humans, delayed immune maturation and delayed production of serum or fecal IgA in early life has been linked to greater risk of atopic disease in later childhood (Kukkonen et al., 2010; Sandin et al., 2011; Orivuori et al., 2014). Further, differential IgA affinity for gut microbiota may be a factor. In their fecal sIgA of 1-year-old infants, Dzidic et al. (2016) observed lower sIgA binding to *Bacteriodes* genus and *Escherichia* species in children who developed atopy and asthma compared to the control group.

Prenatal and postnatal maternal distress have both been linked to childhood atopic disease (Andersson et al., 2016; van de Loo et al., 2016; Tibosch et al., 2011). Consistent with the reported impact of prenatal maternal distress on the IgA-stimulatory microbes, lactobacilli and bifidobacteria (Zijlmans et al., 2015), prenatal depression was a key feature of associated reductions to infant fecal IgA in our study. Plasma B cells, which are responsible for the release of IgA, appear in Peyer's patches around 12–16 weeks of fetal gestation (Brugman et al., 2015). Murine models have shown a lowering of plasma B cell counts after direct exposure to stress due to the actions of glucocorticoids and catecholamines (Martinez-Carrillo et al., 2011), and these hormones in turn, reduced intestinal IgA (Jarillo-Luna et al., 2007). In humans, elevated corticosterone, seen with maternal prenatal stress, is a strong Th2 cytokine inducer and increases allergic responses in the offspring (Cook-Mills, 2015). Of note, observed associations with fecal sIgA were independent of prenatal SSRI use, and theoretically, the activity of SSRIs on serotonin receptors on B cells (Cloez-Tayarani and Changeux, 2007). Hence, in the event that elevated maternal glucocorticoids or catecholamines lower B cells in the human fetus and newborn infant, this effect could lower or delay IgA production in the developing infant independent of serotonin activity.

The chronicity of maternal prenatal depressive symptoms is less well studied but maternal distress often does not end at birth (Beijers et al., 2014). Our results suggest that continued exposure to maternal depression beyond the time period of fetal development has greater influence on infant gut immunity than exposure to maternal pre or postnatal distress in isolation. They were consistent with Jarillo-Luna's murine model of direct stress exposure (Jarillo-Luna et al., 2007) and independent of maternal postnatal behaviours related to depression in our study, such as maternal smoking and reduced breastfeeding. They were also independent of another postnatal environmental factor that influences mental health and infant gut microbial composition – household pets (McConnell et al., 2011; Tun et al., 2017). We found household pet ownership to be associated with lowered fecal sIgA concentrations, which seems contrary to notions of immune stimulation by environmental microbes (Lambrecht and Hammad, 2017). However, pet exposure have shown to reduce the abundance of certain species of lactobacilli and bifidobacteria (Martin et al., 2016; Azad et al., 2013).

In the absence of prenatal depressive symptoms, breastfeeding status greatly affected the association between postnatal maternal depressive symptoms and infant sIgA concentrations. The odds ratio for postnatal depressive symptoms lost significance with the addition of the breastfeeding status variable, suggesting that reduction of breastmilk intake may explain the very low concentrations of infant sIgA seen with maternal postnatal depressive symptoms. Interventions encouraging breastfeeding in depressed mothers will raise infant fecal IgA concentrations; yet, breastfeeding can be a source of stress and frustration in mothers. Of note, breastfeeding status was controlled in final models yielding significant associations for the 'prenatal' and 'pre and postnatal' groups, and pointing to the potential for maternal depressive symptoms to impact gut immunity in breastfed infants as well. sIgA production in breastmilk is reported to be negatively correlated with anxiety, anger and depression, with stronger correlations found for anxiety than depression (Kawano and Emori, 2015). This influence of maternal anxiety on breastmilk sIgA may explain the large variation in fecal IgA concentrations of exclusively breastfed infants observed in our current and earlier study (Bridgman et al., 2016).

The strengths for our study include the measurement of fecal sIgA in a large number of infants from a general population cohort and the administration of a validated questionnaire for maternal depressive symptoms during pregnancy and postpartum (Radloff, 1977). Although our study included infants with fecal samples collected at 6–8 months, postnatal depressive symptoms were assessed after the time of stool collection in many infants. In women with prenatal depression, two recent studies reported little change in postnatal depressive symptom levels over the range of 4–12 months, or 1–12 months (van der Waerden et al., 2017; McCall-Hosenfeld et al., 2016). Hence, using 6-month or even 12-month symptom data would not have biased findings in the pre and postnatal depression group. On the other hand, due to the low number of women who took SSRIs, adjustment for SSRIs may have been inadequate. Finally, since women were not queried on symptoms of anxiety, which can strongly affect breast milk levels of sIgA (Kawano and Emori, 2015), we were unable to assess this source of distress on infant fecal sIgA. Maternal anxiety may also have contributed to the large variation in sIgA concentrations within breastfed infants and our inability to find statistical significance for lower values observed in the DS-exposed breastfed infants.

In conclusion, we found evidence for an association between perinatal depressive symptoms in women and gut immunity in their offspring within the first few months of life. When mothers experienced depressive symptoms during pregnancy and postpartum, infants were more likely to have lower sIgA concentrations in their gut, even after controlling for various covariates. Based on population-level findings, this study highlights the importance of maternal psychosocial well-being during the pre and postnatal periods in shaping the immune health of newborns.

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Conflicts of interest

None to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bbi.2017.10.007.

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