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Gestational Infections and Obesity: Implications for Intellectual Disability Risk

By

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Submitted in Partial Fulfillment of the Requirements

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Abstract

Maternal body weight, measured as Body Mass Index (BMI) and infection during pregnancy are established risk factors of multiple adverse birth outcomes that are also associated with intellectual disability (ID) in children, but little is known of the interaction of these two factors. This retrospective cohort study sought to explore whether BMI is an effect modifier in the association between maternal infection during pregnancy and ID of the child, and to make comparisons between categories of gestational infection. The study sample (n= 124,047 after exclusion) was derived from Medicaid administrative data. After preliminary analysis of interaction, stratified logistic regression analysis was performed to assess magnitude of the effect modification by BMI. After adjusting for confounders, there was evidence that BMI modified the relationship between infection and ID. Underweight and obese mothers who experienced both a general infection (GI) and a sexually transmitted infection (STI) during pregnancy had the highest odds of having a child with ID, when compared to mothers of the same weight category with no infection (ORs 2.76; 95% CI 1.68 – 4.53 & 1.47; 95% CI 1.13 – 1.91). Underweight mothers who experienced both GI & STI during pregnancy also had higher odds of having a child with ID compared to underweight mothers who had either STI or GI only (ORs 2.41; 95% CI 1.44 - 4.03 & 3.76; 95% CI 1.54 - 9.17). There were no differences between STI and GI categories across the BMI strata. These findings aligned with

existing related literature, and contribute to understanding the complexities of the relationships between infection, maternal BMI, and ID.

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List of Abbreviations

AAIDD.....The American Association of Intellectual and Developmental Disabilities

ASD..... Autism Spectrum Disorder

BMI..... Body Mass Index

CDC ..... Center for Disease Prevention and Control

CP.....Cerebral Palsy

DAG.....Direct Acyclic Graph

DDSN.....Department of Disabilities and Special Needs

DOE .....Department of Education

EMH.....Educable Mentally Handicapped

GI ..... General Infection

ID ..... Intellectual Disability

LBW.....Low Birthweight

PMH.....Profoundly Mentally Handicapped

SDE.....State Department of Education

SGA.....Small for Gestational Age

STI.....Sexually Transmitted Infection

TMH.....Trainable Mentally Handicapped

Chapter 1

Introduction

1.1 Background & Significance

1.1.1 Intellectual Disability

Intellectual disability (ID) is a lifelong condition that affects approximately 1.14% of children in the U.S, and often has a significant impact on the families (1). The American Association of Intellectual and Developmental Disabilities (AAIDD) defines intellectual disability as "disability characterized by significant limitations in both intellectual functioning and in adaptive behavior, which covers many everyday social and practical skills"(2). Diagnosis of ID is often complicated due to factors such as varied signs and symptoms, unpredictable timelines, and stigma. Typically, diagnosis occurs during infancy to early childhood, depending on reports of slow development from parents, and confirmation assessment from a psychologist or physician. Due to the stigma of ID in children, many parents are skeptical to report such problems, which leads to a delay in diagnosis(3). The etiology of ID is still largely unknown; 50-60% of cases are attributed to genetic or chromosomal factors which are rarely preventable outside of family planning strategies(4). However, research has suggested that many cases are due to factors that are modifiable, therefore making some cases preventable(4). Research on the prevention of ID could provide at-risk individuals with essential tools that can be utilized through pre-conceptual counseling and other family planning strategies.

1.1.2. Infection

Infection during pregnancy is a known cause of ID through multiple mechanisms. Inflammation is a common immune-response and is often measured using C-reactive protein in an individual (5). During pregnancy, inflammation has shown to increase the risk of multiple adverse birth outcomes including preterm birth, low birthweight (LBW), neonatal brain injury, and adverse neurobehavioral effects, through the mechanisms of hypoxia or ischemia, which increase the probability of low IQ (5, 6). LBW, often a result of gestational inflammation, is a predictor of adverse birth outcomes such as Cerebral Palsy (CP) and ID. However, multiple studies have shown that even in cases of normal birthweight, gestational infection significantly increases the risk of adverse health outcomes such as CP, which is often closely linked with ID(7). Grether et al. suggested this association was due to mechanisms such as fever and inflammation of the genitourinary system(7). Further evidence has supported this idea of immune-mediated mechanisms contributing to ID etiology. A 2015 retrospective cohort study found a 37% increase (OR = 1.37 95% CI 1.28 – 1.47) in odds of autism spectrum disorders (ASD) in women with infection, with no difference in trimester in which the exposure is identified. Furthermore, the infections with the strongest association with ID were found to be bacterial, respiratory, and genitourinary infections(8). Infections such as syphilis, toxoplasmosis, cytomegalovirus, trichomoniasis, and rubella during pregnancy increases the risk of congenital infection, which is also associated with ID in children(9). There has been substantial research of the associations between infection and adverse birth outcomes that have also been linked to ID, but very little research has been done on the causal pathway between infection and ID, and factors that modify this relationship.

1.1.3. Sexually Transmitted Infection

Sexually transmitted infection (STI) during pregnancy has been a longstanding public health problem. According the Center for Disease Prevention and Control (CDC), STIs such as chlamydia, gonorrhea, and syphilis have significantly increased in women in the last decade(10). Various studies have shown an association between various gestational STIs and ID in children(10-13). STIs could be associated with ID in children through various mechanisms such as immune-mediated responses (inflammation, fever), pre-term birth, or through congenital infection. However, little research has been done on the causal pathway from STI, to ID in children with considerations to potential relationship modifiers.

1.1.4 Obesity

Obesity is also a pro-inflammatory condition that has been steadily increasing in prevalence within the last decade. According to the CDC, a woman is considered obese with a body mass index (BMI) of 30.0 or higher. As of 2015, an estimated 38% of females in the United States are considered obese(14). Prior research has shown a relationship between obesity and ID in children through increased risk for preterm birth and inflammation(15-18). Additionally, there has been evidence of obesity being associated with an increased risk and severity of infection, though evidence has been conflicting (18-20).

Obesity is a chronic risk factor with multiple adverse health implications including inflammation and an individual's susceptibility to various infections while simultaneously increasing inflammation(18). As compared to the chronic inflammation caused by obesity, infections cause an acute immune response, which is typically shorter term, but more severe. Therefore, because of the possible relationship between obesity and infection, it is

possible that obesity might be an effect modifier in the association between maternal infections and ID. This study will assess the possible interaction between obesity and maternal infections among pregnant women. These aims could contribute to our understanding of possible preventable factors of ID and have implications for future prevention.

1.2 Aim & Hypotheses

Aim: To explore whether body mass index is an effect modifier in the association between maternal infection during pregnancy and intellectual disability in the child.

H1: BMI will be an effect modifier in the association between maternal infection and intellectual disability, and this will manifest itself most in the obese category.

H2: Stratifying by BMI, the odds of ID will be significantly different between each infection category, with mothers that experience a sexually transmitted infection during pregnancy having greater odds than mothers who experienced a general infection during pregnancy, and mothers that experienced both a general infection & sexually transmitted infection during pregnancy having greater odds than mothers with either a STI or GI alone.

Chapter 2

Literature Review

2.1 Infection & Pregnancy

When a woman is pregnant, their body undergoes a process that lowers the immune system to prevent adverse outcomes such as fetal distress and rejection instigated by immune response. Because of this "immunological shift", pregnant women are often more susceptible to infection during their gestation(21-23). This produces a paradox of health effects to the fetus; although the lowered immune responses protect it from the system itself, having an infection during pregnancy can increase the harm to the fetus. Infections such as rubella, cytomegalovirus, and coxsackie are known teratogenic infections, and often result in fetal rejection, stillbirth, or growth restriction(21). The mechanisms by which infections instigate adverse birth effects are heavily researched; inflammation and in-utero or congenital infection being the most prominent.

2.2 Infection & Intellectual Disability

Though there has been substantial research done on the association between infection and adverse fetal effects such as preterm birth, there is little available literature on the association between gestational infection and ID. The literature that does exist has shown that gestational infections can increase the risk of intellectual disability in children. A 2015 cohort study found that mothers with an infection during pregnancy had

a 30% increase in risk of autism spectrum disorder, and had a greater chance of ASD with ID, rather than without an ID(8). Specific infections such as streptococcus B, cytomegalovirus, rubella, herpes simplex virus, syphilis, toxoplasmosis, and coxsackie are known to be associated with ID(24, 25). The mechanisms of infection increasing the risk of ID in children are similar to, and often mediated by, adverse fetal outcomes such as low birthweight, hypoxia, and inflammation (26).

2.3 Sexually Transmitted Infection & Pregnancy

Many STIs instigate both vaginal and systemic immune responses, which increases risk of adverse effects such as fetal distress, hypoxia, preterm birth, and low birthweight (27). STIs are also associated with a higher risk of congenital infection due to the potential to pass infection through the placenta and the birth canal. Because of this, early diagnosis and treatment of STIs during pregnancy are of utmost importance to preventing negative outcomes to the fetus(28).

2.4 Sexually Transmitted Infections & Intellectual Disability

Much like general infections, significant research has been performed on the relationship between STI and adverse fetal outcomes. Little research has been done linking gestational STI and ID in children, but what research has been performed has shown evidence of an association. Therefore, there is evidence to believe that STIs would also be associated with ID. A 2001 retrospective cohort study found the risk of child ID in women with UTIs were 16% higher than in women without a UTI(13). Additionally, regardless of trimester, the odds of having a child with id in women diagnosed with trichomoniasis were 1.28 (95% CI 1.12 – 1.46) times the odds of having a child with ID

in women without trichomoniasis, and the odds of having a child with ID in women with trichomoniasis during their second trimester were approximately 3 times the odds of having a child with ID in women without trichomoniasis (11). Although these studies assess trichomoniasis, there has been scant research done assessing STIs as a whole, and research comparing the risk of ID in mothers with STIs and in mothers with general infections is even less prominent. More research is needed to continue to understand the relationship of STIs during pregnancy to ID in children.

2.5 Obesity & Pregnancy

Studies have long identified gestational obesity as a risk factor for multiple adverse birth outcomes such as fetal distress, hypoxia, and preterm birth. This is due to inflammation caused by increased adiposity(29). A 2013 cohort study found obese mothers to be 2.01 (95% CI, 1.66-2.45) times as likely than mothers who were normal weight to experience an extreme preterm birth, which is a leading cause of infant mortality and neurocognitive defects(29). Furthermore, morbidly obese mothers were found to have nearly a three-fold increase (95% CI, 2.28-3.92) in extreme pre-term birth risk (29).

2.6 Obesity & Intellectual Disability

The relationship between obesity and infection is not well understood. There have been several studies on the association between obesity and risk for autism spectrum disorder in infants(16, 30). A 2016 meta-analysis found mothers who were obese during pregnancy to be a pooled 1.47 times as likely to have a child with ASD (16). However, less research has been done on maternal obesity and ID within the last decade, though the

existing research does show evidence of an association. A 2013 study found the odds of having a child with ID in women with morbid obesity were 1.52 (95% CI1.30 – 1.77)) times that of women of normal weight(17). Another study found that after adjusting for confounders, obese mothers were 1.64 HR (1.09–2.45 CI) times as likely to have a baby with ID than mothers who were normal weight (31).

2.7 Obesity & Infection

The relationship between obesity and infection is not well understood. Multiple studies have shown that obese individuals have a greater risk of certain infections such as nosocomial, skin infection, and UTIs (31-33). Additionally, the severity of certain infections has been found to be heightened by obesity, and this results in increased inflammation (18, 31). However, there is conflicting research regarding the role obesity plays in other infections such as pneumonia and influenza (34). Regardless, because both infection and obesity are pro-inflammatory conditions that have been found to increase the risk of ID, it is reasonable to hypothesize that when they are both present in pregnant women there is a multiplicative increase in the risk of ID.

2.8 Inflammation

Inflammation is a necessary physiological response to infection. It manifests itself by fever, swelling, redness, and stiffness. It plays a complex role in pregnancy, as there is expected inflammation in normal pregnancies, and maintaining a healthy level is immensely important as it offers protection from infections (35). However, elevated inflammation can cause multiple adverse effects during pregnancy such as fetal distress, preterm birth, or fetal rejection. To mitigate this, during pregnancy there is a

"immunological shift"; that is, hormones modulate inflammatory immune response, and reduce natural killer cells, macrophages, and inflammatory cytokines while simultaneously producing more anti-inflammatory cytokines (23). This reduces inflammatory immune response to infection, and in turn, reduces the risk of fetal rejection. However, in many cases such as with an infection or in obese women, inflammation levels can increase, therefore endangering the fetus. Such circumstances can result in adverse outcomes such as fetal distress and neurological disorders. A recent study found that mothers with a C-reactive protein level that was at the highest quintile, which suggests extensive inflammation, had a 43% higher risk of a child with autism than mothers with CRP levels of the lowest quintile. (5). In another study, research found that, independent of gestational age, elevated inflammation in the mother has been found to increase the risk of brain injury (36). A preliminary Direct Acyclic Graph (DAG) representing the relationship between gestational infection, obesity, and ID in children can be found in Figure 2.1:

Future studies should assess the implications of the associations between infection and ID, including possible mechanisms and effect modifiers. To understand the etiology of ID, researchers must understand and acknowledge the complexities of the causal pathway between preventable risk factors and ID. This paper aims to contribute to this understanding by exploring the relationship between infection, obesity, and ID.

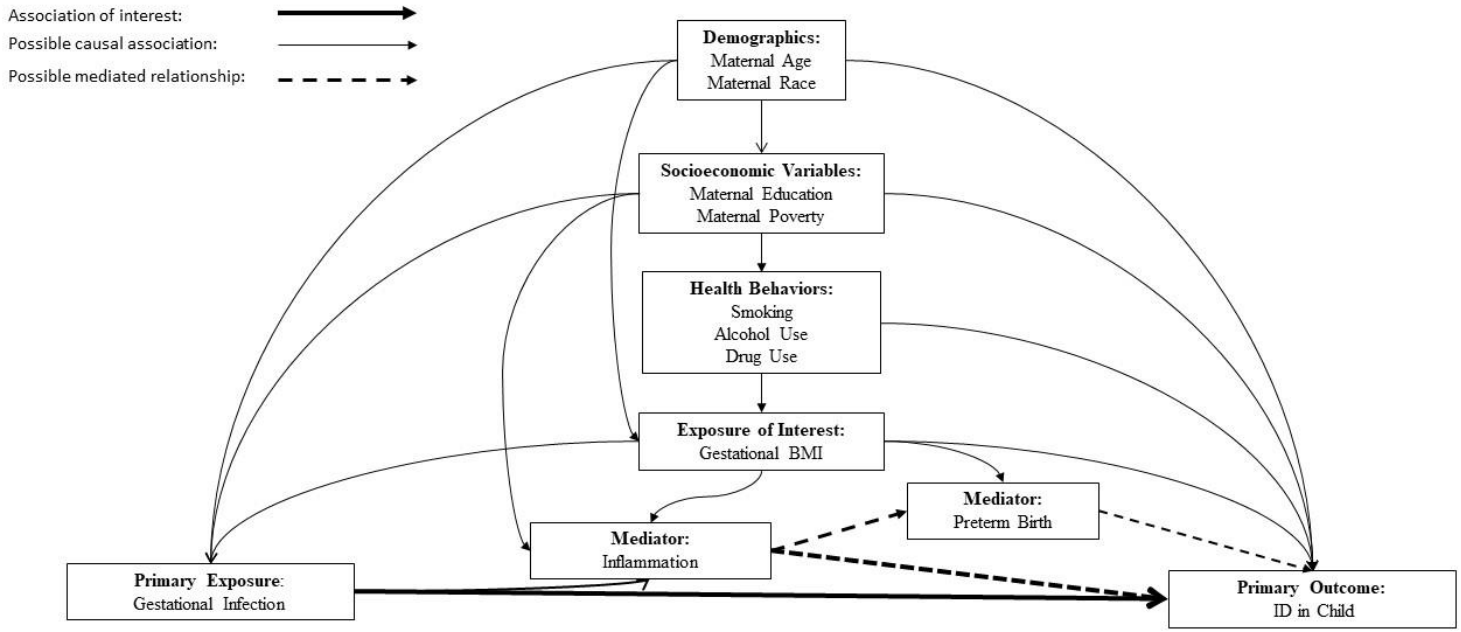

Figure 2.1: Direct Acyclic Graph (DAG) of the Association Between Gestational Infections and Intellectual Disability

Chapter 3

Methods

3.1 Data

We conducted a retrospective cohort study using linked data for pregnant women and their child who were born between the years of 2004 and 2010. Such records included: South Carolina Medicaid records, South Carolina Department of Education (DOE) records, birth certificates, and the South Carolina Department of Disabilities and Special Needs (DDSN). This dataset consists of 124,047 linked maternal and singleton birth records. This study was approved by the Institutional Review Board of the University of South Carolina and is a follow-up study to research performed by Wang et al. which assessed possible prevention of intellectual disability in children(4).

3.2 Data Inclusion & Exclusion Criteria

Data included children of singleton births whose mothers were enrolled in Medicaid during pregnancy and their child remained insured by Medicaid until they were at least three years old, or who were enrolled in public school and were present in the State Department of Education (SDE) files. This study included children who were identified as having an ID or not having an ID by the end of 2013 in either Medicaid, DOE, or DDSN data sets. If a child was identified as having an ID through two or more of the databases, they were included as having an ID in the study. Children diagnosed with known causes of

ID such as an amino acid disorder, deformities of the brain, autosomal deletion, congenital infections, genetic disorders, and fetal alcohol syndrome were excluded.

3.3 Exposures of Interest

Maternal infections were recorded in the Medicaid dataset using ICD-9 codes. These infections included bronchitis, cytomegalovirus, coxsackie, gingivitis, influenza, malaria, mononucleosis, pneumonia, pyelonephritis, rickettsia, rubella, skin infections, tuberculosis, urinary tract infections, chlamydia, gonorrhea, GU infection, syphilis, and trichomonas. Infections were then separated into "STI" and "general infections". Chlamydia, urinary tract infections, gonorrhea, GU infection, syphilis, and trichomonas, and "other STD" were placed into the "STI" category, while bronchitis, cytomegalovirus, coxsackie, gingivitis, influenza, malaria, mononucleosis, pneumonia, pyelonephritis, rickettsia, rubella, skin infections, and tuberculosis were placed in the "General Infection" category. An "Infection Category" variable was added in order to assess the differences in association between Sexually Transmitted Infections and General Infections. Therefore, mothers with neither STI nor general infection fell into Infection Category 1 (no infection), mothers with general infection only were placed in infection category 2 (GI), mothers with only a sexually transmitted infection fell into infection category 3 (STI), and finally, women who experienced both a general infection and sexually transmitted infection during pregnancy fell into infection category 4 (GI & STI).

In order to make inference on the interaction of BMI and infection category, assessment of the continuous variable BMI was performed preliminarily. However, for stratified analysis, the variable was then categorized. BMIs below 18.5 were categorized as underweight, BMIs between 18.5 and 25.0 were categorized as normal weight, BMIs

between 25.0 and 30.0 were categorized as overweight, BMIs above 30.0 were labeled as obese.

3.4 Outcome of Interest

Intellectual disability in children was recorded after follow-up of at least 3 years. A diagnosis within the Medicaid data set required an ICD-9 code of 317, 318, or 319. Within the DOE data set, a diagnosis required either an "educable mentally handicapped" (EMH), "trainable mentally handicapped" (TMH), or "Profoundly mentally handicapped" (PMH) code. These diagnoses were grouped to make the ID variable dichotomous.

3.5 Potential Confounders

Each confounder has had prior research providing evidence of possible association with both STIs and ID as well as Obesity and ID. Confounders that were considered when building the model were small for gestational age (SGA), which was a combination of the child's sex, gestational age, and birthweight, in addition to maternal age, race, education, and receipt of the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) (37-45).

3.6 Statistical Analysis

A mediation analysis was then done for small gestational age, as literature provided evidence to believe it mediated the relationship between Infection Category and ID. The odds of having a child with ID for those with Infection, STI, or obesity were assessed using multiple logistic regression models on SAS 9.4. Descriptive maternal and newborn characteristics were compared between infants with and without ID, and a chi-square test was used to determine statistical significance for unadjusted comparisons.

BMI was first treated continuously in order to efficiently test for interaction. It was noted that BMI proved to be a non-linear variable; therefore, a non-parametric regression was performed to assess the relationship between the odds of ID and BMI. This regression suggested that the association was meaningfully different for women with a BMI less than 19kg/m^2, as compared to women with a larger BMI. To account for this, a linear spline was fitted to the variable to allow the association between BMI and the odds of ID to change at 19 kg/m^2. Once the spline was found significant, an interaction term between the continuous BMI variable, now including the spline, was assessed. Once this term was found significant, BMI was then categorized in order to stratify to produce interpretable odds ratios. The final model assessed is as follows:

ID = INFCAT, BMI, Small Gestational Age, Mother's Age, Mother's Race, Alcohol During Pregnancy, Tobacco During Pregnancy, Drug Use, and Infection*BMI Interaction

Chapter 4

Results

There was a total of 204,282 singleton births between the years of 2004 and 2010. In this study, 42,787 children were excluded that had a known cause of ID, 17,203 were lost to follow up, and 231 only had a single ID diagnosis out of the three linked datasets. As a result, the final study sample included 124,047 mother and children pairs. A flow-chart of all subject exclusions can be found in Figure 4.1, and descriptive data can be found in Table 4.1.

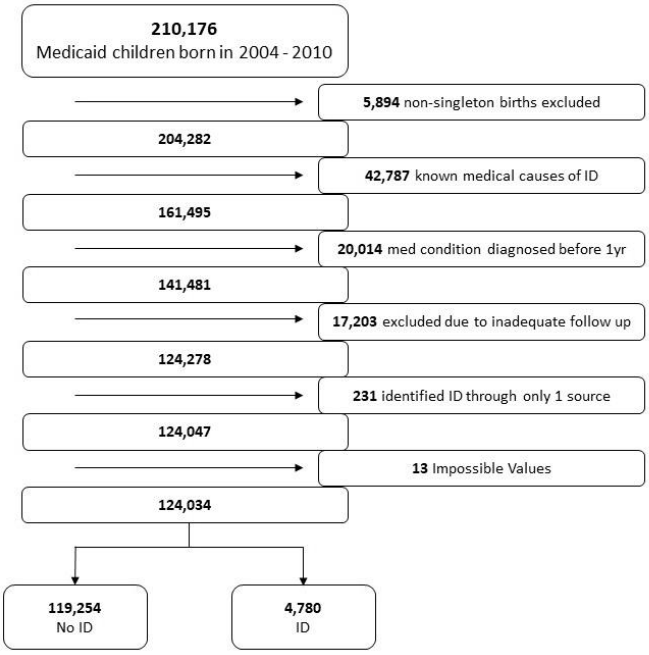

Figure 4.1: Subject Summary

Table 4.1: Study Descriptive Characteristics

Variable	ID (4,781)	No ID (119,266)	P – Value
Mother's Age			
Mean Age	24.32	23.32	<.0001
Mother's Education			<.0001
Less Than Hs Grad	2,031 (42.71%)	43,873 (36.92%)	
Hs Grad & Up	2,724 (57.29%)	74,958 (63.08%)	
Mother's Race			<.0001
Black	2,235 (46.86%)	57,281 (48.05%)	
Other	67 (14.09%)	14,397 (12.08%)	
White	1,863 (39.06%)	47,528 (39.87%)	
WIC			<.0001
No	787 (16.73%)	22,716 (19.37%)	
Yes	3,916 (83.27%)	94,582 (80.63%)	
Mother's BMI			
Mean BMI	28.15	27.43	<.0001
Underweight	405 (8.47%)	8,918 (7.48%)	
Normal Weight	1,616 (33.80%)	45,330 (38.01%)	
Overweight	1,168 (24.44%)	29,783 (24.98%)	
Obese	1,591 (33.28%)	35,224 (29.54%)	
Mother ID			<.0001
No	4,342 (90.84%)	115,034 (96.46%)	
Yes	438 (9.16%)	4,220 (3.54%)	
Baby Birthweight			<.0001
Low Birthweight	371 (7.76%)	7,079 (5.94%)	
Normal Birthweight	4,171 (87.26%)	106,509 (89.31%)	
Heavy Birthweight	238 (4.98%)	5,666 (4.75%)	
Gestational Age			<.0001
<33 Weeks	39 (0.82%)	328 (0.28%)	
33-37 Weeks	363 (7.59%)	7,259 (6.09%)	
37 - 43 Weeks	4,378 (91.59%)	111,667 (93.64%)	
Small for Gestational Age			<.0001
No	3,945 (82.81%)	102,197 (85.79%)	
Yes	819 (17.19%)	16,927 (14.21%)	
Tobacco During Pregnancy			<.0001
No	3,712 (77.66%)	95,615 (80.18%)	
Yes	1,068 (22.34%)	23,639 (19.82%)	
Alcohol During Pregnancy			<.0001
No	4,746 (99.29%)	118,893 (99.70%)	
Yes	34 (0.71%)	361 (0.30%)	
Drugs			<.0001
No	4,523 (94.62%)	116,002 (97.27%)	
Yes	257 (5.38%)	3,252 (2.73%)	
Asthma			<.0001
No	4,169 (87.22%)	108,034 (90.59%)	

Yes	611 (12.78%)	11,220 (9.41%)	
Cerebral Palsy			0.0445
No	4,772 (99.81%)	119,142 (99.91%)	
Yes	9 (0.19%)	112 (0.09%)	
Epilepsy			<.0001
No	60 (1.26%)	2,863 (2.40%)	
Yes	4,720 (98.74%)	116,391 (97.60%)	
Pregnancy Diabetes			0.0027
No	4,471 (93.54%)	112,750 (94.55%)	
Yes	309 (6.46%)	6,504 (5.45%)	
Maternal Hypertension			<.0001
No	3,824 (80.00%)	99,704 (83.61%)	
Yes	956 (20.00%)	19,550 (16.39%)	
Multiple Sclerosis			0.0406
No	4,772 (99.83)	119,160 (99.92%)	
Yes	8 (0.17%)	94 (0.08%)	
Rheumatoid Arthritis			0.1112
No	4,763 (99.64%)	118,968 (99.76%)	
Yes	17 (0.36%)	286 (0.24%)	
Bronchitis			0.0014
No	4,649 (97.26%)	116,791 (97.93%)	
Yes	131 (2.74%)	2463 (2.07%)	
Coxsackie			0.9396
No	4,780 (100.00%)	119,247 (99.99%)	
Yes	0 (0.00%)	7 (0.01%)	
Cytomegalovirus			0.9278
No	4,780 (100.00%)	119,244 (99.99%)	
Yes	0 (0.00%)	10 (0.01%)	
Influenza			0.0791
No	4,733 (99.02%)	118,351 (99.24%)	
Yes	47 (0.98%)	903 (0.76%)	
Gingivitis			0.0142
No	4,766 (99.71%)	119,077 (99.85%)	
Yes	14 (0.29%)	177 (0.15%)	
Malaria			0.934
No	4,780 (100.00%)	119,252 (100.00%)	
Yes	0 (0.00%)	2 (0.00%)	
Mono			0.1679
No	4,778 (99.96%)	119,236 (99.98%)	
Yes	2 (0.04%)	18 (0.02%)	
Pneumonia			0.1443
No	4,762 (99.62%)	118,938 (99.74%)	
Yes	18 (0.38%)	316 (0.26%)	
Rickettsia			0.016
No	4,758 (99.54%)	118,931 (99.73%)	
Yes	22 (0.46%)	323 (0.27%)	

Rubella			0.7902
No	4,779 (99.98%)	119,235 (99.98%)	
Yes	1 (0.02%)	19 (0.02%)	
Skin Infection			0.0379
No	4,648 (97.24%)	116,511 (97.70%)	
Yes	132 (2.76%)	2,743 (2.30%)	
Tuberculosis			0.9146
No	4,780 (100.00%)	119,240 (99.99%)	
Yes	0 (0.00%)	14 (0.01%)	
Infection			<.0001
No	4,452 (93.14%)	112,871 (94.65%)	
Yes	328 (6.86%)	6,383 (5.35%)	
Chlamydia			0.4039
No	4,656 (97.38%)	116,362 (97.57%)	
Yes	125 (2.62%)	2,892 (2.43%)	
Cystitis			0.0002
No	3,680 (76.99%)	94,511 (79.25%)	
Yes	1,100 (23.01%)	24,743 (20.75%)	
Gonorrhea			0.4008
No	4,716 (98.66%)	117,819 (98.80%)	
Yes	64 (1.34%)	1,435 (1.20%)	
G.U. Infection			<.0001
No	3,758 (78.62%)	97,324 (81.61%)	
Yes	1,022 (21.38%)	21,930 (18.39%)	
Other STD			0.0448
No	4,775 (99.90%)	118,946 (99.74%)	
Yes	5 (0.10%)	308 (.03)	
Pyelonephritis			0.4771
No	4,697 (98.26%)	117,334 (98.39%)	
Yes	83 (1.74%)	1,920 (1.61%)	
Syphilis			0.4799
No	4,774 (99.87%)	119,053 (99.83%)	
Yes	6 (0.13%)	201 (0.17%)	
Trichomonas			0.0121
No	4,627 (96.80%)	116,144 (97.39%)	
Yes	153 (3.20%)	3,110 (2.61%)	
STI			<.0001
No	3,163 (66.18%)	82,433 (69.13%)	
Yes	1,617 (33.82%)	36,821 (30.87%)	
Infection Category			<.0001
No Infection	2,989 (62.53%)	78,824 (66.10%)	
General Infection	174 (3.64%)	3,609 (3.03%)	
Sexually Transmitted Infection	1,463 (30.60%)	34,047 (28.55%)	
STI & GI	154 (3.22%)	2,774 (2.33%)	

Means are reported for continuous variables, and frequencies are reported for categorical variables.
P-value is calculated by using chi-squared test.

Because birthweight and gestational age are widely recognized mediators between certain gestational risk factors and ID, a mediation analysis was performed assessing the variables' influence on the relationship between infection category and ID. After mediation assessment was complete, it was concluded that both gestational age and small for gestational age did not significantly mediate the relationship between Infection Category and ID. Results of this analysis can be found in Table 4.2, and the final DAG after analysis can be seen in figure 4.2.

Table 4.2: Mediation Analysis for Small Gestational Age

Variable	**GI**	**STI**	**GI & STI**
OR Without SGA	1.25	1.17	1.44
OR With SGA	1.25	1.17	1.44
Percent Difference	0.00%	0.00%	0.00%
OR Without Gest. Age	1.25	1.17	1.44
OR With Gest. Age	1.24	1.16	1.43
Percent Difference	0.72%	0.77%	0.49%

When selecting a knot for the linear spline regression of the continuous BMI variable, a F-test assessment found the knot to be significant (P-value 0.026). Therefore, the spline was a good fit to the variable, and could be used in the model with an interaction term with Infection Category. An F-test of both the interaction term with BMI and the knot were found significant (P-values .023 and .026, respectively); there is evidence that BMI and infection category do interact. Because of this, in order to assess the effect BMI has on the relationship between gestational infection and ID in children, the analysis was stratified by BMI category.

The results of this analysis can be seen in Table 4.3. Within each stratum, the odds ratios for each infection category change both in magnitude and in significance. There was a 5.17% change in the odds ratios for STIs between the overweight and obese categories. The most substantial change was found between the underweight and obese categories within the GI & STI infection category (87.76%). When comparing individual infection categories, there were no significant differences between STI and GI categories, there was a substantial increase of odds within GI & STI category when comparing to both GI & STI alone. No other differences were found.

Table 4.3: Odds Ratios from Logistic Regression Models of Intellectual Disability for Infection Category Stratified by BMI Category**

	Normal Weight (n = 46,950)		Underweight (n = 9,323)		Overweight (n = 30,956)		Obese (n= 36,818)	
Variable	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
No Infection	**REF**	**REF**	**REF**	**REF**	**REF**	**REF**	**REF**	**REF**
GI	1.26	0.96 - 1.66	0.73	0.34 - 1.58	1.22	0.86 - 1.72	**1.34**	**1.05 - 1.72**
STI	1.12	1.00 - 1.25	1.16	0.92 - 1.47	**1.16**	**1.01 - 1.32**	**1.22**	**1.09 - 1.37**
GI & STI	1.18	0.85 - 1.65	**2.76**	**1.68 - 4.53**	1.32	0.92 - 1.90	**1.47**	**1.13 - 1.91**

Comparing to General Infection

	Normal Weight		Underweight		Overweight		Obese	
Variable	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
GI	**REF**	**REF**	**REF**	**REF**	**REF**	**REF**	**REF**	**REF**
STI	0.89	0.67 - 1.18	1.56	0.72 - 3.39	0.95	0.67 - 1.35	0.90	0.70 - 1.16
GI & STI	0.92	0.61 - 1.41	**3.76**	**1.54 - 9.17**	1.08	0.66 - 1.76	1.09	0.77 - 1.534

Comparing to Sexually Transmitted Infection

	Normal Weight		Underweight		Overweight		Obese	
Variable	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
STI	**REF**	**REF**	**REF**	**REF**	**REF**	**REF**	**REF**	**REF**
GI	1.13	0.85 - 1.50	0.64	0.30 - 1.40	1.05	0.74 - 1.50	1.11	0.86 - 1.43
GI & STI	1.04	0.742 - 1.46	**2.41**	**1.44 - 4.03**	1.14	0.78 - 1.65	1.21	0.92 - 1.575

**Controlling for mother's age, mother's race, alcohol use, tobacco use, drug use, small gestational age

Chapter 5

Discussion

Multiple analyses were run in this study assessing potential interaction and association between maternal infection and obesity and ID in children. Mediation analysis found that SGA was not a mediator in the relationship between maternal infection and ID. After adjusting for multiple confounders, the results found in this study provided evidence that supports the presence of effect modification by BMI; however, this was manifested within underweight mothers rather than obese mothers. Underweight mothers were nearly 3 times as likely to have an intellectually disabled child if they had both a general infection and sexually transmitted infection. In comparison, obese mothers were 1.47 times as likely to birth a child with ID if they had such infections. This nearly 88% difference in stratum-specific odds ratios corroborated the presence of effect modification by BMI. Furthermore, this research provided evidence that partially supported the hypothesis that there was a significant difference between infection categories in their association to ID in children. In underweight mothers, when compared to general and sexually transmitted infections alone, the odds of having a child with ID was greatly increased in mothers that experienced both a GI & STI during pregnancy. However, in every BMI stratum, no significant difference was found between STI and GI categories.

5.1 Stratum Specific Analyses

Within the underweight category, BMI greatly modifies the relationship between infection and ID. Underweight mothers were nearly 3 times as likely to birth a child with

ID if they had both a general infection and sexually transmitted infection. In comparison, obese mothers were 1.47 times as likely to birth a child with ID if they had such infections.

5.2 Comparisons of Infection Categories

Because of the stratified analysis, comparisons of the associations between each infection category and ID could be made. It was hypothesized that mothers with a sexually transmitted infection would have significantly greater odds of having a child with ID as compared to mothers with a general infection. No significant differences in odds of ID were observed in mothers with an STI as compared to mothers with a GI across any of the BMI strata. difference was seen in any BMI category.

Additionally, it was also hypothesized that the odds of having a child with ID in mothers that experience both a GI and an STI during pregnancy would be significantly greater as compared to both general infections and sexually transmitted infections alone. Stratified analysis shows that within underweight women, the presence of both a GI & STI during pregnancy greatly increased the odds of ID in the child when compared to both general infections and sexually transmitted infections alone (OR 3.76 & 2.41, respectively). However, within normal weight, overweight, and obese mothers, no significant differences were found. Additionally, there was no significant difference of increased odds across the BMI strata for STI and general infections.

5.3 The Mechanism: Inflammation

The effect of BMI on the relationship between gestational infection and ID in children is likely due to excess inflammation. A crucial part of the human immunological system, inflammation plays a complex role in pregnancies. Too little inflammation makes a mother, and thus, the baby, more susceptible for infection. However, too much

inflammation can cause severe adverse health outcomes for both the mother and the fetus such as fetal distress and rejection, hypoxia, and neurological outcomes such as ID. Inflammation and BMI have a U-shaped association(47). Underweight individuals experience greater levels of inflammation than those who are normal or overweight. Additionally, underweight mothers are more susceptible to infection, also a pro-inflammatory condition. Therefore, the presence of an infection during the pregnancy of an underweight mother could potentially see inflammation be exponentially increased. This could explain why underweight mothers saw the only difference of odds ratios for mothers who experienced both a GI & STI during their pregnancy. Similarly, obese mothers experience excess inflammation, and the presence of an infection within an obese mother could also cause increased inflammation. This corroborates the significant changes in the odds ratios of infections for underweight and overweight mothers represented in the stratum-specific analyses.

5.4 Strengths & Limitations

The sample size is very large (n = 124,047), and consists of SC mothers covered by Medicaid, which covers pregnant women up to 185% of poverty. Therefore, the study is homogenous, and is representative of the general population of women in SC who are low-income. However, there were several limitations within the study. There was no information on medication within this dataset; and medication taken could disproportionally impact the severity or the impact of the infection in the sample, therefore biasing the result. Additionally, although the presence of infection during pregnancy is noted within this dataset, there is no information on the timeline of infection. Future studies that include this temporal information would allow the researcher to assess the importance

of time of infection in its association to ID in children. Finally, this dataset lists ID as a dichotomous outcome; however, ID is, in reality, a continuous outcome with varying severity. It is possible that certain infections could be differentially associated with mild, moderate, or severe ID. Therefore, future studies should use either the numeric values for the intelligence score, or a categorical variable representing the severity of the ID, rather than the dichotomous outcome used in this study.

5.5 Conclusion

These findings within this retrospective cohort study are in line with previous related literature. This study contributes to understanding the association between maternal infection and ID in children, as well as the effect BMI holds on the relationship. However, further research that thoroughly assesses biological mechanisms, impact of medications, and timeline for infection, continuous measure of maternal BMI, and category of ID, should be done. To further understand the etiology of ID, researchers must understand and acknowledge the complexities of the mechanisms and relationships between infection, obesity, and intellectual disability.

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