PERINATAL, MATERNAL AND ANTENATAL ASSOCIATED FACTORS FOR AUTISM: A CASE CONTROL STUDY

by

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Thesis submitted in partial fulfillment of the requirements
for the degree of
Master of Science (Medical Statistics)

March 2011

ACKNOWLEDGEMENTS

In The Name of Allah, the Most Gracious, the Most Merciful

Praise to Allah S.W.T., the most compassionate and most merciful, whose blessing has helped me through the entire completion at this thesis. I would like to record my deepest gratitude and thank to the following individual who helped me during the preparation of this thesis and during my pursuit of the Master of Science (Medical Statistics) in School of Medical Sciences, Universiti Sains Malaysia, Kelantan.

1. My Supervisor, Dr. Wan Mohd. Zahiruddin Wan Mohamad for his support, encouragement, value advice, comment, suggestion and contribution of his time throughout the research and completion of this thesis.
2. Prof.Madya Dr. Mohd Rusli Abdullah and Prof.Madya Dr. Mohd Jamil Yaacob as my co-supervisor for their supports, suggestion, comments and commitment.
3. Prof Dr. Syed Hatim Noor @ Nyi Nyi Naing, Coordinator of Unit of Biostatistics and Research Methodology, for his encouragement, inspiration, support and commitment in teaching and make me fascinated in statistics studies.
4. Dr. Kamarul Imran Musa, lecturer at Department of Community Medicine who gave his guidance, knowledge and critical thinking in statistical methods.
5. Hospital Pulau Pinang and Hospital Bukit Mertajam for their permission and full cooperation for me to conduct this study especially to Psychiatrists Dr.Yushada Budiman bt. Yusof and Dr. Lai Fong Hwa.

6. Ministry of Health, Malaysia for their permission to use the data in the study specifically Clinical Research Center (CRC) and Institutes of Health (NIH).
7. Human Ethics Committee of USM which approved this research.
8. Universiti Teknologi MARA and Kementerian Pengajian Tinggi Malaysia for their supports during my study in all aspects.
9. All lecturers in the Unit of Biostatistics and Research Methodology and the Department of Community Medicine who have gave their guidance, knowledge and support.
10. My course mates for their moral support, opinions and sharing knowledge throughout this research.
11. My deepest gratitude to my lovely wife (Nor Hazlin bt Ramli), parents (Aishah bt Abdullah & Abdullah bin Marican) and siblings for their endless patient, tolerance, great supports and spared their time for the success of the thesis and course.
12. Last but not least, to others who were directly or indirectly involve in this study.

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LIST OF ABBREVIATIONS

SVD	Spontaneous Vaginal Delivery
LSCS	Lower Segment Caesarean Section
LMSL	Light Meconium Stained Liquor
MMSL	Moderately Meconium Stained Liquor.
TMSL	Tight Meconium Stained Liquor
WHO	World Health Organization
NGO	Non Govermental Organization
CDC	Centers for Disease Control and Prevention
HPP	Hospital Pulau Pinang
HBM	Hospital Bukit Mertajam
UCSF	University of California San Francisco
USM	Universiti Sains Malaysia
SPSS	Statistical Package for Social Science
STATA	Statistics/Data Analysis
cm	Centimeter
gm	Grams
kg	Kilo Grams
SD	Standard Deviation
GOF	Goodness of Fit
CI	Confidence Interval
LR	Likelihood Ratio
MLR	Multivariable Logistic Regression
SLR	Simple Logistic Regression

OR	Odds Ratio
ROC	Receiver Operating Characteristic
SE	Standard Error
PS	Power and Sample Size Calculation
df	Degree of Freedom
G^2	Likelihood Ratio Statistic (Deviance)
X^2	Pearson Chi-Square Statistic
Cpt	Covariate Pattern
SK	Selang Keyakinan (Confidence Interval)

LIST OF SYMBOLS

α	Level of Significance
$1 - \beta$	Power
n	Sample
$<$	Less than
$>$	More than
$\leq$	Less than or equal to
$\geq$	More than or equal to
$\approx$	Approximately
%	Percentage
σ	Standard Deviation
$\Delta\hat{\beta}_j$	Pregibon Delta Beta
$\Delta X^2{}_j$	Delta Chi-Squared
ΔD_j	Delta Deviance
$\hat{\pi}_j$	Estimated Probability
$=$	Equal
$\bar{X}$	Population Mean

FAKTOR BERKAITAN PERINATAL, MATERNAL DAN ANTENATAL TERHADAP PENYAKIT AUTISM: KAJIAN KES DAN KAWALAN

ABSTRAK

Pengenalan: Penyakit autism tergolong dalam kalangan penyakit perkembangan neuro dan boleh diklasifikasikan kepada tiga domain utama iaitu kurang upaya berinteraksi secara sosial, kelewatan berkomunikasi dan tingkah laku pengulangan dan stereotypik. Kebanyakan kajian mencadangkan faktor risiko terhadap autism terdiri daripada tiga faktor besar iaitu faktor persekitaran, genetik dan vaksin.

Objektif: Tujuan kajian ini adalah untuk menyiasat faktor berkaitan perinatal, maternal dan antenatal terhadap kanak-kanak berpenyakit autism di Hospital Pulau Pinang dan Hospital Bukit Mertajam, Pulau Pinang.

Metodologi: Kajian yang melibatkan 312 kes dan kawalan ini telah dijalankan mengunakan data yang diperolehi daripada rekod Hospital Pulau Pinang dan Hospital Bukit Mertajam dari tempoh 2001 hingga 2008. Jabatan yang terlibat adalah Psikiatri, Obstetrik dan Ginekologi dan Jabatan Rekod dan Pengurusan. Kesemua kes yang memenuhi kriteria inklusi dan esklusi di masukkan kedalam kajian ini. Regresi logistic univariat dan regrasi logisitk multivariat digunakan untuk menyiasat faktor risiko prenatal/perinatal terhadap kanak-kanak berpenyakit autism.

Keputusan: Terdapat tujuh faktor risiko yang menyumbang kepada penyakit autism. Faktor-faktor tersebut adalah Umur ibu [Nisbah Odd Terselaras: 1.41; 95% SK:

(1.27, 1.57)], Ibu yang merokok pada lawatan antenatal yang pertama [Nisbah Odd Terselaras: 13.61; 95% SK: (1.87, 99.35)], asfixia ketika lahir [Nisbah Odd Terselaras: 0.35; 95% SK: (0.11, 1.08)], sejarah psikiatri [Nisbah Odd Terselaras: 54.94; 95% SK: (12.07, 250.04)], kandungan Berbilang [Nisbah Odd Terselaras: 4.81; 95% SK: (1.86, 12.45)], kelahiran lebih dari 4 [Nisbah Odd Terselaras: 0.11; 95% SK: (0.03, 0.47)], kelahiran diantara 0 dan 1 [Nisbah Odd Terselaras: 0.19; 95% SK: (0.07,0.55)], bangsa Cina berbanding bangsa Melayu [Nisbah Odd Terselaras: 10.11; 95% SK: (3.61, 28.30)] dan bangsa India berbanding bangsa Melayu [Nisbah Odd Terselaras: 5.14; 95% SK: (1.38, 19.16)].

Kesimpulan: Faktor berkaitan perinatal, maternal dan antenatal yang berhubungkait dengan penyakit autism adalah berasaskan pada ciri-ciri kelahiran, ciri-ciri mengandung dan ciri-ciri keibuan.

Kata kunci: Autism, Autistik, ASD, kelahiran, kes dan kawalan, retrospektif, prenatal, perinatal, maternal, antenatal.

PERINATAL, MATERNAL AND ANTENATAL ASSOCIATED FACTORS FOR AUTISM: A CASE CONTROL STUDY

ABSTRACT

Introduction: Autism disorders are a group of neurodevelopmental disorders which characterized into three main domains which are social interaction impairment, communication delay and repetitive or stereotypic behavior. Many studies had suggested that the risk factors for autism derive from three big factors namely environmental factors, genetic predisposition and vaccine induced.

Objective: The aim of this study was to investigate the perinatal, maternal and antenatal associated factors on autistic disorder children at Hospital Pulau Pinang and Hospital Bukit Mertajam, Pulau Pinang.

Methodology: A case control study involving 312 cases and control was conducted using data retrieved from hospital records at Pulau Pinang hospital and Bukit Mertajam hospital from 2001 to 2008. The departments involved were Psychiatric, Obstetrics and Gynecology and Record and Management Department. All cases which met the inclusion and exclusion criteria were included in the study. Univariable and multivariable logistic regression were used to explore the prenatal/perinatal risk factors associated with autistic disorder children.

Results: There were seven risk factors contributed most to autistic disorder determination. The factors were maternal age [Adjusted OR: 1.41; 95% CI: (1.27,

1.57)], maternal smoking reported at first antenatal visit [Adjusted OR: 13.61; 95% CI: (1.87, 99.35)], birth asphyxia [Adjusted OR: 0.35; 95% CI: (0.11, 1.08)], psychiatric history [Adjusted OR: 54.94; 95% CI: (12.07, 250.04)], multiple gestation [Adjusted OR: 4.81; 95% CI: (1.86, 12.45)], parity for more than 4 [Adjusted OR: 0.11; 95% CI: (0.03, 0.47)], parity between 0 and 1 [Adjusted OR: 0.19; 95% CI: (0.07,0.55)], Chinese race compared to the Malay race [Adjusted OR: 10.11; 95% CI: (3.61, 28.30)] and Indian race compared to the Malay race [Adjusted OR: 5.14; 95% CI: (1.38, 19.16)].

Conclusion: The results suggested that autistic disorders were associated with perinatal, maternal and antenatal factors such as delivery, pregnancy and maternal characteristics.

Keyword: Autism, Autistic, ASD, Prenatal, Perinatal, Maternal, Antenatal, Delivery, Parental, Pregnancy, Case Control, Retrospective, Risk Factor.

CHAPTER 1

INTRODUCTION

1.0 Introduction

Autistic disorders are a group of neurodevelopmental disorders. They are characterized by core deficits in three domains which include social interaction impairment, deficit communication delay and repetitive or stereotype behavior. The question of what constitute the risk factors of the autistic disorders has been debated since 1943 when Leo Kanner (1894-1981), an Austrian psychiatrist introduced the label of early infantile autism (Wikipedia, 2010; Committee on Children with Disabilities, 2001).

Finding on the causes of autistic disorder is one of the most challenging areas of medical sciences. The absence of a clear understanding about what are the causes of autistic disorder makes finding of effective prevention very difficult. It was been widely accepted by scientists are that the predisposition to autism is inherited from the underlying genetic cause of up to 40% (Autistica, 2010). Some studies had suggested that the risk factors for autism came from the three big factors which are environmental factors, genetic predisposition and vaccine induced. Another studies have suggested other risk factors including socioeconomic, perinatal/prenatal and familial/parental risk factors (Larsson *et al.,* 2005; Kolevzon, Gross and Reichenberg, 2007; Brimacombe, Ming and Parikh, 2007). However, there was a study that confirmed the link between sub-prenatal risk factor; maternal age was

found to increase the risk of autism (Yahoo! Malaysia News, 2010). It was confirmed that the risk for women over 40 to have a child later diagnosed with autism was 50% greater than for a mother aged between 25 and 29.

The prevalence of autism according to the Center of Disease Control and Prevention (2007); was 3.4 per 1000 children in the United States of America. Overall, the prevalence was comparable for black and white children (black, 3.4 per 1000 and white, 3.4 per 1000). Furthermore, it was found that one in every 150 children is diagnosed to have autistic disorder. In Malaysia, if one in every 150 children were to be taken as a standard prevalence in Malaysia, there would be more than 3000 new cases each year nationwide (Hariati, 2008). The screening test which was conducted from 2005 to 2006 revealed that the prevalence of the Pervasive Developmental Disorder (Autism, Autism Spectrum Disorder and Asperger) in Malaysia was 6-9 per 1000 (Amar, 2008) and one in every 625 Malaysian children is found to be autistic (Hariati, 2008).

In a nutshell, since there are lots of researches determining the risk factors for autism were done outside Malaysia, there will be a possibility of getting different finding for the local population. The general objective of this research is to explore the perinatal, antenatal and maternal associated factors for autistic disorder children in Malaysia; which may reveal the potential risk factors that might contribute to getting children with autistic disorder. It is also important for the epidemiology and disease prevention in Malaysia to prevent future autistic disorder in Malaysia. It also will improve maternal knowledge about possible risk factors.

1.1 Problem Statement

There is no known unique cause of autism, there is growing evidence that autism can be caused by a variety of problems (Stephen, 2010). There also some indication of a genetic influence in autism. For example that there is a greater likelihood that two monozygotic twins (identical twins) will have autism than two dizygotic twins (fraternal twins). There is also evidence that the genetic link to autism may be a weakened or compromised immune system. However, there are no studies that are known to have examined the association between perinatal, antenatal and maternal factors and autism and most studies on perinatal, antenatal and maternal factors have not been able to adjust for socioeconomic status (Larsson *et al.,* 2005). Based on this statement, this study was conducted to explore the perinatal, antenatal and maternal associated factors that might contribute for autistic disorder in Malaysia. This study involved autistic disorder patients in Pulau Pinang only.

1.2 Significance of the Study

This study proposed to determine the link on perinatal, antenatal and maternal associated factors towards autistic disorder children. It revealed some beneficial outcome for the community, government and the future researchers. The outcomes of the study are:-

1) This study identified the most influence perinatal, antenatal and maternal associated factors for autistic disorder syndrome in Pulau Pinang.
2) This study revealed the chance of getting autistic disorder if the children are predisposed to the risk factors.

Moreover, to the researcher's knowledge, there is no published study that had been done on perinatal, antenatal and maternal associated factors towards autism in Malaysia. Thus, this study may provide some information on the associated factors of perinatal, antenatal and maternal associated factors towards autistic disorder children particularly in Penang, Malaysia.

CHAPTER 2

LITERATURE REVIEW

2.1 Autism

Autism is a severe developmental disorder that begins at birth or within the first two and a half years of life. Some study quote that the autism occurs within 18 to 36 months of the infantile. Based on Robert (1997); autistic disorder always begin in childhood, they often persist into adulthood too. The word "autism" comes from the Greek words – "au", which means "self" and "ism", which indicate that "orientation or state". Autism is the categories as the condition of somebody who is unusually absorbed in himself or herself (Reber, 1985). On the other hand, autism is classified as the chronic neurodevelopmental disorder characterized by social and language impairments and stereotyped, repetitive patterns of behavior (Alexander *et al.,* 2007). Autism is also known as pervasive developmental disorders which used to be known as infantile psychoses which also a term best avoided since it misleads people into thinking that autistic disorders are akin to adult psychoses (Robert, 1997).

The history of autism begin in early twentieth century, where the German psychiatrist Emil Kraepelin classified a series of psychotic disturbances in adults as "dementia praecox" where dementia was defined by Kaepelin as "progressive deterioration" and praecox meant that the disturbance had an early onset. Around the same time, disturbances similar to those identified in adults were beginning to be seen in children as well. There were many comparisons and much debate as to

whether or not adult schizophrenia and the analogous disorder in children were one and the same. Some believed the disorder reported in a small number of children was just an early form of schizophrenia, while others pointed out that, although the disorders were similar, these children were clearly not identical to adults with schizophrenia. For a time in the early 1930s, "childhood schizophrenia" became a general label for these disturbances in children. (Alberto, 2007). Moreover, in 1943, Austrian Psychiatrist and physician Leo Kanner termed the disorder "early infantile autism" and claimed that it was different from the disturbances described by Kraepelin and Bleuler in that it had a very early onset. Based on Certec website, 2003; Leo Kanner described 11 autism children with the following common traits: impairments in social interaction, anguish for changes, good memory, belated echolalia, over sensitivity to certain stimuli (especially sound), food problems, limitations in spontaneous activity and good intellectual potential often coming from talented families.

Based on Alberto (2007); a year after the Leo Kanner described autism characteristics, Austrian pediatrician Hans Asperger published his casework on four children, identifying a similar syndrome he termed as "autistic psychopathy" which he renamed in the 1980's, more appropriately as Asperger's Syndrome which brought the meaning "the shutting-off of relations between self and the outside world." Among these four children, Asperger noted several key features that he had observed as common characteristics of autistic psychopathy. These features included impairments in the areas of speech, nonverbal communication, social interaction, motor coordination, skills and interest, and experiences at school.

The characteristics of autistic disorder is one of the five categories under the heading pervasive developmental disorder which also referred to Autistic Spectrum Disorder in some literature on DSM-IV and is characterized by core set of three primary symptoms which are deficits in social interaction, impairment in communication and the exhibiting of representative and stereotyped behavior (Barlow and Durand, 2007). Based on Robert and Stephan (1997); infantile autism is defined by combination of four set of features such as social impairment, communication impairment, restricted and repetitive activities and interest and early onset.

2.1.1 Deficit in social interaction / Social Impairment

Deficit in the area of social interaction are often thought of as one of the defining characteristics of autism. These symptoms include the lack of social or emotional empathy, the absence of desire to share enjoyment and interactions with others, and noticeable lack of nonverbal communication such as body language, eye contact and gestures. Based on Robert and Stephan (1997); if social interest subsequently develops, as it does in just over 50% of autistic children, problems persist in social responsiveness, reciprocity and the capacity for empathy. The child has difficulty in adjusting his or her behavior according to the social context, and is poor at recognizing other people's emotions and responding appropriately. Interactions with peers are generally very restricted. Even among older high-functioning autistic individuals, a limited ability to form close friendship is probably the most sensitive index of residual social impairments.

2.1.2 Deficit in communication / communication impairment

In addition to deficits in social interaction, autistics exhibit significant impairment in the area of communication. Among these impairments is the inability to sustain or initiate conversation with others or the lack of attempts at communication at all, whether verbal or not. Possible abnormalities include: immediate or delayed parroting of words or phrase (Echolalia), pronominal reversal (for example; the word "you" is for "I"), invented words (neologisms) and repetition of all or part of what is said to them, is another sign of communication delay found in autistic people. Also include under communication issues is the lack of age-appropriate imaginative play. Roughly, 50% of autistics individuals never acquire useful speech (Robert, 1997) but more contemporary research suggests that improvements in early identification of the disorder and improvement in treatment have dramatically reduced that percentage (Bryson, Roger and Fombonne, 2003).

2.1.3 Stereotyped and repetitive behavior

Autistic individuals often adhere to inflexible and ridged non-functional routines and rituals. They may become fascinated with parts of objects or become preoccupied with stereotyped patterns of interest characterized by their unusual intensity or focus (for example; the feel of zips or people's hair). This includes resistance to change, insistence on routines and rituals, hand flapping, twirling, ordering play (for example, lining things up) and attachments to unusual objects (for example; dustbin). When present, they will pretend play is often limited to simple repetitive enactments of just one or two incidents from a favorite story or TV program (Robert, 1997).

2.1.4 Early Onset

Though the disorder is rarely recognized in the first year of life, it is usually clear retrospectively that development was never entirely normal, even though the parents may not have been seriously concerned about early signs of a lack of social interest, for example not liking being cuddled, or not reaching out to be picked up. In a substantial minority of cases, however there is a clear "setback" in the second or third year of life; after a period of normal or near normal development, these children go through a phase of regression when they lose previously acquired skills in social interaction, communication and play (Robert, 1997).

Additional characteristics often observed in autistics individuals but not required for diagnosis are uneven cognition, hyperactivity, attention problems, impulsive and aggressive behavior, self-injury, flat affect and extreme fearfulness (Bargh, 2000). Autistic individuals also may exhibit extreme sensitivity or abnormal responses to touch, sound or visual stimuli (Bargh, 2000; Sattler, 2002). Other disorders often found in autistic individuals at a significantly higher rate than the general population are seizure disorders (16.8% of autistic children), fragile X and tuberous sclerosis (Volkmar, Chawarska and Klin, 2005).

2.1.5 Intellectual Abilities

Among the most fascinating aspects of autistic disorder are the reported cases of individuals displaying remarkable artistic and mathematic abilities. Understandably this condition, which occurs to some degree in approximately 10% of autistics (Pinel,

2003), has generated a great deal of curiosity in the disorder. The movie Rain Man starting Tom Cruise and Dustin Hoffman was loosely based on a real autistic individual. About 75 to 80% of diagnosed autistic individuals score in the range of mental retardation on IQ tests (below 70) (Sattler, 2002) with 50 % scoring in the sever range (below 50) (Barlow and Durand, 2002).

2.2 Associated Factors of Autism

Though autism is considered a lifelong disorder, there is evidence that the symptoms improve with age (Seltzer *et al.,* 2003). A study conducted by Seltzer *et al.,* (2003); examining differences between adolescents diagnosed with autism and older people diagnoses with autism earlier in their lives, found that at least some of the adult population no longer met the diagnostic criteria in one or more of the indicative categories (communication, social interaction, and ritualistic behaviors), but were still below average in areas in which they had improved. Though these results may be the product of differing diagnostic interpretations between age cohorts, it does provide hope for those afflicted by the disorder. Longitudinal studies will have to be conducted to further substantiate these claims.

One generalization is that autistic disorder probably does not have a single cause (Tsai, 2005). Instead, a number of biological contributions may combine with psychosocial influences to result in the unusual behaviors of people with autism. There are two categories of the cause for autism, which are secondary and idiopathic (Reddy, 2005). For secondary cause of autism, there are two subdivided causes which are environmental causes and chromosomal causes. The environmental causes

of autism have been supported in some studies, but also subject to scrutiny in others. Some environmental causes are suggested to be in utero exposures to rubella, valproic acid, thalidomide, and mercury toxicity.

Some non-genetic factors are also considered, such as viral illness and immunological deficiency, originating either before birth or within the first two years of life. Many of the heated debates that occur in the public domain relate to putative environmental triggers, among them the so far unsubstantiated claim that the measles, mumps and rubella vaccination is a contributory cause. Similar claims relate to the measles virus in conjunction with gastric inflammatory disease. The balance of the evidence at present does not favor these hypotheses (Taylor *et al.,* 1999; Halsey and Hyman, 2001; Frith and Hill, 2004). Some research studies have stated that there are some risk factors that might contribute for autism such as Perinatal, Socioeconomic status, Maternal Psychiatric history, prenatal and familial risk factors (Larsson *et al.,* 2005; Kolevzon, Gross and Reichenberg, 2007; Brimacombe, Ming and Parikh, 2007) . For perinatal risk factors there are three categories investigation. Firstly, delivery and newborn characteristics; which are fetal presentation, mode of delivery, apgar score in 5 minutes, birth weight, gestation age at birth and weight for gestation age. Secondly are antenatal characteristics; which are multiple gestation, preeclampsia and number of antenatal visits. Finally, the Maternal characteristics; which described as the number of previous pregnancies, maternal smoking reported at the first antenatal visit, maternal citizenship and maternal and paternal ages (Larsson *et al.,* 2005; Kolevzon, Gross and Reichenberg, 2007). For socioeconomic status, the factor that might be the risk factors for autism are maternal education and parental wealth (Larsson *et al.,* 2005).

Next, the Maternal psychiatric history are defined if the parent have been diagnose and been recorded before the child was born. Based on a population study of autism in United States, there were reported that 89% have familial disorder, 57% reported familial psychiatric disorders, 37% reported developmental disorders and 70% reported medical disorders (Brimacombe, Ming and Parikh, 2007).

2.3 Diagnostic Criteria for Autism

Before proceeding further, it is necessary to break through to outline the diagnostic criteria for autism. Expert analysis of the bizarre speech patterns associated with certain psychiatric disturbances is of primary diagnostic significance. If a mute child persists in stereotyped rituals and strange behavior, a diagnosis of childhood autism is likely to be made. Some experts distinguish this from a similar disorder called childhood schizophrenia, in which previously good general and linguistic development falls apart in association with similarly bizarre behavior (Encyclopedia Britannica, 2010). There are two main diagnostic issues arise with respect to age of manifestation. The first issue is how to classify disorders that appear undifferentiated from autism but which differ in terms of development, the children having been apparently normal until after the age of 30 months. A lifting of the cutoff from 30 months to 3 years removes most of these difficulties without altering the basic concept of the syndrome. The second issue is whether autism that seems to have been preceded by a period of definitely normal development differs in any fundamental way from autism in which development has been abnormal from the outset (Schopler and Mesibov, 1988).

Based on First and Tasman (2004); the restricted repetitive and stereotyped pattern of behavior, interests and activities, which are categorized into four. Firstly, encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal in either intensity or focus. Secondly, apparently inflexible adherence to specific, nonfunctional routines or rituals; then stereotyped and repetitive motor mannerisms (for example, hand or finger flapping or twisting or complex whole-body movements). Lastly, persistent preoccupation with parts of objects.

The set of diagnostic criteria is the concerns of the various aspects of deviance in the development of social relationship. Some delay or impairment in social development is likely to occur as a result of the mental handicap quite independently of the autism. It is not appreciated that it is crucial to define the social abnormalities in terms of deviance in relation to the child's mental age; this means that diagnostic assessment must include a careful and systematic cognitive evaluation (Rutter, 1984). The second Diagnostic criterion comprises abnormalities in communication. At one time these tended to be framed in terms of speech or language impairment, but it is clear that the characteristic features involve deviance rather than delay and the abnormalities extend beyond speech to many aspects of the communicative process (Schopler and Mesibov, 1988).

There are two levels of diagnosing autism in early childhood, which recommended from The American Academies of Neurology, Pediatrics and Childhood Adolescent Psychiatry (Bryson, Roger and Fombonne, 2003). The level one screen includes the checklist for autism in toddlers (CHAT) and the early screening for autism

questionnaire (ESA). The CHAT was an early diagnostic screen designed to identify autism in 18 month old children. However, the follow up studies have found that it missed approximately 80% of cases later diagnosed as autistic (Volkmar, Chawarska and Klin, 2005). These failures lead to the development of the M-CHAT which is designed to be issued to infants aged 24 months and up. This is because the relativity of the recent development, accuracy rates for the M-CHAT and the ESA are still largely unknown (Bryson, Roger and Fombonne, 2003).

The level two screens is the Screening test for autism in toddlers (STAT) (Bryson, Roger and Fombonne, 2003). Moreover, the STAT is designed to observe the behavior of children under two. The primary areas of focus are play, imitation and joint attention. Sensitivity rates of 83% have been reported but there may be inflated due to the fact that it was tested on children whose development was already identified as significant abnormal.

2.4 Epidemiology of Autism

Current research has shown drastic increase in the occurrence of autism over the last decade. The Journal of the American Medical Association reported an increase of almost ten times the number of cases in the United States since past research. This was confirmed by Yeargin-Allsopp *et al.,* 2003; when a total of 987 children displayed behaviors consistent with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for autistic disorder, pervasive developmental disorder–not otherwise specified, or Asperger disorder. The prevalence for autism was 3.4 per 1000. Overall, the prevalence was comparable for black and white

children (black, 3.4 per 1000 and white, 3.4 per 1000). Autism was also found to occur more often in males than females at a four to one ratio (Encyclopedia Britannica, 2010). While there is a statistical occurrence difference between genders, it occurs equally across race, ethnic background and social class (Bargh, 2000). It should be noted that other research states that rises in the prevalence of autism may not be accurate because of changes to diagnostic classifications (Tidmarsh, 2003) as well as an increase of awareness about the disorder.

In Malaysia, over the years, scientists have discovered that autism affects boys more than girls and there is no known cure. Approximately 35 million people worldwide are said to be affected by autism. A local survey conducted a few years ago revealed that one in every 625 Malaysian children is autistic. However, in a US survey in 2007, it was found that one in every 150 children is autistic (Centers for Disease Control and Prevention, 2007). If this were to be taken as a standard in Malaysia, there would be more than 3000 new cases each year nationwide (Hariati, 2008). Based on the Amar, 2008; the screening test done between 2005 and 2006 revealed that the prevalence of the Pervasive Developmental Disorder (Autism, ASD and Asperger) in Malaysia was 6-9 per 1000. However according to the department of Social Welfare (2003); Malaysia has 132,655 people with disabilities registered with the department. They are categorized into four groups as follow:-

1) Visual Impairment – There are 14,154 people registered as visually impaired.
2) Hearing Impairment – There are 22,728 people registered as (deafness to deaf/mute) hearing impairment.

3) Mental Retardation – There are 49,340 people registered as (mental intelligence that does not develop with age such as Down syndrome and slow learning disability) mentally retarded.
4) Physically impaired – There are 45,356 people registered as loss of any limb or handicap at any part of the body and this include those suffering from polio, amputation, paralysis and spastic.
5) Others – There are 1077 persons registered under this group and they are normally those with dual disability or multiple disabilities.

Autistic children are often placed under the mental retardation and hearing disability categories until 2003. Now they are place under the learning disability category.

2.5 Theoretical Framework

The theoretical framework is the foundation on which the entire research project is based. It is a logically developed, described and elaborated network of association among the variables deemed relevant to the problem situation and identified through such processes as interviews, observation and literature survey (Sekaran, 2005). It also a conceptual model of how one theorizes or makes logical sense of the relationship among the several factors that have been identified as important to the problem. From the theoretical framework then, testable hypotheses can be developed to examine whether the theory formulated is valid or not. For this study, the theoretical framework is shown in the figure 2.1:-

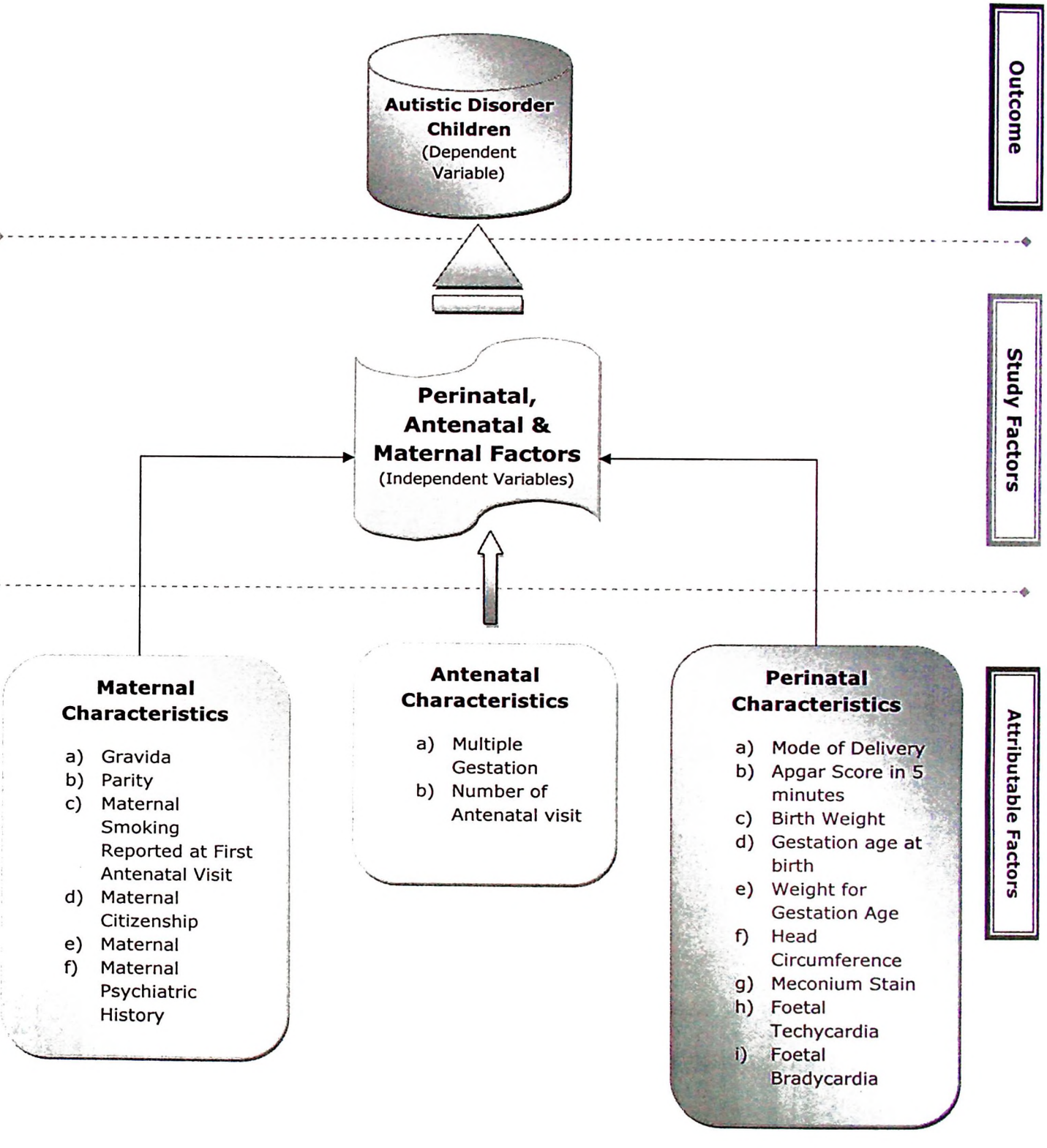

Figure 2.1: ***Theoretical Framework***

CHAPTER 3

OBJECTIVES

3.1 General Objective

To investigate the characteristics and perinatal, antenatal and maternal associated factors on autistic disorder children.

3.2 Specific Objectives

The specific objectives for this study are:-

1) To describe the characteristics of autistic disorder children.
2) To identify the relationship of the associated factors (perinatal, antenatal and maternal factors) with autistic disorder children.

3.3 Research Questions

As exploratory study, the following research questions have been identified:-

1) Is there any relationship between perinatal, antenatal and maternal associated factors and autistic disorder children?

3.4 Hypothesis Statement

1) There is a significant relationship between perinatal, antenatal and maternal associated factors and autistic disorder children.

CHAPTER 4

METHODOLOGY

4.1 Study Design

This study focused only a state in Malaysia which was Pulau Pinang. There were two Hospital will be involved in the study; Hospital Pulau Pinang (HPP) and Hospital Bukit Mertajam (HBM). The judgement why these hospitals selected was because most of Pulau Pinang people prefer these two government hospitals for treatment.

The study design that applied in this study was the unmatched case-control. Based on Gordis (2004); the case control study was use to examine the possible relation of an exposure to a certain disease, the group of individuals with that disease was called cases; and for the purpose of comparison, a group of people without that disease was called as control. The cases for this study were people with autistic disorder; and the controls were people without autistic disorder. The reason why case control design were selected was because there are no need to wait for a long time for disease to occur and these study design also can evaluate multiple possible or potential exposures and it suitable for rare disease outcome.

Because of the difficulty of selecting the match control group for autism disorder children, the researcher used unmatched control group which the control was selected based on the children born within year 2001 and 2008; the reason why from 2001 was because this study was only interested for children below than 10 years old

and after 2 years old (until 2008). This was because the autistic disorder occurs among children between aged 2 to 3 years old and the time that their parent brings the children to hospital is between ages 7 to 10 years old.

For a clear picture, here the following is the example of the case control design for this study:-

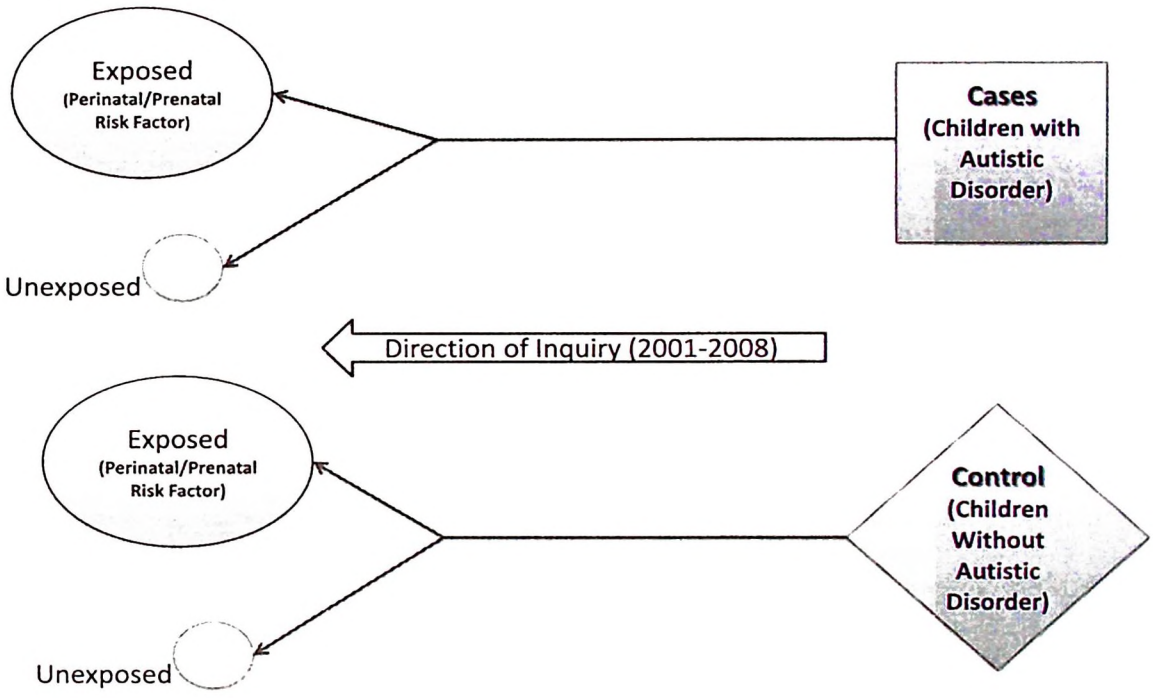

Figure 4.1: ***Case Control Study Design Applied in the Study***

4.2 Study Duration

The study is retrospective case control. The data collection was from 2001 until 2008.

4.3 Reference Population

The reference population for this study was the autistic disorder children in Pulau Pinang.

4.4 Source Population

Source population for cases was the autistic disorder children who was born and registered at Hospital Pulau Pinang and Hospital Bukit Mertajam. For Cases, the registered children with autistic disorder syndrome and who was born at the hospital between 2001 and 2008. For Control, the registered non autistic outpatient children with fever and flu and was born at the hospital between 2001 and 2008.

4.5 Sampling Frame

The sampling frame in this study was divided into two parts which were control and cases. For cases group, the autistic disorder children who were born at Hospital Pulau Pinang or Hospital Bukit Mertajam, Pulau Pinang between 2001 and 2008 who fulfill the criteria. For control group, non autistic disorder children who were born at

Hospital Pulau Pinang or Hospital Bukit Mertajam, Pulau Pinang between 2001 and 2008 who fulfill the criteria.

4.6 Cases and Control

Cases were autistic disorder children who were selected based on inclusion and exclusion criteria. The cases were based from the total population frame in the HPP and HBM, Pulau Pinang. In the record, the diagnosis was written as Autism, ASD, AD, Autistic Spectrum Disorder, Autistic Disorder or Autism Disorder.

Control groups were non autistic disorder children, who only had fever and flu and registered at outpatients' clinic at both hospitals. These groups were based on excused from inclusion and exclusion criteria.

4.7 Inclusion Criteria

The inclusion criteria for this study were; for cases, autistic children aged between 2 to 10 years old and was born at the HPP or HBM. This is because of the autistic disorder begins at birth or within the first two to three years of life. For controls were the patients aged between 2 and 10 years old presented with fever and flu only and was born at the HPP and HBM.

4.8 Exclusion Criteria

The exclusion criteria for this study were the incomplete data records for the main variables of interest more than 30%.

4.9 Sample Size Determination

The sample size was calculated for all variables. All the variables were calculated using two proportions to find the appropriate sample size for the perinatal, antenatal and maternal associated factors for the autistic disorder patients (Naing, 2009). Hence, all the sample size will be calculated by using Power and Sample Size Software (Dupont and Plummer, 1990).

The parameters that were used in the sample size calculation are as below:-

1) ***Type I Error (∝):-*** The type one error probability for a two sided test (Dupont and Plummer, 1990) and the error that results when the null hypothesis is falsely rejected (Everitt, 2006). In this study the type I error was set at 5%.

2) ***Power (1-β):-*** The probability of correctly rejecting the null hypothesis that the relative risk (odds ratio) equals 1 given *n* case patients, *m* control patients per experimental patient, and a Type I error probability (∝) (Dupont and Plummer, 1990). Power gives a method of discriminating between competing tests of the same hypothesis, the test with the higher power being preferred. It is