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Walden University
2011

Abstract

A Sibling Case-Control Study of Maternal Prenatal Body Mass Index as a Risk Factor For Autism Spectrum Disorder

by

Ruth Ann Hendrix

M.P.H., Indiana University, 2005

B.A., Indiana University, 1981

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

Walden University

May 2011

Abstract

The prevalence of autism spectrum disorder (ASD) is estimated to be one in every 150 births. While both genetic and postpartum environmental exposure have been linked to ASD, prenatal maternal weight has not been investigated. The objective of the study is to assess whether overweight or obesity at pregnancy is an important risk factor for the diagnosis of ASD in offspring. A case-control study was designed to answer this question using the public health ecosocial theory. The study population consisted of 70 mothers, who were recruited via the Internet using the viral expansion loop. Multiple logistic regression analysis was used to test the hypotheses. No significant difference in risk of ASD by level of body mass index (BMI) was found after adjusting for covariates. The odds ratio for obese women in comparison to normal or underweight women was 1.19, 95% CI [0.53, 2.66] after adjusting for covariates. Gaining the appropriate amount of weight during gestation, as determined by the Institute of Medicine, was not associated with ASD either, with the odds ratio at 0.67, 95% CI [0.31, 1.48]. The results indicate that BMI category at pregnancy and gestational weight gain were not risk factors for autism in children. The implications for positive social change include a better understanding of maternal prenatal BMI as a risk factor for autism spectrum disorder. Appropriate health information provided to mothers prenatally could result in improved birth outcomes.

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Dedication

This paper is dedicated to all who have gone before in the PhD journey and to the parents of children who are born without healthy biology in any form, in tribute to the lost hopes, and to Adele Bryden.

Acknowledgments

Thanks are given to Mary Link, Hilary Thesmar, and Bob Sullivan who helped me get the start. Thanks also to Dr. Gregory Wilson and Dr. Carole Kacius of the Department of Public Health, School of Medicine, Indiana University for help and support. The completion of this work was made possible by the relentless patience and perseverance of my chair, Dr. James Rohrer. I am eternally grateful to all who helped in any way along an eventful journey of learning. I appreciated all support of the Walden University community. I am thankful to Dr. Hadi Danawi, and Dr. Amany Refaat for their time and help. My family and church community are part of my ecosocial system, essential for my functioning. Feeling blessed to have been born in this place and during this time. Feeling grateful to be able to complete the task.

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Chapter 1: Introduction to the Study

Autism spectrum disorder affects the individual's ability to learn and interact. These children have impairments in social skills, communication, and are incapable of what is considered normal behavior development. In many cases, comorbid conditions may negatively influence intellectual capabilities, resulting in a lower level of learning potential for the person affected. The individual suffers, the familial, and wider social system are also impacted (Ganz, 2007).

Autism spectrum disorders (ASD) include a range of conditions. Those at the higher-functioning end of the spectrum can be active in most aspects of life. Those on the lower end of the scale may have quite limited capabilities (Dawson, Glasson, Dixon, & Bower, 2009). ASDs are also known as pervasive developmental disorders (PDDs), the three most common diagnoses are based on behavioral criteria beginning with those labeled with Asperger syndrome, which may be quite mild, to the midpoint, called pervasive development disorder not otherwise specified (PDD-NOS), and the most severe form, autistic disorder (National Institute of Mental Health, 2009).

The diagnosis is normally made by age three with some children showing what would appear to be normal development up until the sudden onset of symptoms (Nassar, et al., 2009). The neurodevelopmental disorder is classified in Chapter V, Mental and Behavioral Disorders, of the International Classification of Diseases (ICD), currently in the tenth revision. The various classifications for ASD are listed in F84 (World Health Organization, 2009). The standardization of the definition of the disorder in the United States occurred in the early 1990s. Congress passed legislation to ensure those with disabilities would receive federally funded education. At the federal level to improve

fairness in education for every student in 1990, the Individuals with Disabilities Education Act (IDEA) was put into law (U. S. Department of Education, 2003). According to a report to Congress, the number of children served in the educational systems went from less than 1,000 reported for the school year 1990 to 1991 to serving 24,000 in the school year 1993 to 1994 (U. S. Department of Education, 1996). Researchers have found several reasons for the increase, one being the change in definitions, another being substitution of diagnosis, for example, a child may have been previously diagnosed with mental retardation (M. King & Bearman, 2009).

Multiple pathways are suspected in the etiology of autism. Newschaffer et al. reviewed the epidemiological research literature studying the neurodevelopmental condition (Newschaffer et al., 2007). In the genetic epidemiological studies, both genetic links and gene-discovery studies have been utilized to find associations (Mefford et al., 2008; Wang et al., 2009). Prenatal, perinatal, and neonatal risk factors including parental age, parity, fetal distress, and birth weight have been studied (Bilder, Pinborough-Zimmerman, Miller, & McMahon, 2009; Folb et al., 2004; Grether, Anderson, Croen, Smith, & Windham, 2009; Hultman, Sparen, & Cnattingius, 2002). The immunologic, neurologic, and digestive systems of children recently diagnosed with ASD have been studied (Baker, 2008; Wakefield et al., 1998). Both prenatal and postnatal environmental exposures have been studied including prescription medications, metals, alcohol, smoking, illicit drugs, and vaccinations (Bilder et al., 2009; Newschaffer et al., 2007; U. S. Department of Education, 1996).

A gap in the literature exists for prenatal BMI as a risk factor for a child's later diagnosis of ASD. It is known that a healthy BMI and weight gain increases the

possibility of a positive birth outcome (Cedergren, 2006; Khashan & Kenny, 2009). Currently, the rate of overweight and obesity is increasing in the United States. Various researchers have found negative birth outcomes associated when the maternal BMI is outside the normal range (Cedergren, 2004; Nohr et al., 2008; Rosenberg, Garbers, Lipkind, & Chiasson, 2005; Stotland et al., 2005). One gap in the search for the cause of autism spectrum disorder is considering the at pregnancy prenatal body mass (BMI) of mothers of two or more children; one child who is later diagnosed with ASD, one not. Both ASD and obesity rates have increased in the past two decades. The present study assesses whether prenatal BMI is a risk factor for a child's later diagnosis of ASD.

The prevalence reported by the Centers for Disease Control and Prevention is one in 150 children (CDC, 2007b). There is a variation in reported prevalence, but with the standardization of definitions for diagnosis in the early 1990s, the subsequent years led to various reported rates. A recently published study based on surveying parents with no validation of diagnosis was 110 per 10,000 (Kogan et al., 2009). Autism spectrum disorders, also known as pervasive developmental disorders are a range of complex neurodevelopment disorders on a spectrum beginning with the most severe symptoms diagnosed with autism, further towards the middle is pervasive developmental disorder not otherwise specified (PDD-NOS) and at the other end, those with the most mild symptoms are diagnosed with Aspergers. Prevalence in the UK school-based population was 94 per 10,000 (Baron-Cohen et al., 2009). Prevalence has changed over time in Denmark in part to the lowering age in diagnosis, the authors found that better diagnostic criteria with adherence to ICD-10 classification beginning in 1994 the ASD rates were 82 per 10,000 (Parner, Schendel, & Thorsen, 2008). Israeli researchers used the

computerized medical health record reporting 80% male, with a rate of 20 per 10,000 in the population studied (Senecky et al., 2009). Standardization of the diagnosis, services, reporting, and training may attribute to the increase in diagnosis of ASD, which will be discussed more in the next chapter (Dawson et al., 2009; M. King & Bearman, 2009).

The Centers for Disease Control and Prevention (CDC) funds various projects studying adverse health outcomes. The Study to Explore Early Development (SEED) began from the Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) that continues to study the 2,700 children diagnosed with ASD in six states. The study will include research around the question of whether thimerosal, formerly used in MMR vaccines, has impacted ASD rates. The Pregnancy Risk Assessment Monitoring System (PRAMS) collects behavioral information from women who have just given birth. The CDC currently funds the Autism and Developmental Disabilities Monitoring (ADDM) Network in 13 states, plus at the CDC in Atlanta. Those states included in the study are Alabama, Arizona, Arkansas, Colorado, Florida, Georgia, Maryland, Missouri, New Jersey, North Carolina, Pennsylvania, South Carolina, Utah, and Wisconsin (CDC, 2007a). One study using the data revealed disparity in recognition of ASD by ethnicity and race (Mandell et al., 2009). A delay in the diagnosis and therefore, educational interventions, may negatively affect learning. Other research has shown larger schools with bigger budgets were more likely to have higher ASD rates in their school districts than smaller schools (Palmer, Blanchard, Jean, & Mandell, 2005). The increase of the population that has the disorder increasingly affects the educational infrastructure and the economic impact to society.

Problem Statement

Finding the cause or causes of something that affects up to one in 100 children is essential. A healthy weight prior to pregnancy has been shown to increase the likelihood of a healthy baby. Many negative health outcomes both for the mother and the child are associated with being on either extreme of BMI. With the increase of overweight and obese people in the U.S. population, knowing whether overweight or obesity increases the risk of ASD in children needs to be determined. The disorder affects the child and family for the duration of life. The primary independent variable was maternal overweight or obesity before the birth. The dependent variable was ASD status of the offspring.

Nature of Study

This case-control study assessed prenatal overweight or obesity of mothers with at least two children discordant for ASD as the independent variable and its association with autism. The Internet has enabled parents of children with rare diseases to connect and communicate online forming online social groups. The study described in Chapter 3 began with the online social networks for first recruitment. In turn, people who know women who fit the study criteria connected via the viral expansion loop. The research question: Is there a significant difference in the risk for ASD among women who are overweight or obese in comparison to those who are of normal weight or underweight? Since mothers have the highest vested interest in having healthy and successful children, they are the ones most likely to have a driving desire to eliminate another risk factor for autism; thus, connecting, and participating in this study. The objective of the study was to

learn whether excessive maternal weight during early pregnancy is an important risk factor for a later diagnosis of ASD for the children.

The case control study is widely used for the rare disease because of cost-effectiveness. While one in every 150 children is diagnosed with autism spectrum disorder, the developmental disorder is infrequent. The case-control study results in the estimate of odds and is most commonly used for rare health outcomes. The presence or absence of a risk factor can change the risk of a disease or condition outcome. One can select from multiple risk factors to determine if risk increases when a variable is present or absent. Since the design is retrospective and observational, no more harm is incurred to participants. No intervention is done in an observational study.

Purpose of Study

The study sought to answer this question: Is maternal overweight or obesity a risk factor for autism in offspring? Hans Asperger first described the condition in 1938, but the causes of autism spectrum disorder are unknown (Dawson et al., 2009; Newschaffer et al., 2007; Wong & Hui, 2008). The majority of conditions and diseases are from multiple upstream impacts, some identified, but many more unspecified. The study provided new understanding on the impact of a healthy maternal, prenatal BMI on the health of offspring. The case-control study using siblings allows controlling for genetic factors as well as many internal and external environmental factors. In observational research, twins are known to be useful when causation is suspected to be multifactorial, when experiments would not be appropriate, and the sequence of exposures for health outcomes would be similar for the siblings (McGue, Osler, & Christensen, 2010). With the prevalence of autism, a twin study would be impractical, therefore the next closest

study design to fraternal twins was utilized, the sibling study. The relationship of maternal prenatal body mass index for siblings discordant for ASD was considered from two aspects. The primary research questions were:

Research Question 1: Does maternal overweight or obesity impact the risk level for a child's later diagnosis of ASD?

Hypothesis 1

H_0 1: Maternal overweight or obesity prenatally is not a risk factor for ASD.

H_A 1: Maternal overweight or obesity prenatally is a risk factor for ASD.

Research Question 2: Does a healthy GWG for BMI category decrease the risk of ASD?

Hypothesis 2

H_0 2: An unhealthy GWG during pregnancy is not a risk factor for ASD.

H_A 2: An unhealthy GWG during pregnancy is a risk factor for ASD.

After data collection, the BMI was calculated for each pregnancy, the GWG was calculated by subtracting the maximum weight from the weight at pregnancy. Odds ratios were calculated for each BMI category and an appropriate or healthy GWG by BMI category. Odds ratios with 95% confidence intervals were calculated. Chapter 3 provides details of the analysis.

Theoretical Framework

Humanity is social by nature. Both years and quality of life are positively or negatively impacted by a person's social network. The ecosocial theory as described by Krieger portrays the social network by levels, pathways, and power that all combine to impact life outcomes (Krieger, 2008). The health of an individual is determined not only by the genetics that establish the life trajectory, but the environment of the mother during

pregnancy including the social, emotional, and physical surroundings. According to Krieger the integration of the social and biological realms in which we live daily are in a dynamic state of flux. Exposure, susceptibility, and resistance interplay and are impacted by the levels of power influencing the health of an individual over the life span. Accountability comes from the closeness of the social network of the immediate family or from the larger social network including civil, religious, and educational contacts. Just as the social network influences the mother's emotional and physical well being, her total health influences the birth outcome of the offspring. The weight of the mother prior to conception, the pregnancy nutritional status of the mother during fetal formation has the potential to lead to a more positive life trajectory than one where the fetus is undernourished, exposed to the toxins in cigarettes, and frequent high-stress events. Power, the control one has in life for decisions, as given by the elders in a culture also includes where one is in the social ladder, many times determines the economic possibilities for a person. While education is sometimes viewed as a way out of poverty, in general the next generation operates within the same social strata as the previous with the changing of economic level sometimes taking concerted efforts for three generations. The overall health outcome of an individual is determined by the level, pathway, and power of the parents. The cumulative exposure of where one is born in the social context determines the health trajectory of the individual.

Operational Definitions

The study utilized the following definitions and acronyms.

Apgar score rating scale: a scale developed by Virginia Apgar in 1952 measuring the activity, pulse, grimace, appearance, and respiration of newborn babies. Given at one

minute and five minutes after birth with a rating between the optimum of 10 and a low of zero.

Appropriate GWG: a gestational weight gain (GWG) that is within the weight ranges recommended by the IOM for each BMI category (2009)

ASD, ASDs: autism spectrum disorders

BMI: body mass index calculated as weight in kilos divided by height in meters squared

CDC: Centers for Disease Control and Prevention, one of the 11 operating divisions within the U.S. Department of Health & Human Services (DHSS)

GWG: gestational weight gain

LGA: large for gestational age

NIH: National Institutes of Health, another of the DHSS divisions

NIMH: National Institute of Mental Health, one of 27 institutions within the NIH

Normal: the named BMI category from 18.5 to 24.9 kg/m2, the suggested GWG starts at 25 and ends at 35 pounds, from 11.5 - 16 kg (IOM, 2009)

Obese: the name of the grouping for a BMI of 30.0+, the indicated GWG begins at 11, ending at 20 pounds (5 - 9 kg) (IOM, 2009)

Obesity: the condition associated with an abundance of adipose tissue, which has been linked to an increase in risk of various chronic diseases.

OR: odds ratio, the odds of exposure of the disease studied, in case-control studies, OR=AD/BC

Overweight: the category inside the BMI range from 25.0 to 29.9 kg/m^2, the preferred GWG is from 15 to 25 pounds, from 7 to 11.5 kg (IOM, 2009)

SGA: small for gestational age

Underweight: the category of BMI when less than 18.5, the recommended total GWG range is from 28 to 40 pounds (12.5 - 18 kg) (IOM, 2009)

Unhealthy GWG: the gestational weight gain (GWG) is outside the recommended weight as recommended by the IOM

Viral expansion loop: Viral is a term used when information is passed from person to person on the Internet, as the Internet was utilized to gather participants, using various tools possibly including clinics, email, social networks, and web postings. The method is a type of snowballing but using the Internet as the communication medium instead of person-to-person contact. Researchers identified 757 groups on Facebook that were linked by some common disease or disorder (Farmer, Bruckner Holt, Cook, & Hearing, 2009).

WHO: World Health Organization, the United Nations public health branch

Assumptions and Limitations

The case control design is often used when diseases are rare in the population. The epidemiological study category is observational and analytical, while the type of study design is case control. While qualitative studies may lead to interesting findings that later may yield the quantitative research study, the majority of epidemiological research uses quantitative methods. For the weight of evidence, the meta-analysis provides the optimum information for the etiology of a disease, at the other extreme is one person, one case written normally by one doctor.

Epidemiology is the study of patterns of disease across groups of people. The meta-analysis or study of studies is at the highest level of evidence. The gathering of

similar studies can be used to aggregate data for more robust findings. One major limitation is that the quality of the analysis is only as good as the data of the original study. Another level of study quite high and considered the gold standard in the world of clinical trials is the randomized control trial (RCT). A well-designed RCT eliminates many of the biases and confounding inherent in study designs further down the evidence scale for studies by randomly selecting from the population, then further randomizing by study group. In an RCT, both the participants and the administrators may be blinded so that neither group is aware of the participants being the cases or controls. RCTs have the passage of time to study the effect or lack of the intervention. Another type of study is the cohort study where a subgroup of the population is selected, then participates over time. An example of the cohort study is the Framingham Heart Study, which started in 1948, has followed two generations in Massachusetts. The main strength of the cohort study is over time a single exposure can measure multiple health outcomes.

One limitation of the present study is the timeframe since there is variability in the age of diagnosis. One problem in reporting the prevalence of ASD is the variation at which the child is diagnosed. The age of diagnosis varies considerably, therefore, leading to what may appear as differences in prevalence. In a recent study, over 2,568 youths were diagnosed with ASD in a fourteen state study area, where Shattuck et al. found the average age to be diagnosed was 5.7 years (Shattuck et al., 2009). Researchers studied preterm infants for autism using the Modified Checklist for Autism in Toddlers (M-CHAT) which is a widely used to screen young children for ASD (Limperopoulos et al., 2008).

Another limitation of the study is the nature of participants. Those who volunteer for studies are known to be different from the general population; therefore, generalizability of the results may be limited. Those with access to the Internet may be different from the general population. Educational levels were recorded for comparability to the general population. The online survey results were subject to self-report bias. The participatory study involved mothers who were willing to take time from their busy lives to complete the online survey.

Significance of Study

Having a child diagnosed with ASD impacts the individual, the family, the educational network, and the community at large. This retrospective observational research studied whether having a healthy BMI at pregnancy was a risk factor for ASD. The positive social change in my dissertation work was learning whether the optimum BMI when becoming pregnant positively impacted the long-term health of the child. The ripple effect includes a more positive home and school environment. Living and learning with a child diagnosed with autism spectrum disorder can be highly demanding. The observational analytical study of original data of individuals tested the null hypothesis of no difference in maternal BMI of pregnancies of siblings later discordant for ASD. The case-control study looked backward from the disease diagnosis to differences between pregnancies for the siblings using an online survey.

The economic impact of ASD is immense. In 2000, the estimated annual cost was $4,965 per person diagnosed with ASD, rising to $5,979 in 2004 (Leslie & Martin, 2007). Recent research calculated the increase medical costs for children diagnosed with ASD. Shimabukuro, Grosse, and Rice (2008) used data from a private insurance group to learn

the financial impact to the family of a child diagnosed with ASD. In their case control study, insurance records were used to determine both insurance paid and out-of-pocket costs for each year from 1993 to 2003 (Shimabukuro et al., 2008). Inpatient, outpatient, speech and occupational therapy if covered by insurance were included. The patient group consisting of working US population in both government and private companies, there were 6,962 children diagnosed with ASD included in the cost calculation. The costs were compared for the same aged children not diagnosed with ASD. Prevalence ranged from a low of 1.2 for those from 18 to 21 years of age, to a high of 4.4 per 1,000 for those from 5 to 10 (Shimabukuro et al., 2008). The financial burden for each child diagnosed with ASD in the Shimabukuro study was from $4,110 to $6,200 per year. With an estimated 500,000 children diagnosed with ASD, when considering only the increased health care dollars, the burden is more than $2.5 billion every year.

When one considers the cost of ASD for the family and society across the lifespan, the costs are vast. The financial burden on the family and social system continue during the lifetime of the child diagnosed with ASD. Many times the child diagnosed with ASD does not become a productive citizen. A recent researcher calculated the lifetime cost per case at $3.2 million (Ganz, 2007). Using the current U.S. population and the CDC's rate of ASD, the total cost for people alive today is more than $6 trillion. Researchers in Spain estimated the disability-adjusted life years (DALYs) lost at 43,928, 95% CI [28,453, 58,347] for the year 2003 using 0.5 years for those children diagnosed with autism and 0.35 years for those diagnosed with either Asperger or PDD-NOS (Sanchez-Valle et al., 2008). The positive social change is to provide women better information on a healthy BMI for a vigorous baby. While a normal BMI is considered

optimal for a healthy baby, there is a gap in the literature in regards to the later diagnosis of ASD. The study primarily addressed the BMI of the mother at pregnancy confirmation.

Transition Statement

A child without a fully functioning brain who is unable to reciprocate social behaviors, participate in a regular classroom without special help, and engages in repetitive behaviors has a societal cost. To know whether various levels of BMI increased risk of a later diagnosis of ASD was of benefit. To give women another reason to eat a healthy diet, maintain a healthy weight before pregnancy, and for them to know dietary habits may affect the next generation is essential health information. To prevent one case of ASD could potentially result in savings of $3.2 million, but it is the emotional impact that matters more. Parents need to know whether there are potential prenatal BMI influences that affect the future of their unborn child. The next chapter will provide the literature background.

Chapter 2: Literature Review

What did the current epidemiological literature reveal in regards to the causes of autism spectrum disorders when one considers the body mass index (BMI) of the mother? Nearly all diseases and disorders are multifactorial; therefore to have one cause of autism would be highly unlikely. There is much research in regards to the optimal weight gain for mothers during pregnancy. The Institute of Medicine (IOM) report was published in 1990, which has been used for pregnancy weight gain guidelines since that time (Institute of Medicine, 1990). The Committee to Reexamine the Institute of Medicine Pregnancy Weight Guidelines published new recommendations in the summer of 2009 that limit the top weight gain for overweight and obese women (IOM, 2009). Researchers have linked various developmental disorders with undernutrition and overnutrition during pregnancy. A continued healthy weight gain throughout pregnancy is needed for a greater likelihood of a positive pregnancy outcome. While ASDs are not normally diagnosed until age 2 or later, the possibility exists that the beginnings of the disorder may be in the womb. This chapter provides the reader an overview of the current public health literature at the intersection of ASDs and appropriate gestational weight gain (GWG) by BMI category. When there was a lack in the public health literature, the medical or nursing literature was used. The first section reviewed articles on optimal weight gain by BMI category. The next section covered specific issues that women at either end of the weight gain spectrum face either during pregnancy or afterwards. The next section covered other developmental disorders in regards to GWG or other known birth defects. A brief section was included on folic acid since it is known that sufficient folic acid intake has been associated with a decrease in neural tube defects (NTDs). Finally, there was an overview of the

epidemiological literature in regards to known or suspected prenatal factors of ASD. The chapter should provide the reader a basic understanding of current public health literature at the intersection of BMI, GWG, and ASD. The chapter is organized as follows. First the conceptual model used will be described, then the search methodology, followed by an overview of each study included. Next will be a discussion of the articles comparing and contrasting the studies with their relationship to the proposed study, followed by a conclusion with a justification for the proposed research. The goal of the chapter is to place the research in the context of the study described in Chapter 3.

Conceptual Model

The ecosocial model was used to guide the research. The ecosocial model is the most accepted framework currently used in public health. The model recognizes that individuals are not born into a vacuum, but biological and social forces intertwine prior to conception influencing the health outcome of the individual over the lifespan. The predisposition to many chronic diseases is already in the DNA. The female is born with all the eggs she will have. The social network of the mother can impact the health patterns adopted during pregnancy. The new mother can hear advice from friends and family as well as professional health practitioners. At times, new health behaviors may be embraced. If the mother practiced unhealthy behaviors prior to the pregnancy, those habits probably continue. The chains of risk can either be beneficial or detrimental to the developing embryo. Krieger, with the levels, pathways, and power of the ecosocial theory, notes that the embodiment, pathways of embodiment, the cumulative interplay among exposure, susceptibility, and resistance, along with accountability which in turn give the data necessary for epidemiologists to develop the analytical implications and

predictions that come from the person, place, and time of disease (Krieger, 2008). Negative health outcomes have been associated with being on the lower end of the power scale, if one does not see healthy behaviors modeled, how is one to know how to put them into action? Education can be power. Those with more education can educate, but the ability to change human behavior rests at the individual level. It is the mother who decides the quality and the quantity of the nutrition the growing fetus receives. While BMI is not considered a concise measure of nutritional intake, over time, there are trends. Does mother's weight gain during pregnancy impact the growing baby? If there is overconsumption of calories, is the child more likely to be diagnosed with ASD? If the mother was in the obese BMI category prior to the pregnancy, was the child more likely to be diagnosed with autism? Is being obese protective?

Content

The general risk factors for autism spectrum disorder are not known. While there is much information on the guidelines for proper nutrition during pregnancy, the optimal weight gain for each BMI category, and the negative birth outcomes when the weight gain is at either end of the weight gain scale, it is unknown whether any of this increases the risk of a later diagnosis of ASD. There has been much research on the genetic birth disorders (Mefford et al., 2008; Wang et al., 2009). There has been research for certain nutrients that need to be included during pregnancy such as folic acid (Catov, Bodnar, Ness, Markovic, & Roberts, 2007); Helsinki, Trauth, Jernigan, & Kerr, 2004); Mosley et al., 2008). The caloric and nutritional requirements for pregnancy have long been established (Shaw, Carmichael, Yang, Selvin, & Schaffer, 2004). Certain negative brain outcomes later in life have been associated with prenatal factors (Atladottir et al., 2007;

Mongraw-Chaffin et al., 2008; Schaefer et al., 2000; Slickers, Olshan, Siega-Riz, Honein Aylsworth, 2008). However, the association of early prenatal BMI and ASD had not been investigated; the current study sought to find differences during the early prenatal period.

Evidence over the ages has established that the healthiest babies come at full term, which is about 280 days or 40 weeks and weigh about 3300 g. (Evans & Le Hew, 2007). The normal weight mother should gain from ten to 12 kg. Evans and Le Hew recommend for mothers to consume about 2,400 calories per day with about 60 to 80 g of protein (2007). The normal, healthy diet low in sugars and fats, high in fiber is the normal recommendation. Additional intake of folic acid is needed both prior to pregnancy and during gestation (Helsinki, Trauth, Jernigan, & Kerr, 2004; Mosley et al., 2008; Shaw, Carmichael, Yang, Selvin, & Schaffer, 2004). Iron is recommended after 28 weeks of gestation. The normal or healthy weight for a full-term birth is from 2500 g to 4000 g. Babies born outside the normal weight are at greater risk for premature death, later diabetes, and other negative health outcomes (Cedergren, 2006; Kiel, Dodson, Artal, Boehmer, & Leet, 2007; Nohr et al., 2008; Rosenberg, Garbers, Lipkind, & Chiasson, 2005; Stotland et al., 2005). The gestational weight gain (GWG) recommendation for a mother by the healthy BMI category varied depending on the research study.

The safest pregnancy is started when the mother is within the normal BMI range prior to conception. Prepregnancy BMI at either end of the bell curve can lead to negative birth outcomes (Cedergren, 2004; Nohr et al., (2008). If the mother is already underweight, then the nutrients needed for optimal fetal development are unavailable (Stotland et al., 2005). If the mother is either underweight or overweight, then the balance

of nutrients is not available for growth when needed. The cardiovascular system formation begins in the third week with blood flow beginning in the fourth week. The central nervous system begins differentiation at about the fourth week. The brain continues to grow in the womb doubling in size from birth to age five. All the organs of the future child are formed by week twelve of pregnancy (Evans & Le Hew, 2007). Spina bifida can be diagnosed accurately with ultrasound by 12 weeks of gestation. The corpus callosum has formed by the 17th week of development. The healthiest weight gain by BMI category will be presented later in the chapter. Being in the healthy BMI weight category and gaining the appropriate weight gain during pregnancy can increase the likelihood of a healthy birth (Cedergren, 2006). The majority of the articles included were case control studies. Observational descriptive studies are considered appropriate for rare health outcomes. According to the Centers for Disease Control and Prevention, the prevalence of ASDs in the United States is currently reported being one in 150 (2007).

Organization of Review

The following section presents an overview of current research related to the optimal body mass index, gestational weight gain, prenatal micronutrient intakes education, folic acid use, suspected origins of certain birth defects, and advanced parental age. Relevant information from the articles included odds ratios, confidence intervals, study type, and variables studied.

Process for Search Strategy

The PubMed database was utilized for the literature search. The articles gathered for the research foundation started with searches using the terms: epidemiology, public

health, BMI, pregnancy, ASD and adverse pregnancy outcomes. Journal articles reporting the results of studies were included while reviews and meta-analysis articles were excluded. Preference for inclusion was given to those articles published in peer-reviewed journals in the public health journals in the last five years, then supplementing with other sound academic journals. The literature review for ASDs also included the pertinent articles regarding the vaccination association.

The peer-reviewed articles accessed, studied, and then selected based on relevancy. The results of the literature search follow. The study question was based in the current literature at the intersection of prenatal BMI and a later diagnosis of autism.

The following section reviews the recent works done in the areas related to the research study. Articles about optimal body index, gestational weight gain, prenatal nutrition, suspected origins of certain birth defects, and advanced parental age were reviewed. The next section documents the various variables to be included in the study.

Optimal Body Mass Index

It is known that body mass index (BMI) category has been shown to impact adverse medical outcomes for both the mother and baby. Gaining the appropriate weight for the BMI category during pregnancy increases the odds of a healthy birth outcome. Weight gain during a pregnancy that results in the birth of a healthy baby can vary from a negative weight gain to 45 kg. The odds of the baby being born healthy vary significantly depending on the prenatal BMI of the mother. The IOM 2009 recommendations are specific by weight gain category. If the BMI of the mother is less than 18.5, then a weight gain of 12.5 to 18 kg is recommended. For those in the normal BMI category, a gain of 11.5 to 16 kg is recommended. For those overweight, a weight gain of seven to 11.5 kg is

recommended. For those women in the obese category with a BMI over 30, from five to nine kg is recommended (Institute of Medicine, 2009). There is much variation from pregnancy to pregnancy for the same women, the variation increases for women across cultures across the globe. With the current obesity epidemic with the increase in overweight and at risk for obesity with our young in this country, will there be an increase in adverse pregnancy outcomes?

Cedergren has done much of the work surrounding the optimal weight gain by BMI category during pregnancy. Cedergren published an article in 2004 where maternal morbid obesity was considered as a factor for various adverse pregnancy outcomes. In the analytical prospective population-based cohort, the author learned that babies whose mothers are morbidly obese are at a greater risk for an adverse pregnancy outcome. Adverse pregnancy outcomes including preeclampsia, antepartum stillbirth, cesarean delivery, instrumental delivery, shoulder dystocia, meconium aspiration, fetal distress, early neonatal death, and large-for-gestational age were considered. The study included 542,216 mothers (Cedergren, 2004). The controls were in the normal or overweight BMI categories. The obese to morbidly obese were in three different case BMI groups: 29.1 to 35, 35.1 to 40, and BMI greater than 40. Adverse pregnancy outcomes compared resulting in adjusted odds ratios using Mantel-Haenszel technique to determine the risk for the morbidly obese women for preeclampsia was 4.82, 95% CI [4.04, 5.74], antepartum stillbirth 2.79, 95% CI [1.94, 4.02], cesarean delivery 2.69, 95% CI [2.49, 2.90], instrumental delivery 1.34, 95% CI [1.16, 1.56], shoulder dystocia 3.14, 95% CI [1.86, 5.31], meconium aspiration 2.85, 95% CI [1.60, 5.07], fetal distress 5.31, 95% CI [2.12, 2.99], early neonatal death 3.41, 95% CI [2.07, 5.63], and large-for-gestational age

3.82, 95% CI [3.50, 4.16]. The women who were obese and morbidly obese were 1.37 times more likely to have a small for gestational age (SGA) baby with a 95% CI [1.09, 1.71]. (Cedergren, 2004). One weakness of the study is that socioeconomic level was not considered. Women diagnosed with gestational diabetes were not included in the study. Women who are morbidly obese are at a greater risk of a negative outcome during pregnancy, delivery, and the neonatal period (Cedergren, 2004).

In another study, Cedergren found that morbidly obese women had a higher frequency of pregnancy complications and adverse perinatal outcomes (2006). In the prospective population-based cohort the appropriate GWG by BMI category were considered factors in positive birth outcomes. The author divided the 245,526 women into five categories using BMI first, and then three GWG categories. Using the Mantel-Haenszel chi-square, linear trends with weighted linear regression of the log odds ratios were calculated. Of the Swedish obese women, those in the low weight gain category were less likely to develop preeclampsia aOR 0.52, 95% CI [0.42, 0.62], cesarean section aOR 0.81, 95% CI [0.73, 0.90], have an instrumental delivery aOR 0.75, 95% CI [0.63, 0.88], and LGA birth aOR 0.66, 95% CI [0.59, 0.75] (Cedergren, 2006). In the large population-based cohort study using existing medical records recall bias was avoided. GWG could only be calculated for 38% of the women, since there were missing data fields for some of the women. Normal and overweight women who gained more than the recommended weight were more likely to have adverse perinatal outcomes. The author recommended a lower GWG for obese women, with an appropriate weight gain within a healthy BMI category for a healthy perinatal outcome (Cedergren, 2006).

In the 2007 article, Cedergren makes recommendations for healthy weight gain for the different BMI categories. Once again, adverse maternal and natal outcomes including SGA, LGA, preterm birth, preeclampsia, stillbirth, perinatal death, and an Apgar score of less than seven at five minutes were considered. Of the 298,648 mothers in Sweden with children born from 1994-2004, those with sufficient medical records were included (Cedergren, 2007). Adjusted odds ratios using Mantel-Haenszel technique were calculated a 95% confidence ratio reported in graph form, but not listed in texts. The study was a large cohort with evidence for results, giving the study statistical power (Cedergren, 2007). Prenatal and perinatal outcomes that are relatively rare could be included because of the large population. One limitation of the study was only 84% of the births were included, the others lacked either the prepregnancy weight or height or both of the mother. The large cohort study resulted in optimal weight gain guidelines by BMI category (Cedergren, 2007). For those with a BMI less than 20, 4 to 10 kg was the recommendation. For those in the 20-24.9 BMI range, 2 to 10 kg was recommended. For those in the overweight category, a weight gain of less than 9 kg was found to be optimal. For those in the obese or over categories, a GWG of less than 6 kg was recommended (Cedergren, 2007). Cedergren contributed to the 2009 IOM pregnancy weight guidelines.

Another study included 120,250 women in Missouri whose births resulted in a full-term live birth that was done by Kiel, Dodson, Artal, Boehmer, and Leet (2007). The analytical population-based cohort considered pregnancy outcome by weight gain. The adverse outcomes included preeclampsia, Cesarean delivery, SGA, and LGA. Logistic regression using SPSS was used to calculate odds ratios by BMI category. The authors used the National Institutes of Health obesity classes, where Class I has a BMI range

from 30 to 34.9, Class II has a range from 35 to 39.9, and Class III is for those over 40. For those in obese Class II, those losing more than 4.5 kg had the best outcomes with an OR of 0.35, 95% CI [0.2, 0.62] for preeclampsia (Kiel, Dodson, Artal, Boehmer, & Leet, 2007). Those in Class III who did not change weight during pregnancy had an OR of 0.63, 95% CI [0.49, 0.80]; those who lost from one to four kg OR 0.44, 95% CI [0.28, 0.67]; then those losing more than 4.5 kg had an OR of 0.52, 95% CI [0.37, 0.74]. For a cesarean section, women in all three obese categories were at lower risk ranging from 0.63, 95% CI [0.52, 0.77] to 0.88, 95% CI [0.79, 0.98] when they gained four kg or less during pregnancy (Kiel, Dodson, Artal, Boehmer, & Leet, 2007). The authors used birth certificate data, which included the self-report of prepregnancy weight. Another limitation of the study was only full-term, singleton, live births were included. As with all observational studies, the results demonstrate association, not causation. The authors concluded recommending limited or no weight gain for obese women, recommending three different weight gain guidelines (Kiel, Dodson, Artal, Boehmer, & Leet, 2007).

A study in Denmark by Nohr et al. (2008) showed that heavier women needed to gain sufficient weight to prevent a low-birthweight baby. In the cohort study, prepregnancy BMI and GWG were considered as factors for the adverse birth outcomes including SGA, LGA, and low Apgar score. The authors also studied maternal outcomes including diabetes, Caesarean delivery, and postpartum weight retention. For those in the obese prepregnancy BMI category, the adjusted OR was 4.7, 95% CI [4.0, 5.6] for preeclampsia, the aOR was 5.9, 95% CI [4.8, 7.3] for gestational diabetes (Nohr et al., 2008). For the 60,892 full term pregnancies from the Danish National Birth Cohort born from 1996 to 2002, the mean GWG was 15.1 kg. Multiple logistic regression was used to

calculate the adjusted odds ratios. For women in the overweight category, LGA the adjusted OR was 1.7, 95% CI [1.6, 1.8], for obese women LGA aOR 2.9, 95% CI [2.7, 3.2], low Apgar score 1.8, 95% CI [1.3, 2.4]. For pregnancy weight gain, for those gaining less than ten kg, SGA was increased aOR 1.8, 95% CI [1.6, 2.0], while the risk of LGA was decreased 0.7, 95% CI [0.6, 0.8]. For those in the 16-19 kg weight gain category, aOR for LGA was 1.6, 95% CI [1.5, 1.7], those with a greater than 20 kg had an increased risk of LGA 2.6, 95% CI [2.4, 2.8]. Nohr et al. used four categories for BMI and weight gain, also considered post-pregnancy BMI category. One limitation of the study was that self-reported data were used for the pre-pregnancy weight to calculate BMI (Nohr et al., 2008). One of the authors' limitations was generalizability to other populations since most of the women were the same ethnicity. Also, the Danes have used the social health system, whereby many medical procedures are federally mandated. A greater percentage of the women may have participated in prenatal care, which is known to give better health outcomes for the baby. This study concluded that overweight and obese women should lose weight before becoming pregnant. The authors recommended a future randomized control trial where women would be at a healthy weight before pregnancy (Nohr et al., 2008).

Pregnancy is a time when a person is at increased risk for diabetes, especially those in the overweight or obese categories. Rosenberg, Garbers, Lipkind, and Chiasson (2005) studied a cohort of 329,988 singleton births in New York City. The cohort study included births in a three-year period in using vital statistic records. Obesity and diabetes may affect three adverse pregnancy outcomes including Cesarean delivery, preterm birth, and low birthweight. The authors used multiple logistic regression calculating adjusted

odds ratios for the births in 1999, 2000, and 2001. For those whose prepregnancy weight was greater than 136 kg, the aOR was 2.78, 95% CI [2.03, 3.81] for preeclampsia. For those women with hypertension, the adjusted OR for preeclampsia was 10.18, 95% CI [9.37, 11.07]. The authors could not compute BMI for the mothers since height was not recorded in the birth file. There was variation in validity depending on variable. One limitation of the study was that other studies have shown low sensitivity and validity in studies using vital statistic files. The authors used the cutoff of 18.6 kg for weight gain for two categories. For prepregnancy weight, five prepregnancy weight categories, beginning at less than 45 kg increasing by 22.67 kg each (Rosenberg et al., 2005). The general guidelines are for women to be at a healthy weight before conception. Those with low BMI may need to gain more weight, while those that are overweight or obese may need to gain less weight for best birth outcome.

Gestational Weight Gain

While physicians are aware of GWG guidelines, how many advise their patients? In the longitudinal cohort, Stotland et al. studied the relationship of prenatal BMI, target weight gain, and physician's advice for weight gain during pregnancy (2005). In the analytical study, bivariate, multivariate analyses, logistic regression analyses were done on data gathered from 1,198 women in the Bay Area of California. Of those who were overweight, the odds ratios for weight gain above guidelines were 3.79, 95% CI [2.15, 6.60], obese 2.39, 95% CI [1.34-4.27]. One limitation of the study was that some of the data were self-reported and then not validated with the gain in medical records. The authors recommended updated recommendations on how to communicate the optimal GWG by category since the existing ones are not sufficient. Results for women's

prepregnancy weight with weight gain recorded, both ends tended to produce similar results, women in a higher weight category gained more, women in lower categories gained fewer kilograms (Stotland et al., 2005). While GWG is a gross measure of nutrient intake during pregnancy, there are specific micronutrients known to benefit the growing baby.

Prenatal Micronutrient Intakes Education

During the initial prenatal visit, a dietary assessment is normally done. Since the 1990 IOM nutritional guidelines for pregnancy were published, the recommendations were an additional 30 mg of iron, folate only for those known to be deficient for folate intake, and prenatal vitamins were not generally recommended for healthy women (Institute of Medicine, 1990). Research continued to be done around the topic of folate, multivitamin use, choline, and betaine.

Catov, Bodnar, Ness, Markovic, and Roberts (2007) studied the impact of periconceptional multivitamin use and risk of preterm or small-for-gestational-age births. In the analytical case-control study, there were 852 cases and 971 controls. Multinomial logistic models, chi-square, or t-tests were used to calculate adjusted odds ratios. For periconceptional multivitamin users risk of preterm birth, being born at less than 34 weeks had an adjusted OR of 0.29, 95% CI [0.13, 0.64]. The risk of preterm birth from 34 to 37 weeks was not significantly different for users and non-users with an adjusted OR of 1.13, 95% CI [0.74, 1.73]. The authors suggest that nutritional status before pregnancy may be critical in the healthy outcome of a grown, term infant. Unstudied confounders may affect results; dietary folate was not considered. The periconceptional

period is also important in positive pregnancy outcomes (Catov, Bodnar, Ness, Markovic, & Roberts, 2007).

Folic Acid Use

The increase in folic acid intake has been attributed to a decrease in neural tube defects. The neural tube closes at the fourth week of gestation. Folic acid has been added as a supplement in certain foods since 1992 after the CDC made the recommendation. The U.S. and Canadian recommended intakes during pregnancy are 600 μg, while in Britain the recommendations are 300 μg per day (Bender, 2009).

Do women of childbearing age better understand the impact of consuming sufficient folic acid after an educational intervention? Patients need to hear the same message from various health professionals multiple times in order to affect a positive health behavior change. The authors designed a health information session regarding the basic epidemiology of the range of known health benefits of sufficient folic acid intake. Various types of health professionals ranging from doctors to nurses to community health promoters who attended an educational session were asked if they were willing to participate in a study measuring the effects of the program (Helinski, Trauth, Jernigan, & Kerr, 2004). Participants were given a pre-test of folic acid knowledge at the educational session then one month later a post-test survey was administered. Changes in knowledge of folic acid were listed as percentages with *p*-values for participants not knowing the association of folic acid intake and decrease in colorectal cancer risk. Helinksi et al., found in the posttest, 79% answered correctly with a *p*-value of less than 0.01 (2004). The significant change was the awareness of a decrease in risk of certain cardiovascular events with increased folic acid intake. Only 54% responding correctly prior to the

intervention, but on the posttest 81% responded correctly for a *p*-value of < 0.01. Behavior changes with percentages and *p*-values were also listed (Helinksi et al., 2004). The two largest changes in behavior were from 58 to 92% recommending folic acid to their patients or clients with a *p*-value less than .01. The other change was to provide regular preconceptional counseling in regards to folic acid use going from 16 to 62% with a *p*-value of 0.02. Primary care providers were the ones with the largest percentage of change in behavior going from 33 to 66%. One limitation of the Helinski study was the small number of each type of health professional (2004). It is known that the increase in folic acid has resulted in a decrease of certain neural tube defects; this study considers whether an education intervention changed knowledge level or increased likelihood of behavior change. More recent graduates of programs were more likely to be aware of the positive benefits of folic acid intake than those who had graduated years earlier. While there is much information the mother needs to know for optimal prenatal care, often it is not known by the health professionals (Helinski et al., 2004).

Other research has considered the nutritional supplementation of folic acid prior to conception. Mosley et al. performed an analytical multi-center case-control study measuring the impact of folic acid intake and rates of neural tube defects (2008). Participants included women from the National Birth Defects Prevention Study from ten surveillance locations in the United States beginning in 1997. The case group included 565 women and 3963 controls. Bivariate comparisons using chi-square tests and logistic regression were used for analyses. The odds ratios of statistical significance were for anencephaly, which is the lack of complete development of all or part of the brain (Mosley et al., 2008). The neural tube normally closes between the third and fourth week

of pregnancy. If there is no closure, the cells that would normally develop into more complex portions of the brain stop. Of the supplement users, those in the 11th to 30th percentile of folic acid intake ranges had an OR of 2.5, 95% CI [1.4, 4.80]. Those women in the lowest tenth percentile of folic acid intake had an OR of 1.7, 95% CI [0.7, 4.2] (Mosley, et al., 2008). The 31st to 50th percentile folic acid intake group had an OR of 1.3, 95% CI [0.6, 2.8]. The results were inconclusive for folic acid intake in regards to the risk of neural tube defect outcome. There was no dose-response. Authors found that periconceptional supplement use did not reduce the rates of neural tube defects (Mosley, et al., 2008). One limitation of the study was that self-reported data are subject to recall bias. It is well established in nutritional epidemiology literature that past recall on any dietary intake is subject to bias. The authors listed BMI data with four categories. Of the women who had babies diagnosed with neural tube defects, 20% had a BMI greater than 30. In the control group, 15% had a BMI greater than 30 (Mosley et al., 2008).

Other nutrients suspected to impact birth results are choline and betaine. Shaw, Carmichael, Yang, Selvin, and Schaffer (2004) considered periconceptional dietary intakes. The analytical case-control study used a food frequency questionnaire to determine intakes of choline and betaine from three months prior to pregnancy through the first three months of pregnancy. While the U.S. and Canadian adequate intake for choline is 425 mg, there is no evidence to support this intake level (Bender, 2009). The study group included 864 women whose data were collected from 1989 to 1991 in California (Shaw et al., 2004). The risk of neural tube defects (NTDs) in offspring was determined using logistic regression. The risk of NTDs was lower when the mothers were in the upper quartile of both choline and betaine intake. The OR for the group was 0.28,

95% CI [0.12, 0.65]. A principal limitation of the study was that food intakes were self-reported, subject to recall bias (Shaw, Carmichael, Yang, Selvin, & Schaffer, 2004). While micronutrients are important to neonatal development, other environmental factors may influence the outcome.

Suspected Origins of Certain Birth Defects

The search for the etiology of ASD has been varied with researchers concentrating efforts on two major pathways, genetics and environmental exposure. The majority of diseases are multifactorial. The range of structural birth defects is wide with decades of research completed surrounding known chromosomal errors, such as trisomy 13 where a child may have severe physical and mental differences. Mefford et al. sought similarities in a specific region of chromosome 1q21.1 in two groups of patients, one group cognitively normal, the other with autism, or another mental difference (2008). There were 4,737 in the control group, none with deletions of the 1q21.1; three controls had some duplications while 25 of the 5,218 cases had the 1.35-Mb deletion (Mefford et al., 2008). Wang et al. performed data mining on various DNA data including more than 10,000 people (2009). The authors suggested a possible neuronal disconnection syndrome because findings included common genetic variants on 5p14.1 might be significant for ASD (Wang et al., 2009). The genetic component is still being studied; the vaccine controversy has evoked a range of responses by country.

In a recent study published in a journal that specializes in studying aspects of vaccination, Netterlid, Mansson, & Hakansson added parents to the active surveillance in monitoring symptoms of children after they have received vaccinations (2009). The authors reported on moderate and severe symptoms. Only 267 cases of the 7,193 included

in the Swedish study reported 22 negative symptoms out of 120,189 people reported. The study used passive surveillance to report vaccine safety (Netterlid, Mansson, & Hakansson, 2009). Because of the controversy surrounding the vaccinations, parents may be hypersensitive to their children's vaccination adverse responses.

The vaccine controversy began when a British doctor reported that 12 children had developed gastroenterological issues post immunization. Wakefield's study included reports from a collection of doctors each with only a few patients reporting chronic enterocolitis. This suggested a possible environmental cause: the MMR vaccine introduced in Britain in 1988 (Wakefield et al., 1998). The poorly designed study implicated the manufacturers of the MMR vaccine. While the controversy caused much disillusionment with the Lancet, the journal in which Wakefield published, the aftermath is still being felt in the United States today with ongoing federal research. Wakefield is no longer able to practice medicine in England.

In 1999, the Lancet published a new study with a larger number studied, 498 cases of ASD. Taylor et al. concluded there was no causal relationship between MMR vaccination and ASD, reporting an odds ratio of 0.94, 95% CI [0.60, 1.47] for the temporal association (Taylor et al., 1999). In England, the majority of researchers closed the vaccine and ASD association quickly, but the general public did not.

A population-based study including all children born in Denmark from January 1991 through December 1998 concluded no association with timing of vaccination, the date of vaccination, and the development of ASD. Of the 537,303 children included in the study, 738 were diagnosed with ASD. In the unvaccinated group, the relative risk of ASD was 0.92, 95% CI [0.68, 1.24] (Madsen et al., 2002). The study was the first one

considering the entire population of a country. In Denmark, at least at the medical and research level, the vaccine and ASD association was considered closed in 2002.

The World Health Organization's Global Advisory Committee on Vaccine Safety concluded that no evidence existed of a causal association between measles, mumps, and rubella vaccine and ASD (Folb et al., 2004). The evidence continued to build culminating in the evidence review by Demicheli, Jefferson, Rivetti and Price who considered 139 articles published on the topic from 1996 to 2004, including 31 articles for determining no evidence of a link of MMR vaccine to ASD (Demicheli, Jefferson, Rivetti, & Price, 2005). At the meta-analysis level and worldwide level, the question was closed again in 2005.

In the United Kingdom, research published in 2006 revealed a decline in MMR vaccination rates, yet the increase in ASD rates (Wright & Polack, 2006). Baird et al. tested children with ASD and those without, cases $n = 98$, controls positive for educational needs $n = 52$, and normally developing children $n = 90$, all aged 10-12, all vaccinated with MMR. Of all the children, only one child in the control group had symptoms of possible enterocolitis. The virological case-control study found no differences in the levels of measles virus antibodies (Baird et al., 2008).

In the United States, the vaccine and ASD association is still in the process of being determined. Federal legislators with personal family members positive for ASD influenced the federal research agenda. Emotion has been a player in the politics of the vaccine and ASD association. Baker clarifies the history detailing many of the events in the United States (Baker, 2008). The author described the numerous federal agencies, state influences, and individual legislators, all trying to answer the question for parents

about why their child did not have a normally functioning brain. Baker reported thimerosal had been used successfully since the 1920s and 1930s. Due to fear, it was removed from the MMR vaccine by the U. S. Food and Drug Administration (FDA) in the summer of 2001. In the US, the Geiers were also paid professionals testifying on behalf of the alleged victims of the vaccine and ASD controversy. They co-authored a study published in 2008 considering thimerosal exposure and neurodevelopmental disorders including ASD. In the ecological study, individual vaccination records were not matched to the later diagnosis of ASD. The findings, published in Journal of Neurological Sciences, stated weaknesses in the study design, but left the question of the association open for more research (Young, Geier, & Geier, 2008). The Lancet formally retracted the 1998 Wakefield journal article in February 2010. While genetics and environmental exposures may be associated with a later diagnosis of ASD, those two topics were not included in the present study.

The variables assessed as risk factors included season of birth, maternal prenatal intakes, prepregnancy weight change, interpregnancy interval, prepregnancy BMI, and other lifestyle exposures. The outcomes included for the section are neurodevelopmental disorders, persistent cryptorchidism, schizophrenia, bilateral renal agenesis, and oral clefts.

The season of birth was considered as a factor for neurodevelopmental disorders by Atladóttir et al. with their work published in 2007. All children born in Denmark from 1990-1999 were included for a total of 669,995. The authors used Cox regression using spline functions to allow day-by-day analysis of seasonal variation. There was no time of year that was statistically significant for autism spectrum disorders. Since the study

included the entire Danish population, many normal biases were eliminated by the study design. A day-by-day analysis rather than an arbitrary delineation of the season was used to eliminate categorical measurement bias. One limitation of the study was diagnoses were not confirmed by outside review, but to improve the validity a small pilot validation was completed. The authors concluded a preterm birth was more of a predictor for developmental disorders than season of birth (Atladottir et al., 2007).

Other factors that have been considered for birth defects are maternal smoking, alcohol use, and caffeine consumption. Mongraw-Chaffin, Cohn, Cohen, and Christianson considered a son's risk of persistent cryptorchidism in a study published in 2008. In the analytical nested case-control study, the authors found maternal prenatal consumption habits increased the risk of a son being persistent cryptorchidism positive (one or both testes do not descend to the proper location by age one). There were 84 cases and 250 controls in the pregnancy cohort. Mothers that were part of the Child Health and Development Studies living in the San Francisco East Bay area of California were included in the prospective study that used self-reported consumption reports. It was found that mothers who consumed three cups or more of coffee per day were more likely to have offspring positive for the disorder, using conditional logistic regression, the authors reported an OR of 1.43, 95% CI [1.08, 1.91]. The authors found neither smoking nor drinking to be associated with a higher prevalence of persistent cryptorchidism. One limitation of the study was the use of self-reported data. Another was that the caffeine in soda or soft drink consumption was not included in the analysis. Power was not addressed in the article. The median BMI for the group was reported at 22.1 with an interquartile range of 4.2 for cases and a median BMI of 22.0 with an interquartile range

of 2.9 for controls (Mongraw-Chaffin, Cohn, Cohen, & Christianson, 2008). While persistent cryptorchidism is a mechanical type of birth defect, brain development is more complicated.

Another study in California considered maternal prepregnant body mass and risk of schizophrenia in adult offspring. Schaefer et al. completed a nested case-control study with a cohort of births from Prenatal Determinants of Schizophrenia Study, later named the Child Health and Development Study, which included 63 cases and 6,570 controls born from 1959 to 1967 (2000). Multivariate proportional hazards analysis resulted in a prepregnant BMI greater than or equal to 30 of RR 2.9, 95% CI [1.3, 6.6]. Since medical records were used, there was no recall bias for the BMI, but fifteen percent of the women were missing prepregnancy body weight. There was some loss due to follow-up. There was no information gathered on the diets of the mothers, the authors noting that GWG could be used as a gross measure of nutritional intake (Schaefer et al., 2000). The study considered prepregnant body mass as a risk for an adulthood mental ailment. The authors included an extensive discussion section considering various possible prenatal factors that could lead to poor prenatal neurodevelopment (Schaefer et al., 2000).

Lifestyle factors and age are known risk factors for many diseases. Slickers, Olshan, Siega-Riz, Honein, and Aylsworth considered maternal body mass index and lifestyle exposures as risk factors for bilateral renal agenesis or hypoplasia (Slickers, Olshan, Siega-Riz, Honein, & Aylsworth, 2008). In the analytical case-control study, the following were considered as risk factors: BMI greater than 30 prior to pregnancy, smoking during periconceptional period, and binge drinking during the second month of pregnancy. There were 75 cases and 868 controls from the National Birth Defects

Prevention Study in the United States. The CDC conducted the study in ten different states including certain children born from 1997 to 2003. Univariate and bivariate analysis, then logistic regression finding a BMI greater than or equal to 30 resulted in an adjusted OR of 1.90, 95% CI [1.00, 3.59]. According to Slickers and the other authors, those mothers who reported smoking during pregnancy resulted in an adjusted OR of 2.08, 95% CI [1.11, 3.90] (2008). Binge drinking during the second month of pregnancy resulted in an adjusted OR of 3.64, 95% CI [1.19, 11.1]. Slickers et al. considered a narrow window during pregnancy during renal development. Study limitations included the use of self-reported weight and recall bias for several exposures (2008). The authors suggest the second month of pregnancy may be a critical time of prenatal development (Slickers et al., 2008). Every day is important during the prenatal period for neural development.

A case-control study in Australia revealed comorbidity of other birth defects with ASD. Dawson, Glasson, Dixon and Bower used the Western Australian Birth Defects Registry to study the association of birth defects and ASD finding an OR of 2.0, 95% CI [1.1, 4.3], but those with Asperger syndrome did not show a statistical significance OR 0.5, CI [0.2, 1.9]. The authors suggest the possibility that prenatal environmental factors may be associated with ASD. In the study, the control group had 465 with 481 sibling controls and 1313 population controls (Dawson et al., 2009).

Ultrasound can be used to diagnose cleft palates beginning at about the tenth week of pregnancy. Villamor, Sparen, and Cnattingius (2008) considered the risk of oral clefts with prepregnancy body weight and the pause between pregnancies. In the analytical population-based cohort study in Sweden, births from 1992 to 2004 were

included. The researchers measured the effect of change in BMI from first pregnancy to second pregnancy, age, increase of BMI units, and pregnancy interval. There were 220,328 Swedish births included in the study which used multivariate logistic regression to find that when there was a greater than 48 month interval, adjusted OR was 2.80, 95% CI [1.36, 5.78]. Villamor, Sparen, and Cnattingius suggested weight gain between pregnancies, rather than just the obesity that was associated with an increase in oral clefts (2008). The authors did not consider reported dietary prenatal intake. Another limitation of the study was that since the nationwide birth registry was used, there might have been undiagnosed stillbirths. The study considers interpregnancy weight gain (Villamor, Sparen, & Cnattingius, 2008). It is known that an increase in age increases the risk of disease, what of the increase of parental age as a risk factor for neurodevelopmental disorders?

Advanced Parental Age

Since age is a factor in many diseases and negative birth outcomes, Durkin et al. considered age as a risk factor for autism spectrum disorder (2008). The CDC sponsored a study to consider parental age as a risk factor. In the analytical case-cohort design, the authors used a ten state group, consisting of 1,251 cases and 253,347 controls. The adjusted OR when maternal age at delivery was over 40 was found to be 1.3, 95% CI [1.1, 1.6]. When the father was 40 or older at delivery, the adjusted OR was 1.4, 95% CI [1.1, 1.8]. The eldest parental category was the only age group for each that was statistically significant (Durkin et al., 2008). Total weeks gestational age of less than 28 weeks resulted in an adjusted OR of 2.5, 95% CI [1.6, 3.9], while those born from 28 to 36 weeks had an adjusted OR of 1.4, 95% CI [1.2, 1.7], thus suggesting that a 40-week

gestation is important for complete neural development. While the authors note that the effect is modest, there are public health implications (Durkin et al., 2008).

Research Variables

Research variables included were season of birth, gestational weight gain, birth order, prepregnancy BMI, and family history. The outcome measured was ASD in the siblings of the case control study. The following is a discussion of independent variables in the current literature with outcomes including neurodevelopmental disorders, persistent cryptorchidism, schizophrenia, bilateral renal agenesis, and oral clefts.

All the major organs are formed by the twelfth week of development. While the cells are differentiating into various parts of the central nervous system in varying rates depending on the week, brain growth inside the skull is linear from 29 to 41 weeks. At birth, the head is about half the size of the adult skull. Perinatal risk factors for infantile autism were considered in a Swedish study published in 2002. Hultman, Sparen, and Cnattingius considered age, parity, smoking habits, country of birth of mother, hypertensive disease, diabetes, pregnancy bleeding, mode of delivery, season of birth, gestational age, birth weight, congenital malformations, and Apgar score at five minutes (Hultman et al., 2002). In the analytical nested case-control study, 408 cases were matched to 2,040 controls using the Swedish Birth Registry for those born from 1987-1994. Hultman, Sparen, and Cnattingius identified unfavorable perinatal conditions that could lead to a child's later diagnosis of infantile autism (2002). Conditional logistic regression was used to analyze the various factors. Of significance were maternal birth outside Europe and North America OR 3.0, 95% CI [1.7, 5.2], birthweight for gestational age less than two standard deviations OR 2.1, 95% CI [1.1, 3.9], and Apgar score at five

minutes being six or less the OR was 3.2, 95% CI [1.2, 8.2]. While the study population was large, various risk factors were considered, resulting in significant findings (Hultman et al., 2002).

Delivery, newborn characteristics, pregnancy, and parental characteristics were found to be important in the later diagnosis of autism. Delivery and newborn characteristics including fetal presentation, mode of delivery, Apgar score at five minutes, birth weight, gestational age at birth, weight for gestational age; parental characteristics including multiple gestation, preeclampsia, number of antenatal visits; parental characteristics including number of previous pregnancies, maternal smoking as reported, maternal citizenship, and age of both parents were considered in the 2005 study published by Larsson et al. The Danish cohort of all children born after 1972 to 1999 resulting in the inclusion of 698 cases matched to 17,450 controls. Cases were diagnosed with autism before 1999, with 25 controls matched by gender, birth year, and age (Larsson et al., 2005). Conditional logistic regression resulted in a significant find with an adjusted OR for breech presentation of 1.63, 95% CI [1.18, 2.26], Apgar score from one to seven at five minutes 1.89, 95% CI [1.10, 3.27]; gestational age at birth being less than 35 weeks 2.45, 95% CI [1.55, 3.86]; schizophrenia-like psychosis 3.44, 95% CI [1.48, 7.95]; and affective disorder 2.91, 95% CI [1.65, 5.14]. Factors found not to be significant included substance abuse, birth order, frequency of prenatal visits, birthweight for gestational age, maternal age, paternal age, maternal education, parental wealth, and number of pregnancies. Because multiple gestations were excluded and limits of coverage for some variables, Larsson et al., only included 595 participants in the adjusted analyses (2005). The authors found associations with regard to socioeconomic status

(SES) in the large cohort. Results found parental age not to be a significant risk factor for autism, contrary to another study. In Denmark, the birth records have been computerized since January 1, 1973 (Larsson et al., 2005).

Season of birth was studied in a group of children born from 1982 to 2002. In the analytical case-control study, day of birth and gender were considered as risk factors for ASD (Lee et al., 2008). The cases included 907 singletons and 161 multiple births. The controls were 1,416,932 singleton births in Maryland and 41,079 multiple births across the United States. The cases were diagnosed at the Kennedy Krieger Institute. Non-parametric time-series analyses and relative risks from Poisson regression were completed. The data were analyzed in various stages, first using the Rayleigh test to consider the frequency of case-control births by day of the year. Lee et al. used the Hilbert-Huang Transform Toolbox to perform an Empiric Mode Decomposition (EMD) on the time series over the 20 years of data (2008). Then the Poisson regression was done to estimate relative risk with 95% confidence intervals. The only confidence interval in text was for December births, with a relative risk of 0.18, 95% CI [0.04, 0.82], the rest were shown graphically. For inclusion in the ASD group, diagnosis was made using the standards of the American Psychiatric Association, DMS-IV-TR (2000). The Childhood Autism Rating Scale was also used. One limitation was some of the case births might have been included in the control group (Lee et al., 2008). Since many births are scheduled for various reasons, the natural delivery date may have been more relevant, but birth delivery method was not considered. Gestation ages were not available from the participants in the control group, therefore, the comparison could not be made (Lee et al., 2008).

A Danish study considered perinatal risk factors for ASD. Authors Maimburg and Vaeth considered obstetric factors included parental age, maternal citizenship, birthweight of baby, gestational age, Apgar score, irregular fetal position, and congenital malformations (2006). In the analytical population based matched case-control study which included 473 cases and 4730 controls, the authors used conditional logistic regression finding an adjusted OR for BMI less than 18.5 to be 0.8, 95% CI [0.4, 1.3]. For those mothers with BMI greater than 30, the adjusted OR was 0.7, 95% CI [0.2, 1.7]. The variable of statistical significance used by Maimburg and Vaeth was use of medicine during pregnancy with an adjusted OR of 1.5, 95% CI [1.1, 2.1] (2006). Of the cases, only 20% were female and the average age at diagnosis of ASD was 4.57 years. The data were gathered over a ten-year period, with better diagnostics and improved validity over time of measurements (Maimburg & Vaeth (2006). The authors considered BMI as a risk factor, dividing into three groups. Ten percent of the cases had a BMI of less than 18.5, while only six percent of the controls did. Adjusted odds ratios were not calculated per BMI category (Maimburg & Vaeth, 2006).

The same authors also considered risk of developing autism after assisted conception. Maimburg and Vaeth did an analytical population based case control study considering conception status, mother's age, maternal country of origin, parity, multiplicity, birth weight, gestational age, and diagnosed birth defects (2007). The authors found that children born as a result of assisted conception were less likely than others to be diagnosed with ASD. Conditional logistic regression was used with the 461 cases and 461 controls; the OR was 0.37, 95% CI [0.14, 0.98]. While the population-based study design was strong, the article was not published in a public health journal.

The authors suggested further studies considering folic acid intake both before and during pregnancy (Maimburg & Vaeth, 2007).

Birthweight and total gestational weeks can impact fetal growth. Schendel and Bhasin conducted an analytical nested case-control from a Georgia cohort using the Metropolitan Atlanta Developmental Disabilities Surveillance Program (2008). There were 565 cases and 578 controls born from 1981 to 1993 from the population-based study using medical records for data analyses. Unconditional logistic regression was used to compute adjusted odds ratios and 95% confidence intervals. While much data were presented, the two variables found to be significant were less than a full term pregnancy and a birthweight less than or equal to 2499 grams. The adjusted OR for infants born with both factors was 9.9, 95% CI [1.3, 6.6). While much data stratification was done, the numbers were small for some of the categories. The authors found impaired fetal growth as a factor for many developmental outcomes (Schendel & Bhasin, 2008).

A recent California study considered parental age as a risk factor for autism. King, Fountain, Dakhlallah, and Bearman used autism diagnostic records of a large cohort born from 1992 to 2000, then matching birth records to assess the impact of parental age on a later diagnosis of ASD (2009). The authors grouped parents by year of diagnosis, with only an advanced paternal age remaining a factor over time, with an OR of 1.29, 95% CI [1.03, 1.6] to 1.71, 95% CI [1.41, 2.08], authors stated was inflated due to pooling of data (M. D. King, Fountain, Dakhlallah, & Bearman, 2009).

Summary

A healthy environment for natal development includes sufficient nutrition throughout pregnancy. As to nutritional supplements, in 1990 the IOM recommended an

additional 30 mg of iron per day during the last two trimesters of pregnancy (Institute of Medicine, 1990). Additional folate was only recommended when there was a known deficiency for the individual. Prenatal vitamins were not recommended for the majority of women. New nutritional guidelines have not been published by the IOM, but micronutrient needs during pregnancy continue to be studied. Catov, Bodnar, Ness, Markovic, and Roberts considered multivitamin use by BMI category, finding that preconceptional multivitamin use did not affect the premature birth rate. The results suggested periconceptional multivitamin use may reduce the risk of small for gestational age (SGA) babies for non-obese women (Catov et al., 2007). While the 1990 IOM guidelines have no suggested additional intake of folate acid for pregnant women, in 1992 the Public Health Service recommended the addition of 0.4 mg of folic acid per day for women of childbearing age in order to decrease the risk of having a pregnancy affected with spina bifida or other NTDs. The 2009 IOM dietary reference intake for choline, the RDA is 450 mg per day, and folate is 600 µg (IOM, 2009). Helinski, Trauth, Jernigan, and Kerr (2004) considered the effect of a public health promotion program about folic acid benefits with various health professionals, learning that more recent graduates were more likely to recommend current information on the benefits of folic acid use than those who had been practicing for some years. While women need to know evidence-based guidelines for nutrition before becoming pregnant, there is still much to learn for optimal pregnancy outcome. After fortification of grains, Mosley et al. found no statistical significance with the increase in folate intake and a decrease in neural tube defects for babies born after 1997 (Mosley et al., 2008). One limitation of the study was the fortification of grain began in the United States in January 1998; there would have

been some overlap of women getting part of their folic acid from the food chain and some from supplements. In the analysis, the study was based on self-reported data, which did not differentiate between the possible sources of maternal micronutrient intake. No baseline was done considering the folic acid in the mother's diet and with all self-reports, reports were subject to bias. Micronutrients also studied were choline and betaine as the exact combination of nutrients for optimal neurological growth during gestation, which is not known. Shaw, Carmichael, Yang, Selvin, and Schaffer concluded that the addition of these two micronutrients with the choline decreased the likelihood of a neural tube defect (2004). The balance of macronutrient and micronutrient intake during pregnancy increases the probability of a baby being born without birth disorders.

The current IOM pregnancy weight gain guidelines for underweight (BMI <18.5) women are to gain from 12.5 to 18 kg. Yet, underweight women tend to gain less and obese women tend to gain more. Cedergren found that morbidly obese (BMI 40+) women are automatically in the high-risk pregnancy category (Cedergren, 2004). Kiel et al. recommended different GWG by BMI obese category, with a range of gain for each: Class I from 4.5 to 11.3; class II up to four kg; and class III also up to four kg (Kiel et al., 2007). The 1990 IOM guidelines had a minimum GWG recommendation for those in the obese BMI category, but no maximum. The 2009 IOM pregnancy weight gain guidelines for those with a BMI equal to or higher than 30.0 are from five kg to nine kg. In the New York study group, 18.4% gained 18.6 kg plus (Rosenberg et al., 2005). In the Danish group, the average GWG was 15.1 kg, with the obese group gaining an average of 10.5 kg (Nohr et al., 2008). In 2006, Cedergren published optimal GWG by BMI category with only one recommendation for the obese group. For women in the underweight

category, the recommendation was to gain from four to ten kg. For pregnant women in the normal or average BMI range, a weight gain from two to ten kg, and those in the overweight less than nine kg, and obese less than six kg (Cedergren, 2007). In summary, there is some disagreement about optimal GWG for those in the obese range. Cedergren and Kiel groups both recommended lower weight gains for those women whose BMI is greater than 30. Cedergren recommending less than six kg and not differentiating between the obese categories, while Kiel recommended separate GWG guidelines for each of the three obese categories with class I to gain between 4.5 to 11.3 kg, class II from zero to four kg, and class III from zero to four. The IOM guidelines of 2009 recommend a weight gain from five to nine kg for those in the obese category for singleton pregnancies.

Appropriate weight gain by BMI category has been associated with better birth outcomes. Stotland et al. (2005) focused on patient education of appropriate weight gain by BMI category finding that health care providers did not give sufficient education to women for the optimal GWG by BMI category. Of overweight women, 24% gained more than IOM guidelines. Of all women in the study, 79% were within IOM guidelines, with 12% below the recommended GWG. For women with high prepregnancy BMI, 9% gained above the guidelines (Stotland et al., 2005). Even with the existing GWG recommendations, physicians were not informing a third of their patients of the benefits of appropriate weight gain.

Risk factors that have been considered for various developmental disorders, birth defects, agenesis of body parts, and mental disorders include season of birth, smoking, caffeine consumption, alcohol consumption, BMI, lifestyle exposures, prepregnancy

weight change, and interpregnancy interval. The ideal developmental environment would include optimal nutrients, hydration, environmental factors, excluding unneeded or harmful chemicals and stressors. There may be a lack of nutrients, mom may smoke and drink excessively, and maybe it is harmful to be born in December. The Danish study published by Atladóttir et al. (2007) considered four neuropsychiatric developmental disorders that are most common. Hyperkinetic disorder, obsessive-compulsive disorder, Tourette syndrome, and autism spectrum disorder are all diagnosed early in childhood and at times occur with one another. The day-by-day analysis of birthdates revealed no seasonality pattern (Atladóttir et al., 2007). When only considering ASD, Lee et al. (2008) reported a significant decrease in risk for those born in December, but overall births were also lower for the month. Mongraw-Chaffin et al. only prenatal lifestyle factors were considered for risk of persistent cryptorchidism in the study done in California (2008). The authors found only slightly increased risk with caffeine consumption, while smoking and alcohol consumption showed no increase of risk (Mongraw-Chaffin et al., 2008). Hultman, Sparén, and Cnattingius (2002) found seasonality not to be a factor for ASD. Another study considered both maternal BMI and lifestyle factors for bilateral renal agenesis, finding a BMI greater than 30, smoking, and binge drinking all increased the risk (Slickers et al., 2008). Schaefer et al. (2000) also found high BMI to increase the risk of schizophrenia in adult offspring. When pregnancy interval and prepregnancy weight change was considered for risk of oral clefts, the authors found when there was an increase of more than three units, the risk was 2.3 times higher (Villamor et al., 2008). Together these findings suggest that significant changes in nutrient intake do affect birth outcomes.

Some studies only considered ASD as the outcome. Of the possible parental factors, those that have been considered as a risk factor were age, birthplace, psychiatric history, socioeconomic status, and assisted conception. Perinatal and prenatal risk factors considered have included multiple gestations, preeclampsia, number of antenatal visits, low birth weight, preterm birth, and others. Durkin et al. found conflicting results, reporting risk of ASD increased with parental age, but the risk of the firstborn being three times greater than those siblings born afterwards (Durkin et al., 2008). The Swedish study by Hultman, Sparén, and Cnattingius (2002) found significant risks included maternal smoking, maternal birth outside Europe, cesarean delivery, SGA, low Apgar score after five minutes, and congenital malformations. Larsson et al. (2005) found breech presentation, low Apgar score, gestational age at birth less than 35 weeks, and parental psychiatric history to all be significant for the later diagnosis of ASD for the baby. In Denmark, the findings were risk of ASD increased with maternal factors of age greater than 35, foreign citizenship, use of medication during pregnancy, low birth weight and congenital malformations (Maimburg & Vaeth, 2006).

Those factors not found to be significant were head circumference, maternal diabetes, being a twin, season of birth, socioeconomic status, weight for gestational age, parity, parental age, number of antenatal visits, birth interventions, pathological cardiotocography, green amnion fluid and acidosis during delivery (Durkin et al., 2008; Hultman et al., 2002; Larsson et al., 2005; Maimburg & Vaeth, 2006).

Assisted conception was a variable found to be protective for ASD (Maimburg & Vaeth, 2007). The suggestion would be that those who are making a consistent effort to generate offspring should be consuming nutrients for the optimal nutritional needs of the

baby. Schendel and Bhasin studied birthweight and gestational age as risk factors for autism and other developmental disabilities. Their findings suggested impaired fetal growth could be a factor for children with autism (Schendel & Bhasin, 2008). Using the best guidelines for optimal GWG by BMI category results in the best natal outcome. Hultman, Sparén, and Cnattingius (2002) suggest that intrauterine and neonatal factors may be at work for the cause of autism. The research suggested the prenatal BMI category and appropriate GWG by BMI category might be factors for optimal development conditions during pregnancy.

Conclusion

The gap in the research for the prenatal predictor of ASD is BMI category. By analyzing the reported prenatal weights of women who have borne children later diagnosed with ASD and some children free of the life-long disorder, the literature gap will be filled. The appropriate weight gain by BMI category a risk factor for a later diagnosis of ASD will also be learned. We know the initial weeks of pregnancy are critical for the development of the organs and body systems. During the most critical periods of pregnancy, the embryo and fetus rely only on the mother for essential growth.

Health professionals utilize evidence-based guidelines in order to educate women about healthier choices in order to increase the odds of a healthier birth outcome. There was a gap in the literature at the intersection of BMI and autism. It is known, that for the best-predicted postnatal outcome, the mother should gain weight appropriate for the respective BMI category.

The next chapter describes the study to answer the research question. While some research has been done regarding mental wellness of offspring, a sibling study had not

been done comparing the BMI of the mother at early pregnancy. It was not known whether the mother was more likely to be heavier for the child later diagnosed with ASD. According to the IOM, it is known that a baby is more likely to be healthy if the mother gains weight within the healthy guidelines for her respective BMI category.

Chapter 3: Research Method

Introduction

The study investigated the hypothesis of whether maternal overweight or obesity during early gestation was a risk factor for a later diagnosis of ASD, a disorder that affects more than 2 million Americans. This chapter includes a description of the study design, the sample population, the variables, participant protection, and ethical issues. The study investigated the hypothesis of whether maternal overweight or obesity during early gestation was a risk factor for a later diagnosis of ASD, a disorder that affects more than 2 million Americans. The study design and reasons for selecting a case control are established. The research design will be discussed first, followed by the setting and sample, the data collection tools, and the data collection process. The analysis section includes a description of each variable and then the appropriate statistical analysis to answer the study question. A section describing the Institutional Review Board (IRB) process is presented to describe the participants' protection. Study limitations and the summary are also presented. The chapter describes in detail the methods used in the matched case control study to consider a difference of BMI during sibling pregnancies, with two live births later resulting in siblings discordant for ASD.

Research Design and Approach

The following section includes a description of the research design and why the study design was selected. The section explains the study design limitations with the rationalization for the research type. The case-control study is the best for researching rare health outcomes. The sibling design is similar to the twin design for control of confounders. McGue, Osler, and Christensen (2010) further validated the use of

observational studies when causation is multifactorial. The researchers noted that when an experimental design may not be possible, or ethical, the use of twins for the study can be beneficial (McGue, Osler, & Christensen, 2010).

Description

The case-control study is used when comparing risk factors for uncommon diseases. The study was observational and looked back over time to understand the differences of factors between groups. The design is frequently used for uncommon health outcomes for practicality. There are certain biases inherent in the design.

The case-control quantitative observational study compared differences in BMI category between pregnancies. The study had several limitations. Selection bias occurs when the group studied varies significantly from the general population. It is well established that people who volunteer for research studies are different from the general population. The self-selection bias will exist. Those who do not participate in the study may have quite different results, therefore, the generalizability of the study is limited. The viral recruitment method was used for recruitment. Those with access to the Internet may be different from the general population in regards to education level, which was addressed by study design. While the healthy worker effect bias may not be present, the Internet-connected participant bias was present since the majority of participants were gathered via the Internet. The second type of bias potentially present was information or misclassification bias. The data were self-reported. This was a participatory research project for mothers of children diagnosed with ASD. They were using social networks for social support or entertainment. Effort was required for participation; therefore, the

results may not be generalizable to the general public, as it is known that those who volunteer for research are not the same as the general population.

Study Problem

The etiology of ASDs is unknown. Early pregnancy is a time of the formation of all the major body systems. It was not known whether being in the healthy BMI category mattered for a child's later diagnosis of ASD. Using siblings as controls eliminates many of the differences between women. The case-control study design allows comparison of autism risk when the mothers were obese for one sibling but not for the other. The risk of maternal prenatal body mass index for autism was considered from two aspects.

H_0 1: Maternal overweight or obesity prenatally is not a risk factor for ASD.

H_0 2: An unhealthy GWG during pregnancy is not a risk factor for ASD.

An additional study purpose was to examine the relationship of a later diagnosis of ASD with several risk factors of pregnancy including anemia, high blood pressure, a mental health condition, a move during pregnancy, level of prenatal care, and season of birth. Confounders considered were birth order, gender known prior to birth, and gender of the siblings.

Setting and Sample

Information was gathered for more than 120 pregnancies. In the case-control study, participants are divided into cases and controls based on the exposure or disease outcome. Case-control studies can match at different levels including birth cohort, neighborhood, hospital, and so on. The health outcome was ASD. Those siblings with ASD were the cases; those without ASD were in the control group.

Population

The sample came from the population of females of childbearing age from 1992 to 2007. English-speaking women who had access to the Internet, knew someone who had access to the Internet, or knew someone who was aware of the study were included if they completed the entire online survey. Women were eligible for participation if they had at least two children who were born between January 1, 1992 and December 31, 2007 with a minimum of 36 weeks of gestation.

Sampling Method

The approach used to gather participants was nonprobability using convenience sampling. Participants were recruited on the Internet using the viral expansion loop, which is the online equivalent of word of mouth, beginning with online advocacy groups, including Autism Speaks and statewide autism groups (Autism Speaks). Email recruitment was also done including colleagues and their social networks directing potential participants to a webpage with a brief overview of the study, a button to download the forms, and a link to the online portion of the data gathering survey website (http://www.surveymonkey.com/).

To encourage recruitment to ensure a sufficient sample size gift cards were given. Two randomly selected participants received gift cards of U.S. $30.00 each. Participants had a 2 in 80 chance of winning a $30.00 gift card. The random number generator was used in Stata with the first two matches being selected to receive the gift cards. The gift cards were emailed 30 days after the close of study participant recruitment. The incentive encouraged participation thereby increasing sample size.

Sample Size

The sample size of 120 was selected for sufficient power. OpenEpi's sample size for unmatched case control studies was used (Dean, Sullivan, & Soe, 2009). A two-sided confidence level of 95% with 80% power, the ratio of controls to cases at one to one, the estimate of 35% controls exposed with the anticipated odds ratio of 3.0, results in a required sample size of 110. If 55% are exposed and the least extreme odds ratio to be detected is 3.0, then a sample size of 126 was required (Dean, Sullivan, & Soe, 2009).

Eligibility Criteria

Those eligible for participation were mothers who have two biological offspring discordant for ASD. Inclusion criteria included being a mother whose children were born with at least 36 weeks gestation from January 1, 1992 to December 31, 2007 diagnosed with autism, Asperger syndrome, or PDD-NOS. The participants were mothers who provided the prenatal data. One child was diagnosed with ASD, one child was not. The health outcome registered was ASD; which is normally diagnosed by the age of three, therefore, the end birthdate for inclusion in the study was December 31, 2007. The online recruitment began in the United States, so it was anticipated for the majority of the participants to be U.S. residents using the English language.

Characteristics of Selected Sample

The population studied consisted of mothers of at least two children discordant for ASD. Maternal information was gathered on the Internet questionnaire using SurveyMonkey (see http://www.surveymonkey.com/). A copy of the survey is included in the appendix section of this document. Sibling data included maternal weight when she learned she was pregnant, birthdate, whether the mother was diagnosed with a mental

health condition, anemia, or high blood pressure during pregnancy. Birth order, birthdate, the gender of the child, whether the gender was known prior to birth, whether the family moved during pregnancy, prenatal health care visits, and maximum weight gain during the pregnancy were all requested. After the dataset was complete with all needed data, any paper forms were filed under lock and key. Only the investigator had access to the paper surveys of the participants. The data gathered online were downloaded from SurveyMonkey. The computer was password protected, the personal identifiers including name, email address, physical address, maternal birthdate, and computer ID were removed for all data analysis.

Instrumentation and Materials

The data were acquired one of two ways. The first option was the online option, using SurveyMonkey for the consent and all questions. The second option was to download the forms, print, complete the consent and the survey, then mail it to the post office box or submit it to the investigator. The majority of the surveys were completed online. Since there were fewer than five submitted in paper form, no analysis was done to consider differences between the groups.

The reliability of maternal weight was verified using the repeated measures as recorded since the current weight, then four other pregnancy weights were recorded. The mother's current weight was reported, as were the weights at pregnancy for each of the offspring, and the maximum weight for each pregnancy. The validity of maternal height is subject to less bias than self-reported weight. Extreme outliers were confirmed or corrected with the participants via email.

A complete set of data was necessary consisting of the online information with the consent form. If the participant completed the survey online, they were contacted at least one time to remind them to send the missing or errant data. If unable to obtain complete information, the participant was excluded from the research. It was essential to have the complete set of variables for each sibling.

Description of Data

The following information was gathered for each record: maternal birthdate, maternal education, sibling birth order, sibling birthdate, maximum gestational weight gain, date of consent, date of child's ASD diagnosis, birth location. Maternal BMI was calculated using the standard BMI formula (weight in kg divided by height in meters^2) after conversion to metric measurements. Weight at the time the pregnancy was known and was used to calculate the main variable of interest. Variation in weight gain from pregnancy to pregnancy would be expected.

There were missing data. Variables with more than 30% unreported were not included in the regression analysis. For the maximum weight reported, coding errors were considered first, then the weight confirmed when necessary. With the five weights given, extremes were verified with the participants.

The data were cleaned. With each variable, a frequency was done, the outliers were verified, then discarded if outside two standard deviations of the mean. If the variable was necessary for calculations for the study, the participant was notified to attempt verification via email. Each variable was considered individually, then as a group. Since the majority of the data were received directly from SurveyMonkey, the other records were checked and verified for correct entry.

Dependent Variable

The dependent variable was ASD In a case-control study, the dependent variable determines the research group. The cases were those diagnosed with ASD, those siblings without ASD were the controls. The observational study considers various factors that may possibly impact an increased risk of the disease outcome. The disease outcome in this study was autism.

Independent Variables

The primary independent variables were BMI category at pregnancy and healthy gestational weight gain. Measures were converted from U.S. measures to metric as needed. Underweight was a BMI less than 18.5 with the total recommended GWG from 12.5 to 18 kg. The normal BMI category is from 18.5 to 24.9 with the suggested GWG from 11.5 to 16 kg. For those women who are overweight (BMI 25- 29.9), a weight gain from 7 to 11.5 kg was proclaimed to be optimum. For women with a BMI greater than 30.0, a weight gain from 5 to 9 kg is considered best by the experts (IOM, 2009). A healthy BMI was in the normal category for analysis. A new binary variable was created, labeled appropriate GWG. The secondary independent variables were birth order, birthdate, gestational weight gain, high blood pressure, anemia, gender of the child, if the gender was known prior to pregnancy, prenatal care visits, a residential move during the pregnancy, family history of ASDs, and mental health conditions. Demographic information was included to predict the generalizability of the study results. Those variables were education level of mother, birthplace of mother, age, marital status, and home ownership.

Data Collection and Analysis

The data were entered into a file using only necessary variables. The analyses were done using Epi Info, Version 3.5.1 (U. S. Department of Health and Human Services, 2010). GWG was calculated for each pregnancy by subtracting the at pregnancy weight from the maximum weight for the respective pregnancy, BMI at pregnancy, then two new variables were calculated. A healthy BMI range at pregnancy included both the normal and overweight categories. The second calculated variable was appropriate weight gain for BMI category. The dependent variable was ASD, the main independent variable was maternal BMI at early pregnancy. Odds ratios were calculated for the categorical variables. The two-sided test at the $\alpha = .05$ level of significance was used. If p was less than or equal to α, the null hypothesis was rejected. Confidence intervals of 95% were calculated. Regression analysis was run for the major variables studied including appropriate gestational weight gain, BMI category at pregnancy, and gestational weight gain. The primary independent variable was maternal prenatal BMI category.

Protection of Participants' Rights

The U.S. Department of Health and Human Services (HHS) regulations regarding human subject protection were used to ensure that patient rights were protected. The Institutional Review Board (IRB) at Walden University was utilized for proper adherence to all research procedures. The IRB approval number was 02-15-10-0332414. The NIH standards for research were followed. All participants in the study completed informed consent. Since primary data were used and were identifiable, informed consent was done via the Internet. The form was included in the online survey. It was also available for

download, then completed by the participant and submitted to the researcher. The study added to the scientific base of knowledge for the etiology of ASD.

The observational study used online questions, making the risk to the participants minimal. The identity of the individual was used for initial data analysis, thereafter the private identifiable records were removed. The paper surveys were kept under lock and key with only the investigator having access. The records will be destroyed seven years after the last journal article is published for the study.

Summary

This chapter described the methods that were used to complete the quantitative case control study to consider prenatal overweight or obesity as a risk factor for a later neurodevelopmental outcome in the offspring. The observational design inflicts no additional harm to the families that have been impacted by the diagnoses of ASD for a family member. The study results will quantify the risk associated with prepregnancy BMI category and a later diagnosis of a child with a developmental disorder.

The null hypothesis was there is no difference in the odds of ASD for mothers who were overweight or obese in comparison to those who were normal weight or underweight. While it is known that case-control studies are subject to various biases, the study type is considered the best study for rare health outcomes, being both timely and cost effective. The next chapter will present the results and show whether there was a significant difference in BMI and GWG for the pregnancies.

Chapter 4: Results

Autism was not found to be dependent on obesity at pregnancy for the participants in this study. The study revealed no association between a healthy gestational weight gain by BMI category and the later diagnosis of ASD. The following chapter describes the data collected, lists the results, and reports the findings for the main study variables. The first research question: Does maternal overweight or obesity impact the risk level for a child's later diagnosis of ASD?

H_0 1: Maternal overweight or obesity prenatally is not a risk factor for ASD.

H_A 1: Maternal overweight or obesity prenatally is a risk factor for ASD.

The second research question: Does a healthy GWG for BMI category decrease the risk of ASD?

H_0 2: An unhealthy GWG during pregnancy is not a risk factor for ASD.

H_A 2: An unhealthy GWG during pregnancy is a risk factor for ASD.

After data collection, the BMI was calculated for each pregnancy, the GWG was calculated by subtracting the maximum weight from the weight at pregnancy. Odds ratios were calculated for each BMI category and an appropriate or healthy GWG by BMI category. Odds ratios with 95% confidence intervals were calculated. Confounders considered were birth order, gender known prior to birth, and gender of the siblings. The descriptive statistics are presented. The results of the data analysis are described by the main research question. First, the two-way associations between autism and demographic, socioeconomic, and familial variables are reported. Second, the multiple logistic regression results are presented. The conclusion summarizes the findings in terms of the research question.

Descriptive Statistics

Results of the descriptive analysis include characteristics of the participants, variables common to both pregnancies, and information specific to each pregnancy (see Appendix A). The majority of the women completed the user-friendly survey on computers. Less than five participants used the print option. Of the 81 who began the survey, 70 completed it with adequate information. The response rate was not possible to calculate. There is no national registry for ASD in the United States, so the denominator would be an estimate. Of those who began the online survey, 86% completed. The study was conducted in June and July 2010.

Characteristics of the study sample

Characteristics of the study sample are presented in Table 1. Maternal age was calculated from the birth date, as a continuous numerical variable. The average participant age was 37.1 years (± 6.6), ranging from 23 to 54. Both the mode and the median were 35. The birth location of the mother was requested and, if born abroad, the country of birth was recorded. The variable was analyzed as a categorical nominal variable. Five were born in Indiana, 56 in other U.S. states, and nine mothers were born outside the United States. Marital status was requested using a nominal categorical variable with space allowing participants to write in another status. The family size of the study participants was not large with an average of 2.4 children per family and a range from two to five children.

Table 1

Characteristics of Study Sample, N=70

Variable	*N* (%)
Maternal age (%)	69 (99)
Median in years	35
Nativity	
In the U.S.	61 (87)
Outside the U.S.	9 (13)
Marital status	
Married	59 (84)
Divorced or other	11 (16)
Total number of children in family	
Two	48 (69)
Three or more	22 (31)
Education	
Less than high school	0 (0)
Completed high school	10 (14)
Some college or technical school	28 (40)
Completed college- bachelor	17 (24)
Graduate degree	15 (21)
Housing- own home	53 (76)
Rent or other	17 (24)

Family characteristics

Several factors were considered for family characteristics. One was birth order, which can be used as a proxy for maternal age. The next was a family history of ASD and a mental health condition. Since these are more descriptive than analytical, only the basic information will be included. The participants could answer both family health questions with a yes, no, or other response. There was also space for comments. The two variables were categorical and dichotomous. Birth order was determined by the birthdates for the siblings. The child later diagnosed with autism was born first in 61% of the sample. Of the participants, 30% reported a family history of ASD for a close relative. Thirty percent

also reported some sort of familial mental health disorder. The majority of the women were well educated, had smaller families, were married, and owned their own homes. The next section will describe the variables that pertained to each of the pregnancies.

Pregnancy variables

The first section will present reportable pregnancy health factors including high blood pressure, anemia, and a mental health condition. One potential stressor, a residential move during pregnancy, was observed. These pregnancy variables are dichotomous. Prenatal care is considered essential in our country, therefore, while the data requested was categorical, for analysis, the data were reported as dichotomous, either 11 or more prenatal visits or fewer. The results of the birth season are presented. Two variables for gender were included, one was whether the gender was known before birth, and the gender of the child.

Health factors

Anemia was reported for 22% of the pregnancies. High blood pressure was reported for 12% of the pregnancies. A mental health condition was reported diagnosed at some point for 31% of the pregnancies. For the family health, 43% reported a mental health condition in the family, while 30% reported an immediate family member that had been diagnosed with ASD. A move during pregnancy was reported by 27%. The women went to the doctor frequently receiving prenatal care, with 73% reporting 11 plus visits for each pregnancy. Since this information was not the core research, the data are presented in Table 7, later in the chapter.

Seasonality

The time of year the baby is born has been linked to several adverse health outcomes. The season of the year was determined. The Julian day is the running number of day for the calendar year, for example January 1, is Julian day 1; February 2 is Julian day 33, and so on. After calculating the Julian day of birth, the means were calculated and compared using the *t*-test. The mean birthdate for those diagnosed later with autism was Julian day 190 or July 9 for a non-leap year, for those undiagnosed, the mean was 199 or July 18. The *t*-statistic was 0.52, with a *p*-value of .60. There was not a significant difference. In order to do further analysis, categories were done using the sun cycle for seasons: spring, summer, winter, and fall. Then frequencies by season and autism were done (see Table 2).

Table 2

Season of Birth, N=140

Season of birth	ASD + (*n*=70)	%	ASD (*n*=70)	%
Spring	22	31%	14	20%
Summer	18	26%	25	36%
Fall	13	19%	18	26%
Winter	17	24%	13	19%

From the data, it appeared a birth in the summer and fall was protective against autism, which led to the analysis dividing those born in the summer and fall into one group; winter and spring in the other. The OR for a winter or spring birth was 2.00, 95% CI [1.02, 3.93], with a *p*-value of less than .05. Of the children included in the study, a birth in the winter or spring increased the odds of later being diagnosed with autism.

Being born in the summer or fall was a protective risk factor, therefore combined for later analysis.

Gender

Both gender variables were dichotomous. Since males are diagnosed at a higher rate, female was the reference category. Many times, the families are aware of the gender of the offspring prior to the birth. The results are as follows. To be male resulted in an OR of 4.14, 95% CI [1.93, 8.88], with a *p*-value of less than .001. The variable describing whether the parents were aware the gender of the offspring prior to the birth was not significant. The OR was 0.82, 95% CI [0.39, 1.72], with a *p*-value of .31. Being male was significant, while knowing the gender prior to birth was not.

Body Mass Index and Gestational Weight Gain

The main study questions results are provided in the following section. The hypotheses are listed, followed by the results and analysis.

H_0 1: Maternal overweight or obesity prenatally is not a risk factor for ASD.

H_0 2: An unhealthy GWG during pregnancy is not a risk factor for ASD.

The participants reported five weights that were compared for consistency:

1. Current weight.
2. Weight at pregnancy for child later diagnosed with autism.
3. Maximum pregnancy weight for the child later diagnosed with autism.
4. Weight at pregnancy for the child not diagnosed with autism.
5. Maximum pregnancy weight for the child not diagnosed with autism.

GWG was calculated for each pregnancy, BMI at pregnancy and two new variables were calculated. The first dichotomous variable was being in a healthy BMI

range at pregnancy, which included those in both the normal and overweight categories. The second was appropriate weight gain for BMI category. Table 3 shows the association between BMI category at pregnancy and ASD. No significant difference in autism risk was found by level of BMI. Among mothers who were obese at the time of delivery, 53% of births produced an autistic child and 47% did not, with a *p*-value of .34. The primary hypothesis for the study was to learn whether there was a significant association between the BMI categories and the odds of ASD. There was not a significant association. The null hypothesis was there was no difference in the early pregnancy prenatal maternal BMI. The null hypothesis was retained.

Appropriate GWG

Another question was whether being in the appropriate GWG category appropriate for BMI at pregnancy was a risk factor for a later diagnosis of ASD. Only 24% of the women gained the appropriate weight for their respective BMI category. The variable was not significant (See Table 4). The OR was 0.67, 95% CI [0.31, 1.47], with a *p*-value of .16. The mother gaining the appropriate weight during pregnancy was not a significant risk factor for a later diagnosis of ASD in the offspring (See Table 3).

Table 3

Association Between Appropriate GWG and ASD, N=140

Variable	ASD +	%	ASD -	%
GWG appropriate for BMI category				
Underweight/Normal (<24.99)	10	7%	13	9%
Overweight (25-29.99)	2	1%	5	4%
Obese (30+)	2	1%	1	1%
Total	14	10%	19	14%
GWG not according to IOM guidelines				
Underweight/Normal (<24.99)	32	23%	25	18%
Overweight (25-29.99)	10	7%	13	9%
Obese (30+)	14	10%	13	9%
Total	56	40%	51	36%

Specific variables of significance

Bivariate tests assessing the association between maternal weight and the odds of ASD were not significant. However, when other variables including season of birth, high blood pressure, gender, and whether gender was known at birth were added.to the calculations. then there were significant findings. The following table reveals the odds ratios and confidence intervals (Table 4). The odds ratio calculations resulted in no statistically significant findings by BMI category. Birth by season also resulted in no statistically significant findings. When summer and fall births were combined, then the OR was 0.50, 95% CI [0.25, 0.98], with a *p*-value of less than .05. The other variable of significance was gender. Being male resulted in an OR of 4.14, 95% CI [1.93, 8.88], with a *p*-value of less than .001.

Table 4

Bivariate Tests of Association Between Covariates and ASD, N=140

Variable	Odds ratio	95% CI	*p*-value
BMI Category			
Underweight (BMI < 18.5)	2.48	[0.61, 10.01]	0.10
Normal (18.5-24.99)	1.00	[0.51, 1.94]	0.50
Overweight (25-29.99)	0.60	[0.26, 1.36]	0.11
Obese (30+)	1.19	[0.53, 2.66]	0.34
Season of birth			
Summer	0.62	[0.30, 1.29]	.10
Fall	0.66	[0.29, 1.48]	.16
Winter	1.41	[0.62, 3.17]	.21
Spring	1.83	[0.85, 3.97]	.06
Birth season summer or fall	0.50	[0.25, 0.98]	.02*
GWG appropriate for BMI category	0.67	[0.31, 1.47]	.16
Gender known prior to birth	0.82	[0.39, 1.72]	.31
High blood pressure diagnosed	0.66	[0.31, 1.37]	.13
Gender = male	4.14	[1.93, 8.88]	< .001***

Note. *$p < .05$, ***$p < .001$

Multiple Logistic Regression Analysis

The following section reports the findings of the multiple logistic regression analysis (see Table 5). The odds ratios using a 95% confidence interval with the *p*-values will be presented. Being born in the summer or fall was protective, OR 0.46, 95% CI [0.22, 0.97], *p*-value is equal to .04. The other variable of significance was gender. The OR for male was 4.30, 95% CI [1.93, 9.56], *p*-value is less than .01. The variables that were not statistically significant for this portion of the analysis included BMI in the overweight or obese category at pregnancy, appropriate GWG for BMI category, and

high blood pressure. Being born in the summer and fall or fall appeared to be protective. Male gender was statistically significant with other variables included being in either the underweight or overweight category at pregnancy, having the appropriate weight gain for BMI at pregnancy, being diagnosed with high blood pressure proved the best fit. The test statistic was 22.35, with seven degrees of freedom since there were seven variables considered in the analysis, and a *p*-value of less than .01. The number of degrees of freedom is determined by the number of independent variables included for the comparison. The birth season in summer or fall was protective, as was being in the overweight category at pregnancy, but the latter was not statistically significant. Being male and having high blood pressure diagnosed during pregnancy appeared to impact risk, as did being underweight at pregnancy.

Table 5

Multiple Logistic Regression analysis of ASD

Variable	Odds Ratio	95% CI	*p*-value
Birth season summer or fall, as opposed to winter or spring	0.46	[0.22, 0.97]	0.04*
BMI at pregnancy: Obese (30+)	0.95	[0.38, 2.39]	0.91
BMI at pregnancy: Overweight (25-29.9)	0.49	[0.19, 1.27]	0.14
GWG appropriate for BMI category	0.64	[0.27, 1.55]	0.33
Gender known prior to birth	0.66	[0.29. 1.50]	0.32
High blood pressure diagnosed	2.17	[0.66, 7.09]	0.20
Male gender	4.30	[1.93, 9.56]	0.00***

Note. * $p < .05$ for birth season of summer or fall, *** $p < .001$ for male gender

Interaction

While several tests were done to test interaction, the one of interest was the interaction variable for seasonality and male. The test statistic was 25.72 with seven degrees of freedom. The interaction with seasonality was statistically significant with a *p*-value less than .01. When the interaction of being male was combined with being born in the summer or fall, the interaction term was significant. However, since the birth season was no longer significant, the model was discarded (Table 6).

Table 6

Multiple Logistic Regression Analysis with Interaction

Variable	Odds Ratio	95% CI	*p*-value
Birth season summer or fall	1.45	[0.38, 5.59]	0.59
BMI at pregnancy Obese	1.25	[0.48, 3.27]	0.64
BMI at pregnancy Overweight	0.56	[0.21, 1.51]	0.25
BMI at pregnancy Underweight	3.34	[0.70, 15.97]	0.13
GWG appropriate for BMI category	0.62	[0.25, 1.53]	0.30
High blood pressure diagnosed	2.32	[0.68, 7.90]	0.18
Male gender	9.89	[2.80, 34.90]	0.00***
Birth season summer or fall * Male	0.18	[0.03, 0.96]	0.04

Note. *** p < .001 male gender

Findings

The risk of ASD was not significantly different between BMI categories in this case-control study, where the health outcome measured was ASD. The risk of ASD in the offspring was not affected by maternal prenatal BMI. Gaining the appropriate amount of

weight during gestation, as determined by the IOM also did not impact the health status of the child in regards to ASD. Gender was the significant risk factor for autism. A birth in the summer or fall was protective for autism.

The following table displays a data summary of the findings of the study in one table. Please note that background information of the women and the study variables of significance are included. Table 7 is a numerical format of the variables of significance either before, during, or after the entire pregnancy period.

Table 7

Odds ratios for ASD

Exposure or Condition	Odds Ratio	95% CI	*p*-value
BMI at pregnancy Underweight (<18.5)	2.48	[0.61, 10.01]	.10
BMI at pregnancy Normal (18.5 -24.9)	1.00	[0.51, 1.94]	.50
BMI at pregnancy Overweight (25.0-29.9)	0.60	[0.26, 1.36]	.11
BMI at pregnancy Obese (30+)	1.19	[0.53, 2.66]	.34
Healthy BMI at pregnancy	0.66	[0.31, 1.37]	.13
GWG appropriate for BMI category	0.67	[0.31, 1.48]	.16
Anemia	1.28	[0.58, 2.86]	.28
High blood pressure	1.99	[0.69, 5.72]	.10
Mental health issue	1.00	[0.49, 2.04]	.50
Male gender	4.14	[1.93, 8.88]	< .001***
Gender known prior to birth	0.82	[0.39, 1.73]	.31
Prenatal visits	0.86	[0.41, 1.82]	.35
Move during pregnancy	1.16	[0.55, 2.44]	.35
Birth season summer or fall	0.5	[0.25, 0.98]	.02*

Note. * $p < .05$, *** $p < .001$

Conclusion

The study's two research questions dealt with the relationship of maternal prenatal body mass index for siblings who were discordant for ASD.

H_0 1: Maternal overweight or obesity prenatally is not a risk factor for ASD.

H_0 2: An unhealthy GWG during pregnancy is not a risk factor for ASD.

Neither of the null hypotheses could be rejected. Autism was not found to be dependent on obesity at pregnancy for the participants in this study. The study revealed no association between a healthy gestational weight gain by BMI category and the later diagnosis of ASD. The other relationships studied included anemia, high blood pressure, a mental health condition, gender, gender known before birth, prenatal visits, a move during pregnancy, birth order, and season of birth. In the secondary analysis, the variables of significance were season of birth and gender. Males are at a higher risk of autism, 81% of those with autism in the study sample were male. The confounding of significance was birth season with gender. Being born in the summer or fall was protective for the study group. The next chapter will discuss the findings and place them within the larger body of research presented in Chapter 2.

Chapter 5: Discussion, Conclusions, and Recommendations

According to the results of this study, being overweight or obese during pregnancy is not a risk factor for ASD. Having a healthy BMI is important for overall health and longevity, but in regards to ASD, being overweight or obese during pregnancy is not a risk factor. This study does not give women in childbearing age another reason to be at a healthy weight before and during pregnancy. The major study variables had no statistical significance and were not associated with an increase in the diagnosis of autism. However, two secondary variables proved to have significance: gender and seasonality. Males have an increased risk of being diagnosed with ASD and children born in summer or fall appeared to have a lower risk of ASD.

Interpretation of Findings

The gap in the research on BMI at pregnancy and GWG as risk factors for autism was investigated. While the IOM recommends a healthy weight gain during pregnancy and the CDC recommends a healthy BMI always, neither is a risk factor for ASD. The ecosocial theory, grounded in location with all the environmental and social impacts that have the potential for one to have optimal health, was the theoretical construct from which the study began (Krieger, 2008). The women were recruited using online social networks. The women who participated in the study were more likely to own homes, have some postsecondary education, have smaller families, and have multiple visits to their health care provider during pregnancy. In this study, 46% of the women had bachelors' degrees; in the Durkin study on socioeconomic inequality and rates of ASD, 30% of the people living in the census blocks with higher rates of ASD had completed a bachelors' degree (Durkin et al., 2010). The generalizability of the study may be limited

due to these factors. External validity was demonstrated with similarity of findings including weight gain during pregnancy and male prevalence to previously completed studies. Optimal gestational weight gain by BMI category and being obese were not factors for a healthy baby outcome in this study. The following section will place the study findings in the literature review presented in Chapter 2.

Maternal BMI at Pregnancy

The mother being obese at pregnancy was not a risk factor for a child's later diagnosis of ASD. The 2004 Cedergren study in Sweden revealed women who were obese or morbidly obese were more likely to have adverse pregnancy outcomes. Those with odds ratios greater than 2.0 included preeclampsia, antepartum stillbirth, cesarean delivery, shoulder dystocia, meconium aspiration, fetal distress, early neonatal death, and large-for-gestational age (Cedergren, 2004). Autism was not found to be dependent on obesity at pregnancy for the people in this study. The dependent variable for the study was ASD. For children whose mothers were in the obese category at pregnancy in this study, the OR was 1.19, 95% CI [0.53, 2.66]. Being obese at pregnancy was not a risk factor for a child's later diagnosis of ASD. If the mother was in the normal or overweight category at pregnancy, there was no increase in risk of the offspring being later diagnosed with ASD. For mothers in the normal or overweight category at pregnancy, the OR was 0.66, 95% CI [0.31 to 1.37]. Maternal prenatal BMI at pregnancy was not a risk factor for ASD. In a study on healthy renal development during pregnancy by Slickers et al. (2008), the authors found a BMI greater than 30 to result in an OR of 1.90, 95% [1.00, 3.59].

Optimal Weight Gain by BMI Category

The study revealed no association between a healthy gestational weight gain by BMI category and the later diagnosis of ASD. A previous study from Sweden revealed that gestational weight gain by BMI category found normal and overweight women who gained more than the recommended weight were more likely to have adverse perinatal outcomes (Cedergren, 2006). The study results show that appropriate GWG by BMI category for the women in the study was not a risk factor for a child's later diagnosis of autism. The OR was 0.67 for all BMI categories, 95% CI [0.31, 1.48]. Optimal weight gain by BMI category during pregnancy was not a risk factor for ASD.

Weight gain above the GWG guidelines increased the risk of averse birth outcomes. Stotland et al. (2005) found that in women who were overweight, the odds ratio for weight gain above the guidelines was 3.79, 95% CI [2.15, 6.60]. For women in the obese category, the OR was 2.39, 95% CI [1.34, 4.27]. The findings from both the Stotland study and the present study were that women gained more than the recommendations. The present study revealed no negative health effect from the increase in weight during pregnancy. The OR was 0.67, 95% CI [0.31, 1.48], indicating that there was no increase in risk of autism due to a weight gain greater than the IOM recommendations.

The majority of the women in the study did not gain the appropriate weight for their BMI category. Combining all the BMI categories, only 24% of the women gained the appropriate weight suggested by the IOM. In the obese category, 90% of the women were not within the appropriate weight range. For the overweight category, 77% were not in the suggested weight range. The average weight gain for all the pregnancies in the

study was 14.91 kg (32.9 lb). The results for average weight gain were similar to the findings of a Danish study, where the average GWG was 15.1 kg (Nohr et al., 2008). In the Nohr study, for women in the obese category at pregnancy, the average GWG was 8.6 kg. The range of weight gain suggested from the IOM is from 11.5 to 16 kg or from 25 to 35 pounds for women in the healthy BMI category (IOM, 2009).

Family and Mental Health History

Depression and other mental health conditions can adversely impact health. While mental health was not a major study question for the current study, depression and family history of mental health conditions could impact health. Nearly one-third (31%) of the women reported having a mental health issue during pregnancy. In examining the family history of the women in the study, 43% of the families had mental health conditions as part of the family medical history and 30% reported an immediate family member who had been diagnosed with ASD.

Gender

Two aspects of gender were considered in the study. The first was whether the gender of the child was known before birth. The second was gender of the siblings. Knowing the gender of the child before birth was not a risk factor for ASD, OR = 0.82, CI [0.39, 1.72], *p*-value of 0.31. It is well established in the literature that males have a higher rate of autism. A study conducted in Israel found 80% of the children diagnosed were male (Senecky, 2009). The findings of the current study reported 81% male for those diagnosed with ASD.

Birth Order

Birth order served as a proxy in this study for parental age as several studies have shown that birth order and parental age are significant predictors of ASD (Durkin et al., 2008; Larsson et al., 2005; Hultman et al., 2002). While a higher maternal age or paternal age was not considered in the study, birth order was considered. The OR for a child being born first, therefore, the mother being younger, was 2.73 95% CI [1.37, 5.45]. The results here mirror those found in the Hultman study which was a population study done in Denmark (2008). The Durkin study considered age at becoming a parent, which is different from birth order (2008). In this study, the mothers were younger on average at the birth of the child positive for autism. The child with ASD was born first in 61% of the pregnancies.

Seasonality

In this study, a birth in the summer or fall suggested being protective for autism. Lee et al. (2008) showed a protective effect for children born in December, while the present study showed a decrease in risk for the children if they were born in the summer or fall. In the Lee et al. study, there were higher rates of ASD for children born in April, June, and October (2008). The OR for children in the present study was 0.50, the 95% CI [0.25, 0.98] for those born in summer or fall. One limitation of the current study was the small sample size. The interval chosen was season, with natural breakpoints, almost equal in length, and easily understood. The Lee study showed a lower risk for those born in December, this study showed a decrease for those born in the summer or fall, the different findings suggest the need for further studies (Lee et al., 2008).

Conclusions

Not being at a healthy weight at pregnancy did not affect the risk of autism for the offspring. Season of birth may be a risk factor for autism, but more studies need to be done. While being male and a birth in the winter or spring were shown to be risk factors in the regression analysis, the GWG and BMI category at pregnancy were not found to be risk factors. It is recommended for further studies to be done considering seasonal flu during early pregnancy.

Implications for Social Change

The findings from the study suggest BMI at pregnancy and GWG by BMI category were not risk factors for a child's later diagnosis of ASD. Mothers can know that being overweight or obese at or prior to pregnancy did not increase the risk of the child being later diagnosed with autism. The gap in the literature is filled by the results. A tangible improvement from this study, could be for women to be confident in the IOM guidelines for GWG by BMI category in regards to a later diagnosis of ASD for their children. Communities do not need to create interventions and programs for young women who are either considering becoming parents or already pregnant at least in regards to ASD. The social networks in which they participate daily, sharing their struggles, gives them a sharing space for rare health outcomes such as ASD. The study sought to answer this question: Is maternal overweight or obesity a risk factor for autism in offspring? While the study purpose was to give women another reason to be a healthy weight, the results were that the women participated in research, and encouraged other women during the research process, the researcher was allowed temporary entry into their lives. Communications on the social blogs and emails with the participants increased

connectivity. Social change begins with one person in their environment and spreads outwards. These women are making a positive impact with one another, which was evident even though I was only an observer.

Recommendations for Action

The action required from the study results includes dissemination of the information back to the participants and to the social networking sites on the Internet. It is possible that the stress levels of these mothers could be lowered, since they would be aware that a higher BMI or a higher GWG was not a risk factor for autism in their unborn children. The results from this study do not suggest that a healthy BMI or an appropriate GWG for BMI category impact the health outcome autism. The results will be posted on the social network sites, sent to the participants, submitted to a public health journal for possible publication, and presented at a statewide public health conference.

Recommendations for Further Study

The new questions or the ones that need further study are seasonality, gender, and other prenatal influencers on early pregnancy. Since both GWG and BMI at pregnancy were at the end of the first trimester, other first trimester factors could be further studied. With the seasonality question unsettled, it may be of benefit to consider influenza cycles by latitude and geographical region. Another potential study area could be in underweight mothers. The social networks could be utilized to learn more about the etiology of ASD.

Concluding Statement

Maternal current health status as measured by BMI does not impact a child's later diagnosis of ASD. The study raised several questions that need to be addressed in future studies including the gender issue and birth seasonality. The ability of mothers to

produce healthy offspring is essential for the continuation of our species. Several factors of pregnancy around the topic of BMI were addressed in this study. BMI at pregnancy was not shown to impact the risk of autism, therefore woman can be confident that their weight was not a factor. The purpose of a dissertation is not to answer the larger questions in life. The study recruited participants from social network sites and the Internet to study questions surrounding BMI at pregnancy. The participatory study results were posted on the site. The mothers on these social networking sites continue in the daily struggles of their children. Gaining the appropriate weight during pregnancy by BMI category as recommended by the Institute of Medicine was not a risk factor for a child's later diagnosis of autism. Being in a healthy BMI category also was not a risk factor. The search for the causes of autism continues. A healthy society begins with the birth of a healthy baby. Public health begins with each mom, is impacted by each health decision of the individual, and paid for by all. All public health begins at home.

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Appendix A: Online Survey

The purpose of this study is to determine if the early pregnancy weight differs by pregnancy for women who have a child later diagnosed with autism spectrum disorder. Body mass index is the main study variable; another will be birth order.
Your responses are confidential, only the accumulated information from all participants in the study will be presented.
The approximate time to complete this survey is less than 20 minutes. The FIRST set of questions is about the child diagnosed with autism spectrum disorder.
I appreciate your time.

This page contains the consent form which includes details of the study. Your electronic signature is required below to be included in the study.

CONSENT FORM You are invited to take part in a research study of considering prenatal body mass index (BMI) at 12- weeks of pregnancy as a risk factor for a child's later diagnosis of autism spectrum disorder (ASD). You were chosen for the study because you have two healthy children: one who has been diagnosed with ASD, one not. This form is part of a process called "informed consent" to allow you to understand this study before deciding whether to take part.
A researcher named Ruth Ann Hendrix, who is a doctoral student at Walden University, is conducting this study.

Background Information: The purpose of this study is to determine if there are things that happen during the early pregnancy period that may contribute to a child's later diagnosis of autism. Body mass index is one thing to be studied; another will be birth order, and other events listed in the questionnaire.

Procedures: If you agree to be in this study, you will be asked to either: 1. Complete this consent form and survey online;
OR 2. Print the consent form with survey, scan, and submit either electronically to ruthann.hendrix@waldenu.edu
or U.S. mail to: Ruth Ann Hendrix Walden University PO Box 68 Cortland, IN 47228

Voluntary Nature of the Study: Your participation in this study is voluntary. This means that everyone will respect your decision of whether or not you want to be in the study. No one at Walden University will treat you differently if you decide not to be in the study. If you decide to join the study now, you can still change your mind during the study. If you feel stressed during the study you may stop at any time. You may skip any questions that you feel are too personal. You may choose to withdraw any time by notifying the researcher.
There will be minimal risk to you. The potential benefits will be to future mothers who will have more information to ensure a healthy pregnancy for a healthy child.

No compensation will be given to be in the study. To increase participation, a random lottery of those who have completed this survey, will be done on September 30, 2010. Two randomly selected participants will each receive a $30 online gift card from Amazon.com. The card will be sent either electronically or via U.S. mail.

Any information you provide will be kept confidential. Only the researcher will have access to the personal identifiers. All data will be collected, aggregated, and analyzed. The results will only be given in a combined form. The researcher will not use your information for any purposes outside of this research project. Also, the researcher will not include your name or anything else that could identify you in any reports of the study. You may ask any questions you have at any time, you may contact the researcher either by phone 812.497.3099 or 812.707.1452 or email ruthann.hendrix@waldenu.edu. If you want to talk privately about your rights as a participant, you can call Dr. Leilani Endicott. She is the Walden University representative who can discuss this with you. Her phone number is 1-800-925-3368, extension 1210. Walden University's approval number for this study is 02-15-10-0332414 and it expires on February 14, 2011.

You may keep a copy of this form.

Statement of Consent: I have read the above information and I feel I understand the study well enough to make a decision about my involvement. By signing below, I am agreeing to the terms

described above.

***1. Your full name:**

***2. Date of consent**

Today's date MM/DD YYYY /

****3. Participant's Written or Electronic* Signature (Please enter your full name again.)**

Electronic signatures are regulated by the Uniform Electronic Transactions Act. Legally, an "electronic signature" can be the person's typed name, their email address, or any other identifying marker. An electronic signature is just as valid as a written signature as long as both parties have agreed to conduct the transaction electronically.

4. Name

***5. What is your birthdate?**

MM/DD YYYY /

***6. Where were you born? City, state or country if outside U.S.**

7. What is your marital status?

- Married
- Single
- Divorced
- Living with partner
- Other

***8. What is your height?** In feet, then inches, rounding up to the nearest inch.

Feet Inches

***9. What is your current early morning weight in pounds?**

***10. Do you know your Body mass index?**

- Yes
- No

If yes, what is it?

Other

***11. How many children do you have?**

- 2
- 3
- 4
- 5
- 6
- 7+

***12. Please indicate your highest level of education.**

- Less than high school
- High school
- 2 years technical school
- Some college
- Bachelors degree
- Masters degree
- PhD

Other (please specify)

13. Do you own your own home?

Yes
No
Rent

The questions on this page are about your child who HAS been diagnosed with autism spectrum disorder.

14. Child's name

***15. Birthdate** Please enter month, day, and year. MM/DD/YYYY

***16. What is the gender of your child?**

Boy
Girl

***17. Did you receive prenatal care during this child's pregnancy? If so, please select the approximate number of visits.**

none
1-5
6-10
11+
Don't recall

18. Did you know the gender of the baby prior to your child's birth?

Yes
No
Do not recall

Other comment

***19. Did you move during this pregnancy?**

Yes
No
Do not recall
Other

***20. What was your approximate weight when you learned you were pregnant with this baby?**

***21. What was your maximum weight during this pregnancy?**

22. Do you recall being diagnosed with anemia during this pregnancy?

Yes
No
Do not recall

23. Were you diagnosed with high blood pressure during this pregnancy?

Yes
No
Do not recall

If yes, please write the approximate week or month of pregnancy.

24. Do you recall any mental health issues or stress during this pregnancy?

Yes
No
Do not recall.

The questions on this page are about your child who HAS NOT BEEN diagnosed with autism spectrum disorder.

25. Child's name

***26. Birthdate** Please enter month, day, and year. MM/DD/YYYY

***27. What is the gender of your child?**

- Boy
- Girl

***28. Did you receive prenatal care during this child's pregnancy? If so, please select the approximate number of visits.**

- none
- 1-5
- 6-10
- 11+
- Don't recall

29. Did you know the gender of the baby prior to your child's birth?

***30. Did you move during this pregnancy?**

- Yes
- No
- Do not recall

***31. What was your approximate weight when you learned you were pregnant with this baby?**

***32. What was your maximum weight during this pregnancy?**

- Yes
- No
- Do not recall
- Other

33. Do you recall being diagnosed with anemia during this pregnancy?

- Yes
- No
- Do not recall

34. Were you diagnosed with high blood pressure during this pregnancy?

- Yes
- No
- Do not recall

If yes, please write the approximate week or month of pregnancy.

35. Do you recall any mental health issues or stress during this pregnancy?

- Yes
- No
- Do not recall

If yes, please comment.

Other family history and some contact information.

36. Is there a family history of autism spectrum disorders?

- Yes
- No
- Do not recall

If so, please comment.

37. Is there a family history of any mental health disorder?

- Yes
- No
- Do not know

If yes, please comment.

38. If you wish to be included in the drawing for the gift card, please include either your email address or your postal address.

39. Please use this space for any additional comments you would like to make. Thank you.

Thanks so much for your time today. You are finished!

Curriculum Vitae

Ruth Ann Hendrix

Objective

Work in the field of epidemiological research in order to affect change in policies for individuals first, then populations to live their maximum lifespan in good health. All public health begins with the individual.

Education

May 1981, BA, Portuguese, Indiana University
May 1981, Certificate in Latin American Studies, Indiana University
May 2005, Master of Public Health, Concentration in Epidemiology, Department of Public Health, School of Medicine, Indiana University

Positions Held

*February 1989 to present, Corporate Secretary, Director, Rose Acre Farms, Inc.
*May 2004 to September 2005, Research Assistant, Bowen Research Center, Geographical Information System (GIS) implementation for AHEC, Bowen and the Family Practice Residency Clinic in Indianapolis.
*May 2003 to January 2004, Interviewer, Indiana Perinatal Network, Inc. Responsible for consent, authorization, pediatric and postpartum surveys for study at various public health clinics in Marion County, Wishard Hospital, Methodist Hospital
*Spring 2005, Survey Administrator, Indiana Department of Health, Youth Risk Behavior Survey

Conference Presentations

"Choices at Life's End," poster, IPHA, Bloomington, May 2003, 2005
"Choices at Life's End," poster, IRHA, French Lick, June 2003, June 2005
"Local Choices at Life's End," poster, IPHA, West Lafayette, May 2004
"A GIS Study of the Community Benefits of a Family Practice Residency"
September 2004 Bowen Research Center Lecture Series
September 2004 Fourth National Workshop On The Community Benefits Of Family Practice Residency Programs
American Public Health Assoc., Philadelphia, December 2005
"Aspects of statistics: Traffic fatalities & alcohol. Walden University, Minneapolis, MN, July 2007
"Public health informatics in a rural county: efficiency, redundancy, and bureaucracy," poster, American Public Health Assoc., Washington, DC, November 2007
"Nutritional epidemiology: Community summer intervention: Lipoprotein levels." Walden Residency, Dallas, TX February 2008.

Organizations
Delta Omega, Honorary Society in Public Health, 2007, Beta Zeta Chapter
American Public Health Association
Indiana Public Health Association
Airplane Owners and Pilots Association
Simplified Spelling Society
American Egg Board, Alternate for West North Central States, Nutrition Committee
Jackson County Leadership, graduate 2006
Jackson County Community Service Council, Vice President
Jackson County Community Foundation Board Member, Governance Committee
Indiana Youth Institute, Board member, Secretary-Treasurer
Egg Industry Center, Advisory member

Volunteer Experience
Fall 2002 to Fall 2007, Volunteer
Jackson County Juvenile Detention Center, Brownstown
Learning with youth on health, social, religious and family issues thru the Bible

May 2003 to present, Member
Jackson County Community Service Council, Seymour
Local leaders of the various service agencies meet most months to connect for collaboration and education, currently serving as Vice President

Spring 2003 to Spring 2005, Volunteer
ASAP, Adolescent Substance Abuse Prevention
Present with other IUPUI students to Indianapolis Public Schools students.

Computer Skills
Microsoft Office-proficient; Epi Info, Stata, SPSS, SAS– beginning;
GIS ArcMap 9.0- intermediate

Licenses and Certificates
Protecting Human Research Participants, NIH, January 1, 2010
Human Participants Protection Education for Research Teams, NIH, June 4, 2003
HIPAA Privacy Training, Marion County Health Dept., June 5, 2003
Human Subjects Protection, Indiana University, June 18, 2003

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