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Association of NSAIDs and Acetaminophen Prescriptions During Pregnancy With Autism Spectrum Disorders in the Child

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ASSOCIATION OF NSAIDS AND ACETAMINOPHEN PRESCRIPTIONS DURING PREGNANCY WITH AUTISM SPECTRUM DISORDERS IN THE CHILD

by

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Dedication

This dissertation is dedicated to my family including my parents, my wife, and kids. My father, Late Dr. Bodiuzzaman Chowdhury, has been an inspiration for me though I lost him at a very early age. However, I have always tried to be like him and whenever I am demoralized during my PhD journey, I have been reenergized by the reminiscences of my father. Being widowed at the age of 33, my mother, Mrs. Rokeya Zaman, has been holding our family together for the last 40 years. She is the iron lady who made all her three sons well educated, well mannered, and better human beings. It is my mother for whom I am what I am. No word will be sufficient to express my gratitude to her. My wife, Salma Morium, has supported me in all sorts of issues during my stay in the USA, and was beside me whenever I needed her. She provided me with mental strength and taught how to focus and persevere. Finally, my kids, Ayaan and Alayna, were the windows through which I could have the refreshing air. They were my cheerleaders and I want to dedicate my dissertation to them as well.

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Abstract

Neurodevelopmental disorders in children including Autism Spectrum Disorders (ASD) and Intellectual disability (ID) are the topics of growing concern and recently many studies looked for the risk factors of these disorders. Although antidepressants and antiepileptics consumption during pregnancy have been reported to be associated with ASD, the effect of NSAID or acetaminophen, two most common drugs used during pregnancy, have been under researched. We conducted a prospective cohort study linking data from Medicaid, Department of Education, and Department of Disabilities and Special Needs with birth certificate data from mothers and children between 2010-2017. Beside exposure variables, NSAID and acetaminophen, and outcome variables, ASD and ID, other covariates included were maternal age, race, BMI, preeclampsia, gestational diabetes, smoking, and infection which were ascertained using causal diagram. Later. we measured the direct and indirect effects of NSAID use on ID. For acetaminophen, we conducted systematic review and meta-analysis because of underrepresentation of acetaminophen prescription in our data sources. There were 153,562 mother-child pairs of whom 3859 mothers were exposed to NSAID prescription during pregnancy, and the rest were unexposed. Regarding the outcome variable, 1018 children were flagged as ASD only, 6300 as ID only, and 1939 children had ASD with ID. Our main exposure variable, NSAID prescription was associated with ID with an adjusted odds ratio of 1.52. The sensitivity analysis also gave us similar findings. We found a significant mediation effect of

birthweight on ID. Very low birth weight mediated the association of NSAIDs on ID (OR:1.21, 95% CI: 1.06 – 1.40) when 40.9% of the effects of NSAIDs on ID was mediated through very low birthweight. When we categorized birthweight as low birth weight versus others, the direct effect was 1.42 (95% CI: 1.03-1.96) and the indirect effect was 1.10 (95% CI: 1.06-1.15) and 27.1% of the effects were mediated. The systematic review included 67,319 mother-child dyads in total. There was heterogeneity among the studies (I^2: 94%). The pooled odds ratio for the association between acetaminophen exposure during pregnancy and ASD in the child was 1.29 (95% CI: 1.17, 1.41). Our findings warrant further research on the research question and inform the scientific community and the relevant stakeholders regarding the risks of taking NSAIDs and acetaminophen.

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Preface

I have been a physician since 2004 in Bangladesh, a country from South Asia. After working as a clinician for about 8 years, I decided to switch my career to a public health professional to work for mass population, rather treating individual patients. To fulfil this goal, I got my MPH from James P Grant School of Public Health, BRAC University in 2013. Since then, I have been involved in public health research. I have been interested in autism research because the prevalence of autism has been increasing for the last few decades both in the USA and Bangladesh, my home country. I found it very interesting to look for the relationship between Non-Steroidal Anti-Inflammatory Drugs (NSAID) intake during pregnancy by the mothers and development of autism in their offspring.

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List of Abbreviations

ADHD ..... Attention Deficit Hyperactivity Disorder

AIC ..... Akaike Information Criterion

ANC ..... Ante Natal Care

APA ..... American Psychiatric Association

ASD..... Autism Spectrum Disorders

BIC ..... Bayesian Information Criterion

BMI ..... Body Mass Index

CDC ..... Centers for Disease Control and Prevention

CNS..... Central Nervous system

COX ..... Cyclooxygenase

DSM-III.....Diagnostic and Statistical Manual of Mental Disorders, Third Edition

DSM-IV .....Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

DSM-V.....Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

FHDR..... Finish Hospital Discharge Register

GDM ..... Gestational Diabetes Mellitus

HR..... Hazard Ratio

ID ..... Intellectual Disability

IDEA ..... Individuals with Disabilities Education Act

IL ..... Interleukins

INF ..... Interferons

IRB ..... Institutional Review Board

NICU ..... Neonatal Intensive Care Unit

NIDDK ..... National Institute of Diabetes and Digestive and Kidney Diseases

NSAIDs ..... Non-Steroidal Anti-Inflammatory drugs

OCD ..... Obsessive Compulsive Disorder

OR ..... Odds Ratio

OTC ..... Over the Counter

RR ..... Relative Risk

PDD-NOS ..... Pervasive Developmental Disorder – Not Otherwise Specified

SC ..... South Carolina

SCAN ..... South Carolina Community Assessment Network

SCDDSN ..... South Carolina Department of Disabilities and Special Needs

SCDE ..... South Carolina Department of Education

SCDHEC ..... South Carolina Department and Environment Control

SCDHHS ..... South Carolina the Department of Health and Human Services

SCRFA.....South Carolina Revenue and Fiscal Affairs

SGA.....Small for Gestational Age

TNF- α..... Tumor Necrosis Factor- alpha

USPSTF .....US Preventive Services Task Force

Chapter 1: Introduction

1.1. Background

Autism Spectrum Disorders (ASD) comprise a set of early-onset neurodevelopmental syndromes which are characterized by difficulties in social communication and unusually restricted repetitive behavior and narrow interests.(1-3) The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-5) describes ASD as having two main areas of impairment: "social communication" and "restrictive, repetitive patterns of behavior, interests and activities" where the differences in sensory perception are included in the latter domain.(4) In 2012, the global prevalence of ASD was estimated to be 0.62% although the data were not available from many underdeveloped countries;(5) whereas, in the developed world, the prevalence has been estimated to be at least 1.5%.(6) Studies conducted in Asia, Europe, and North America reported prevalence of ASD between 1-2%.(7) In United States, the Centers for Disease Control and Prevention (CDC) estimated prevalence of ASD among children aged 8 years was 1.69% in 2014 which was about 2.5 times higher than the prevalence in 1990.(7-9)

The risk factors associated with ASD include both parental characteristics, and prenatal and perinatal exposures.(8, 10-25) Some old studies identified mothers with higher income and more education as high risk groups which might be caused by ascertainment bias or reporting bias since the more educated segment of the society seem to be more

concerned about the health related issues.(24, 25) Among the prenatal risk factors, the notable ones are advanced maternal or parental age,(11, 13, 16) prenatal medication use by the mother,(11, 16) parental psychiatric history of schizophrenia or psychosis,(14) pre-pregnancy overweight or obesity,(24, 25) presence of maternal hypertension or diabetes,(11, 12, 16, 24, 25) maternal fever during pregnancy,(26) short interval between pregnancies,(24, 25) excessive weight gain during pregnancy,(24, 25) preeclampsia,(15-17) and some genetic, inflammatory, and environmental factors.(18, 20-23) The perinatal factors related to ASD include maternal hemorrhage,(11, 12) preterm birth,(12-14, 16) abnormal presentation,(12, 14, 16) low Apgar scores,(12, 14) low birth weight,(12, 13, 16) induced labor,(24, 25) delayed labor,(24, 25) and major central nervous system (CNS) anomaly.(24, 25)

Although the etiology of ASD is still ambiguous, the studies suggested that the susceptibility to ASD could be partially attributable to genetic and familial factors.(27-29) Some familial diseases that have also been cited as risk factors for ASD include thyroid problems, diabetes, rheumatoid arthritis, depression, anxiety, Attention Deficit Hyperactivity Disorder (ADHD), Obsessive Compulsive Disorders (OCD) or speech and language problems in one or both of the parents.(29) However, some studies suggested that children exposed prenatally to antidepressants are at higher risk of ASDs.(30-34) At mechanistic level, inflammatory and apoptotic mechanisms have also been reported to be responsible for ASD since inflammatory mediators like Interleukins (IL), Tumor Necrosis Factor (TNF-α), and Interferons are found at higher levels and Tryptophan is found deficient among children with autism.(35-43) Maternal intake of Vitamin D, Vitamin B, and Folic Acid during pregnancy has been shown to be moderately protective against

ASD.(44-50) Prenatal antibiotics exposure was found to be a mild risk for ASD in a few studies, however it was not possible to distinguish between the infection associated with the antibiotic use and the antibiotic alone.(51) Higher concentration of umbilical cord acetaminophen metabolites has been reported to be significantly associated with higher odds of ASDs in comparison to lower concentrations in a recent study,(52) although the half-life of acetaminophen is 2-3 hours after therapeutic dosage.(53) Perinatal induction of labor and postnatal exposure of anesthetics and antibiotics are also associated with higher ASD risk.(51, 54)

Recent literature and systematic reviews in the past five years suggest proinflammatory conditions during pregnancy including diabetes,(55-57) hypertension/pre-eclampsia,(17, 19, 58, 59) pre-pregnancy obesity,(56, 57, 60) and infections,(61-63) are associated with ASD.(64) Since proinflammatory conditions of the mothers are associated with higher risk, it is plausible that anti-inflammatory drug intake during pregnancy could have protective effects. However, despite having evidence of association of proinflammatory conditions with ASD, there have been limited research on the impact of maternal intake of non-steroidal anti-inflammatory drugs (NSAIDs) on ASD of the offspring. Hence, this study aims to assess the relationship between NSAIDs intake during pregnancy and ASD of the children.

1.2. Highlights of the dissertation

This dissertation is presented in eight chapters. Chapter 1 contains a brief background and notion of the contents of the whole paper. Chapter 2 presents the literature review conducted in preparation for this dissertation. The 3rd chapter delineates the objectives of the study along with the detailed methodology the author utilized to answer

the research questions. Chapter 4, Chapter 5, and Chapter 6 presents three manuscripts developed for this dissertation. In Chapter 4, we looked for the relationship of NSAID prescription during pregnancy among Medicaid insured mothers associated with ASD and ID among their children. Chapter 5 is a systematic review and meta-analysis that explored the prenatal exposure of acetaminophen on ASD. We found an association between NSAID with Intellectual disability and in Chapter 6 we looked for the mediation effect of preeclampsia and birthweight between our exposure and outcome. Chapter 7 includes a overall discussion that ties all the three papers together and finally, Chapter 8 contains the bibliography. In this paper, we utilized the Vancouver style for referencing.

Chapter 2: Literature Review

2.1. Autism Spectrum Disorders: Definition and diagnostic criteria

In 1943, after careful and systematic observations on 11 children with a previously unrecognized syndrome, Leo Kanner described their specific characteristics, later termed as autism, to differentiate from children with other psychiatric disorders.(65) Despite providing vivid description of the characteristics, this paper did not operationalize the diagnostic criteria. Later, in 1956, Kanner and Eisenberg, identified five diagnostic features of which they selected two criteria, a profound lack of affective contact, and repetitive, ritualistic behavior, as essential.(66) This reduction of essential symptoms to two led to much confusions and arguments among the clinicians, diagnosticians, scientists regarding defining autism.(67, 68) After a couple of decades, Rutter (1978) suggested four criteria for defining childhood autism with many examples from his own research and clinical experiences.(67-69) These were – (a) Impaired social development which has a number of special characteristics out of keeping with the child's intellectual level; (b) delayed and deviant language development that also has certain defined features and is out of keeping with the child's intellectual level; (c) 'insistence on sameness' as shown by stereotyped play patterns, abnormal preoccupations or resistance to change, and (4) onset before 30 months.(67) The American Psychiatric Association (APA) used 'pervasive developmental disorder' for the general category of autism in Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III) and defined 'infantile autism' as lack of responsiveness

to others; language absence or abnormalities; resistance to change or attachment to objects; the absence of schizophrenic features; and onset before 30 months.(65, 66) APA revised the criteria in 1987 and 1994.(66, 67) Most recently in 2013, the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) describes autism as having two main areas of impairment: "social communication" and "restrictive, repetitive patterns of behavior, interests and activities" where the differences in sensory perception are included in the latter domain.(4) In DSM-V there were some key changes to ASD diagnosis the most important of which was the single diagnosis of ASD that replaced the different subdivisions in the earlier versions – autistic disorder, Asperger's disorder, and pervasive developmental disorder – not otherwise specified (PDD-NOS).(4)

2.1. Factors associated with ASD

2.1.1. Risk groups

The children of the mothers of advanced age group were found to be more susceptible to ASD in different studies.(11, 13, 16, 24, 68-70) One of those studies also reported high maternal parity as a risk factor for ASD of the children although this has neither been supported nor rejected by other studies.(24) A few studies suggested that genetic changes responsible for ASD have been correlated with paternal age.(13, 71-73) According to some studies, women from higher income groups are more likely to have a child diagnosed as ASD.(24, 25) A number of studies postulated air pollution as an risk factor for ASD, suggesting that urban population are more prone to have ASD.(6, 74-79)

2.1.2. Familial or genetic factors

It has been evident that there is a huge genetic heterogeneity in ASD, involving both a locus heterogeneity and an allelic heterogeneity.(80, 81) The concordance in ASD diagnosis is observed in identical twin pairs at rates of 60-90%, whereas rates among non-identical twins are estimated at 3-31%.(82-88) Besides, specific genetic syndromes like Tuberous sclerosis, epilepsy, Rett syndrome, Fragile-X syndrome, or cytogenetic abnormalities are found to be associated with ASD.(89-94) Overall, it has been suggested that genetic factors play an important role in causation of ASD.

2.1.3. Prenatal factors

Several studies have been done to identify prenatal risk factors associated with ASD. Some factors like maternal place of residence like geographic areas with cooler climate,(11, 13, 16) pre-pregnancy overweight,(24, 25) presence of pre-pregnancy hypertension or diabetes,(11, 12, 16, 24, 25, 95) history of multiple pregnancy,(69) and parental history of psychiatric illnesses, especially schizophrenia and bipolar disorder.(14, 95, 96) These factors can be termed as pre-pregnancy or general risk factors for ASD which may also include short interval between pregnancies,(24, 25) and previous fetal loss.(11, 97) On the other hand, there are some factors which are experienced by the mothers during the pregnancy period. These factors are prenatal medication use,(11, 16) maternal fever,(26) excessive weight gain during pregnancy,(24, 25) gestational diabetes,(11) and preeclampsia.(10, 11, 13, 15-17, 50, 69, 95) Other prenatal risk factors are maternal exposure of second-hand smoke and air pollution,(6, 69, 77, 78, 95, 98) gestational respiratory infections,(68) and fetal distress.(68) Conversely, maternal intake of folic acid, vitamin D,(99, 100) and Vitamin B complex(101) have been associated with reduction in

ASD risk.(6, 102-104) Moreover, several of these vitamins and minerals are found in lower concentrations in children with ASD compared to their peers.(101, 105)

2.1.4. Perinatal factors

Several research activities identified a number of perinatal and postnatal factors associated with ASD. Among the maternal perinatal factors, maternal hemorrhage,(11, 12, 69, 98) induced, obstructed, or delayed labor,(24, 25, 68, 69) and breech presentation(24) have been reported. The perinatal factors related to the children include preterm birth and prematurity,(12-14, 16, 68-70) abnormal presentation,(12, 14, 16) low Apgar scores,(12, 14) low birth weight,(12, 13, 16, 69) being male in sex,(70) intrapartum hypoxia,(13, 68, 69) delayed crying,(68) major CNS anomaly,(24, 25) macrocephaly,(94) and neonatal jaundice.(68)

2.2. Individual risk factors for ASD

2.2.1. Maternal age

There have been different studies that put forth evidence of an association between advanced maternal age and ASD of their children.(11, 13, 16, 24, 68-70) Yaniv et al. (2010) conducted a retrospective cohort study among 45,033 nulliparous women with singleton gestation and found a significant linear association between maternal age and adverse perinatal outcomes.(106) A case cohort study with 1994 birth cohort in the US documented a 30% increase in odds of having ASD among the children of mothers aged ≥ 35 years in comparison to mothers aged 25-29 years.(107) Another cohort study using Danish National Psychiatric Register found that maternal age was associated with a greater risk of ASD (hazard ratios ranging from 1.21 (1.10-1.34) to 1.65 (1.09-2.48) depending on

combinations of different age categories.(108) A systematic review and meta-analysis, conducted by Sandin et al. (2012), included 16 epidemiological studies with 25,687 ASD cases and 8,655,576 controls. This study reported an adjusted relative risk of 1.52 (1.12-1.92) comparing mothers ≥35 years with mothers aged 25-29 years.(109) A relatively recent systematic review found that the lowest maternal age category was associated with a reduced risk of ASD in the offspring and an increased risk among the older age categories.(110) A paper by Lee et al. (2014) suggested that the increased risk of ASD in the offspring of older mothers probably involves the interaction of multiple risk factors.(111)

2.2.2. Maternal race

Maternal race is reported to be associated with ASD in offspring in many studies conducted in different parts of the world, although the results are not consistent. A population-based study in the US found that white children had a lower risk of having ASD in comparison to foreign born black mothers, central/south American, Filipino and Vietnamese, US born Hispanics and African American children.(112) In a retrospective cohort study in Australia indigenous women were 50% less likely to have a child with ASD than Caucasian, non-immigrant women. Conversely, the black women had 3.5 times the odds of having a child with ASD than Caucasian women.(113) However, in a secondary data analysis from the Pennsylvania Autism and Developmental Disabilities Surveillance Program reported, the authors reported a higher prevalence of ASD diagnosed among the white children compared to African American children using DSM-IV criteria (92% vs 81%; $p = .005$).(114) Overall, among hundreds of reports there are few differences in the prevalence of ASD by race, however diagnosis in African American children occurs later

than in White children.(115, 116) These differences are likely caused by racial disparity in detection or identification of ASD among children.(115, 117)

2.2.3. Preeclampsia

Clinically, preeclampsia is defined by hypertension and proteinuria during pregnancy, with or without pathologic edema. However, pathologically, it is a disorder of widespread vascular endothelial malfunction and vasospasm that occurs after 20 weeks of gestation and can present as late as 4-6 weeks postpartum.(118) As mentioned earlier, preeclampsia is an established risk factor for ASD.(10, 11, 13, 15-17, 19, 50, 58, 64, 69, 95) The Childhood autism risks from Genetics and the Environment (CHARGE) study, a population based case-control study, found that children with ASD were more than twice as likely to have been exposed to preeclampsia in utero in comparison to control children.(19) Dachew et al. (2018) conducted a meta-analysis of 10 epidemiological studies and concluded that the risk of ASD was 32% higher in offspring of the mothers having preeclampsia in comparison of the children whose mothers were not preeclamptic.(58) An analysis of 87,677 births insured by South Carolina Medicaid program between 1996-2002 found maternal preeclampsia to be significantly associated with higher odds of ASD.(17) A very recent meta-analysis of relevant case-control and cohort studies revealed that the pooled estimates of ORs and RRs for association between preeclampsia and ASD are statistically significant [OR:1.36 (1.12-1.60) & RR: 1.30 (1.20-1.41)].(119) A population based cohort study in Sweden involving all singleton live births between 1982-2010 reported that preeclampsia was associated with a 25% increase in likelihood of ASD [HR:1.25 (1.19-1.30)].(59) This same group conducted a cross-family analysis to examine

the intergenerational association between preeclampsia and ASD and reported a 25% increase in the likelihood of ASD of the children if the mothers had preeclampsia.(120)

2.2.4. Gestational diabetes mellitus

According to National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), gestational diabetes mellitus (GDM) develops during pregnancy and is usually diagnosed in the 24^{th} to 28^{th} week of pregnancy.(121) A retrospective longitudinal cohort study including 322,323 singleton children found that maternal GDM diagnosed by 26 weeks' gestation was found to be significantly associated with ASD in offspring.(55) A study with a subset of Boston birth cohort involving 2734 children who completed at least one postnatal study visit between 1998 and 2014 found that GDM, when combined with obesity, significantly increased the risk of ASD [HR: 3.04 (1.21-7.63)].(57) Sacks et al. (2016) conducted a population based cohort study with 231,271 deliveries and found a possible association with GDM and ASD.(122) A systematic review and meta-analysis of 16 epidemiological studies examining the association between GDM and ASD demonstrated a significant association with 48% increase in risk of ASD in offspring if the mothers had GDM.(123) A recent meta-analysis looking for prenatal, perinatal, and postnatal factors associated with ASD also endorsed GDM as a potential risk factor for autism.(124) Another meta-analysis that looked at the risk of ASD in the offspring among mothers with diabetes both before and during pregnancy found that the risk of ASD among mothers with GDM was 48% more in comparison to the mothers without GDM.(125) Thus, an increasing body of evidence has been being generated in favor of GDM to be a risk factor for ASD.

2.2.5. Infection

The relationship between prenatal infections and ASD is complicated by the numerous types of infectious agents, body system infected and severity of the infection. A study was conducted using the Danish Medical Birth Register and was restricted to infections requiring hospitalizations only. This study documented a three-fold increase of ASD risk for mothers hospitalized due to viral infection in the first trimester, and a 42% increase of risk for mothers hospitalized due to bacterial infection in the second trimester.(126) Goines et al. (2011) found that increased mid-gestational IFN-γ, IL-4, and IL-5 were associated with increased risk of ASD which is suggestive of the association between maternal infection during pregnancy and ASD.(127) There are additional studies that report an association between maternal infection and ASD risk.(128, 129) A population based cohort study in Taiwan found a significant association of visits for genital infection and bacterial infection in the third trimester with ASD.(130) As a potential indicator of inflammation, maternal fever has also been found to be associated with ASD in offspring.(131) And in terms of infectious agents influenza(26) and cytomegalovirus (132) have been associated with risk factors for ASD. A meta-analysis involving more than 40,000 ASD cases from 15 epidemiological studies showed that maternal infection during pregnancy was significantly associated with the increased risk of ASD and the risk was modulated by the type of infectious agent, time of exposure, site of infection, and hospitalization.(133)

2.2.6. Obesity

Despite the fact that there are mixed reports about the association of maternal pre-pregnancy obesity and ASD, a meta-analysis found an increased risk of ASD in children

of women who were obese during pregnancy with the pooled adjusted OR of 1.47 (95% CI: 1.24-1.74).(134) The CHARGE study also reported similar results [OR: 1.67(1.10-2.56)].(56) The Norwegian Mother and Child Cohort Study, a prospective population based study involving 92,909 children, reported 73% increased risk of ASD in children of obese parents in comparison to normal weight ones.(135) Many other studies identified maternal obesity as a potential risk factor for developing ASD or other neuropsychiatric disorders in the offspring.(136-141) Some other studies documented similar results by describing the association of ASD with maternal pre-pregnancy body mass index.(142-144)

2.2.7. Smoking and air pollution

Several studies examined the association between maternal smoking during pregnancy and ASD risk, but the results have been equivocal.(145-150) A number of meta-analyses and other studies were performed that found no association between smoking and ASD in offspring.(145, 147, 149) A case-control study conducted with 3,958 ASD cases and 38,983 controls reported the association was confounded by sociodemographic characteristics of parents such as education, income, and occupation.(146) A population-based nested case-control study from Finish Hospital Discharge Register (FHDR) documented 20% higher risk among the children whose mothers smoked throughout the pregnancy period in comparison to those whose mothers were non-smokers. However, they found that smoking exposure limited to the first trimester was not associated with ASD.(150) An interesting study by Golding et al. (2017) found an association between maternal grandmother smoking in pregnancy and granddaughters having adverse scores in Social Communication and Repetitive Behavior measures were independently predictive of diagnosed autism.(151) In addition, a meta-analysis utilized ‘population smoking

metrics' (*population smoking prevalence to include second hand smoke*) as moderators and found significant results using World Health Organization data suggesting the importance of investigating this research question more rigorously.(148) Second-hand smoking exposure of the mother during pregnancy and air pollution have also been suggested as a risk factor for ASD in a number of studies. (6, 69, 77, 78, 95, 98)

2.2.8. Gestational age and birthweight

A retrospective cohort study, conducted in California USA, found increased ASD risk in preterm Small for gestational Age (SGA) infants.(152) Lampi et el. (2012) conducted a population-based case-control study in Finland and found increased risk for childhood autism among very low (<1500 g) and moderately low (<2500 g) birthweight, very low gestational age (less than 32 weeks), and SGA infants.(153) A retrospective cohort study in Atlanta, Georgia demonstrated two-fold increased risk of ASD for infants with birthweight of <2500 g and preterm birth at <33 weeks' gestation.(154) Another large study in Canada with a total of 218,110 singleton births observed a gradual increased risk of ASD with shorter gestation.(155) A prospective multi-center birth cohort study of 10-year-old children born at 23-27 weeks' gestation found that low gestational age and very low birthweight are strongly associated with ASD.(156) Thus, through the evidence generated from different types of epidemiological studies, it can be inferred that both gestational age (low) and birthweight (low) are important risk factors for development of ASD in children.

2.2.9. Drugs

Different drugs and pollutants have been reported as risk factors for ASD. A large population-based cohort study in Denmark following 655615 children reported that

maternal use of valproate during pregnancy, even after adjusting for maternal epilepsy, was associated with a significantly increased risk of ASD.(157) Similar results were found in many other studies regarding the relationship of antiepileptic drug use during pregnancy and ASD.(158-161). A population-based nested case-control study in Sweden reported the association of in-utero exposure to both selective serotonin reuptake inhibitors (SSRI) and non-selective monoamine reuptake inhibitors (tricyclic antidepressants) with the increased risk of ASD.(162) This finding was supported by a cohort study conducted in Quebec, Canada where they found that SSRIs, taken during second and/or third trimester, increase the risk of ASD in children, even after controlling for maternal depression.(30) However, some other studies nullified this finding which warrants further studies.(31, 34, 163) Maternal use of acetaminophen was suggested to be related to ASD in offspring through empirical data and ecological studies.(52, 164-168) As mentioned earlier, perinatal induction of labor and postnatal exposure of anesthetics and antibiotics are also associated with higher ASD risk(51, 54).

2.3. Proinflammatory conditions during pregnancy

A proinflammatory condition is a phenomenon which triggers the immune cells to be active and thus promotes inflammation(169-171) and a stress response(171). The pregnancy period is proinflammatory since it is associated with immunosuppression especially in the first trimester(172, 173). The literature has identified a few proinflammatory conditions which are associated with ASD and those are preeclampsia, gestational diabetes, infection, and obesity. It has been found that the inflammatory cytokine production is increased by pro-inflammatory T-cells along with a decrease in regulatory and anti-inflammatory cytokines among preeclamptic women resulting in a

proinflammatory state(174-176). Gestational diabetes has also been reported to increase the synthesis of proinflammatory cytokines like TNF-α, IL-6, and IL-1(177, 178). Any infection during pregnancy is also regarded as proinflammatory since it is associated with increased production of TNF-α and IL-1 and oxidative stress(179-182). Maternal obesity, is also associated with increased secretion of chemokines such as leptin, IL-6, TNF-α, monocyte chemoattractant factor-1, and resistin(183). Cytokines also reduces production of adiponectin, and thus is likely to be increased in pro-inflammatory state and oxidative stress(184). All those proinflammatory conditions have been cited as risk factors for ASD in different studies as mentioned above in the prior sections.(10, 11, 13, 15-17, 50, 69, 95)

2.4. NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of analgesic medications that are widely used globally to reduce pain, fever, and inflammation(185). Most NSAIDs are over the counter medications that do not require a prescription, however some NSAIDs are combined with prescription drug. NSAIDs have several effects including anti-inflammation, analgesic, antipyretic effects and inhibition of thrombocyte aggregation(185). They are also known as cyclooxygenase (COX) inhibitors since they work by inhibiting the activity of COX-1 and COX-2 enzymes(186). Most NSAIDs are non-selective inhibiting both, whereas some others are selective to COX-2 only and are known as COX-2 inhibitors(187). Non-selective NSAIDs include salicylates (Aspirin), Propionic acid derivatives (Ibuprofen, Naproxen, Ketoprofen, Oxaprozin), Acetic acid derivatives (Indomethacin, Ketorolac, Diclofenac, Aceclofenac), Enolic acid derivatives/Oxicams (Piroxicam, Tenoxicam, Phenylbutazone), Anthranilic acid derivatives/Fenamates (Mefenamic acid, Meclofenamic acid). On the other hand selective

COX-2 inhibitors/Coxibs are Celecoxib, Rofecoxib, and Valdecoxib.(188) In some states over-the-counter medications are covered by Medicaid plans and thus there is a record of their dispensing in the Medicaid Prescription file.

NSAIDs, if given in high doses during pregnancy, are potential risk factors for adverse maternal and fetal effects like prolongation of labor in mothers, spontaneous abortion/miscarriage, low birth weight, constriction of the ductus arteriosus, renal dysfunction, congenital cardiac malformations, orofacial clefts and hemostatic abnormalities in the fetus and neonates.(189-193) However, despite these adverse effects, US Preventive Services Task Force (USPSTF) recommends 81mg of Aspirin daily, which is an NSAID, as preventive medication in women at risk for pre-eclampsia.(194) However, we could not find any literature that described the effect of Aspirin, or any other NSAID intake during pregnancy on the brain and behavioral development of the offspring.

Chapter 3: Objectives and Methodology

3.1. Objectives

The main goal of this study was to ascertain the relationship between NSAIDs and acetaminophen exposure during pregnancy and development of ASD among the offspring. The specific objectives were:

Specific Aim I: To measure the prevalence of ASD and ID among the 3-7 years' children of Medicaid insured mothers in South Carolina during 2010-2017

Specific Aim II: To measure the association of NSAIDs and acetaminophen prescribed for the women during pregnancy and development of ASD and ID among their children in South Carolina during 2010-2017

Specific Aim III: To measure the direct and indirect effect of NSAIDs on ASD considering the birthweight and preeclampsia as potential mediators

3.2. Methodology

3.2.1. Data Sources

Primarily the study has been conducted utilizing four different South Carolina public data sources that were linked through a unique identifier. The data sources included South Carolina Medicaid individual billing files from 2010-2017, South Carolina Department of Disabilities and Special Needs (SCDDSN) service files, South Carolina

Department of Education SCDE) school records, and South Carolina Department of Health and Environmental Control (SCDHEC) Vital Records from 2010-2017.

Medicaid data has been commonly used as an administrative database in health services research.(195) In South Carolina the Department of Health and Human Services (SCDHHS) is the Medicaid agency and the data are shared between SCDHHS and the SC Revenue and Fiscal Affairs (SCRFA) office that is the repository of numerous state health and social service datasets.

Medicaid data files contain information that is used for billing including diagnosis and procedure codes from hospital, outpatient and community health services utilization, long term care, and pharmacy/medication claims.(195) The Medicaid dataset allowed us to link mothers to their children using unique identifiers for the individuals and the mother-child pairs. This same data source allowed us to identify children with ASD using the billing claims, which used ICD9 and ICD10 codes for diagnosis and treatment services. According to ICD-9 criteria, autism was assigned to the code 299.00 for current or active state, and code 299.01 for residual state. We also looked for other components of ASD that include Asperger syndrome (299.80 to 299.81) and pervasive developmental disorder, not otherwise specified (299.90 to 299.91). For the datasets after 2015, we used ICD-10 codes to identify children with ASD and looked for codes F84.0 to F84.9. Each claim record had either an ICD-9 or, an ICD-10 code to justify the service provided and we required that an inpatient hospital stay had an Autism code or there were at least two Autism codes used in the outpatient setting at least 10 days apart. The requirement for two codes in the outpatient setting allowed excluding children who had the code for evaluation, but the child tested negative.

The second data source was the SC Department of Disabilities and Special Needs (SCDDSN) which provides direct services to children and adults with qualifying disabilities. In the SCDDSN dataset there is an indicator variable that is used to identify children who have been tested and diagnosed with ASD, including those who are receiving early intervention autism services through the SCDDSN Autism Division.(196)

We also used the SC Department of Education (SCDE) dataset to identify additional children who were receiving either Part B or part C 'Individuals with Disabilities Education Act (IDEA)' early intervention and school based special education services for Autism in public schools. Autism, as defined by IDEA, refers to "a developmental disability significantly affecting verbal and nonverbal communication and social interaction, generally evident before age three that adversely affects a child's educational performance".(48)

Birth certificate data has been available at South Carolina Department and Environment Control (SCDHEC) where all births of SC residents are documented.(197) We obtained information related to child's year of birth, birthweight, sex, estimated gestation, Neonatal Intensive Care Unit (NICU) admissions, pregnancy complications, and the number of mother's prenatal visits, BMI, and presence of infection from this dataset.

3.2.2. Study setting

The study has been conducted in the context of South Carolina since the data sources utilized are of this state. South Carolina is a state in the southeastern United States bordered to the north by North Carolina, to the southeast by the Atlantic Ocean, and to the Southwest by Georgia across the Savannah river. According to United States Census Bureau estimation of July 1, 2018, the population of South Carolina was 5,084,127 which

was 9.92% higher than that of 2010.(198). Of the population of SC, 68.5% were White, 27.3% were African Americans, and the rest comprised American Indian, Asian, Alaska native, Hawaiian, or Pacific Islander.(198) The median household income was $51,015 and the population living in poverty was 15.3%.(198) In South Carolina, health insurance coverage is provided to pregnant women with low income through Medicaid which continues for 60 days after the baby's birth and the infant is covered up to age one. To qualify for this program, a woman must be pregnant, a South Carolina resident, a US citizen or lawful permanent resident alien, a Social Security Number holder, and having individual annual income up to 194% of poverty level(199-201) although it was 185% before 2014.(201-203)

3.2.3. Study population

According to South Carolina Department of Health and Environmental Control (SCDHEC) birth certificate records, the number of babies delivered between 2010 and 2017 in South Carolina was 242,510. However, we included children at least 3 years of age in the study because it has been reported that although autism can be detected as early as 18 months of age, it is usually diagnosed at or around the age of 3 years.(204-206) After adequate data cleaning and implying the inclusion criteria, the final sample size was 153,562. Figure 3.1 illustrates STROBE flow chart for our study population.

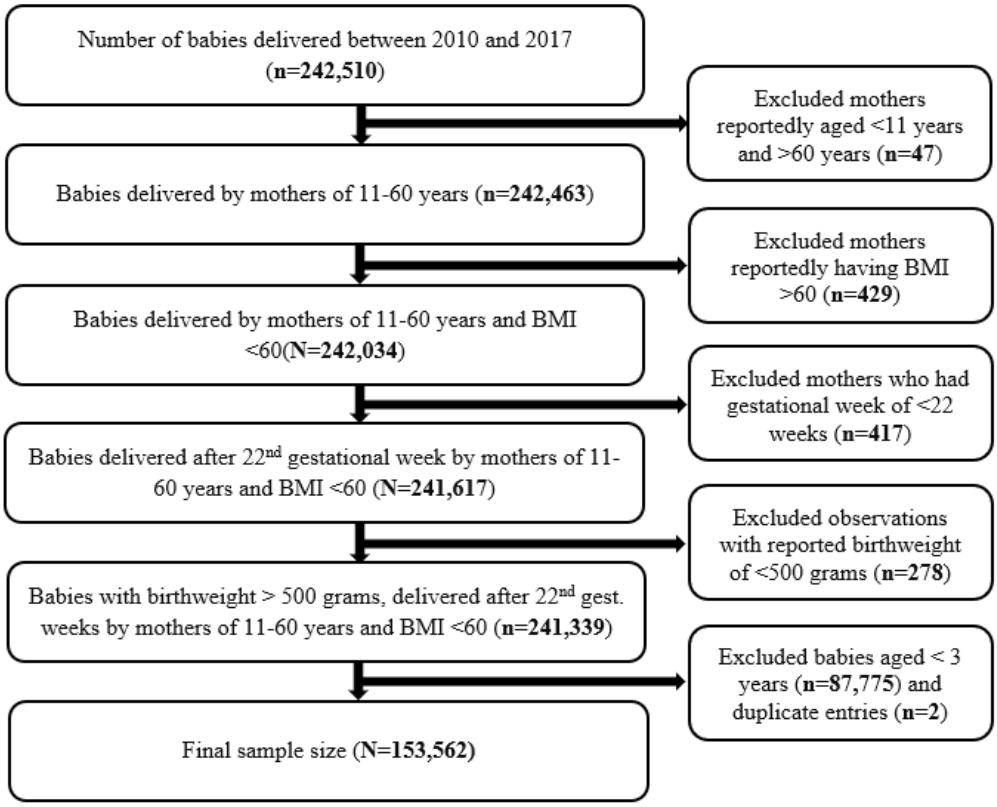

Figure 3.1: Strobe flow chart for the study population

3.2.4. Directed Acyclic Graph (DAG)

To address Objectives 2 and 3 we developed directed acyclic graph (DAG) to ascertain the confounders we need to adjust for (Figure 3.2). We utilized the DAGitty software version 3.0 to illustrate the causal diagram and to determine the confounders. From the causal diagram, we identified that minimal sufficient adjustment set contained maternal age, race, preeclampsia, infection, gestational diabetes, smoking, body mass index, and Kotelchuck index. The Kotelchuck index is also called the Adequacy of Prenatal Care Utilization (APNCU) index that uses two crucial elements from birth certificate data related to initiation and utilization of prenatal care services.(207)

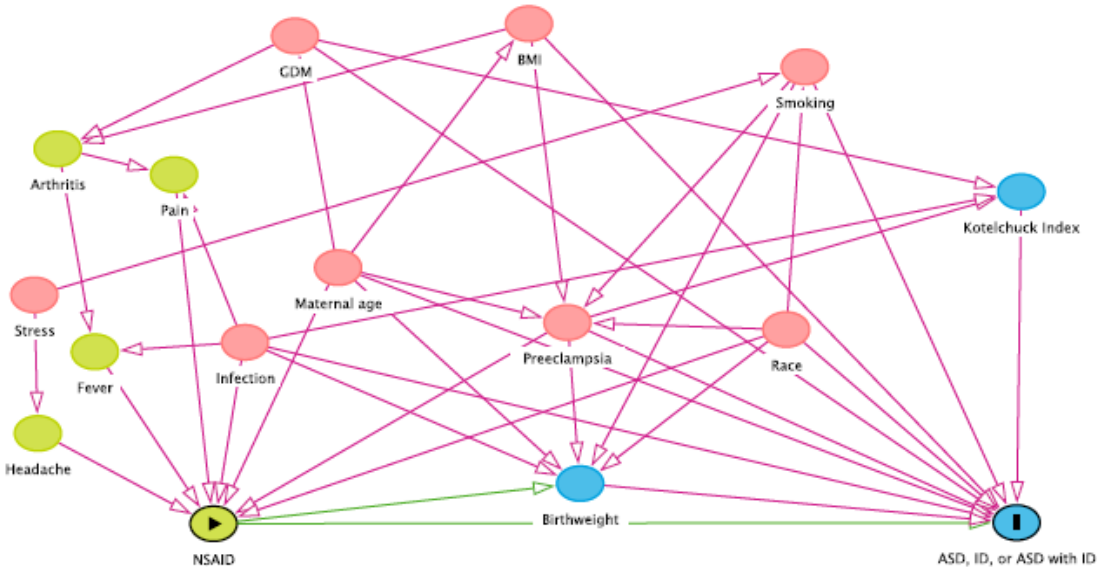

Figure 3.2: Directed acyclic graph showing the relationship among the variables

3.2.5. Variables

The main exposure variable was 'NSAID prescriptions during pregnancy' which was recorded as 'YES' if the observations were found to have a Medicaid pharmacy entry for the receipt of a supply of any Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) during the pregnancy period. The other exposure variable, Acetaminophen prescription, was also obtained from Medicaid dataset. From the same dataset, the categorical outcome variable was determined through International Classification of Diseases (ICD) codes. ASD was determined from ICD-9 codes of 299.0 and 299.1 and ICD-10 codes of F84.0 to F84.9. On the other hand, Intellectual disability (ID) was determined from ICD codes 317.0-319.0 and ICD-10 codes of F70-F79. The outcomes were also flagged in SCDDSN and SCDE datasets. The categories of outcome variable were ASD only, ID only, ASD with ID, and neither ID or ASD.

The other variables were maternal age, maternal race, Children's age, children's gender, body mass index (BMI), birthweight, gestational age, preeclampsia, gestational diabetes (GDM), infection, smoking, Kotelchuck index, and plurality. Among these, preeclampsia, GDM, infection, and smoking were binary variable delineated as either presence or absence of these (YES/NO). Maternal age, BMI, and children's age and birthweight were continuous variables. However, later, maternal BMI was categorized into 4 categories, which were Underweight (<20kg/m^2), Normal (20-25 kg/m^2) , Overweight (25-30 kg/m^2), and Obese (30 kg/m^2), and children's birthweight was also categorized into 4 categories: Extremely Low birthweight (<1000gms), Very Low Birthweight (≥1000 & <1500gms), Low birthweight (1500-2500gms), and Normal (≥2500gms). The other categorical variables were maternal race (White, Black, and others), Children's gender (Male, Female), gestational age (<32 weeks, 32-37 weeks, and more than 37 weeks), Kotelchuck index (Inadequate, Intermediate, Adequate, and Adequate+), and plurality (Singleton, Twin, and Triplet).

3.2.6. Data analysis

The prevalence of ASD and ID among the children of Medicaid insured mothers between 2010-2017 were measured by frequency distribution. The baseline characteristics of the study participants were discerned through descriptive statistics. Any significant difference between the exposed and unexposed group regarding those characteristics was determined by the chi-square test or t-test. Some variables underwent Fisher's exact test when the sample subset was small. Since the outcome variable was categorical (ASD only, ID only, and ASD with ID), we conducted multinomial logistic regression for unadjusted and adjusted analysis. In the final model, we adjusted for the confounders identified from

the DAG. To measure the direct and indirect effects, we used SAS macro by L. Valeri and TJ Vanderweele.(208, 209) All data linkage and analysis will be performed using SAS™ version 9.4. The details of the methods are outlined in the following chapters.

3.3. Methods used for systematic review

We conducted a systematic review to see the effect of acetaminophen exposure during pregnancy with ASD since in our datasets, acetaminophen exposure was underrepresented.

3.3.1. Registration of the review

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2009 framework guideline and checklist to conduct this systematic review.(210) Our PROSPERO registration number was CRD42020213917.(211)

3.3.2. Eligibility criteria

We reviewed all the scientific articles, published in English, up to September 2020. Although the preferred study type was Randomized Controlled Trial (RCTs), we found no RCT of acetaminophen in pregnant women. Therefore, we only included cohort studies in our final selected articles. The exposure and comparison ascertainment did not consider the usage of any concomitant NSAID. There was no age, ethnicity, or socio-economic status preference for the study population.

3.3.3. Data sources and Search strategy

The databases we used for our systematic review were MEDLINE, EMBASE, and Cochrane Reviews to identify all the available manuscript that studied the association between in-utero exposure of acetaminophen and risk of ASD irrespective of study types. We identified the studies using the keywords and appropriate Medical Subject Heading

(MeSH) terms: “autism”, “ASD”, “autism spectrum disorder”, “acetaminophen”, “paracetamol”, “Tylenol”, “pregnancy”, and “prenatal” in different combinations. We also searched published systematic reviews, other online resources, and conference abstracts to identify all relevant studies and also contacted the authors of the final selected articles for clarification about methods through personal correspondence.

3.3.4. Study selection and data extraction

Two investigators (MAKC and RDG) independently searched the databases for the selection of the articles. Although they independently screened titles, abstracts and full texts, any disagreement was resolved by consensus, or by consultation with the study supervisor. After finalizing the articles, a standardized data extraction form was developed and piloted, based on the Cochrane data abstraction template.(212) The extractable data items were study title, publication year, population description, study setting, inclusion and exclusion criteria, methods of participant recruitment, study objective, study start and end date, study design, outcome measures, exposure, data analysis, bias assessment, and results.

3.3.5. Risk of bias assessment

The risk of bias was assessed both within and across the studies using utilized “Tool to Assess Risk of Bias in Cohort Studies” from Evidence Partners contributed by the CLARITY group at McMaster University and published by Evidence Partners(213) where we assessed the risk of bias analyzing 8 different questions.

3.3.6. Synthesis of results

Primarily, the findings have been described as narrative synthesis with the explanation of the summary measures (Hazard ratios, Risk ratios, or Odds ratios). We conducted the meta-analysis to get the pooled estimates using the Microsoft Excel 2016 as suggested by Neyeloff et al. (2012).(214) Heterogeneity was assessed using the I^2 statistics, when I^2 values of 75%, 50%, and 25% represented high, medium, and low heterogeneity, respectively. Forest plots were generated from the same software to illustrate our findings. Random effects models were used since there was high heterogeneity. Statistical significance was defined using a 2-sided alpha level of 0.05.

More detailed description of the methodology is provided in Chapter 4, 5 and 6.

Chapter 4: Relationship of NSAID prescription during pregnancy among Medicaid insured mothers with autism spectrum disorders and intellectual disability among their children: findings from a prospective cohort study[1]

[1] Chowdhury, MAK. To be Submitted to *Journal of Autism and Developmental Disorders.*

4.1. Abstract

Introduction: Autism Spectrum Disorders (ASD) and Intellectual disability (ID) may occur individually or concomitantly, but their relationship with NSAIDs intake by their mothers during pregnancy is not well understood.

Methods: We conducted a prospective cohort study linking data from Medicaid, Department of Education, and Department of Disabilities and Special Needs with birth certificate data from mothers and children between 2010-2017. Our main exposure variable was NSAID prescription, and the outcome variables were ASD, ID, and ASD with ID. The other covariates included in the model were maternal age, race, BMI, preeclampsia, gestational diabetes, smoking, and infection. The confounders were ascertained using causal diagram. We conducted multinomial logistic regression since our outcome variable was categorical. We also conducted sensitivity analysis considering 'alcohol use' as an unmeasured confounder and calculated E-value.

Results: Of 153,562 study participants, 3859 mothers were exposed to NSAID prescription during pregnancy, and the rest were unexposed. Regarding the outcome variable, 1018 children were flagged as ASD only, 6300 as ID only, and 1939 children had ASD with ID. The identified risk factors for ASD were mothers' age, race, BMI, preeclampsia, and gestational diabetes Whereas for ID only, NSAID prescription, mothers' age, race, BMI, preeclampsia, and smoking were the risk factors. Our main exposure variable, NSAID prescription was associated with ID only with an adjusted odds ratio of 1.52 (p-value:<0.0001). The sensitivity analysis also gave us similar findings.

Conclusion: Our findings identified a 52 percent higher risk for ID among children whose mothers took NSAIDs during pregnancy, however, demonstrate the need for more

specific research on both the biologic plausibility using animal models and the generalizability to other maternal-child populations using other data sources, are needed to validate the effect of NSAIDs prescription during pregnancy on ASD and ID disability among children.

4.2. Introduction

Autism Spectrum Disorders (ASD) and Intellectual disability (ID) may occur individually or concomitantly, but in varying rates.(1-3) ASD comprise a set of early-onset neurodevelopmental syndromes which are characterized by difficulties in social communication and unusually restricted repetitive behavior and narrow interests.(4-6) The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-5) describes autism as having two main areas of impairment: "social communication" and "restrictive, repetitive patterns of behavior, interests and activities" where the differences in sensory perception are included in the latter domain.(7) On the other hand, IDs are characterized by social, cognitive, and adaptive skill deficits which is often accompanied by stereotypies and challenging behaviors.(1, 8-17)

In 2012, the global prevalence of ASD was estimated to be 0.62% although the data were not available from many underdeveloped countries;(18) whereas, in the developed world, the prevalence has been estimated to be at least 1.5%.(2) Studies conducted in Asia, Europe, and North America reported prevalence of ASD between 1-2%.(19) In United States, the Centers for Disease Control and Prevention (CDC) estimated prevalence of ASD among children aged 8 years was 1.69% in 2014 which was about 2.5 times higher than the prevalence in 1990.(19-21) Similarly, a systematic review of US studies on the prevalence of intellectual disabilities reported that the prevalence of ID among children

ranges between 1.1% to 1.34%.(3) A study in Finland reported the prevalence to be 1.17%.(22)

A study conducted among 2,208 children with both ASD and ID identified through the South Carolina Autism and Developmental Disabilities Network reported that the prevalence of ASD in people with ID to be 18.04% while the ASD rate in the general population was between 0.60% and 1.11%.(23) Other studies have reported ASD co-occurring with ID,(1, 24-26) although there are numerous reports of ASD in people with normal intelligence.(1, 27) The needs for the persons with co-occurring ASD and ID are different from individuals with ASD or ID alone.(28, 29)

Thus, three distinct groups prevail related to these disorders - persons with ID, persons with ASD, and persons with both ASD and ID.(30) Many studies have explored the risk factors for ASD and ID,(20, 31-40) however, no study explored the relationship between Non-Steroidal Anti-Inflammatory Drugs (NSAID) prescription during pregnancy associated with ASD or ID of the offspring. Our study aimed at identifying any association of NSAID prescription with three distinct groups of ASD alone, ID alone, and ASD with ID.

4.3. Methods

4.3.1. Study design and data sources:

We conducted a prospective cohort study utilizing four different South Carolina public data sources that were linked through a unique identifier. The data sources included South Carolina Medicaid individual billing files, South Carolina Department of Education (SCDE) school records, South Carolina Department of Disabilities and Special Needs

(DDSN) and South Carolina Department of Health and Environmental Control (SCDHEC) Vital Records of 2010-2017. Medicaid supported pregnant women up to 185% of poverty and children who were identified at high risk for disability during that period.(41, 42) Children are covered by SC Medicaid, without consideration of parental income, under the Katie Beckett Medicaid waiver if they have long-term disabilities or complex medical needs.(43, 44) Thus, some children with ASD and ID are identified in Medicaid, which is an entitlement program, even when they are not served by SCDE or DDSN. SCDE is also an entitlement program; however, not all children in our study were old enough to qualify for school services, beginning at 3 years of age for children with disabilities and special needs, or they were schooled in settings, such as private schools or home schools, which are not captured by SCDE data.(45, 46) DDSN is a state service program that provides services and supports for citizens of all ages with ASD and ID. Nonetheless, DDSN is not an entitlement, thus some children are on waiting lists for ASD and ID services.(47)

4.3.2. Study participants:

According to South Carolina Department of Health and Environmental Control (SCDHEC) birth certificate records, the number of babies delivered between 2010 and 2017 in South Carolina was 242,510. However, we included children at least 3 years of age in the study because it has been reported that although autism can be detected as early as 18 months of age, it is usually diagnosed at or around the age of 3 years.(48-50) After adequate data cleaning and implying the inclusion criteria, the final sample size was 153,562. The study participants included the Medicaid insured mother/children pairs who gave birth to their children between 2010-2014. In total, there were 153,562 children. Of the study participants, 3859 mothers were exposed with NSAID prescription during

pregnancy and the rest were unexposed. Regarding the outcome variable, 1018 children were flagged as ASD only, 6300 as ID only, and 1939 children had ASD with ID. The details have been presented in Figure 4.1.

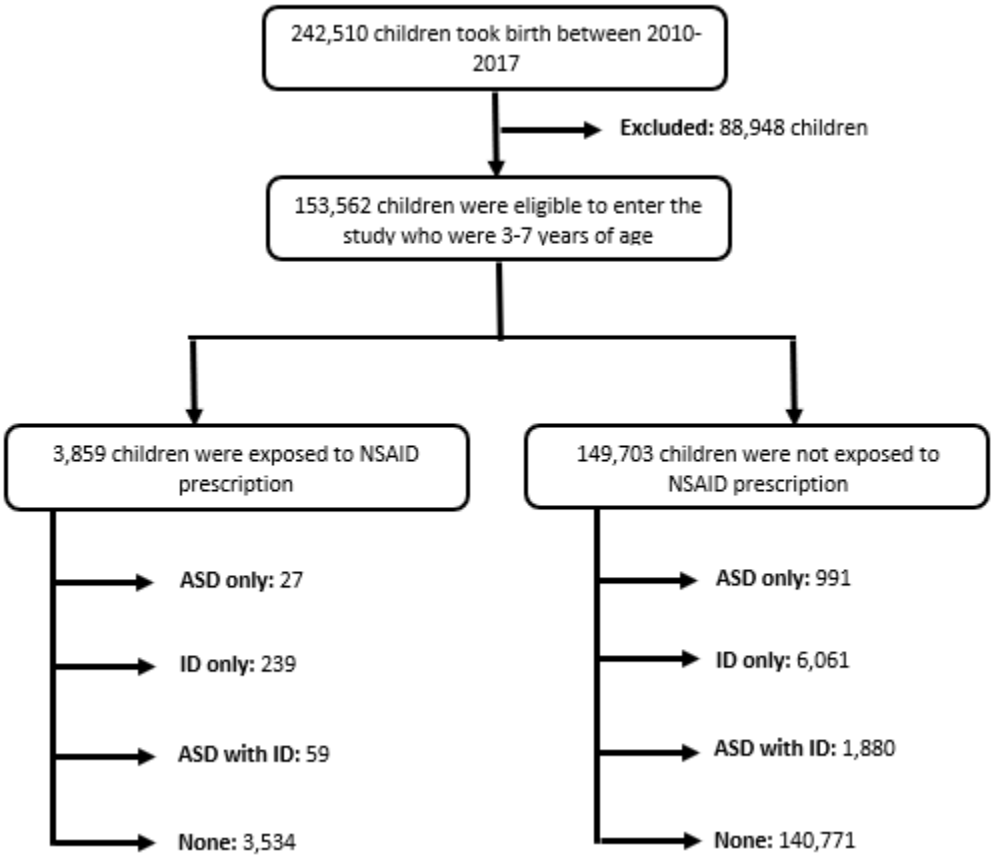

Figure 4.1: Study participants of the study analyzing the relationship of NSAID prescription during pregnancy with ASD and ID

4.3.3. Variables of interest:

The main exposure variable was 'NSAIDs during pregnancy' which is recorded as 'YES' if a woman received a supply of any Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in the Medicaid pharmacy file during the pregnancy period. All systemic prescription NSAID medications, including both COX-1 and COX-2 enzyme inhibitors,

were considered. Other demographic variables included mother's age, race, children's age, children's sex. Maternal Body mass index (BMI), Number of Ante natal care (ANC) visits, Birthweight, smoking status, gestational age, Kotelchuck index, gestational diabetes, preeclampsia, and infection during pregnancy. Among these maternal age, children's age, BMI, gestational age, and birthweight were recorded continuous variables. However, gestational age, BMI, and birthweight have also been analyzed as categorical variables. The other categorical variables were maternal race and Kotelchuck index. The other explanatory variables were binomial (Yes/No).

Our outcome variable was a categorical variable where the categories were ASD only, ID only, ASD and ID, and none. The ASD and the ID variables were based on a flag in the SCDE or the DDSN file, which was used to qualify for ASD or ID service. The flag for ASD and ID was assigned after extensive testing by psychologists, physicians, and other professionals. All children with ASD and ID do not receive SCDE or DDSN services, thus, we also used to Medicaid file to identify children with ASD and ID. ASD was determined from ICD-9 codes of 299.0 and 299.1 and ICD-10 codes of F84.0 to F84.9. On the other hand, Intellectual disability (ID) was determined from ICD codes 317.0-319.0 and ICD-10 codes of F70-F79.

4.3.4. Data analysis:

The baseline characteristics of the study participants were analyzed using descriptive statistics and the significant differences were determined by the chi-square test. Since the outcome variable is categorical, we used multinomial logistic regression models for unadjusted and adjusted analysis. However, we chose the confounders through utilization of directed acyclic graph (DAG) as shown in Figure 4.2. The variables required to adjust

were maternal age, race, preeclampsia, infection, gestational diabetes, smoking, and body mass index.

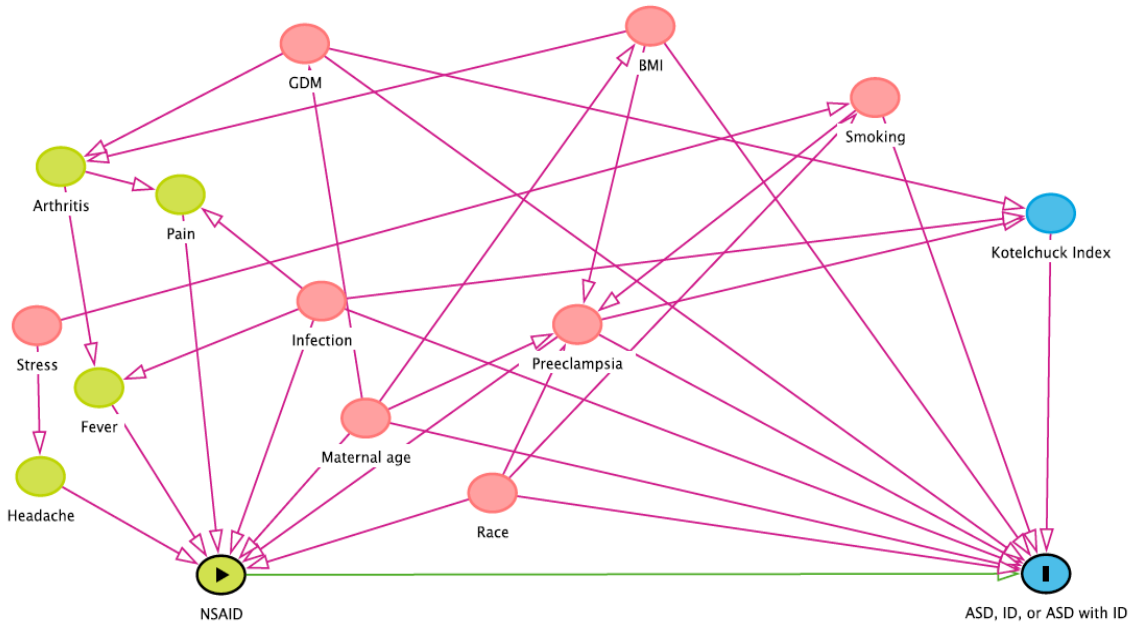

Figure 4.2: Directed Acyclic Graph (DAG) to ascertain the relationship among the variables

Later, we conducted a sub-group analysis considering the outcome detected by SCDDSN and SCDE datasets. We considered this subgroup analysis because SCDDSN detects ASD based on DSM-5 definition and SCDE conduct screening for the children through administering questionnaire, both of which are more uniform in comparison to the simple use of ICD codes from Medicaid data. We also conducted a sensitivity analysis to check our findings in the method shown by VanderWeele and Arah considering Alcohol consumption as unmeasured confounder,(51) and calculated the E-value.(52) For the sensitivity analysis, we considered alcohol consumption as an unmeasured confounder. A meta-analysis showed that maternal alcohol use was associated with ID of their children (OR:1.63, 95% CI: 1.49-1.78).(39) On the other hand, a study conducted in South Africa

identified migraine headache as an associated factor of alcohol use (OR: 1.61, 95% CI: 1.07-2.43).(53) We could not find any direct association of NSAID intake with alcohol use. Since, NSAID is widely used as a treatment of migraine attacks, we considered headache as a proxy variable for NSAID.(54, 55) On the other hand, regarding ASD, a multi-site case control study reported null effect of alcohol use with an OR of 0.80 (95% CI: 0.60-1.10).(56) The sensitivity analysis was conducted using Microsoft Excel 2016. We also calculated E-value using the following formula as demonstrated by VanderWeele and Ding.(52)

$$\text{E-value} = \text{OR} + \text{sqrt}[\text{OR} \times (\text{OR}-1)]$$

All other analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

4.3.5. Ethical considerations:

The study data were linked by the SC Revenue and Fiscal Affairs Office and provided to investigators as a deidentified dataset. Therefore, the University of South Carolina Institutional Review Board (IRB) reviewed the study and declared the deidentified data study had exempt status.

4.4. Results

Of the study participants, 2.5% had NSAID prescriptions (our main explanatory variable) during the pregnancy time. The mean mother's age was 24 years (SD: 5.4) and the mean children's age was 5 ± 1.4 years. Of the study participants, about 54% were Whites, 44% were African Americans, and about 2% were constituted by the other races. There were almost equal numbers of males (51%) and female (49%) among the children.

The mean birthweight was 3.16 ± 0.6 kilograms. Most (89%) of the children had a normal birthweight of more than 2500 grams while about 9% were of low birth weight (2000-2500 grams). The rest of 2% were of either extremely low birth weight or low birth weight babies. The mean gestational age was 38.3 ± 2.2 weeks. Most of the babies were born full term (88%) while about 2.6% were born before 32 weeks and the rest were born between 32 and 37 weeks of gestation. The mean BMI was 27.8 ± 7.4 kg/m2. About a third (30.6%) of the mothers had between 20-25 kg/m2 of BMI while 13.6% were underweight, 24% were overweight, and the rest were obese. Regarding the other risk factors, 5.8% had pre-eclampsia, 5.1% had gestational diabetes, 9.8% had infection, and 26.4% were smokers. Regarding Kotelchuck index, 24.5% had inadequate, 6.4% had intermediate, 25.2% had adequate, and the rest 45% had adequate plus index. Nearly all of the children were born from singleton pregnancy and about 2.8% were from multiple-birth pregnancies. The socio-demographic and clinical characteristics are presented according to the different categories of our outcome variables in Table 4.1.

Table 4.1: Socio-demographic and clinical characteristics of the study participants

Variables	ASD only (n=1018)	ID only (n=6,300)	ASD with ID (n=1,939)	None (n=144,305)	p-value
Maternal age (years)	24.8 ± 5.7	24.5 ± 5.7	25.4 ± 5.9	24.0 ± 5.4	<0.0001
Maternal race					
White	631 (62.0)	3,249 (51.6)	1,135 (58.5)	78,264 (54.2)	<0.0001
African American	375 (36.8)	2,980 (47.3)	779 (40.2)	63,459 (44.0)	
Others	12 (1.2)	71 (1.1)	25 (1.3)	2,582 (1.8)	
Children's age (years)	5.2 ± 1.4	5.0 ± 1.4	5.2 ± 1.4	5.0 ± 1.4	<0.0001
Children's gender					
Male	798 (78.4)	3,786 (60.1)	1,508 (77.8)	72,168 (50.0)	<0.0001
Female	220 (21.6)	2,514 (39.9)	431 (22.2)	72,137 (50.0)	
Birthweight (kilograms)	3.2 ± 0.6	2.7 ± 0.9	3.0 ± 0.9	3,1 ± 0.6	<0.0001
Normal	885 (86.9)	4,350 (69.1)	1590 (82.0)	130,215 (90.2)	<0.0001
Extremely Low	7 (0.7)	500 (7.9)	65 (3.6)	619 (0.4)	
Very Low	9 (0.9)	471 (7.5)	59 (3.0)	1,083 (0.8)	
Low	117 (11.5)	979 (15.5)	225 (11.6)	12,388 (8.6)	
Gestational age (weeks)	38.1 ± 2.2	36.3 ± 4.3	37.5 ± 3.2	38.4 ± 1.9	<0.0001
<32 weeks	24 (2.4)	1,122 (17.8)	148 (7.6)	2,734 (1.9)	<0.0001
32-37 weeks	115 (11.3)	898 (14.3)	230 (11.9)	12,544 (8.7)	
>37 weeks	879 (86.3)	4,280 (67.9)	1,561 (80.5)	129,027 (89.4)	
NSAID prescription	27 (2.7)	239 (3.8)	59 (3.0)	3,534 (2.5)	<0.0001
Body Mass Index (kg/m^2)	28.4 ± 8.1	28.7 ± 7.9	29.0 ± 8.0	27.7 ± 7.4	<0.0001

Normal	280 (27.5)	1,736 (27.6)	539 (27.8)	44,430 (30.8)	
Underweight	139 (13.7)	771 (12.2)	206 (10.6)	19,779 (13.7)	<0.0001
Overweight	235 (23.1)	1,567 (24.9)	450 (23.2)	35,080 (24.3)	
Obese	364 (35.8)	2,226 (35.3)	744 (38.4)	45,016 (31.2)	
Preeclampsia	86 (8.5)	487 (7.7)	157 (8.1)	8,180 (5.7)	<0.0001
Gestational Diabetes	59 (5.8)	383 (6.1)	143 (7.4)	7,279 (5.0)	<0.0001
Infection	82 (8.1)	605 (9.6)	166 (8.6)	14,195 (9.8)	0.0610
Smoking	203 (20.0)	1,141 (18.1)	374 (19.3)	23,504 (16.3)	<0.0001
Kotelchuck index					
Inadequate	177 (22.3)	1,319 (27.0)	329 (22.4)	27,981 (24.5)	
Intermediate	330 (6.7)	86 (5.9)	38 (4.8)	7,302 (6.4)	<0.0001
Adequate	196 (24.7)	987 (20.2)	331 (22.5)	29,067 (25.5)	
Adequate +	383 (48.2)	2,258 (46.1)	724 (49.3)	49,738 (43.6)	
Plurality					
Singleton	983 (96.6)	5,825 (92.5)	1,849 (95.4)	140,458 (97.3)	
Twin	35 (3.4)	450 (7.1)	85 (4.4)	3,799 (2.6)	<0.0001
Triplet	0 (0.0)	25 (0.4)	5 (0.3)	48 (0.03)	

Our main explanatory variable NSAID prescription was found to be associated with ID only in both unadjusted and adjusted analysis. The children with the mothers who had NSAID prescription were 52% more likely to have ID in comparison to the children whose mothers did not have NSAID prescription. Maternal age was associated with all three categories of the outcome variable. With each unit increase of age, the odds of ASD only increases by 4%, the odds of ID only increase by 2%, and the odds for ASD with ID also increases by 2%. After controlling for other variables, White race was a risk factor for development of ASD and ASD with ID. The odds of having ASD among the children of the mothers with preeclampsia were 33% higher than that of the children of the mothers without preeclampsia (p-value: <0.01)and the odds ratio for ASD with ID was 1.47 (p-value = <0.01). The odds of ID only for the children of smoker mothers were 18% higher than that of non-smoker mothers' children while the odds for ASD with ID for smokers' children was 20% higher than the comparator. The gestational diabetes was associated with ASD only (p-value:0.03). Infection was not associated with any of the outcome variables with or without adjusting for the confounders. Regarding BMI, being in the obesity group for the mothers seem to be more at risk of having children with ASD only, ID only, or ASD with ID. The odds of having ID only among the overweight mothers were 11% higher than that of the mothers with normal BMI. The findings from unadjusted and adjusted analyses are presented in Table 4.2.

Table 4.2: Adjusted and Unadjusted odds ratios

Variables	ASD only		ID only		ASD with ID	
	UOR	**AOR**	**UOR**	**AOR**	**UOR**	**AOR**
NSAID prescription	1.09	1.23	1.57***	1.52***	1.25	1.08
Mothers' age	1.03***	1.04**	1.02***	1.02***	1.05***	1.02***
Mothers' Race						
White	1.00	1.00	1.00	1.00	1.00	1.00
African American	0.73***	0.87**	1.13***	1.15***	0.85**	0.75***
Others	0.58	0.65*	0.66**	0.58**	0.67*	0.67
Preeclampsia	1.54**	1.33**	1.39***	1.32***	1.47***	1.47**
Smoking	1.28**	1.20**	1.14**	1.18***	1.23**	1.20*
Gestational diabetes	1.16	1.20*	1.22**	1.10	1.50***	1.00
Infection	0.86	0.94	0.97	0.97	0.80	0.88
Body Mass Index						
Normal	1.00	1.00	1.00	1.00	1.00	1.00
Underweight	1.12	0.88	0.99	1.01	0.86	1.13
Overweight	1.06	1.01	1.14**	1.11**	1.06	1.05
Obese	1.28**	1.26***	1.26***	1.17***	1.36***	1.26**

***<0.0001, **<0.01,* <0.05

We have conducted a sub-group analysis considering the outcome detected by SCDDSN and SCDE datasets and found similar results with significant association of NSAID prescription with risk of ID. The sub-group analysis also did not show any association of our exposure variable with ASD or ASD with ID. (Supplementary material).We also conducted a sensitivity analysis considering alcohol use an unmeasured confounder. The sensitivity analysis for the association between NSAID and ID shows that the true odds ratio is 1.30 (95%CI: 1.14, 1.49) considering exposure-unmeasured confounder OR of 1.61 and unmeasured confounder-outcome OR of 1.63. When we considered ASD as the outcome variable during the sensitivity analysis the true OR we found was 1.35 (95% CI: 1.04-1.75) which means that if we could adjust for unmeasured confounder the mothers who used NSAID during pregnancy would have found to be at more risk of having children with ASD. Table 3 shows the sensitivity analysis:

Table 4.3: Sensitivity analysis with 'alcohol use' as the unmeasured confounder

Outcome Variable	Observed Exposure-Outcome OR	Exposure-Unmeasured confounder OR	Unmeasured confounder-Outcome OR	True OR
Intellectual Disability	1.52	1.61	1.63	1.30
	1.33 (LCI)	1.61	1.63	1.14
	1.74 (UCI)	1.61	1.63	1.49
Autism Spectrum Disorder	1.23	1.61	0.80	1.35
	0.95 (LCI)	1.61	0.80	1.04
	1.60 (UCI)	1.61	0.80	1.75

The E-value was found to be 1.92. So, the observed OR between NSAID and ID of 1.52 could be explained by the alcohol use that was associated with both exposure and outcome by an OR of 1.92 folds each, above and beyond the measured confounders. The

E-value for NSAID and ASD was 2.04 when we considered ‘alcohol use’ as an unmeasured confounder.

4.5. Discussion

Overall, the prevalence of ASD only, ID only, and ASD with ID were 0.66%, 4.10%, and 1.26%, respectively. The prevalence of NSAID prescription was 3.8% among children with ID only which was significantly higher than the same of other categories. And the variables significantly associated with the ID only group were: NSAID prescriptions, mothers’ age, race, BMI, smoking status, and preeclampsia. In addition, we also identified maternal age, race, preeclampsia, gestational diabetes, and obesity as risk factors for ASD, which have also been evident in many studies.(31-33, 37, 57, 58)

It is noteworthy that preeclampsia was positively associated with ASD only, ID only, and ASD with ID in our study. Other researchers have identified preeclampsia as a potential risk factor for ASD.(35, 59, 60) This is an important finding since the US Preventive Services Task Force (USPSTF) recommends NSAIDs for pregnant women at risk for preeclampsia.(61) Thus, if our findings are replicated using other data sources the recommendation to reduce preeclampsia would have to be balanced by the need to reduce ASD or intellectual disability. The data reviewed in the USPSTF recommendation includes numerous studies about the association of NSAIDs and ASD, but it does not include any literature about the association of NASAIDs and ID, or ASD and ID.

The prevalence of ID in our study was similar to the reported ID prevalence by SC Autism and Developmental Disabilities Network.(23) The increased prevalence is likely due to the Katie Beckett Waiver in South Carolina Medicaid that allows children with ID to qualify for Medicaid without consideration of the parental income or assets.(62) Thus,

among the children qualified for Medicaid in South Carolina, a higher-than-expected proportion have ID as their eligibility determinant, compared to children on Medicaid in other states who do not have the Katie Beckett waiver.(62) We found that the odds of having children with ID of the mothers who had NSAID prescription was 52% higher than that of the mothers who did not have any NSAID prescription during pregnancy. However, we did not find any association of NSAID prescription with ASD, and ASD with ID. A prospective cohort study involving 6,876 mothers suggested that prenatal exposure of NSAID prescription was associated with attention problems of the children.(57) Another study showed that consuming NSAIDs during pregnancy may affect children's brain.(63) However, there has not been many studies done on this topic and thus we cannot reach any conclusion yet.

Mothers' age has been found to be positively associated with all the outcome variable categories. Advanced maternal age is also an established risk factor for ASD and ID (20, 31, 33, 35-37, 39, 64-66). Similarly, ID of the children has also been associated with maternal age as evident by many studies across the world (20, 39, 59, 67). Maternal race has been identified as a significant risk factor for ASD, ID, and ASD with ID. In comparison to Whites, being African American seemed to be protective for ASD and ASD with ID which aligns with the findings of many other studies (68, 69). BMI is another risk factor that has been significantly associated with ASD only, ID only, and ASD with ID constituting 26%, 17%, and 26% higher odds than normal weighed mothers. Regarding the association between maternal BMI, there have been inconclusive findings reported by different studies (70-72). In our study, gestational diabetes was found to be associated with ASD only. A large population-based cohort study with more than 2.3 million individuals

found that there was strong relationship of Diabetes mellitus with ASD, ID, or Attention Deficit Hyperactivity Disorder (ADHD) (73). Unlike our study, Smoking was found to be associated with increased odds for all the outcome categories. Oother studies analyzing reported conflicting results for the association of smoking and ASD reported conflicting results (74-76). The subgroup analysis and sensitivity analysis for ID have endorsed our findings. However, when we conducted sensitivity analysis for ASD, we found significant association with NSAID while adjusting for unmeasured confounder 'alcohol use' which calls for further rigorous scientific study.

Strengths of this study include its large sample size and study design. Moreover, very few studies explored the association of NSAID prescription with ASD and ID, individually and collectively. The sensitivity analyses and calculation of E-value have also strengthened our study findings. The main limitation of our study lies in the unavailability of the exposure data for NSAID usage without prescription. However, a study reported that missing OTC drug exposure is not a large source of bias especially when the overall prevalence of drug usage is below 35%,(76) and several studies reported that the prevalence of OTC NSAID usage during pregnancy is well below that level of 35%.(77, 78) Despite this limitation, administrative pharmacy records are commonly used as a source for medication exposures and are not subject to recall bias. Finally, as is generally the case with medication studies outside a controlled experiment, we cannot confirm details about the women's NSAID-taking behaviors.

In conclusion, maternal exposure to prescription NSAIDs was associated with ID, but not ASD or ASD with ID. Our findings warrant the need for more specific research on both the biologic plausibility of NSAIDs being causally associated with ID and the

generalizability of the effect of NSAIDs prescription during pregnancy on intellectual disability in the child, using other linked maternal-child datasets.

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4.7. Supplementary material

Table 4.4: Supplementary table presenting sub-group analysis

Variables	ASD only		ID only		ASD with ID	
	AOR	p-value	AOR	p-value	AOR	p-value
NSAID prescription	1.12	0.5261	1.50	<0.0001	0.87	0.7288
Mothers' age	1.05	<0.0001	1.02	<0.0001	1.04	0.0013
Mothers' Race						
White	1.00	-	1.00	-	1.00	-
Black	0.79	0.0002	1.13	<0.0001	0.91	0.4627
Others	0.58	0.0440	0.68	0.0008	0.90	0.8093
Preeclampsia	1.29	0.0215	1.32	<0.0001	1.82	0.0027
Smoking	1.18	0.0310	1.18	<0.0001	0.93	0.6581
Gestational diabetes	1.21	0.0991	1.11	0.0450	0.91	0.7307
Infection	0.98	0.8411	0.96	0.2775	0.51	0.0144
Body Mass Index						
Normal	1.00	-	1.00	-	1.00	-
Underweight	0.83	0.0801	1.00	0.9756	0.99	0.9640
Overweight	0.99	0.9525	1.10	0.0063	0.90	0.5285
Obese	1.25	0.0034	1.18	<0.0001	1.16	0.3446

Chapter 5: Prenatal exposure to acetaminophen and risk of autism spectrum disorder: a systematic review and meta-analysis[2]

[2]Chowdhury, MAK. To be Submitted to *Pharmacoepidemiology and Drug Safety*.

5.1. Abstract

Introduction: Acetaminophen is the most commonly used medication during pregnancy. Recent studies suggest an association between acetaminophen usage during pregnancy and neurodevelopmental disorders in their children which has been biologically explained by the oxidative stress produced by the drug during pregnancy. Therefore, we conducted a systematic review to evaluate the literature examining the risk of autism among children of the mothers who had used acetaminophen during pregnancy.

Methods: We followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2009 framework guideline and checklist to conduct this systematic review. We searched MEDLINE, Embase, and Cochrane databases for relevant studies up to September 2020. The review process was conducted by two researchers individually and any concern was sorted out with the help of a senior of the team. Finally, three studies met the inclusion criteria and were selected for narrative synthesis and meta-analysis. The risk of bias was assesses using a standardized tool. A Random effects model was utilized for meta-analysis since there was heterogeneity (I^2: 94%).

Results: The review included 67,319 mother-child dyads in total. The exposure and outcome ascertainment differed among the studies. The follow up ranged from 5 years to 20 years. The pooled risk ratio for autism was 1.29 (95% CI: 1.17, 1.41).

Conclusion: We found a 29 percent evaluated risk for ASD. However, this systematic review warrants further investigation of the research question in order to establish the generalizability of the selected study results.

PROSPERO registration: Done in October 2020 (CRD42020213917)

5.2. Introduction

Acetaminophen (also known as ‘Paracetamol’, ‘Panadol’, or ‘Tylenol’) is an effective analgesic and antipyretic agent.(1-3) Among all the ‘Over-the-counter (OTC)’ drugs, acetaminophen is the most commonly used drug for fever and pain management (4, 5). Since acetaminophen is considered safe for pregnant women, it continues to be the most common medication used to relieve the aforementioned symptoms.(6, 7) Studies conducted in the United States and Europe suggest that about 50% of pregnant women use acetaminophen at least once during their pregnancy period (8). However, there has also been evidence of harmful effects on children due to maternal acetaminophen exposure, including increased risk for development of asthma,(9, 10) cryptorchidism,(11, 12) and neurodevelopmental disorders.(7, 13-17) Despite these reports on adverse impact of acetaminophen intake during pregnancy, in 2015, the U.S. Food and Drug administration (USFDA) released a safety announcement regarding potential limitation of those studies and continued with the previous recommendations for pain and fever management during pregnancy.(18)

Different studies reported different types of neurodevelopmental disorders associated with Acetaminophen exposure during fetal life that includes behavioral problems,(7, 19) low intelligence quotient (IQ),(15, 20, 21) Attention Deficit Hyperactivity Disorder (ADHD),(16, 17, 22) and Autism spectrum disorder (ASD).(23-26) The underlying pathophysiology regarding how acetaminophen affects fetal brain is still being explored both in animal models and humans.(12, 27-31) A study on in vitro developing mouse cortical neurons found a detrimental effect of acetaminophen on cortical neuron function.(27) Other rodent studies suggested that acetaminophen toxicity causes neuronal

apoptosis and consequently disruptive brain development through inhibition of fetal testosterone production.(30, 32) Another mechanism of pathogenesis indicated by several studies is through inhibition of cyclooxygenase-2 enzyme which may alter brain functions.(31, 33, 34) These mechanisms produce free oxygen radicals which can cross the blood-placental barrier and may cause neuro-developmental disorders in the fetus.(28)

The impact of acetaminophen on ASD has only recently been explored,(35) but it is an important topic in public health since the prevalence of autism is increasing throughout the world.(36) There has been one systematic review and meta-analysis,(37) but in that review, the outcome was not autism exclusively, rather they included both ADHD, ASD, conduct disorders. Moreover, the authors included case-control studies in their review, and they reported ASD together with emotional problems. Furthermore, after the publication date of that meta-analysis, a few other publications described the relationship between acetaminophen and autism.(38-43) Therefore, we conducted a systematic review and meta-analysis, using articles published through September 2020, to assess the association between in-utero acetaminophen exposure and risk of autism.

5.3. Methods

5.3.1. Registration of the review

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2009 framework guideline and checklist.(44) According to the guideline of the PRISMA checklist, we have registered our systematic review protocol at the PROSPERO registry of systematic reviews in October 2020 (CRD42020213917).(45)

5.3.2. Eligibility criteria

We planned to review all the scientific articles, published in English, up to September 2020. Although the preferred study type was Randomized Controlled Trial (RCTs), we found no RCT of acetaminophen in pregnant women. Therefore, we only included cohort studies in our final selected articles. We excluded case-control studies to get similar measures of effect and biases. Across the analyses described in the collected studies, the effect measures for our outcome 'autism' included hazard ratios, risk ratios, incidence rate ratios, odds ratios, or coefficients. The exposure and comparison ascertainment did not consider the usage of any concomitant NSAID. There was no age, ethnicity, or socio-economic status preference for the study population. The Population, Intervention, Comparison, Outcome (PICO) framework for our systematic review is given as Figure 5.1 below.

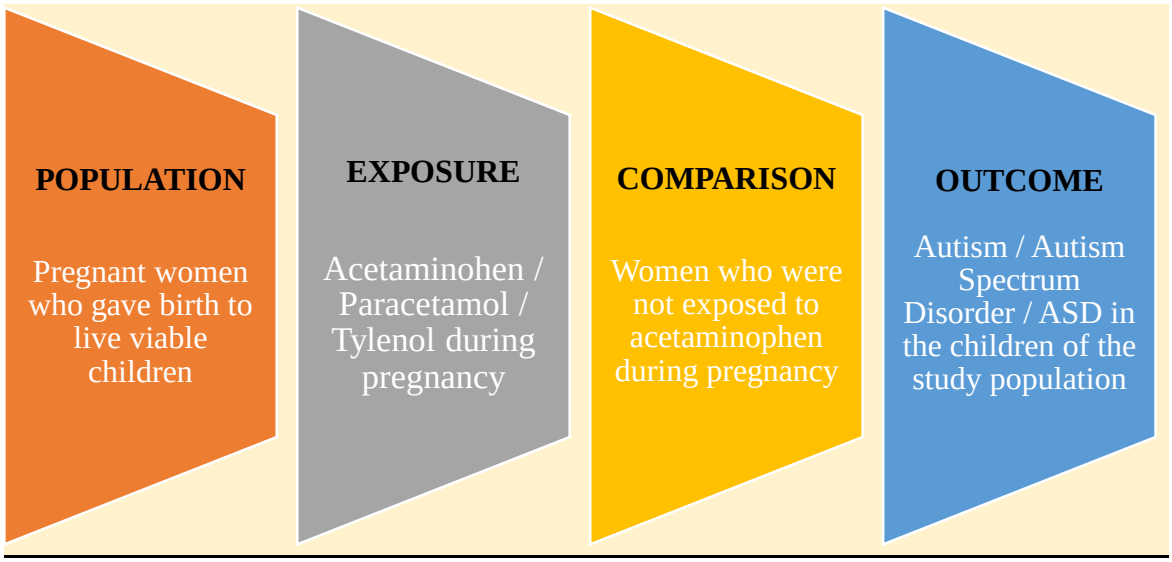

Figure 5.1: PICO framework for the systematic Review

5.3.3. Data sources and Search strategy

The databases we used for our systematic review were MEDLINE, EMBASE, and Cochrane Reviews to identify all the available manuscript that studied the association between in-utero exposure of acetaminophen and risk of autism irrespective of study types. We identified the studies using the keywords and appropriate Medical Subject Heading (MeSH) terms: “autism”, “ASD”, “autism spectrum disorder”, “acetaminophen”, “paracetamol”, “Tylenol”, “pregnancy”, and “prenatal” in different combinations. We also searched published systematic reviews, other online resources, and conference abstracts to identify all relevant studies. Finally, when appropriate and necessary, we contacted the authors of the final selected articles for clarification about methods [Personal correspondence].

5.3.4. Study selection and data extraction

Two investigators (MAKC and RDG) independently searched the databases for the selection of the articles. Although they independently screened titles, abstracts and full texts, any disagreement was resolved by consensus, or by consultation with the study supervisor (SM). After finalizing the articles, a standardized data extraction form was developed and piloted, based on the Cochrane data abstraction template.(46) The first author (MAKC) extracted the data and consulted with RDG and SM if there were any issues. The extractable data items were study title, publication year, population description, study setting, inclusion and exclusion criteria, methods of participant recruitment, study objective, study start and end date, study design, outcome measures, exposure, data analysis, bias assessment, and results.

5.3.5. Risk of bias assessment

The risk of bias was assessed both within and across the studies using utilized "Tool to Assess Risk of Bias in Cohort Studies" from Evidence Partners contributed by the CLARITY group at McMaster University and published by Evidence Partners(47) where we assessed the risk of bias analyzing 8 different questions. Again, two investigators independently filled out the forms relevant to study bias assessment and rated the studies as 'Good', 'Fair', or 'Poor'. Any inconsistency was resolved by consensus, or by consultation with the senior authors.

5.3.6. Synthesis of results

Primarily, the findings have been described as narrative synthesis with the explanation of the summary measures (Hazard ratios, Risk ratios, or Odds ratios). We also described how the authors obtained the effect measures with appropriate numerators and denominators where applicable.

5.3.7. Statistical analysis

We conducted the meta-analysis to get the pooled estimates using the Microsoft Excel 2016 as suggested by Neyeloff et al. (2012).(48) Heterogeneity was assessed using the I2 statistics, when I2 values of 75%, 50%, and 25% represented high, medium, and low heterogeneity, respectively. Forest plots were generated from the same software to illustrate our findings. Random effects models were used since there was high heterogeneity. Statistical significance was defined using a 2-sided alpha level of 0.05.

5.4. Results

We found 90 articles from MEDLINE (31), EMBASE (51), and Cochrane Reviews (8) when we applied our search terms in the respective databases. Two additional articles were identified from manual searches from conference proceedings and gray literature. After removal of duplications and articles with languages other than English, 68 articles were eligible for title and abstract screening. Based on our predefined eligibility criteria, 24 articles were selected for full text review. We excluded 21 articles for reasons related to article types, study design, inappropriate exposure and outcomes, and animal studies. We included 3 articles in this systematic review which encompassed 67,310 mother-child pairs among whom 460 children had autism. The selection process is depicted in Figure 5.2.

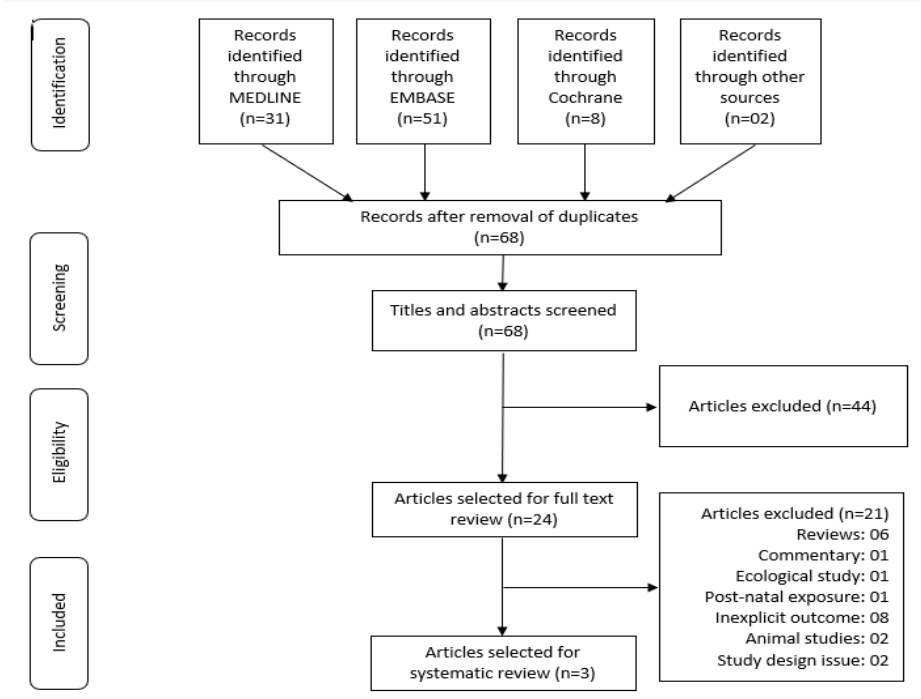

Figure 5.2: Preferred Reporting Items for Systematic Reviews (PRISMA) flow diagram for selecting the articles published to ascertain the association between acetaminophen intake during pregnancy and autism in the children through cohort study till September 2020

None of the selected studies was identified as “poor” after risk of bias assessment. The reviewers have identified all 3 studies between “good” and “fair” because of a few risks in exposure ascertainment, outcome assessment and cohort follow up duration. Moreover, we could not assess whether all the possible confounders have been considered in these studies. The details of risk of bias assessment are provided in Table 5.1.

Table 5.1: Findings from risk of bias assessment

Articles	Was selection of exposed and non-exposed cohorts drawn from the same population	Can we be confident in the assessment of exposure?	Can we be confident that the outcome of interest was not present at the study?	Did the study match for all variables that are associated with the outcome or adjust for them?	Can we be confident in the assessment of the presence or absence of prognostic factors?	Can we be confident in the assessment of outcome?	Was the follow up of cohorts adequate?	Were co-interventions similar between groups?
Avella-Garcia CB et al., 2016	Yes	Probably Yes	Yes	Probably Yes	Probably Yes	Yes	Probably Yes	Yes
Liew Z et al., 2016	Yes	Probably No	Yes	Probably Yes	Probably Yes	Probably Yes	Yes	Yes
Ji Y et al., 2016	Probably Yes	Yes	Yes	Probably Yes	Probably Yes	Probably Yes	Probably Yes	Yes

These cohort studies were conducted in three different countries in Europe and North America. One of the studies (Avella-Garcia, 2016) was conducted in four different Spanish cities (Asturias, Gipuzkoa, Sabadell, and Valencia)(16) while Ji et al. (2019) conduced their study in Boston, USA.(39) The other study utilized the Danish National Birth Cohort.(15) All those articles were published after 2015. However, the timelines for the studies were different from one another ranging from 1998 to 2018. The sample size also varied between the studies, ranging from 996 in study conducted in Boston, USA(39) to 64,322 from Danish National Birth Cohort(15). The duration of the cohort follow up for the studies were 20 years(39), 12.7 years(15), and about 5 years(16). In keeping with our research question, the exposure was acetaminophen in all these three articles although the method of ascertainment of exposure was not the same. Garcia et al. and Liew et al. interviewed the women prospectively utilizing a standard questionnaire (face-to-face and telephone interviews) whereas Ji et al. measured cord plasma metabolites of acetaminophen as the exposure status. The metabolites which were measured included unchanged acetaminophen, acetaminophen glucuronide, and 3-(N-acetyl-L-cystein-S-yl) acetaminophen. The authors of the papers utilized different approaches for outcome ascertainment. Garcia et al. ascertained the outcome of autism from the Childhood Autism Spectrum Test (CAST) score while the other two used International Classification of Diseases 9th and 10th version (ICD-9 and ICD-10) codes for autism. All the selected articles mentioned possible biases in their respective studies. The important components of the studies are summarized in Table 5.2.

Table 5.2: Glossary of the selected articles

Author	Journal & Publication year	Study site & Timeline	Study population	Exposure assessment	Outcome assessment	Bias ascertainment
Avella-Garcia CB et al.	International Journal of Epidemiology 2016	Spain 2004 - 2008	• The parent study had 2644 mother-child pairs from Spanish birth cohort. • CAST score was available for 1467 children	Interviewing participants – face to face	CAST13 scores	• Sensitivity analysis was conducted. • No differential loss to follow up. • Unmeasured genetic confounding • Exposure misclassification
Liew Z et al.	International Society for Autism Research 2016	Denmark 1996 - 2002	• In total, 101,041 pregnancies were enrolled in Danish National Birth Cohort • This study was limited to 64,322 children and their mothers	Interviewing participants – telephone	ICD-9 & ICD-10 codes (Only hospital data)	• Large sample ensured generalizability. • Multiple imputation for missing value • Less chance of recall bias for exposure assessment • Valid outcome assessment • Unmeasured confounding

Ji Y et al.	JAMA Psychiatry 2020	USA 1998 - 2018	• For this study, the Boston birth cohort enrolled 3183 mother-infant dyads. • Of them, 996 had sufficient cord plasma sample for metabolite survey, and 66 had ASD	Cord plasma metabolites	ICD-9 & ICD-10 codes (Electronic Medical Records)	• Absence of true unexposed groups • Unmeasured confounding • There has been issues regarding generalizability

Despite having similar study design, and the same exposure and outcome, the selected studies used different measures of association in their analysis. Avella-Garcia et al. (2016) considered the outcome autism as continuous variables,(16) while in the Ji et al. paper the outcome was categorical.(39) In the Liew paper, the outcome was time to event.(15) Thus, for statistical analysis, the studies utilized linear regression, logistic regression, and Cox proportion hazard regression, respectively. The studies also included the variables adjusted for in the final model. Table 5.3 outlines the measures of association, analysis strategy, and the variables in the final model.

Table 5.3: Measures of association, analysis strategy, and variables adjusted for in the final model in the selected articles.

Articles	Measure of association	Analysis strategy	Variables adjusted for in the final model
Avella-Garcia, 2016	Incidence Risk ratio	• Linear regression • Negative binomial regression	• City, child gender, age at testing, gestational age at birth, and maternal social class, education, mothers' IQ, chronic illness, fever during pregnancy, urinary infection during pregnancy.
Liew, 2016	Hazard ratio	• Cox proportional hazard regression	• Child's sex, birth year, maternal age at childbirth, parity, socioeconomic status, smoking, alcohol drinking during pregnancy, and maternal pre-pregnancy body mass index, self-reported maternal psychiatric illness
Ji, 2020	Odds ratio	• Adjusted logistic regression	• Maternal age at delivery, maternal race/ethnicity, maternal educational level, marital status, stress during pregnancy, smoking before or during pregnancy, alcohol use before or during pregnancy, maternal body mass index, parity, child's sex, delivery type, preterm birth, and low birth weight.

The study by Garcia et al., presented their results as beta coefficients and found no significant results overall regarding increase of the CAST score for detecting autism when adjusted for confounders. In a stratified analysis by sex, they reported significant result in for male children.(16) However, we calculated the crude Risk Ratio for this study and found that to be significant for males and females (1.34, 95% CI: 1.17, 1.53). In the Liew et al. paper the authors presented hazard ratios separately for ASD with or without hyperkinetic symptoms.(15) They reported significant results for the former and no association between acetaminophen exposure and ASD without hyperkinetic symptoms. Again, we calculated the crude RR which was 1.21 (1.07 – 1.37). The Ji paper reported their findings for acetaminophen metabolites separately. The authors presented adjusted Odds ratios for cord blood unchanged acetaminophen and cord acetaminophen burden having first tertile as the reference group since there were no true unexposed group.(39) In both these cases, the third tertile showed significant results. For cord acetaminophen glucuronide and cord 3-(N-acetyl-L-cystein-S-yl) acetaminophen, there were some cases for whom these metabolites were not detected, and the authors utilized this group as the reference category. The study reported significant finding for cord acetaminophen glucuronide, and our calculated crude RR was 1.34 (0.78 – 2.30). As shown in Figure 5.3, our meta-analysis suggests that acetaminophen use during pregnancy is significantly associated with an increased risk of ASD (RR = 1.29, 95% CI:1.17, 1.41, I^2=94%).

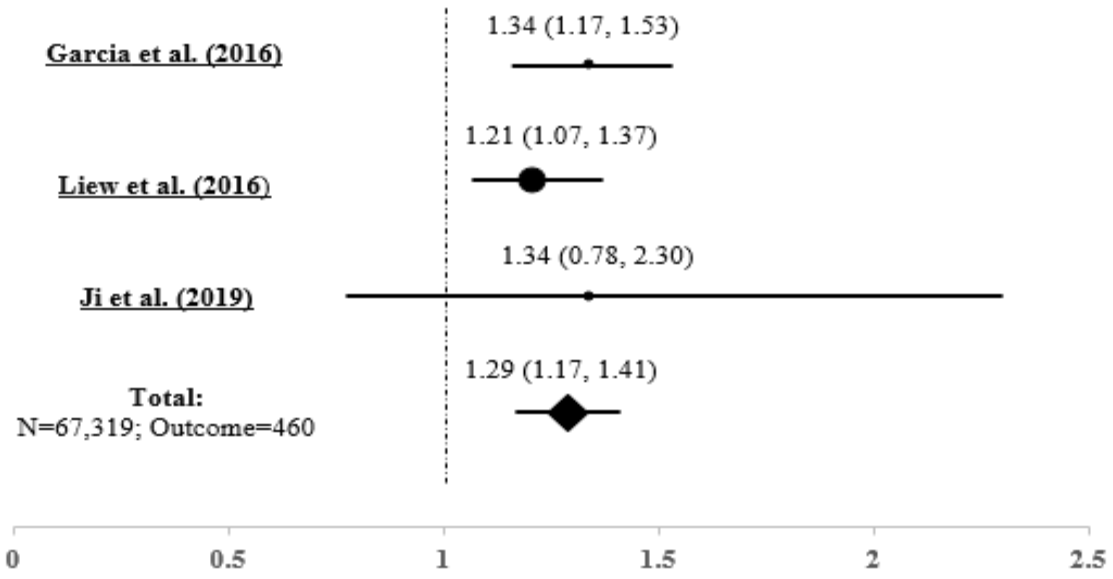

Figure 5.3: Forest plot showing Risk ratios (RRs) and confidence intervals (CIs) from a random effects meta-analysis of 3 cohort studies on the risk for autistic spectrum disorder after exposure to acetaminophen during pregnancy.

5.5. Discussion

This systematic review and meta-analysis unique in a way that no other study, to our knowledge, has examined the association of acetaminophen exposure during pregnancy and children's ASD exclusively. However, there has been another article that examined the association of the same exposure with neurodevelopmental outcomes including ASD(37) up to January 2017, whereas we included studies up to October 2020. For the eligibility criteria, Masarwa, R., et al., selected both cohort and case-control study designs, and ADHD and ASD as outcomes. On the contrary, we included only cohort studies and ASD as the only outcome. In this way, we excluded three papers that were included by Masarwa et al.(37) For example, we excluded a study that reported the outcomes of psychomotor delays, behavioral problems, and temperament.(19)

Our meta-analysis suggests that children of mothers who used acetaminophen during their pregnancy period have a 29% higher risk of ASD in comparison to children whose mothers did not use acetaminophen during pregnancy. Our study findings support the meta-analysis finding of Masarwa et al. that showed the RR of 1.19 (95% CI: 1.14, 1.25).(37) There have also been research reports that demonstrated the biological plausibility of this association either through neuro-disruptive mechanisms or oxidative stress in utero.(12, 13, 28, 30, 49, 50)

However, there are some limitations to our approach. Firstly, there were differences in exposure ascertainment. Two of the three selected articles used interviews for exposure ascertainment, one of which was face-to-face and the other was telephone interviews.(15, 16) This created a potential for bias since the validity depends upon how the questions are worded. But more importantly, the third article ascertained the exposure by biochemical measurement(39) using the cord plasma metabolites collected at birth. There are several issues regarding exposure ascertainment in this way since measuring once at birth only confirms exposure during peripartum period, since the half -life of acetaminophen is just a few hours.(51) Moreover, the acetaminophen metabolites are excreted through urine mostly within 24 hours.(51, 52) Thus, this exposure ascertainment by plasma biomarker estimation at birth will not provide an idea whether the mother was exposed to acetaminophen during the in-utero brain development of her child. The study did not measure acetaminophen sulfate, a major acetaminophen metabolite, which could have evaluated cord acetaminophen burden.(39, 53) For the other acetaminophen metabolites, they compared no detection of metabolites in the cord, and this does not represent the absence of exposure during the pregnancy period. Secondly, this study did not have a true

comparator.(39) They categorized the unchanged cord acetaminophen into tertiles and presented their findings accordingly considering the lowest tertile as the reference. Thirdly, the outcome ascertained differed among the studies when one of the articles measured Childhood Autism Spectrum Test (CAST) scores while the others used international classification of Disease (ICD) codes. However, CAST scoring system has been regarded as a good predictor of autism.(54-56) A study conducted in UK by Williams et al. on 1,925 children reported sensitivity of 100% and specificity of 97% of this test although the positive predictive value was 50% only.(56) Another study conducted in China reported good test-retest reliability (kappa=0.64) with the cut-off score of 15 out of 39 which has been a well-accepted cut-off value now.(55) However, CAST scoring is still not widely used as a diagnostic tool, rather it is more used as a good screening tool.(54) However, despite this, CAST score is a better indicator of the outcome than the ICD codes since we do not get much information from the ICD codes regarding how the diagnosis was confirmed. Among the other two studies, one used only the hospital registry while the other used the physician diagnosed electronic medical registry. Finally, they presented three different effect measures with different statistical analyses strategies. Garcia et al. used linear regression and negative binomial regression and presented incidence risk ratio (IRR),(16) Liew et al. used Cox proportional hazard regression,(15) and Ji et al. utilized adjusted logistic regression.(39) Fourthly, the number of the papers included is very low which impacts the heterogeneity and may result in bias.(57).

The main strength of this study lies in its specificity of the research question and corresponding eligibility criteria. This is the first systematic review and meta-analysis that examined the association between maternal usage of acetaminophen during pregnancy and

Autism Spectrum Disorders (ASD) through analyzing cohort studies only. We conducted an extensive search for available literature published till October 2020 and utilized standard methods for data extraction. We utilized Preferred Reporting Items for Systematic Reviews (PRISMA) flow diagram for selecting the articles.(44) Since the selected articles were heterogenous in nature, we applied random effects model to pool the results.

Our findings suggest a need for detailed, methodologically sound investigations of the risk of ASD due to acetaminophen use during pregnancy. Until a clear causal pathway is established, the findings of these studies should not be overstated since acetaminophen is one of the most widely used medicine across the globe.

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Chapter 6: NSAID usage during pregnancy, mediated through birthweight, is associated with the development of intellectual disability: findings from prospective data.[3]

[3]Chowdhury, MAK. To be Submitted to *Neonatology*.

6.1. Abstract

Introduction: Although many risk factors have been identified for ID, the effect of non-steroidal anti-inflammatory drugs (NSAID) usage during pregnancy was unexplored. We estimated direct and indirect effects of NSAID on ID while considering preeclampsia and birth weight as potential mediators.

Methods: We conducted this retrospective cohort study using the datasets from Medicaid, Department of Education, Department of Disabilities and Special Needs, and birth certificate from South Carolina between 2010-2017. We used multiple logistic regression to identify factors associated with ID. Subsequently, we conducted the mediation analyses using the SAS version 9.4.

Results: Out of 153,562 children born to Medicaid mothers during the study period, 2.5% of the mothers had NSAID prescription while 5.4% of the children were diagnosed with ID. The factors associated with ID were NSAID prescription during pregnancy, child's sex and birthweight, maternal age, race, BMI, smoking, gestational diabetes, Kotelchuck index, and multiple pregnancy. The odds of having a child with ID among the mothers who had an NSAID prescription during pregnancy was 27% higher than that among the mothers who did not have an NSAID prescription (aOR: 1.27, 95% CI: 1.12-1.45). We found a significant mediation effect of birthweight on ID. Very low birth weight (<1500 grams) mediated the association of NSAIDs on ID (OR:1.21, 95% CI: 1.06 – 1.40). The indirect effect was 1.12 (95% CI: 1.06-1.18) and 40.9% of the effects of NSAIDs on ID was mediated through very low birthweight. Similarly, when we categorized birthweight as low birth weight (>2500 grams) versus others, the direct effect was 1.42

(95% CI: 1.03-1.96) and the indirect effect was 1.10 (95% CI: 1.06-1.15) and 27.1% of the effects of NSAIDs on ID were mediated through birthweight.

Conclusion: The use of NSAIDs during pregnancy is associated with an increased risk for ID, partially mediated through birthweight. It is clinically relevant because NSAIDs are recommended for women at risk for preeclampsia by both the American College of Obstetrics and Gynecology and the US Preventive Services Task Force.

6.2. Introduction

An intellectual disability (ID) is a neurodevelopmental disorders which has onset during the developmental period and is characterized by "developmental deficits that produce impairments of personal, social, academic or occupational functioning" according to Diagnostic and Statistical Manual, Fifth edition (DSM-5).(1) IDs are characterized by social, cognitive, and adaptive skill deficits which is often accompanied by stereotypies and challenging behaviors.(2-5) ID is the only condition, among the neurodevelopmental disorders, that demonstrates substantial deficit in in intellectual function although it shares many features with other disorders including communication disorders (language disorder, speech sound disorder, childhood-onset fluency disorder, social communication disorder), autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), and motor disorders (developmental coordination disorder, stereotypic movement disorder, tic disorders).(6)

A US systematic review suggested that the prevalence of ID among children ranges between 1.1% to 1.34%.(7) Another study in Finland reported the prevalence to be 1.17%.(8) A study conducted among 2,208 children with both ASD and ID identified through the South Carolina Autism and Developmental Disabilities Network reported that

the prevalence of ASD in people with ID to be 18.04% while the ASD rate in the general population was between 0.60% and 1.11%.(9) However, different epidemiological studies in United States show that the range of prevalence of ID vary widely depending on the denominator (or source of the underlying population including Medicaid insured mothers, school based counts, or service delivery systems), from 8.7 to 36.8 per 1,000.(10)

A systematic review and meta-analysis involving 17 studies showed that advanced maternal age, maternal black race, low maternal education, multi parity, maternal alcohol use, maternal tobacco use, maternal diabetes, preeclampsia, maternal epilepsy and maternal asthma, preterm birth, male sex and low birth weight were significantly associated with increased risk of ID(11), although some other studies also included antidepressant or antiepileptic drug exposure during pregnancy as risk factors for ID.(12-15)

NSAIDs have several effects including anti-inflammation, analgesic, antipyretic effects and inhibition of thrombocyte aggregation.(16) Aspirin, a very common NSAID, has been found to be preventive for preeclampsia with Odds Ratio of 0.86 (95% CI: 0.76, 0.96),(17) and has been recommended, since 2014, by the US Preventive Services Task Force (USPSTF) and the American College of Obstetricians and Gynecologists (ACOG) for pregnant women at risk for preeclampsia.(18) Moreover, preeclampsia is a known risk factor for ID, for instance, a meta-analysis involving 17 studies showed that the mothers having preeclampsia were at 33% more at risk of having children with ID in comparison to the mothers without preeclampsia (OR: 1.33; 95% CI:1.24-1.42).(11, 19)

NSAIDs have the potential to produce free oxygen radicals which can cross the blood brain barrier and may result in neurodevelopmental abnormalities in the offspring.(20, 21) However, no study reported an association of Non-Steroidal Anti-

inflammatory Drugs (NSAID) intake during pregnancy with ID. The aim of this paper was to study the impact of NSAID prescriptions during pregnancy with ID of the offspring, and the direct and indirect effects of preeclampsia and birthweight as potential mediators.

6.3. Materials and Methods

6.3.1. Study population

The analyses were conducted on the prospective data of 153,562 mother-child pairs from the South Carolina Medicaid data 2010-2017. SC Medicaid enrolls women up to 185% of the federal poverty level, during pregnancy and infancy.(22, 23) In addition, SC has the Katie Beckett Waiver that allows children to remain on Medicaid if they have a condition that requires high levels of care regardless of family income. (23, 24) Therefore, there is likely an overrepresentation of children with ID and other neurodevelopmental conditions in the study population. These data were linked to South Carolina Department of Education (SCDE) public school records, South Carolina Department of Disabilities and Special Needs (DDSN) service and support records and South Carolina Department of Health and Environmental Control (SCDHEC) Vital Records of 2010-2017. The SCDE services children ages 3-22 in regular and special education, however some children in SC attend private school and others are home schooled. The SCDE data system allows us to access children with ID and ASD placements among those attending public school and those homeschool using SCDE endorsed curriculum. The decision to place a child in a special education placement is made by a team of educational professional with the results from formal psychological and medical testing. The DDSN is a state-based provider of disability testing and services for residents of SC at all ages for ID and other lifelong neurodevelopmental disabilities. To receive services and supports from DDSN there is

extensive testing by a licensed psychological and a medical evaluation. Not all residents of SC with ID and ASD take advantage of this state service, thus there are children with ID who are not in the DDSN dataset. Finally, SCDHEC has the birth certificate for every live born child born in the state, and this system includes numerous demographic and medical variables about the mother and child at the time of birth.

6.3.2. Variables

Exposure variable: The main exposure variable was Non-steroidal anti-inflammatory drugs (NSAIDs) prescriptions during the pregnancy. NSAID prescriptions have been ascertained from the pharmacy list in the Medicaid data. NSAIDs are a class of analgesic medications that are widely used globally to reduce pain, fever, and inflammation.(16) Most NSAIDs are over the counter medications that do not require a prescription, some NSAIDs are combined with prescription drug. SC Medicaid pays for both prescription and over the counter medication for members during pregnancy so NSAIDs would be recorded in the pharmacy list even if a prescription was not sent. They are also known as cyclooxygenase (COX) inhibitors since they work by inhibiting the activity of COX-1 and COX-2 enzymes.(25). Most NSAIDs are non-selective inhibiting both, whereas some others are selective to COX-2 only and are known as COX-2 inhibitors.(26) Non-selective NSAIDs include salicylates (Aspirin), Propionic acid derivatives (Ibuprofen, Naproxen, Ketoprofen, Oxaprozin), Acetic acid derivatives (Indomethacin, Ketorolac, Diclofenac, Aceclofenac), Enolic acid derivatives/Oxicams (Piroxicam, Tenoxicam, Phenylbutazone), Anthranilic acid derivatives/Fenamates (Mefenamic acid, Meclofenamic acid). On the other hand, selective COX-2 inhibitors/ Coxibs are Celecoxib, Rofecoxib, and Valdecoxib.(27) We have defined a mother exposed

to NSAIDs if she had prescriptions of any type of NSAIDs during the pregnancy period and considered it as a binary variable (Yes/No).

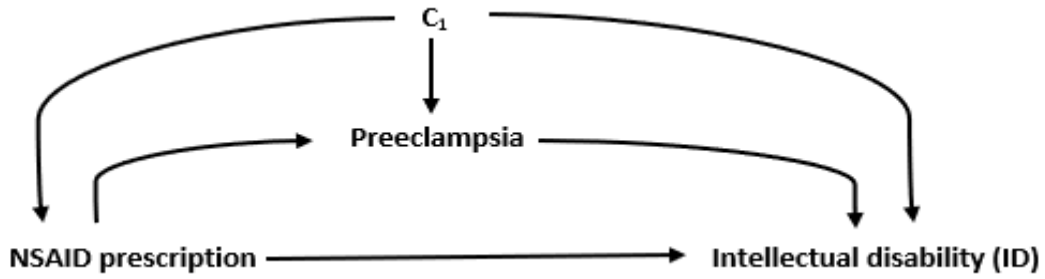
Mediators: We considered preeclampsia as a potential mediator since we hypothesized that some of the effect of NSAIDs on ID could be mediated through the proinflammatory condition of preeclampsia. In 2014, during our study period, the US Preventive Services Task Force (USPSTF) made a B grade recommendation for 81 mg of Aspirin daily after 12 weeks of gestation, as preventive medication in women at risk for preeclampsia.(18) In our dataset, preeclampsia was a binary variable (Yes/No) obtained from SC birth certificates and Medicaid data. We also analyzed the data considering birthweight as a potential mediator since some research showed that NSAID usage during pregnancy is a risk factor for low birth weight,(28, 29) which in turn, is associated with ID.(19, 30) In our data, birthweight was a continuous variable which was later categorized to 'Normal' (>2500 grams), 'Low Birth Weight – LBW' (1500-2500 grams), and 'Very Low Birth Weight – VLBW' (<1500 grams). We conducted two mediation analyses for the mediator 'birthweight' considering this as binary variable, one as 'VLBW and others' and the other as 'LBW and others'.

Outcome variable: Intellectual disability (ID) has also been a binary variable where the variable was denoted as 'YES" when we detected Medicaid ICD-9 codes 317-319 or a specific genetic syndrome code 758.0-758.3, 759.81-759.89, 760.71, or ICD-10 codes of F70-F79. We also identified ID in public school special education records (SCDE) or the centralized state disability service agency dataset (SCDDSN). We considered IDs irrespective of having concurrent autism spectrum disorders.

Covariates: The covariates of our analysis included maternal age, race, gestational diabetes, preeclampsia, body mass index (BMI), smoking status, Kotelchuck index, and plurality, and child's sex and birthweight. All these variables were determined either from Medicaid dataset or SC birth certificate dataset. Variables were dichotomous or categorical: race ('White' or 'Black'), age ('less than 30 years' and '30 years or more), Kotelchuck index (Inadequate and adequate), and child's sex (Male and Female).

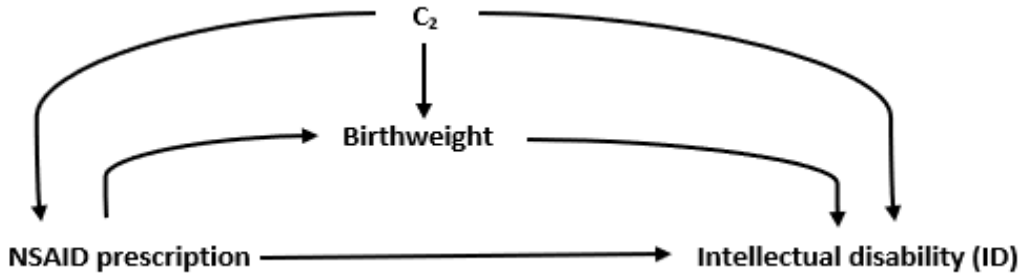
6.3.3. Statistical analysis

The baseline characteristics of the study participants were analyzed using descriptive statistics and the significant differences were determined by the chi-square test for the categorical variables and t-test for continuous variables. Since the outcome variable is binary, we used logistic regression models for unadjusted and adjusted analysis. We also evaluated the total, direct, and indirect effects of NSAID usage during pregnancy by the mothers on ID of their children, with preeclampsia and birthweight as mediators, using the mediation macro in SAS version 9.4. With this method, we attempted to decompose the total effect of NSAID on ID into a direct effect (not mediated by preeclampsia or birthweight) and indirect effect (mediated by preeclampsia or birthweight).(31) Diagrammatic representations of these effects are described in the causal directed acyclic graph (DAG) in Figure 6.1 and 6.2.



C1 = Maternal age, race, gestational diabetes, smoking, BMI, Kotelchuck index, children's sex, plurality

Figure 6.1: DAG for the effect of NSAID on ID mediated by preeclampsia



C2 = Maternal age, race, gestational diabetes, smoking, BMI, Kotelchuck index, children's sex, plurality

Figure 6.2: DAG for the effect of NSAID on ID mediated by birthweight

We used the SAS macro developed by Valeri and VanderWeele(32,22) to evaluate the natural direct effect, natural indirect effect, and total effect of NSAID prescription during pregnancy on ID of the children with preeclampsia and birthweight as mediators from a cohort data.(34) We assumed that there were, first, no unmeasured confounding of exposure (NSAID prescription) and outcome (ID); second, no unmeasured confounding of mediators (preeclampsia or birthweight) on outcome (ID); third, no unmeasured confounding of the exposure–mediator relationship; fourth, that no exposure-outcome

confounder was affected by exposure; and finally, that the outcome was rare.(33,35). VanderWeele showed that under these assumptions, the odds ratio (OR) for total effects evaluating exposure and outcome in the presence of a mediator can be decomposed into ORs for direct and indirect effects and this OR approximates the relative risk.(35) We have presented our findings as natural direct effect (NDE) and natural indirect effect (NIE) which have also been decomposed the pure and total NDE and NIE, respectively. In our study, NDE was the effect of the exposure NSAID use in pregnancy on the outcome, ID, among mothers not having preeclampsia (or a normal weight baby), and NIE was the effect of preeclampsia (or low birthweight) on ID among mothers using NSAID including interaction between NSAID use and preeclampsia (low birthweight). We also estimated the pure indirect effect which was the effect of preeclampsia (or low birthweight) on ID when women did not take NSAIDs and the total direct effect which was the effect of NSAID use on ID among women with preeclampsia (or low birthweight babies) and the interaction between NSAID use and preeclampsia (or low birthweight). Finally, we measured the proportion of the effect mediated by using the following formula from VanderWeele and Vansteelandt (2010):(35):

Proportion mediated = [(NDE*(NIE-1)) / (NDE*NIE – 1)],

where, NDE = Natural Direct Effect and NIE = Natural Indirect Effect

6.3.4. Ethical consideration

The study data were linked by the SC Revenue and Fiscal Affairs (RFA) Office, which is the repository of state datasets that assigns a unique identifier to every person. RFA matched mothers and newborns and sent the study group a deidentified dataset.

Therefore, the University of South Carolina Institutional Review Board (IRB) reviewed the study and declared the deidentified data study had exempt status.

6.4. Results

In this retrospective study of 153,562 mother-child pairs, 8,239 (5.4%) of the children were diagnosed as having ID. Among the mothers of the children, 3.859 (2.5%) had NSAID prescriptions during their pregnancy. Among the mothers who had NSAID prescription during pregnancy 6.8% had preeclampsia whereas this proportion was 5.8% among the rest of the mothers. However, when we considered the children with ID, this proportions get significantly higher (11.1% and 7.7% respectively). The characteristics of the study population by the status of intellectual disability are presented in Table 6.1.

Table 6.1: Characteristics of the study participants [N = 153,562]

Variables	Children with ID (n=8,239)	Children without ID (n=145,323)	Total (N=153,562)
Maternal age (years), mean ± SD	24.7 ± 5.8	24.0 ± 5.4	24.0 ± 5.4
Less than 30 years	6,598 (80.1)	121,824 (83.8)	128,422 (83.6)
30 years or more	1,641 (19.9)	23,499 (16.2)	25,140 (16.4)
Maternal race			
White	4,384 (53.2)	78,895 (54.3)	83,279 (54.2)
Black	3,759 (45.6)	63,834 (43.9)	67,593 (44.0)
Others	96 (1.2)	2,594 (1.8)	2,690 (1.8)
Children's age (years), mean ± SD	5.1 ± 1.4	5.0 ± 1.4	5.0 ± 1.4
Children's gender			
Male	5,294 (64.3)	72,966 (50.2)	78,260 (51.0)
Female	2,945 (35.7)	72,357 (49.8)	75,302 (49.0)
Birthweight (kilograms), mean ± SD	2.8 ± 0.9	3.2 ± 0.6	3.2 ± 0.6
Normal (> 2500 gm)	5,940 (72.1)	131,100 (90.2)	137,040 (89.2)

Low Birthweight	1,204 (14.6)	12,505 (8.6)	13,709 (8.9)
Very low birthweight	1,095 (13.3)	1,718 (1.2)	2,813 (1.8)
Gestational weeks, mean ± SD	36.6 ± 4.1	38.4 ± 1.9	38.3 ± 2.2
Preterm	2,398 (29.1)	15,417 (10.6)	17,815 (11.6)
Full term	5,841 (70.9)	129,906 (89.4)	135,747 (88.4)
NSAID prescription	298 (3.6)	3,561 (2.5)	3,859 (2.5)
BMI (kg/m^2), mean ± SD	28.8 ± 8.0	27.7 ± 7.4	27.8 ± 7.6
Normal	3,252 (39.5)	64,628 (44.5)	67,880 (44.2)
Overweight or Obese	4,987 (60.5)	80,695 (55.5)	85,682 (55.8)
Preeclampsia	644 (7.8)	8,266 (5.7)	8,910 (5.8)
Gestational Diabetes	526 (6.4)	7,338 (5.1)	7,864 (5.1)
Infection	771 (9.4)	14,277 (9.8)	15,048 (9.8)
Smoking (n=153,433)	1,515 (18.4)	23,707 (16.3)	25,222 (16.4)
Kotelchuck index (n=121,246)			
Inadequate or intermediate	2,064 (32.4)	35,498 (31.0)	37,562 (31.0)
Adequate or more	4,300 (67.6)	79,384 (69.0)	83,684 (69.0)
Plurality			
Singleton	7,674 (93.1)	141,441 (97.3)	149,115 (97.1)
Multiple	565 (6.9)	3,882 (2.7)	4,447 (2.9)

We found that along mothers with an NSAID prescription, maternal age, race, children's sex, BMI, smoking, gestational diabetes, birthweight, and multiple pregnancy were significantly associated with ID and hence, we considered them as confounders. In our study, after adjusting for the confounders, the odds of having a child with ID was 27% higher among the mothers who had NSAID prescription during pregnancy in comparison to the mothers without an NSAID prescription. The detailed finding for the multivariate analyses were provided in Table 6.2.

Table 6.2: Factors associated with Intellectual Disability (Adjusted Odds ratios)

Variable	aOR (CI)	P-value
NSAID prescription	1.27 (1.12 - 1.45)	0.0002
Age: 30 years or more vs. others	1.22 (1.15 - 1.29)	<0.0001
Race: White vs. Black	1.09 (1.04 - 1.15)	0.0002
Children's sex: Male vs. Female	1.87 (1.78 - 1.96)	<0.0001
Preeclampsia	1.06 (0.97 - 1.16)	0.2000
BMI: Overweight / Obese vs. normal	1.14 (1.09 - 1.20)	<0.0001
Smoking	1.10 (1.04 - 1.17)	0.0015
Gestational diabetes	1.23 (1.12 - 1.36)	<0.0001
Birthweight		
Very Low birthweight vs. Normal	13.90 (12.77 - 15.13)	<0.0001
Low birthweight vs Normal	2.11 (1.97 - 2.26)	<0.0001
Adequate Kotelchuck index	0.90 (0.86 - 0.94)	<0.0001
Multiple pregnancy	1.29 (1.17 - 1.44)	<0.0001

NSAID prescription increased the risk of ID by 27% (aOR 1.27, 95 % CI: 1.12, 1.45) after adjusting for the confounders. Table 6.3 shows the mediation analysis for the effects of NSAID prescription on ID mediated through preeclampsia and birthweight using the SAS mediation macro. The indirect effect through preeclampsia was not statistically significant, and therefore, we conclude that the effect of NSAID prescription on ID was a direct effect. When birthweight was categorized into 'VLBW and others', the direct effect was measured as OR of 1.21 (1.06-1.40) while the indirect effect was 1.12 (1.06-1.18). About 40% of the total effect was mediated through birthweight. When birthweight was categorized as 'LBW and others' the OR for direct effect was 1.42 (1.03-1.96) and the indirect effect was 1.10 (1.06-1.15). The percentage of mediated effect was 27.1% in the

latter case. In both the cases, the Pure Indirect Effect (PIE) and Total Natural Indirect Effect (TNIE) were similar.

Table 6.3: Total, direct, and indirect effects of NSAID prescription and intellectual disability mediated by preeclampsia and birthweight using SAS mediation macro (Odds Ratio scale)

Mediator	TDE	PIE	NDE	NIE	TE	% Mediated
Preeclampsia	1.20* (1.04-1.38)	1.00 (0.99-1.00)	1.20* (1.04-1.38)	1.00 (0.99-1.00)	1.20* (1.04-1.38)	0% -
VLBW vs. others	1.27** (1.10-1.46)	1.16*** (1.13-1.20)	1.21** (1.06-1.40)	1.12*** (1.06-1.18)	1.41*** (1.23-1.63)	40.9 (17.4-76.1)
LBW vs. others	1.41* (1.04-1.740)	1.09*** (1.07-1.11)	1.42* (1.03-1.96)	1.10*** (1.06-1.15)	1.55** (1.12-2.14)	27.1 (10.9-67.3)

†*TDE: Total Direct Effect; PIE: Pure Indirect Effect; NDE: Natural Direct Effect; NIE: Natural Indirect Effect; TE: Total Effect*

6.5. Discussion

In our study, the adjusted odds ratio (aOR) for the association of NSAIDs with ID was 1.27 (1.12-1.45). The other risk factors identified in our study were advanced maternal age (>30 years), White race, male sex of the children, overweight or obesity, smoking, having gestational diabetes, adequate Kotelchuck index, multiple pregnancy and adequate Kotelchuck index. In our investigation of mediation by preeclampsia status and birthweight we found very different results. We did not identify mediation through preeclampsia, although 7.8% of the mothers of children with ID had preeclampsia and 5.7% of the mothers of children without ID had preeclampsia. There was however mediation by birthweight. The proportion of very low birthweight (VLBW) children in the ID group was 12.3% compared to 1.2% in the no ID group and the aOR for ID was 13.90 (12.77 - 15.13)

for the VLBW group. The total direct effect of NSAIDs on ID was 1.21 (1.06-1.40) and the indirect effect through VLBW was 1.12 (1.06-1.18). The Odds ratios for LBW (< 2500 grams vs.≥2500 grams) were 1.42 and the indirect effect was 1.10. Birthweight mediated 40.9% of the association of NSAIDs and VLBW, and 27.1% of the association between NSAIDs and LBW, respectively.

The prevalence of ID varies,(36) as evident by a meta-analysis of population-based studies(37) however the CDC, in collaboration with the National Center for Health Statistics (NCHS) reported ID prevalence among children ages 3-17 years during the period 2014-2016 was between 1.10-1.34%.(38) The higher prevalence of ID in our study may be due to the Katie Beckett Medicaid waiver which ensured qualifying children regardless of income are included in the Medicaid system, therefore disproportionately including more children with ID in both the numerator and the denominator.(23, 39)

We identified the same set of potential confounders as previous reports including maternal age,(11, 13, 40, 41) race,(11, 42, 43) child sex,(44, 45) maternal obesity or overweight,(46-48) maternal smoking,(49, 50), preeclampsia with ID, gestational diabetes,(11, 51, 52) multiple pregnancy,(53-55) and very low-birth-weight.(11, 41) A few studies have explored the association of NSAIDs with two other neurodevelopmental outcomes of attention deficit hyperactive disorder (ADHD) and Autism Spectrum Disorder (ASD),(56) but none with the ID outcome. We also looked for literature to identify studies regarding the effect of NSAID usage on other pregnancy outcomes and found that NSAID increases the risk of miscarriage and spontaneous abortion.(57-61) Thus, we can say the association of NSAID with ID or other neurodevelopmental outcomes in the child could have been higher if we took the pregnancy losses into account.

According to our study, NSAID use in the absence of preeclampsia and low birthweight (NDE) use was positively associated with ID, suggesting that NSAID use by mothers not at risk of preeclampsia may raise the risk of ID in the baby. Moreover, the Pure Indirect Effect (PIE: effect of birthweight when NSAID=0 for all mothers) and Natural Indirect Effect (NIE: effect of birthweight when NSAID=1 for all mothers) of birthweight on ID in both the categories we used as mediators, are similar. A possible explanation could be that NSAIDs prescribed to high-risk mothers had a beneficial effect on the preeclampsia and fetal survival, and surviving babies were at higher risk of ID. In this case a possible beneficial effect of NSAIDs on high-risk mothers would be underestimated. Another reason could be that there were unknown common causes of preeclampsia and ID, and birthweight and ID (unmeasured mediator-outcome confounding). Thus, NSAID use during pregnancy may have a harmful impact on ID on mothers without risk factors for preeclampsia or low birth weight. NSAIDs might, however, have a beneficial effect for mothers with risk factors for preeclampsia, the group for whom NSAIDs are recommended.

Our study had some limitations. Firstly, we used administrative data that did not include the frequency or timing of NSAID use, only the filling of a prescription for these drugs. Moreover, we did not have the actual data on frequency of NSAID usage with or without prescription. However, a study reported that missing OTC drug exposure is not a large source of bias.(62) Despite this limitation, administrative pharmacy records are commonly used as a source for medication exposure related studies and are not subject to recall bias. Finally, the omission of fetal deaths and still births bias the findings. We do not

know if the deaths were more prevalent among the NSAID exposed group which would bias the study to the null, and our results would be an underestimate of the true effect.

The main strength of our study was the large sample size and the ability to capture the key variables. Furthermore, to our knowledge, this is the first study exploring the association of NSAIDS with ID, using mediation through birthweight. This study could be used to develop an animal model and it should be replicated using additional data sources, so that we can establish the causal association of NSAIDs usage during pregnancy and ID.

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Chapter 7: Discussion and Conclusion

7.1. Summary of results

We found that the prevalence of ASD was 1.93% and the prevalence of ID was 5.4%. However, the prevalence of ASD only, ID only, and ASD with ID were 0.66%, 4.10%, and 1.26%, respectively. Of the study participants, 2.5% had NSAID prescriptions (our main explanatory variable) during the pregnancy time. Though we could not establish any association of NSAID prescription with ASD, we found that the children with the mothers who had NSAID prescription were 52% more likely to have ID in comparison to the children whose mothers did not have NSAID prescription. Black children were 13% less at risk of having ASD only while the White children 15% more likely to have ID only. Preeclampsia had similar effects on ASD and ID with the adjusted ORs of 1.33 (95% CI: 1.13-1.57) and 1.32 (95% CI: 1.20-1.45) respectively. Smoking also had similar effects on ASD and ID with the adjusted OR estimates of 1.20 (95% CI: 1.07-1.35) and 1.18 (95% CI: 1.10-1.26). Gestational diabetes has been identified as a risk factor for ASD only (aOR 1.20, p-value = 0.035). Obesity has also been found to be significantly associated with ASD (aOR 1.26, p-value = <0.0001) and ID (aOR 1.17, p-value = <0.0001). We have conducted a sub-group analysis considering the outcome detected by SCDDSN and SCDE datasets and found similar results with significant association of NSAID prescription with risk of ID. We also conducted a sensitivity analysis considering alcohol use an unmeasured confounder. The sensitivity analysis for the association between NSAID and ID shows that the true odds ratio is 1.30 (95%CI: 1.14, 1.49). When we considered ASD as the outcome

variable during the sensitivity analysis the true OR we found was 1.35 (95% CI: 1.04-1.75) which means that if we could adjust for unmeasured confounder the mothers who used NSAID during pregnancy would have found to be at more risk of having children with ASD.

Since we found an effect of NSAID prescription during pregnancy with ID of the children, we conducted a mediation analysis to measure the direct and indirect effects considering preeclampsia and birthweight as mediators separately. The indirect effect through preeclampsia was not statistically significant, and therefore, we concluded that the effect of NSAID prescription on ID was a direct effect. When birthweight was categorized into 'VLBW and others', the direct effect was measured as OR of 1.21 (1.06-1.40) while the indirect effect was 1.12 (1.06-1.18). About 40% of the total effect was mediated through birthweight. When birthweight was categorized as 'LBW and others' the OR for direct effect was 1.42 (1.03-1.96) and the indirect effect was 1.10 (1.06-1.15). The percentage of mediated effect was 27.1% in the latter case.

To ascertain the association of acetaminophen usage during pregnancy and ASD in the children, we opted for systematic review due to abundant usage of acetaminophen as Over-the-counter drugs. After applying our inclusion and exclusion criteria, we finally included three articles in this systematic review which encompassed 67,310 mother-child pairs among whom 460 children had autism.(52, 165, 166) These three cohort studies were conducted in three different countries in Europe and North America. The sample sizes varied between the studies, ranging from 996 to 64,322. The duration of the cohort follow-up for these studies were 20 years, 12.7 years, and about 5 years. The exposure ascertainment also differed between the studies. Garcia et al. and Liew et al. interviewed

the women prospectively utilizing a standard questionnaire (face-to-face and telephone interviews),(165, 166) whereas Ji et al. measured cord plasma metabolites of acetaminophen as the exposure status.(52) The authors of the papers also utilized different approaches for outcome ascertainment. Garcia et al. ascertained the outcome of autism from the Childhood Autism Spectrum Test (CAST) score(165) while the other two used International Classification of Diseases 9th and 10th version (ICD-9 and ICD-10) codes for autism.(52, 166) Despite having similar study design, and the same exposure and outcome, the selected studies used different measures of association in their analysis. Avella-Garcia et al. (2016) considered the outcome autism as continuous variables,(165) while in the Ji et al. paper the outcome was categorical.(52) In the Liew paper, the outcome was time to event.(166) The study by Garcia et al., presented their results as beta coefficients and found no significant results overall regarding increase of the CAST score for detecting autism when adjusted for confounders.(165) However, we calculated the crude Risk Ratio for this study and found that to be significant (1.34, 95% CI: 1.17, 1.53). Liew et al. (2016) reported significant results for ASD with hyperkinetic symptoms.(166) Again, we calculated the crude RR which was 1.21 (1.07 – 1.37). The Ji paper presented adjusted Odds ratios for cord blood unchanged acetaminophen and cord acetaminophen burden having first tertile as the reference group since there was no true unexposed group(52) and the crude RR was 1.34 (0.78 – 2.30). Our meta-analysis suggests that acetaminophen use during pregnancy is significantly associated with an increased risk of ASD (RR = 1.29, 95% CI:1.17, 1.41, I^2=94%). However, as seen from the I^2 value, there was heterogeneity between the studies.

7.2. Discussion

The prevalence of autism in our study was 1.93% (N=153,562] which aligns the claim by Lyall et al. that the prevalence of autism was at least 1.5% in developed world.(6) Studies conducted in Asia, Europe, and North America reported prevalence of ASD between 1-2% (7). The prevalence of ASD among children aged 8 years was 1.85% as shown by autism and developmental disabilities monitoring network in 11 sites of United states.(8, 215) Our study findings are also in concordance with many studies which reported the prevalence to be between 1-2% in the USA.(7-9)

The prevalence of ID in our study was higher than the reported ID prevalence by SC Autism and Developmental Disabilities Network.(216) The increased prevalence is likely due to the Katie Beckett Waiver in South Carolina Medicaid that allows children with ID to qualify for Medicaid without consideration of the parental income or assets.(217) Thus, among the children qualified for Medicaid in South Carolina, a higher-than-expected proportion have ID as their eligibility determinant, compared to children on Medicaid in other states who do not have the Katie Beckett waiver.(217) However, a meta-analysis of population based studies showed that the prevalence of ID may vary largely.(218)

Like our study, advanced maternal age is an established risk factor for ASD.(10, 11, 13, 14, 16, 18) Similarly, ID of the children has also been associated with advanced maternal age as evident by many studies across the world.(8, 15, 219, 220) Maternal race has also been identified as a significant risk factor for ASD and ID. In comparison to Whites, being African American seemed to be protective for ASD which aligns with the findings of many other studies (113, 221). Similar result was found in a secondary data

analysis from the Pennsylvania Autism and Developmental Disabilities Surveillance Program (114). This might be due to underrepresentation of Blacks in relation to autism detection and treatment.(117, 222) However, we found the opposite result for ID when the Blacks seemed to be at more risk. In our study, the obese mothers were found to be at 26% and 17% more at risk of having children with ASD and ID respectively. Regarding the association between maternal BMI, there have been inconclusive findings reported by different studies.(142, 144, 223) Our finding suggests that there is a need for more concrete evidence to document the association of maternal BMI with ASD and ID. In our study gestational diabetes was found to be associated with ASD only. A large population-based cohort study with more than 2.3 million individuals found that there were strong relationship of Diabetes mellitus with ASD, ID, or Attention Deficit Hyperactivity Disorder (ADHD).(224) Smoking has been another risk factor for both ASD and ID according to our findings although other studies analyzing the association of smoking and autism reported conflicting results (147-149). However, a California statewide cohort study found that smoking is also associated with ASD without ID.(225) Another study from intergenerational Danish cohort reported increased odds of ID among those exposed to maternal smoking in pregnancy after confounder adjustment.(226) Conversely, a meta-analysis of 15 epidemiological studies reported a null association.(147) It is noteworthy to note that we found that preeclampsia was positively associated with both ASD and ID.

Preeclampsia has been well established as a risk factor for ASD and ID.(15-17, 24, 219) This is an important finding since the US Preventive Services Task Force (USPSTF) recommends NSAIDs for pregnant women at risk for preeclampsia.(194) Thus, if our findings are replicated using other data sources the recommendation to reduce

preeclampsia would have to be balanced by the need to reduce intellectual disability. The data reviewed in the USPSTF recommendation includes numerous studies about the association of NSAIDs and ASD, but it does not include any literature about the association of NASAIDs and ID, or ASD with ID.

We did not find an association of NSAIDs with ASD, but we did find an association of NSAIDs with ID, another lifelong disability. However, NSAIDs are potential risk factors for adverse maternal and fetal effects like prolongation of labor in mothers, spontaneous abortion/miscarriage, low birth weight, constriction of the ductus arteriosus, renal dysfunction, congenital cardiac malformations, orofacial clefts and hemostatic abnormalities in the fetus and neonates.(189-193) Moreover, a prospective cohort study involving 6,876 mothers suggested that prenatal exposure of NSAID prescription was associated with attention problems of the children.(227) Another study showed that consuming NSAIDs during pregnancy may affect children's brain.(228) On the other hand, we found that the odds of having children with ID of the mothers who had NSAID prescription was 52% higher than that of the mothers who did not have any NSAID prescription during pregnancy. A few studies have explored the association of NSAIDs with two other neurodevelopmental outcomes of attention deficit hyperactive disorder (ADHD) and Autism Spectrum Disorder (ASD),(227) but none with the ID outcome. We also looked for literature to identify studies regarding the effect of NSAID usage on other pregnancy outcomes and found that NSAID increases the risk of miscarriage and spontaneous abortion.(191, 192, 228-230) Thus, we can say the association of NSAID with ID or other neurodevelopmental outcomes in the child could have been higher if we took the pregnancy losses into account.

Later, we looked for the direct and indirect effects of NSAIDs on ID considering preeclampsia and birthweight as potential mediators. We identified birthweight as a potential mediator for the effect of NSAID on ID. Though no other study looked for this mediation effect, a study by Griffith et al. reported birthweight to be a mediator between the effect of preeclampsia on intellectual disability.(15) In our study, the Pure Indirect Effect and Natural Indirect Effect of birthweight on ID were similar. A possible explanation could be that NSAIDs prescribed to high-risk mothers had a beneficial effect on the preeclampsia and fetal survival, and surviving babies were at higher risk of ID. In this case a possible beneficial effect of NSAIDs on high-risk mothers would be underestimated. Another reason could be that there were unknown common causes of preeclampsia and ID, and birthweight and ID (unmeasured mediator-outcome confounding). Thus, NSAID use during pregnancy may have a harmful impact on ID on mothers without risk factors for preeclampsia or low birth weight. NSAIDs might, however, have a beneficial effect for mothers with risk factors for preeclampsia, the group for whom NSAIDs are recommended.

We conducted a systematic review and meta-analysis to ascertain the effect of NSAID on ASD. The narrative synthesis suggested that there was heterogeneity among the selected studies which was later supported by the meta-analysis with an I^2 of 94%. Our meta-analysis suggests that children of mothers who used acetaminophen during their pregnancy period have a 29% higher risk of ASD in comparison to children whose mothers did not use acetaminophen as medication during pregnancy. Our study findings support the meta-analysis finding of Masarwa et al. that showed the RR of 1.19 (95% CI: 1.14, 1.25).(231) There have also been research reports that demonstrated the biological

plausibility of this association either through neuro-disruptive mechanisms or oxidative stress in utero.(232-237)

7.3. Limitation of the study

The main limitation of our study lies in the unavailability of the exposure data for NSAID usage without prescription. However, a study reported that missing OTC drug exposure is not a large source of bias especially when the overall prevalence of drug usage is below 35%,(238) and a number of studies reported that the prevalence of OTC NSAID usage during pregnancy is well below that level of 35%.(239, 240) Despite this limitation, administrative pharmacy records are commonly used as a source for medication exposure related studies and are not subject to recall bias. The omission of fetal deaths and still births bias the findings. We do not know if the deaths were more prevalent among the NSAID exposed group which would bias the study to the null, and our results would be an underestimate of the true effect.

Regarding the limitation of the systematic review, firstly, there were differences in exposure ascertainment. The differences in exposure ascertainment could result in a potential for bias since the validity depends upon how the questions are worded. Moreover, one of the articles ascertained the exposure by biochemical measurement(52) using the cord plasma metabolites collected at birth. There are several issues regarding exposure ascertainment in this way since measuring once at birth only confirms exposure during peripartum period, since the half -life of acetaminophen is just a few hours.(241) Moreover, the acetaminophen metabolites are excreted through urine mostly within 24 hours.(241, 242) Secondly, the same study did not have a true comparator.(52) They categorized the unchanged cord acetaminophen into tertiles and presented their findings accordingly

considering the lowest tertile as the reference. For the other acetaminophen metabolites, they compared no detection of metabolites in the cord, and this does not represent the absence of exposure during the pregnancy period. Thirdly, the outcome ascertained differed among the studies when one of the articles measured Childhood Autism Spectrum Test (CAST) scores while the others used international classification of Disease (ICD) codes. However, CAST scoring system has been regarded as a good predictor of autism.(243-245) A study conducted in UK by Williams et al. on 1,925 children reported sensitivity of 100% and specificity of 97% of this test although the positive predictive value was 50% only.(245) However, CAST scoring is still not widely used as a diagnostic tool, rather it is more used as a good screening tool.(243) Among the other two studies, one used only the hospital registry while the other used the physician diagnosed electronic medical registry. Finally, they presented three different effect measures with different statistical analyses strategies. Garcia et al. used linear regression and negative binomial regression and presented incidence risk ratio (IRR),(165) Liew et al. used Cox proportional hazard regression,(166) and Ji et al. utilized adjusted logistic regression.(52) Fourthly, the number of the papers included was very low which impacts the heterogeneity and may have resulted in bias.(246)

7.4. Strengths of the study

Strengths of this study include its large sample size and study design. Moreover, to our knowledge, no other study explored the association of NSAID prescription with ASD and ID, individually and collectively. The sensitivity analyses and calculation of E-value have also strengthened our study findings. Moreover, the mediation analysis to answer our research question related to direct and indirect effects of NSAID on ID using two different

mediators is also unique. The main strength of our systematic review lies in its specificity of the research question and corresponding eligibility criteria. This is the first systematic review and meta-analysis that examined the association between maternal usage of acetaminophen during pregnancy and Autism Spectrum Disorders (ASD) through analyzing cohort studies only. We conducted an extensive search for available literature published till October 2020 and utilized standard methods for data extraction. We utilized Preferred Reporting Items for Systematic Reviews (PRISMA) flow diagram for selecting the articles.(210)

7.5. Conclusion

Our study found that NSAID usage during pregnancy causes risk of intellectual disability of the children. The meta-analysis documented association between acetaminophen exposure during pregnancy and autism. We also identified birthweight as a mediator of NSAID's effect on development of ID. Our findings warrant the need for more specific research on both the biologic plausibility of NSAIDs being causally associated with ID and the generalizability of the effect of NSAIDs prescription during pregnancy on intellectual disability in the child, using other linked maternal-child datasets.

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