FINAL COMPREHENSIVE REPORT

I. Introduction

A. Nature of the research problem

Epilepsy, autism spectrum disorders (ASD), and attention deficit hyperactivity disorder (ADHD) are neurologic conditions that affect a large number of children and can cause significant lifelong disability. While evidence suggests significant genetic components of these conditions, studies have shown that genetic factors do not fully explain the risk.

B. Purpose, scope, and methods of the investigation

The aim of this project is to answer the research question: Do genitourinary infections during pregnancy result in an increased risk for epilepsy, autism spectrum disorders, and attention deficit hyperactivity disorder in children? To answer the research question we used a cohort of over 152,000 Medicaid maternal-child pairs, in a retrospective cohort design. We utilized a retrospective cohort study design, with South Carolina Medicaid data. Data for mothers were linked to that for children. We studied children born from 1996 through 2002, with follow-up through 2008.

C. Nature of the findings

We found that maternal genitourinary (GU) infection was associated with increased risk of epilepsy and ADHD, but not ASD. For epilepsy, there was interaction between infection and maternal epilepsy, such that the effect of infection was significantly greater in women who had a diagnosis of epilepsy themselves. We also conducted analyses of pre-eclampsia as a risk factor, and found pre-eclampsia was associated with significantly greater risk for intellectual disability, ASD, ADHD, and cerebral palsy.

II. Review of the Literature

Definition, Prevalence, and Risk Factors for Epilepsy

"The epilepsies are a heterogeneous collection of neurological conditions and syndromes characterized by recurrent, unprovoked, paroxysmal seizure activity"[1]. The recurrent and unprovoked nature of the seizure activity is an important criterion, as it distinguishes epilepsy from seizures that occur due to an acute systemic or central nervous system condition (febrile seizures, for example). The prevalence of epilepsy in children is generally around 0.5%[2-7]. Between 55 percent and 75 percent of cases of epilepsy have unknown causes[8-14]. The prevalence of epilepsy is substantially higher in children with another neurologic condition (such as mental retardation or cerebral palsy)[8-13].

Known risk factors for epilepsy include congenital malformations and metabolic disorders, history of febrile seizures, seizures within the first 28 days of life, traumatic brain injury, central nervous system (CNS) infections, and family history of seizures[15]. CNS infection (such as meningitis) is believed to account for approximately 3 to 6 percent of cases of epilepsy[8-13]. Two recent studies have identified maternal infection as a risk factor for epilepsy[16-17]. Whitehead[16] linked maternal and child medical records for children born from 1986 through 2001 and found that maternal infection during pregnancy (defined as lower urinary tract infection[UTI], group B streptococcal infection, chronic intrauterine infection, sexually transmitted diseases [STDs], varicella, mycoplasma disease, and bacterial infections) was associated with increased risk (RR = 1.3, 95% CI 1.0 – 1.6). The study did not analyze the different infections separately, stratify by

timing of infection, or account for the possible effects of antimicrobial treatment. Therefore, application to clinical practice is limited.

Sun[17] utilized a structured interview to assess the presence of UTI, vaginal candidiasis, genital herpes, and genital warts. UTI was significantly associated with increased risk of epilepsy for full term and preterm infants, and for infections occurring in all three trimesters of pregnancy. Second trimester vaginal candidiasis was significantly associated with epilepsy in preterm infants. Genital herpes and genital warts were not significant; trichomoniasis, gonorrhea, and Chlamydia were not assessed.

Definition, Prevalence, and Risk Factors for Autism Spectrum Disorders

Autism spectrum disorders (ASD) are characterized by deficits in the domains of social interaction and communication, plus repetitive or stereotypic behavior[18]. Autism represents the most precise diagnosis and requires symptoms in each domain for diagnosis[19]. Asberger's Disorder is another important ASD, which involves impairment in social function and the presence of restricted repetitive and stereotyped patterns of behavior, interests, and activities, resulting in clinically significant impairment in social, occupational, or other important areas of functioning[19]. A final category is pervasive developmental disorder not otherwise specified, which includes children who have significant impairment but do not meet criteria for autism or Asberger's Disorder. The prevalence of autism is approximately 1 to 2 per 1,000, while the combined prevalence of any ASD is approximately 6 per 1,000 children[20]. Autism is strongly heritable, as evidenced by a 69% concordance rate in monozygotic twins[21]. Risk factors include male sex[22], paternal age[23-24], and possibly maternal age[25-27]. Pregnancy related risk factors include uterine bleeding, caesarian section, low birthweight, preterm birth, and low APGAR score[28-31]. An association with maternal cytomegalovirus and rubella infection has been observed[32], and animal studies have demonstrated the potential for the maternal immune response to viral infection to produce autistic-like behavior in offspring[33]. A case control study found that maternal urinary tract infection ($p = .03$) and maternal viral infection ($p = .000$) were significantly more common in mothers of children with autism[34]; however, the study relied on maternal self report. We are aware of no studies investigating prospectively identified maternal GU infections as potential risk factors.

Definition, Prevalence, and Risk Factors for Attention Deficit Hyperactivity Disorder

For a diagnosis of ADHD to be made, the Diagnostic and Statistical Manual of Mental Disorders IV Text Revision (DSM IV)[35] requires the presence of significant symptoms of inattention and/or hyperactivity-impulsivity. Some symptoms must have been present before age 7, and symptoms must be present in two or more different settings. ADHD may be diagnosed as predominantly inattentive type, predominantly hyperactive-impulsive type, or combined type. The DSM IV states the prevalence of ADHD is approximately 3 to 5 percent in school age children[35], but epidemiologic studies have estimated the prevalence at 11 to 16 percent[36]. ADHD is believed to have a genetic component, as evidenced by a higher concordance for clinically diagnosed hyperactivity in monozygotic (51 percent) than dizygotic (33 percent) twins[37]. Males are at greater risk than females[38]. Additional risk factors included low birth weight[39] and maternal tobacco use during pregnancy[40].One case control study found a significant association between severe respiratory infection during pregnancy and ADHD[41], and another found that women of children with autism were significantly more likely to report having had a viral

exanthem during pregnancy[42]**.** We have found no studies investigating maternal GU infections and ADHD.

Maternal GU Infection and Neurologic Impairment

There is a well-known association between maternal TORCH infections and adverse neurologic outcomes in children[43]. There is mounting evidence that non-viral GU infections can be harmful to the fetal brain as well. Leviton and Gilles[44] reported that maternal UTI resulted in increased risk of fetal death. Their explanation for the causal link between maternal UTI and death is related to endotoxin insults to glial cells in the maturing forebrain. Glial cells, destined to become oligodendroglia and to lay down and maintain myelin, are either destroyed (causing necrosis) or transformed (resulting in hypertrophic astrocytes and damaged glia). This process can lead to periventricular leuko-encephalopathy (PVL) and death[44]. Other have added that neurologic injury may also occur by means such as fetal hypoperfusion, or by the initiation of a deleterious inflammatory response in the mother or fetus[45-46]. Infection may also increase the risk of neurologic conditions by increasing the risk of preterm birth.

The association between maternal infection and infant/child outcomes is particularly well established for cerebral palsy (CP)[47]**.** Generally, two approaches have been used to establish the link between infection and CP, one focusing on the documented presence of organisms in the amniotic fluid or chorioamnion and the other on the presence of inflammatory mediators. Both approaches support the premise that infection is a significant cause of CP. An association between intrauterine infection/inflammation and CP has been demonstrated for both term and pre-term[48-52] infants, though not necessarily for very preterm infants (<32 weeks of gestation)[53-54], implying that gestational age remains an important consideration when examining the impact of maternal infection on neurologic morbidity in children.

McDermott et al found that maternal UTI was significantly associated with mental retardation/developmental delay in children, but only when untreated[55]. Mann, McDermott, et al similarly found that trichomoniasis in the second half of pregnancy is associated with increased risk of MR, especially if not appropriately treated[56].

III. Study Design and Methods

A. Study design

We utilized a retrospective cohort study design.

B. Population studied

The study population consisted of children whose births were paid for by South Carolina Medicaid and their mothers. The study included births from 1996 through 2002, with child follow-up through 2008.

C. Sample selection

All Medicaid births from 1996 through 2002 were included initially. Children with diagnosed chromosomal or genetic abnormalities, brain injuries, central nervous infections, and other high risk infections were excluded, as were multiple gestations.

D. Instruments used

We utilized billing and other administrative data.

E. Statistical techniques employed

For the majority of the analyses, we utilized logistic regression. For most analyses, logistic regression was performed using generalized estimating equations (PROC GENMOD in SAS 9.1) with the binomial distribution and the logit link function. The exchangeable structure was used to model the correlation of the responses from the subjects. In some cases we limited the sample to only the first birth during the study period, and used PROC LOGISTIC.

We controlled for potential confounders using multiple regression techniques. We generally treated gestational age or birth weight (a proxy for gestational age that also captures impaired fetal growth) as potential mediators. That is, we considered that infection (and pre-eclampsia, for the additional analyses) could increase the risk of adverse neurologic outcomes by way of increased risk of preterm birth or low birth weight. Therefore, we typically did not control for gestational age or birth weight in the initial modeling, but added it in a later step to examine its effect on the initial association.

Our initial plan was to investigate the role of antibiotic treatment for infection as a risk factor for infection. However, we found that many women received multiple antibiotics following an infection diagnosis, but these drugs often did not follow recommendations for treating the specific infection diagnosed. Therefore it was difficult to classify these women accurately as 'treated' or 'untreated.' We also noted that for many of the specific infections, cell sizes were fairly small, and dividing the cases into treated and untreated women produced imprecise estimates of treatment effects. Finally, we found that many women had multiple infections during pregnancy, some of which appeared to have been adequately treated and some of which were not. Due to all these problems we decided to abandon our goal of testing the effect of treatment and focus instead on the associations between infection (and, later, pre-eclampsia) and childhood neurocognitive conditions.

IV. Detailed Findings

Epilepsy

For the paper on epilepsy, we used proportional hazards regression modeling to estimate the relative hazard of developing epilepsy. 1.7 percent of the children in the cohort were diagnosed with epilepsy. Previous research has demonstrated a much higher risk of epilepsy in children whose mothers have epilepsy. For that reason, we obtained an indicator variable based on whether the mother had a diagnosis of epilepsy in the Medicaid billing records during her pregnancy. This was the case for 389 women. We considered the possibility that GU infection could have a different effect on risk of epilepsy in these women (the maternal diagnosis of epilepsy being a proxy for increased inherited risk of the condition). We tested for an interaction between maternal epilepsy and infection status, and it was statistically significant ($p = .004$). When we stratified the analysis by maternal epilepsy status, we found that GU infection was much more strongly associated with risk of epilepsy if the mother was epileptic (HR = 3.64, $p = .001$) than if she was not (HR = 1.24, $p < .0001$). We interpreted this as likely evidence of a gene-environment interaction, which merits additional study to identify potential candidate genes and mechanisms.

Table 1. GU Infection and Epilepsy

	Mother With Epilepsy			Mother Without Epilepsy		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**
Any GU Infection	3.64	1.65, 7.99	.001	1.24	1.14, 1.35	<.0001
First Trimester Infection	2.76	1.35, 5.62	.005	1.20	1.06, 1.36	.003
Second Trimester Infection	1.74	0.82, 3.72	.152	1.14	1.02, 1.26	.015
Third Trimester Infection	2.80	1.39, 5.64	.004	1.13	1.02, 1.25	.019

Models are stratified on maternal race and age, child's sex, preterm birth and low birth weight. Separate models were estimated for women with and without epilepsy, because there was a significant interaction between maternal epilepsy and infection.

Autism Spectrum Disorders

We found that 0.54% of children were diagnosed with an ASD by at least two health care providers. Maternal GU infection was not significantly associated with ASD. However, we found that pre-eclampsia was significantly associated with risk of ASD (OR = 1.85, p<.0001). (Just over 6% of women had pre-eclampsia during pregnancy.) The association with pre-eclampsia became only slightly weaker when controlling for low birth weight (< 2500 grams) (OR = 1.69, p = .0005), indicating that the association was primarily attributable to other factors (not the effect of pre-eclampsia on risk for LBW).

Table 2. Infection, Pre-Eclampsia, and Autism Spectrum Disorders

Variable	**OR**	**95% CI**	**P**
Pre-eclampsia/eclampsia	1.85	1.38, 2.47	<.0001
GU infection	1.07	0.89, 1.29	.475
Maternal age	1.04	1.03, 1.06	<.0001
White race	1.05	0.87, 1.27	.617
$\geq$ 12 years education	1.13	0.92, 1.39	.252
Birth year	1.05	1.00, 1.10	.059
Male sex	5.68	4.41, 7.35	<.0001
Alcohol use	1.40	0.65, 3.00	0.395
Tobacco use	1.02	0.80, 1.30	0.900
Down syndrome	6.74	2.98, 15.24	<.0001
Fragile X syndrome	9.63	1.24, 75.01	.031
Brain anomaly	8.23	3.40, 19.93	<.0001

Table 3. Predictors of ASD, Controlling for Low Birth Weight

Variable	OR	95% CI	P
Pre-eclampsia/eclampsia	1.69	1.26, 2.28	.0005
GU infection	1.07	0.88, 1.29	.514
Maternal age	1.04	1.03, 1.06	<.0001
White race	1.12	0.92, 1.37	.252
≥ 12 years education	1.14	0.93, 1.41	.205
Birth year	1.04	1.00, 1.09	.070
Male sex	5.81	4.50, 7.52	<.0001
Alcohol use	1.34	0.62, 2.90	0.450
Tobacco use	0.97	0.76, 1.24	0.786
Down Syndrome	6.05	2.66, 13.78	<.0001
Fragile X Syndrome	10.10	1.30, 78.56	.027
Brain anomaly	7.24	2.96, 17.69	<.0001
Birth weight (kg)	0.78	0.67, 0.91	.001

Attention Deficit Hyperactivity Disorder

ADHD was diagnosed by one provider in 6.9% of children and by two or more providers in 9.0% of children in the cohort. To reduce the likelihood of bias due to the inclusion of some 'cases' who may not have truly had ADHD, we limited the modeling to children who either had no diagnosis of ADHD or were diagnosed by two or more providers. GU infection was significantly associated with increased risk of ADHD (OR = 1.30, $p < .0001$). Interestingly, pre-eclampsia was also significant (OR = 1.20, $p = .0006$). These associations were present when controlling for both gestational age and birth weight.

Table 4. Predictors of Attention Deficit/Hyperactivity Disorder

	OR	95% CI	P
Pre-eclampsia	1.20	1.08, 1.32	.0006
GU Infection	1.30	1.24, 1.37	<.0001
> 12 years education	0.88	0.83, 0.93	<.0001
Maternal age	0.99	0.989, 0.999	.026
White race	2.27	2.15, 2.39	<.0001
Female sex	0.32	0.31, 0.34	<.0001
Maternal alcohol	1.04	0.81, 1.34	0.738
Maternal tobacco	1.52	1.43, 1.61	<.0001
Oldest age in Medicaid	1.34	1.33, 1.36	<.0001
Birth weight (kg)	0.99	0.93, 1.04	.628
Gestational age (wks)	0.98	0.980, 0.995	.011

We analyzed the effects of specific GU infections, with and without controlling for gestational age and birth weight. The results are shown in the table below. We found that

trichomoniasis, Chlamydia/non-gonococcal urethritis, UTI, and vulvovaginal candidiasis were all significantly associated with increased odds of ADHD, both before and after controlling for gestational age and birth weight.

Table 5. Specific GU Infections and ADHD Diagnosed by More Than One Provider

	Not Controlling for Gestational Age and Birth Weight			**Controlling for Gestational Age and Birth Weight**		
	OR	**95% CI**	**P**	**OR**	**95% CI**	**P**
Pre-eclampsia	1.29	1.16, 1.44	<.0001	1.26	1.13, 1.40	<.0001
Maternal education	0.91	0.86, 0.97	.002	0.91	0.86, 0.97	.002
Trichomoniasis	1.22	1.04, 1.44	.016	1.22	1.04, 1.44	.017
Chlamydia/NGU	1.45	1.06, 1.99	.020	1.44	1.05, 1.98	.023
Gonorrhea	1.04	0.76, 1.43	.817	1.04	0.75, 1.42	.832
UTI	1.26	1.18, 1.35	<.0001	1.26	1.18, 1.35	<.0001
Candidiasis	1.20	1.04, 1.38	.011	1.20	1.05, 1.39	.001
Maternal age	0.993	0.988, 0.999	.017	0.993	0.988, 0.999	.019
White race	2.22	2.09, 2.35	<.0001	2.25	2.12, 2.39	<.0001
Female sex	0.32	0.31, 0.34	<.0001	0.32	0.30, 0.34	<.0001
Maternal alcohol	1.07	0.82, 1.41	.621	1.07	0.81, 1.40	.643
Maternal tobacco	1.53	1.43, 1.63	<.0001	1.51	1.41, 1.61	<.0001
Oldest age in Medicaid	1.35	1.33, 1.37	<.0001	1.35	1.33, 1.37	<.0001
Birth weight (kg)	NA	NA	NA	0.96	0.90, 1.02	.149
Gestational age (wks)	NA	NA	NA	0.988	0.97, 1.01	.165

Pre-eclampsia and Intellectual Disability

We analyzed the association of pre-eclampsia with intellectual disability (ID). For this analysis, ‘cases’ of ID were limited to children receiving special education in public schools or receiving mental retardation services from the South Carolina Department of Disabilities and Special Needs (DDSN). Only children who had enrolled in public schools or were receiving mental retardation services from DDSN were included in the analysis. Approximately 2 percent of children met the case definition. When not controlling for low birth weight, pre-eclampsia was associated with a 58% increase in the odds of ID (OR = 1.58, $p < .0001$). Controlling for low birth weight reduced but did not eliminate the association (OR = 1.28, $p = .006$). We also tested the effect of further restricting ‘cases’ of ID to children who were receiving DDSN services or were classified as ‘trainable mentally handicapped’ or ‘profoundly mentally handicapped’ by the school system. We considered these children to have moderate to profound ID. The effect of pre-eclampsia was even stronger for these children (OR = 2.07, $p <.0001$ without controlling for low birth weight; OR = 1.46, $p = .004$ when controlling for low birth weight). We conclude that pre-eclampsia is associated with increased risk of ID, and that the association is partially, but not completely, accounted for by low birth weight.

Table 6. Pre-Eclampsia and Confirmed Intellectual Disability

	Model One (without low birth weight)		Model Two (with low birth weight)	
Variable	**Odds Ratio (95% CI)**	**P value**	**Odds Ratio (95% CI)**	**P value**
Pre-Eclampsia	1.579 (1.334, 1.870)	<0.0001	1.277 (1.074, 1.518)	0.0057
Maternal age	1.036 (1.027, 1.045)	<0.0001	1.034 (1.025, 1.043)	<0.0001
White race	0.534 (0.480, 0.593)	<0.0001	0.564 (0.507, 0.660)	<0.0001
≥ 12 years of education	0.577 (0.519, 0.640)	<0.0001	0.594 (0.534, 0.660)	<0.0001
Birth year	0.827 (0.802, 0.852)	<0.0001	0.822 (0.798, 0.848)	<0.0001
Female sex	0.486 (0.438, 0.540)	<0.0001	0.472 (0.425, 0.524)	<0.0001
Low birth weight (<2500 g)	NA	NA	2.526 (2.229, 2.863)	<0.0001

Pre-Eclampsia and Cerebral Palsy

We analyzed the association between maternal pre-eclampsia and cerebral palsy (CP). This is a controversial area of research, because previous researchers have found increased risk of CP in full term infants whose mothers had pre-eclampsia, but reduced risk of CP in preterm infants exposed to pre-eclampsia (compared to other preterm infants). Because of the potential for pre-eclampsia to 'cause' CP by way of preterm birth (pre-eclampsia is a frequent cause for medically indicated preterm delivery) and the strong association between preterm birth and CP, we decided to categorize pre-eclampsia based on the timing of initial diagnosis (< 37 weeks or >= 37 weeks).

Our results were similar to those previously reported: pre-eclampsia was associated with significantly increased risk in full term but not preterm infants. In addition, only early pre-eclampsia appeared to be important.

Table 7. Pre-Eclampsia and CP

First Pre-Eclampsia Diagnosis	OR for CP in Preterm Infants	P	OR for CP in Term Infants	P
Any Pre-eclampsia	NA	NA	1.74 (0.86, 3.53)	.124
< 37 weeks	0.73 (0.42, 1.26)	.256	3.46 (1.42, 8.41)	.006
≥ 37 weeks	NA	NA	0.96 (0.31, 2.99)	.939

Model is adjusted for maternal age and race, genitourinary infection in the first two trimesters, and child's sex.

We considered the likelihood that the lack of an effect in preterm infants could be due to the presence of other high risk conditions in these infants (since preterm birth is never a 'normal' occurrence). Pre-eclamptic mothers were far more likely to deliver preterm, so the overall impact of pre-eclampsia including any effect mediated by prematurity is important to capture. Therefore, we repeated the analysis, categorizing children by their pre-eclampsia/preterm status, and using full term infants not exposed to pre-eclampsia as the referent group. This analysis showed that, compared to full term infants without exposure to pre-eclampsia, preterm infants with pre-eclamptic mothers were at far greater risk of CP. Early CP was also associated with increased risk in infants who delivered at term.

Table 8. Pre-Eclampsia and Cerebral Palsy

Pre-Eclampsia-Preterm Status	OR	95% CI	P
No Pre-eclampsia, Full Term Birth	REF	REF	REF
Early Pre-eclampsia, Preterm	5.88	3.40, 10.17	<.0001
Early Pre-eclampsia, Full Term	3.41	1.40, 8.31	.007
No Pre-eclampsia, Preterm	8.12	6.49, 10.17	<.0001
Late Pre-eclampsia, Full Term	0.95	0.31, 2.98	.936

V. Discussion and Interpretation of Findings

A. Conclusions to be drawn from findings

We found that maternal GU infection was associated with increased risk of both epilepsy and ADHD, but not ASD. These associations were present after controlling for confounders. The greatest impact of infection appeared to be on the risk of epilepsy, in children whose mothers were documented as having epilepsy themselves.

Though it was not part of the original plan for the study, we also examined the association between pre-eclampsia and neurodevelopmental outcomes in children. We found that pre-eclampsia was associated with increased risk of ASD, epilepsy, ADHD, intellectual disability, and cerebral palsy. In most cases, the effect of pre-eclampsia remained a significant event when controlling for gestational age or birth weight. For cerebral palsy, early pre-eclampsia was associated with increased risk overall and in full term infants but not when limiting the sample to preterm infants. However, we believe the most likely explanation of this finding is the presence of other risk factors in preterm children, since preterm children with pre-eclampsia exposure were in fact at significantly greater risk than children born full term.

B. Explanation of study limitations

The biggest limitation of this project is that we relied upon billing data and other administrative data for all of the analyses. Clearly, the study would be strengthened by direct ascertainment and confirmation of exposure and outcome status. However, we believe the strength and consistency of the findings argue for their veracity.

C. Comparison with findings of other studies

Evidence is accumulating to show that maternal infection is associated with increased risk of adverse neurodevelopmental outcomes in children. This study supports and expands that hypothesis. The findings relating to an increased effect of infection on epilepsy risk in children whose mothers have epilepsy provide evidence for a gene-environment interaction, which is novel and merits further study.

D. Possible application of findings to actual MCH health care delivery situations

These findings highlight the important of preventing GU infections, when possible, in pregnant women. In particular, recommendations to avoid sexually transmitted infections (via abstinence, monogamy, and/or condom use) during pregnancy would seem to be very important for reducing adverse neurodevelopmental disability in children.

F. Policy implications

Programs for reducing sexual risk taking in high risk women have the potential to reduce rates of significant childhood disabilities such as epilepsy and ADHD.

F. Suggestions for further research

Additional research is needed, particularly focused on establishing the mechanism(s) by which maternal infection may impair fetal brain development. For example, is the effect of infection only present in the context of intrauterine or systemic infection, or is an effect present even when infection is limited to the vagina, cervix, or bladder? Similarly, are the associations due to direct effects of infecting organisms, or are they mediated by other biologically active substances such as cytokines?

Additional research is also needed to examine the mechanism(s) by which pre-eclampsia may increase the risk of adverse child outcomes.

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VI. List of products

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