J. Perinat. Med.
27 (1999) 441–450

Prenatal and perinatal risk factors for autism

Larry Burd, Robin Severud, Jacob Kerbeshian, and Marilyn G. Klug

University of North Dakota School of Medicine and Health Sciences, The North Dakota Fetal Alcohol Syndrome Center and Altru Health Systems, Departments of Pediatrics and Neuroscience, Grand Forks, USA

1 Introduction

Autism and the other pervasive developmental disorders have an infant and childhood onset and often result in severe lifelong impairments. Mental retardation and epilepsy are common comorbid conditions. Most persons with autism or pervasive developmental disorder require care throughout their life span. Institutionalization is a frequent outcome.

The etiology of these disorders is incompletely understood. There is a substantial genetic contribution to these disorders. The recurrence risk of autism in siblings of autistic probands is 2 to 5% [5, 13, 36, 31]. This represents about a fifty-fold increase in risk over the general population where the population prevalence is 1 in 2,500 or 0.04% [13, 31]. In families with multiple cases of autism the recurrence risk is about 8% which is over 200 times the general population risk [32]. The average concordance risk from several twin studies is 3 to 9% for dizygotic twins and 64 to 81% for monozygotic twins [5, 35, 37, 31]. The monozygotic/dizygotic twin concordance ratio is 25 [31]. While genetic disorders are commonly comorbid with autism no genetic disorder is uniformly associated with autism, and similar cases of autism occur in children with and without genetic disorders. Given the variability in autism, even in groups of children who have the same genetic disorder, it seems likely that environmental factors play an important role in the development of these disorders and may influence severity. Pleiotropy (the variable expression of a single gene disorder) may explain some of the variance in phenotypes. However, the genetic mechanism in autism is unknown.

Several environmental factors increasing risk for autism have been described in the past. Among these has been congenital rubella [12] and cytomegalovirus infection [24, 13]. Earlier studies have examined the role of prenatal and perinatal events as risk factors for autism. This work has not produced a consistent set of risk factors (for reviews see Nelson [29] and Tsai [38], and Gillberg [18]). Research in this area has been complicated by the use of variable case definitions for autism and the pervasive developmental disorders and use of divergent risk factors that are not directly comparable. Other problems involved differing study methodologies, small sample sizes and the use of variable information sources such as interviews with the families of autistic patients [16, 23]. Some studies do not list the data sources [22, 20]. As a consequence, there is no current consensus about the role of prenatal and perinatal risk factors in autism. If prenatal or perinatal risk factors that are in a causal chain influencing either the severity of or the risk of developing autism could be identified, this data could have important implications in prevention and treatment. These risk factors and the temporal unfolding of risk would both be appropriate to target as starting points to initiate interventions that may decrease both the severity and prevalence of the disorder.

Environmental risk factors occurring during the prenatal and perinatal periods of development have been found to be etiologically important de-

terminants of developmental disorders [33]. The roles of prenatal exposure to maternal smoking in attention deficit hyperactivity disorder [27] or conduct disorder [39] and prenatal alcohol exposure and the resulting fetal alcohol syndrome [11, 4] are examples. Some children with fetal alcohol syndrome also have autism [28].

A limited review of previously published studies relevant to autism is presented in table I [7, 14, 15, 16, 17, 18, 21, 22, 23, 26, 30]. We have included only studies that compared cases and controls. We were especially interested in studies, which had utilized birth certificate data. Gillberg and Gillberg [18] developed an optimality score for pre and perinatal risk factors and used 25 cases of autism and 25 controls to demonstrate that the cases had decreased optimality scores. However, as the table demonstrates, no consistent pattern of findings is apparent across the studies. Studies using birth certificate data as the primary source of data could not be found.

We have demonstrated an alternative strategy for pursuing the potential relationship between prenatal and perinatal risk factors and developmental disorders [11]. This strategy combines a statewide diagnostic registry linked with data from birth certificate files. This methodology was derived from previous studies of risk factors for infant mortality and has been very useful in the identification of possible environmental risk factors [8, 10].

This methodology provides three distinct advances in research in developmental disorders. The first is a low cost strategy to control for interview or data extraction bias. The birth certificate data are collected by persons having no connection with the research project (or even knowledge of the project). The second is that birth certificate data provides access to a very large and usually a very complete data set. The third is that this type of data provides access to a very large number of potential controls that can be matched on a variety of factors. These include year and month of birth, the county of birth, and sex and race matching.

Birth certificate data should become even more useful in the future since the revision of the United States Standard Certificate of Live Birth revision in 1989. In this version many new items were added, including a switch to a check box format from open-ended questions. The new birth certificate data may also be used to develop national files of linked birth and death certificates [25]. This would represent an important advance in large-scale studies developmental disabilities.

The initial studies linking a diagnostic registry of patients with developmental disabilities and their birth certificate data was conducted with a registry of patients with fetal alcohol syndrome [11] and sudden infant death syndrome [8]. Names of the children from a diagnostic registry and their birth dates were forwarded to the State Health

Table I. A review of previously published studies of prenatal, perinatal and neonatal data in persons with autism and pervasive developmental disorders

Case-Control Studies

Variables	Levy	Deykin	Lobascher	Deb	Mason-Brothers	Finegan	Lord	Bryson	Cryan	Piven	Gillberg
Maternal Age				−	−	−		−	−	−	+
Maternal Education									−		+
Maternal Weight Gain		+									−
Gestation Length			+	−	−	−	+	+	−	−	+
Birth-weight		+		−	+	+		−			−
Apgar I	−			−	−	+		−			+
Apgar 5					−			+			+
Meconium Staining	−			−	−	−		+		−	−

(−) = negative finding (+) = positive finding (blank) = not addressed in given study

dology provides three distinct ad-
esearch in developmental disorders.
a low cost strategy to control for in-
lata extraction bias. The birth certifi-
collected by persons having no con-
the research project (or even knowl-
project). The second is that birth cer-
provides access to a very large and
ry complete data set. The third is that
data provides access to a very large
otential controls that can be matched
of factors. These include year and
rth, the county of birth, and sex and
ig.

ate data should become even more
e future since the revision of the
s Standard Certificate of Live Birth
1989. In this version many new
dded, including a switch to a check
rom open-ended questions. The new
ate data may also be used to de-
al files of linked birth and death
25]. This would represent an impor-
in large-scale studies developmen-
s.

udies linking a diagnostic registry of
developmental disabilities and their
te data was conducted with a regis-
ts with fetal alcohol syndrome [11]
nfant death syndrome [8]. Names of
from a diagnostic registry and their
vere forwarded to the State Health

nd neonatal data in persons with autism

Lord	Bryson	Cryan	Piven	Gill-berg
	−	−	−	+
		−		+
				−
+	+	−	−	+
	−			−
	−			+
	+			+
	+		−	−

in given study

Department. Individual birth certificate data was extracted and entered into a file, and a series of controls were identified. Birth certificate data for the controls was obtained from the same computerized birth certificate registry. We have now utilized this methodology to compare children with a diagnosis of autism or pervasive developmental disorder in North Dakota with controls to determine if we could identify prenatal or perinatal risk factors.

2 Method

Since 1980 we have maintained an autism registry at our clinic. Since the publication of the DSM-III in 1980, the data base has been expanded to include cases of autism, pervasive developmental disorders and autistic disorder as subsequent versions of the DSM have been developed. In the current registry the term autism would encompass patients meeting criteria in one of the three versions of the Diagnostic and Statistical Manual (DSM-III, DSM-III-R and DSM-IV) (American Psychiatric Association, 1980, 1987, 1994) [1, 2, 3].

In 1984 and 1985 we conducted a statewide prevalence study of autism and pervasive developmental disorders [9]. We contacted all physicians who were known to see children with developmental disabilities, all special education directors, all residential care facilities, parent support groups, clinical psychologists, and the state's comprehensive evaluation center. This study identified 59 cases of autism in North Dakota children. A recently completed 12-year follow-up of this data identified only one additional case of autism meeting the 1986 study inclusion criteria who had not been identified in the initial survey. These 60 cases and 84 additional patients were from the North Dakota Autism and Pervasive Developmental Disorder Registry. The registry lists all children and adults who had been seen since 1980 at the state's comprehensive evaluation center or who had been seen by JK. This produced a final list of 144 patients.

The project was approved by the Institutional Review Board of the University of North Dakota. We then forwarded a list of these patients, including their first names, last names, middle initials, dates of birth, sex, and no other information to the North Dakota Health Department. The Health Department then identified all patients who had North Dakota birth certificates.

We then selected five controls for each case from the computerized North Dakota birth certificate registry maintained by the North Dakota Health Department since the mid 1970's. Computer access to all birth records facilitates access and decreases costs for research, especially when selecting multiple controls and when using matching. The number of controls was selected to maximize the power of the study. Since it is expensive and time consuming to obtain additional cases of autism or PDD, adding multiple controls from a computerized data base is an inexpensive strategy to increase the power of the study to detect differences. Since the ability to increase power drops off rapidly above five controls per case, we used five controls per case [34]. The controls were matched by sex, the year of birth and month of birth. Matching for sex was considered important since males have autism three to five times more frequently than females. This sex difference has been identified in nearly all studies of autism. Matching on the year of birth was used to control for differences in obstetrical and neonatal medical practice over the wide age span of these subjects. Matching on month of birth was used to control for effects of month of birth or season of birth, which occurs in many developmental disabilities.

Since the cases and controls were matched, they were linked during the analysis (each case and the five matched controls) using the method described by Schilleschman [34]. The analysis was completed using the Number Cruncher Statistical System [19].

3 Results

We forwarded a list of 144 patients with autism to the Health Department, and they were able to identify 78 (54 %) with North Dakota birth certificates. The most common reason for not locating a birth certificate was a birth occurring in another state. We did examine the adoption files and used several other strategies to maximize the number of matches. In order to maximize confidentiality, the controls were not identified to us by name. The birth certificate data was obtained from three versions of the US standard certificate of live

birth. This birth certificate is completed while the baby is in the hospital. The variables include a record of maternal and paternal data, prenatal care birth information, and newborn data. In previous studies we have examined issues of data quality on birth certificates [11, 8]. We used data that we had found to be accurate and complete. Due to poor data quality, alcohol exposure and smoking were excluded. Due to incompleteness, birth defects and syndrome identification data was also excluded.

The total case population in the study was comprised of 55 males (70 %) and 23 (30 %) females. Since we matched on sex, we also had 275 male and 115 female controls. The mean age of the subjects was 212.5 months (sd 74.3) with a range from 77 to 348 months. The age of the matched controls was 212.6 months (sd 74.8) with a range of 77 to 348 months. The mean age of the males was 201.4 months (sd 71.1), and that of the females was 239.4 months (sd 75.2).

Table II presents the categorical variables from the cases and controls. In some cases the number of cases and controls may differ due to missing data. Only cases where complete data from their matched controls was available were used in the univariate analysis. Two variables, birth weight (less than 2500 grams, OR = 2.40 [95 % CI 1.13 to 5.10], p = 0.036) and mothers education (less than grade 12, OR = 2.25 [95 % CI 1.21 to 4.20], p = 0.016), were significant when compared to their matched controls. Four other variables that approached but did not reach significance were: mothers race as white (OR = 2.47 [95 % CI 0.97 to 6.26] p = 0.056); other terminations of pregnancy (OR = 0.44 [95 % CI 0.20 to 1.00] p = 0.067); apgar 5 (OR = 2.21 [95 % CI 0.86 to 5.65] p = 0.086; and gestation less than 36 weeks (OR = 2.71 [95 % CI 0.97 to 7.61], p = 0.059).

Table III presents a comparison of autism and controls for continuous variables in the data set. The birth weight for the two groups was significant (the mean for cases was 3239 grams and 3403 grams for controls). The difference was 164 grams (t = 2.14; p = 0.03). The one and five minute apgar scores were significantly different. For the one minute apgar, the mean for cases was 6.9 and 7.6 for controls for a difference of 0.7 (t = 2.54; p = 0.01). For the five minute apgar, the mean score for the cases was 8.5 and for the controls was 8.8 for a difference of 0.4 (t = 2.07; p = 0.39). Mother's education was 12.3 years for the cases and 12.9 years for the controls for a difference of 0.68 years (t = 2.8; p = 0.005). The father's age for the cases was 30.2 years and for the controls was 28.2 years for a difference of 2.1 years (t = −2.91; p = 0.004). The month prenatal care was begun was 2.7 months for the cases and 3.2 for the controls for a difference of 0.44 months (t = 2.21; p = 0.027).

Optimality scores were created to assess the number of risk factors for the cases and controls [18]. Each risk factor present was assigned a score of one point. Due to the low number (15) and similarity of risk factors, only a total optimality score was computed. Possible optimality scores ranged from zero to fifteen. Figure 1 shows the step graph of cumulative percentages for both cases (dashed line) and controls (solid line) by total optimality score. The scores for the cases and controls were very similar.

Univariate tests and Optimality scores, however, do not indicate which set of risk factors best predict membership to case or control groups when considering their relationships with each other. Univariate tests only investigate the relationship between cases and controls one variable at a time. Optimality scores do look at more than one risk factor together, but do not specify which factors occur the most frequently for each case or control group at each level of optimality. We expanded on the analytic strategy of Gillberg and Gillberg [18] by utilizing logistic regression modeling for this data. Logistic modeling allow for consideration of multiple risk factors simultaneously and controls for confounding from the variables included in the analysis [35].

We then developed a model to predict autism from this data. The variables that were found to be significant in the univariate analysis were used to develop regression models. The final logistic regression models were comprised of four and five variables (table IV). Two logistic regression models were considered. One model had mother's education, father's age, other terminations of pregnancy by the mother, month prenatal care began and birth weight as predictors. All predictors were significant at the .05 level. The model Chi-

core for the cases was 8.5 and for the
s 8.8 for a difference of 0.4 (t = 2.07;
Mother's education was 12.3 years for
nd 12.9 years for the controls for a
f 0.68 years (t = 2.8; p = 0.005). The
for the cases was 30.2 years and for
was 28.2 years for a difference of 2.1
−2.91; p = 0.004). The month prena-
s begun was 2.7 months for the cases
the controls for a difference of 0.44
2.21; p = 0.027).

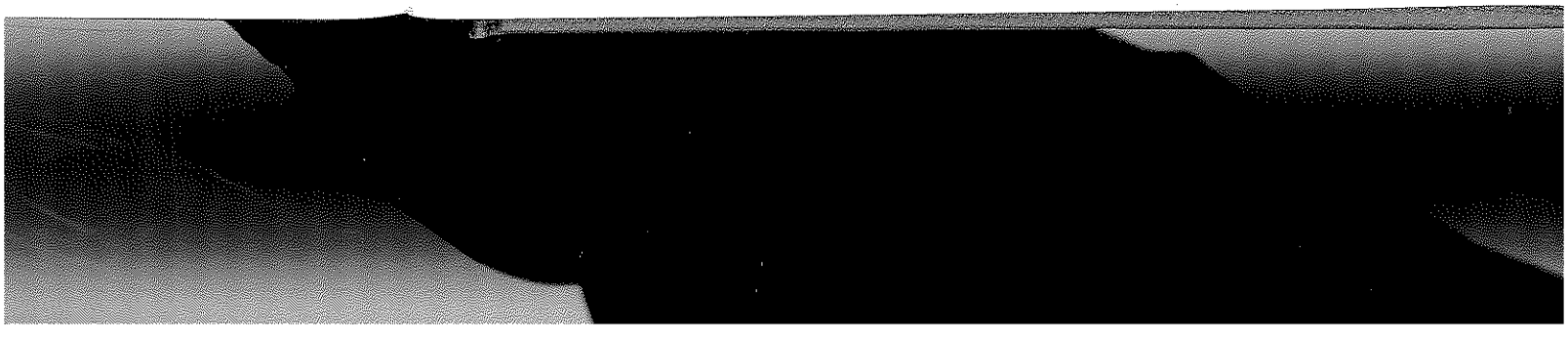
scores were created to assess the
isk factors for the cases and controls
risk factor present was assigned a
e point. Due to the low number (15)
ty of risk factors, only a total optimal-
was computed. Possible optimality
ed from zero to fifteen. Figure 1
tep graph of cumulative percentages
ses (dashed line) and controls (solid
l optimality score. The scores for the
ntrols were very similar.

ests and Optimality scores, however,
ate which set of risk factors best pre-
rship to case or control groups when
their relationships with each other.
ests only investigate the relationship
es and controls one variable at a time.
cores do look at more than one risk
ier, but do not specify which factors
st frequently for each case or control
h level of optimality. We expanded
tic strategy of Gillberg and Gillberg
zing logistic regression modeling for
gistic modeling allow for consider-
tiple risk factors simultaneously and
confounding from the variables in-
analysis [35].

veloped a model to predict autism
ta. The variables that were found to
t in the univariate analysis were used
egression models. The final logistic
odels were comprised of four and
s (table IV). Two logistic regression
considered. One model had moth-
n, father's age, other terminations of
the mother, month prenatal care be-
weight as predictors. All predictors
ant at the .05 level. The model Chi-

Table II. Results of comparisons of categorical variables for 78 cases of autism and five matched controls per case using North Dakota birth certificate data

Variable	Case		Control		p	O. R.
	N	(%)	N	(%)		
Birth Weight						
< 2500	11	(31)	25	(69)	0.036	1.13 < 2.40 < 5.10
≥ 2500	67	(16)	365	(84)		
Apgar 1						
< 6	8	(27)	22	(73)	0.122	0.82 < 1.98 < 4.75
≥ 6	41	(16)	223	(84)		
Apgar 5						
< 8	7	(29)	17	(71)	0.086	0.86 < 2.21 < 5.65
≥ 8	42	(16)	228	(84)		
Infant White						
No	8	(25)	24	(75)	0.287	0.75 < 1.74 < 4.04
Yes	70	(16)	366	(84)		
Mother's Age						
< 20 or > 30	26	(20)	102	(80)	0.246	0.84 < 1.41 < 2.38
20 to 30	52	(15)	288	(85)		
Mother's Education						
< 12	17	(28)	43	(72)	0.016	1.21 < 2.25 < 4.20
≥ 12	61	(15)	347	(85)		
Mother White						
No	7	(32)	15	(68)	0.056	0.97 < 2.47 < 6.26
Yes	71	(16)	375	(84)		
Father's Age						
< 20 or > 30	31	(21)	120	(79)	0.157	0.90 < 1.48 < 2.45
20 to 30	47	(15)	270	(85)		
Father's Education						
< 12	14	(25)	43	(75)	0.129	0.91 < 1.77 < 3.41
≥ 12	64	(16)	347	(84)		
Father White						
No	4	(33)	8	(67)	0.121	0.76 < 2.63 < 9.10
Yes	46	(16)	242	(84)		
Live Births Now Dead						
Yes	4	(33)	8	(67)	0.122	0.76 < 2.58 < 8.79
No	74	(16)	382	(84)		
Other Terminations						
Yes	7	(9)	71	(91)	0.067	0.20 < 0.44 < 1.00
No	71	(18)	319	(82)		
Trimester Care Started						
> 1st	19	(14)	115	(86)	0.437	0.44 < 0.77 < 1.35
1st	59	(18)	275	(82)		
Prenatal Visits						
< 5	4	(11)	34	(89)	0.405	0.20 < 0.57 < 1.64
≥ 5	74	(17)	356	(83)		
Gestation						
< 36	6	(33)	12	(67)	0.059	0.97 < 2.71 < 7.61
≥ 36	43	(16)	233	(84)		



Square was 36.6, 5 d.f., p = .0001 and 64% of the cases were correctly classified. However, the Hosmer-Lemeshow Chi-Square was 15.993, d.f. = 8, p = .042, indicating a lack of fit for the model [35]. The second model contained all the previously mentioned variables except for birth weight which was removed in this model since it was the last variable added in the stepwise regression. All variables in this model were significant predictors at the .05 level. The model Chi-Square was 31.083, d.f. = 4, p = .001 and 61% of the cases were correctly classified. The Hosmer-Lemeshow Chi-Square for this model was 3.673, d.f. = 8, p = .885 indicating a much better fit with the data.

4 Discussion

In a case control study of 78 cases of autism and 390 matched controls we identified seven variables, three of which are categorical, six continuous, and two that are in both groups. We used matching to control for the effects of year of birth, sex, changes in medical care, and season of birth. The results of the univariate analysis identified seven significant variables in this study

Table III. Results of comparisons of continuous variables for 78 cases of autism and five controls per case using North Dakota birth certificate data

Variable	N	Mean	Stand. Dev.	t	d.f.	p
Birth Weight						
Case	78	3239.6	671.37	2.137	466	0.033
Control	390	3403.8	608.41			
Apgar 1						
Case	49	6.918	2.050	2.545	292	0.011
Control	245	7.592	1.612			
Apgar 5						
Case	49	8.449	1.385	2.070	292	0.039
Control	245	8.829	1.250			
Mother's Age						
Case	78	26.064	6.003	−0.935	466	0.350
Control	390	25.454	5.104			
Mother's Educ.						
Case	78	12.256	1.996	2.810	466	0.005
Control	390	12.931	1.922			
Father's Age						
Case	78	30.282	7.478	−2.907	466	0.004
Control	390	28.149	5.556			
Father's Educ.						
Case	78	12.859	2.459	1.040	466	0.299
Control	390	13.141	2.129			
Prenatal Care Start Month						
Case	78	2.718	1.318	2.213	466	0.027
Control	390	3.146	1.604			
Prenatal Visits						
Case	78	9.321	3.562	−1.267	466	0.206
Control	390	8.792	3.319			
Gestation						
Case	49	39.143	2.828	1.535	292	0.126
Control	245	39.857	3.001			

.885 indicating a much better fit

n

trol study of 78 cases of autism and controls we identified seven vari- of which are categorical, six con- wo that are in both groups. We used control for the effects of year of anges in medical care, and season of sults of the univariate analysis iden- significant variables in this study

autism and five controls per case using

t	d.f.	p
2.137	466	0.033
2.545	292	0.011
2.070	292	0.039
−0.935	466	0.350
2.810	466	0.005
−2.907	466	0.004
1.040	466	0.299
2.213	466	0.027
−1.267	466	0.206
1.535	292	0.126

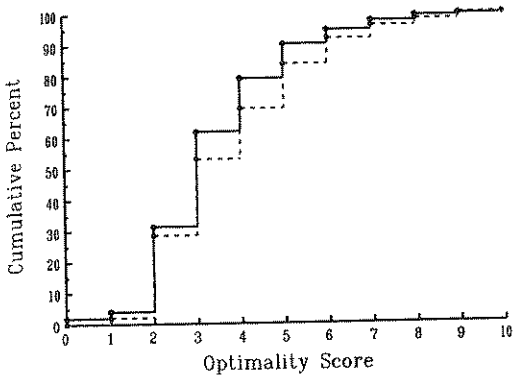


Figure 1. Cumulative percent of reduced optimality in cases and controls. Cases = dashed line, controls = solid lines.

which were: birth weight, apgar score at one and five minutes, mother's education, father's age, the trimester prenatal care started, and terminations of a prior pregnancy. Three additional variables, mother's race, apgar 5 and gestation of less than 36 weeks, approached significance at the .05 level.

We then used stepwise conditional logistic regression analysis to control for confounding from other significant variables and produced two final models, which were comprised of four and five variables (table IV). In the five variable model birth weight in grams was a risk factor (OR = 1.01), suggesting that for each gram reduction in birth weight, the risk of autism increased by a very small amount compared to the matched controls. For each year of difference in parents' education between the cases and controls (lower education was the risk factor for autism), the risk of autism increased 25%. Each month prenatal care was delayed increased the risk of autism 29%. Having had a previous termination of pregnancy increased the risk of autism 236% compared to controls who did not have a termination of pregnancy. We identified one variable (father's age) which was associated with risk reduction. A one-year decrease in the age of the father decreased the risk of autism by 6% compared to the controls. When viewed as a composite of risk the model was highly significant but produced a model, which was a poor fit with the data in this sample. Eliminating birthweight decreased the model chi-square but produced a substantial improvement in goodness of fit (table IV).

The prevalence of low birth weight babies in our sample was high (11/78 or 14%) in the cases

Table IV. Logistic regression of significant variables from 78 cases of autism and five controls per case. The final two models consisted of four or five variables

Variable	Model 1		Model 2	
	Coeff	O. R.	Coeff	O. R.
Intercept	−1.693		−.450	
Mother's Education	.217	1.24	.239	1.27
Father's Age	−.067	.94	−.063	.94
Other Terminations	1.213	3.36	1.027	2.79
Month Prenatal Care Began	.261	1.30	.258	1.29
Birth Weight	.000483	1.00		
Model parameters				
Chi-Square	36.616		31.083	
p-value	.0001		.0001	
Hosmer-Lemeshow				
Chi-Square	15.993		3.673	
p-value	.042		.885	

compared to 7% in the controls producing an odds ratio of 2.4 for autism in low birth weight infants compared to matched controls. However, this data does not indicate if low birth weight is a cause or consequence of autism. The issues of the relationship between prenatal and perinatal variables and autism is complex and has been discussed elsewhere [6]. The direction of the association between low birth weight and autism will require further study.

None of the variables which emerged as risk factors in this study appear to be either necessary or sufficient for the development of autism. This was the same conclusion reached by Bolton [6] in a study of obstetric risk factors for autism. However, this study does offer strong support for viewing these risk factors as important in cases of autism. As a result we are unwilling to dismiss them as consequences of the disorder without further study. If after replication studies consistent potential risk factors are identified further studies should be designed to elucidate if these risk factors act as additive liabilities of risk for the development of autism or are markers of complicated pregnancies resulting from the genetic influences that resulted in autism in that person. This effort will likely require both a large sample and a sophisticated design since the risk factors in this study are complex constructs and cannot be clearly categorized as environmental or genetic or as cause or consequence of autism. Like most factors influencing human behavior they probably represent an expression of an interaction of these influences.

This study may have limited clinical implications. First, the results may alert clinicians to specific signs that may be useful in developing a clinical history in patients presenting for evaluation. Second, the cluster of variables identified here may be useful as part of a screening tool for autism. Thirdly, clinicians may benefit from adding the birth certificate to the clinical record of patients with autism. Fourthly, clinicians may be able to utilize this data to discuss the role of pregnancy as a factor in the development of autism with parents. This would likely be reassuring to parents, especially mothers, of children with autism.

The methodology presented here has several important limitations that need to be considered. There are limitations in both the quality and completeness of the data from the birth certificates. In North Dakota the quality of data for both alcohol use and smoking is poor. When we examined the birth certificate data for a population of children with a diagnosis of fetal alcohol syndrome in North Dakota the birth certificate data identified only 6% as having been alcohol exposed. This was much different from the data on prenatal alcohol exposure we obtained from the mothers or other sources during our evaluations of these children. Due to the poor quality and missing data in this area we excluded alcohol exposure and maternal smoking as variables in this study.

The next issue is the quality of the data for cases in the registry. Since most registries span decades the inclusion and exclusion criteria change. In most cases the registry data will encompass several versions of diagnostic nomenclatures. This occurred in our study which spanned three versions of the Diagnostic and Statistical Manual of Mental Disorders. Several other issues can also be concerns. Will the registry include autism and profound mental retardation? Will cases of autism occurring in severely abused and neglected children be included? Will children with genetic disorders and autism be listed on the registry?

In this study we have demonstrated a registry birth certificate linkage model as a strategy to identify potential risk factors for childhood mental illness. The data developed from this model also has both clinical and public health implications. A replication of this study would be very valuable in determining the prevalence of these risk factors among persons with autism in other clinical settings.

Abstract

Aim: To identify pre- and perinatal risk factors for autism.
Method: Case control study. We matched names of patients from North Dakota who met DSM criteria for autism, a pervasive developmental disorder, and autistic disorder with their birth certificates. Five matched controls were selected for each case.
Results: Univariate analysis of the 78 cases and 390 controls identified seven risk factors. Logistic modeling to control for confounding produced a five variable

ata to discuss the role of pregnancy
the development of autism with par-
ould likely be reassuring to parents,
others, of children with autism.

logy presented here has several im-
ations that need to be considered.
itations in both the quality and com-
the data from the birth certificates.
ota the quality of data for both alco-
moking is poor. When we examined
ificate data for a population of chil-
liagnosis of fetal alcohol syndrome
ota the birth certificate data iden-
% as having been alcohol exposed.
h different from the data on prenatal
sure we obtained from the mothers
es during our evaluations of these
to the poor quality and missing data
we excluded alcohol exposure and
king as variables in this study.

e is the quality of the data for cases
. Since most registries span decades
and exclusion criteria change. In
e registry data will encompass sev-
of diagnostic nomenclatures. This
ur study which spanned three ver-
)iagnostic and Statistical Manual of
lers. Several other issues can also
Will the registry include autism and
tal retardation? Will cases of autism
severely abused and neglected chil-
led? Will children with genetic dis-
ism be listed on the registry?

we have demonstrated a registry
te linkage model as a strategy to
tial risk factors for childhood men-
e data developed from this model
clinical and public health implica-
cation of this study would be very
termining the prevalence of these
nong persons with autism in other
s.

eir birth certificates. Five matched con-
ed for each case.
iate analysis of the 78 cases and 390
d seven risk factors. Logistic modeling
confounding produced a five variable

model. The model parameters were $\chi^2 = 36.6$ and $p < 0.001$. The five variables in the model were decreased birth weight, low maternal education, later start of prenatal care, and having a previous termination of pregnancy. Increasing father's age was associated with increased risk of autism.

Conclusion: This methodology may provide an inexpensive method for clinics and public health providers to identify risk factors and to identify maternal characteristics of patients with mental illness and developmental disorders.

Keywords: Autism, case control, pervasive developmental disorder, prenatal care, risk factors.

References

[1] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (DSM-III). Washington DC, American Psychiatric Association 1980
[2] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (DSM-III-R). Washington DC, American Psychiatric Association 1987
[3] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). Washington DC, American Psychiatric Association 1994
[4] Bagheri M, L Burd, JT Martsolf, MG Klug: Fetal alcohol syndrome: maternal and neonatal characteristics. J Perinat Med 26 (1998) 262
[5] Bailey, A, A LeCouteur, I Gottesman, PK Bolton, E Simonoff, E Yuzda, M Rutter: Autism as a strongly genetic disorder: Evidence from a British twin study. Psychol Med 25 (1995) 63
[6] Bolton PF, M Murphy, H Macdonald, B Whitlock, A Pickles, M Rutter: Obstetric complications in autism: consequences or causes of the condition? J Am Acad Child Adol Psychiat 36 (1997) 272
[7] Bryson S, I Smith, D Eastwood: Obstetrical suboptimality in autistic children. J Am Acad Child Adol Psychiat 27 (1988) 418
[8] Burd L: Prevalence of prone sleeping position and selected infant care practices in North Dakota infants: a comparison of Caucasians and Indians. Pub Health Rep 109 (1994) 446
[9] Burd L, W Fisher, J Kerbeshian: A prevalence study of pervasive developmental disorders in North Dakota. J Am Acad Child Adol Psychiat 32 (1987) 1283
[10] Burd L, J Gregory, R Ford: Incidence rates and risk factors for SIDS. Fed Pract 11 (1994) 53
[11] Burd L, J Martsolf, M Klug: Children with fetal alcohol syndrome in North Dakota: a case control study utilizing birth certificate data. Add Biol 1 (1996) 181
[12] Chess S: Follow-up report on autism in congenital rubella. Journal of Aut Child Schiz 7 (1977) 68
[13] Ciaranello RD: Linkage and molecular genetics of infantile autism in: Watson SJ: Biology of Schizophrenia and Affective Disease. American Psychiatric Press, Washington DC 1996
[14] Cryan E, M Byrne, A O'Donovan, E O'Callaghan: Brief report: A case-control study of obstetric complications and later autistic disorder. J Aut Devl Dis 26 (1996) 453
[15] Deb S, K Prasad, H Seth, JM Eagles: A comparison of obstetric and neonatal complications between children with autistic disorder and their siblings. J Intellect Disabil Res 41 (1997) 81
[16] Deykin E, B MacMahon: Pregnancy, delivery, and neonatal complications among autistic children. Am J Dis Child 134 (1980) 860
[17] Finegan J, B Quarrington: Pre-, peri, and neonatal factors and infantile autism. J Child Psychol Psychiat 20 (1979) 119
[18] Gillberg C, I Gillberg: Infantile autism: A total population study of reduced optimality in the pre-, peri-, and neonatal period. J Aut Dev Dis 13(2) (1983) 153
[19] Hintze J: Number Cruncher Statistical System. MicroHelp and Microsoft. Kaysville, UT 1992
[20] Knobloch H, B Pasamanick: Some etiologic and prognostic factors in early infantile autism and psychosis. Pediatrics 55 (1975) 182
[21] Levy S, B Zoltak, T Saelens: A comparison of obstetrical records of autistic and nonautistic referrals for psycho educational evaluations. J Aut Dev Dis 18 (1988) 573
[22] Lobascher M., P Kingerlee, S Gubbay: Childhood autism: An investigation of aetiological factors in twenty-five cases. Brit J Psychiat 117 (1970) 525
[23] Lord C, C Mulloy, M Wendelboe, E Schopler: Pre- and perinatal factors in high-functioning females and male with autism. J Aut Dev Dis 21 (1991) 197
[24] Lotspeich LJ, RD Ciaranello: The neurobiology and genetics of infantile autism. Int Rev Neurobiol 35 (1993) 87
[25] Luke B, L Keith: The United States standard certificate of live birth. J Rep Med 36 (1991) 587
[26] Mason-Brothers A, E Ritvo, C Pingree, PB Petersen, WR Jenson, WM McMahon, BJ Freeman, LB Jorde, MJ Spencer, A Mo: The UCLA-University

of Utah epidemiologic survey of autism: Prenatal, perinatal, and postnatal factors. Pediatrics 86 (1990) 514

[27] Milberger S, J Biederman, S Faraone, L Chen, J Jones: Is maternal smoking during pregnancy a risk factor for attention deficit hyperactivity disorder in children? Am J Psychiat 153 (1996) 1138

[28] Nanson JL: Autism in fetal alcohol syndrome: a report of six cases. Alcoholism: Clin Exp Res 16 (1992) 558

[29] Nelson K: Prenatal and perinatal factors in the etiology of autism. Pediatrics 87 (1991) 761

[30] Piven J, J Simon, G Chase, M Wzorek, R Landa, J Gayle, S Folstein: The etiology of autism: pre-, peri- and neonatal factors. J Am Acad Child Adol Psychiat 32 (1993) 1256

[31] Risch N, D Spiker, L Lotspeich, N Nouri, D Hinds, et al.: A genomic screen of autism: Evidence for a multilocus etiology. Am J Genet 65 (1999) 493

[32] Ritvo ER, BJ Freeman, C Pingree, A Mason-Brothers, L Jorde, WR Jenson, WM McMahon, PB Petersen, A Mo, A Ritvo: The UCLA-University of Utah epidemiologic survey of autism: prevalence. Am J Psychiat 146 (1989) 194

[33] Saugstad LF: Optimality of the birth population reduces learning and behavior disorders and sudden infant death after the first month. Acta Paediatr [Suppl] 429 (1999) 9

[34] Schilleschman J: Case control studies: Design, conduct and analysis. Oxford University Press, New York 1982

[35] Schlesselman JJ: Case-Control Studies: Design, Conduct, Analysis. Oxford University Press, New York 1982

[36] Smalley SL, RF Asarnow, A Spence: Autism and genetics: a decade of research. Arch Gen Psychiat 45 (1988) 953

[37] Steffenburg S, C Gillberg, L Hellgren et al: A twin study of infantile autism in Denmark, Finland, Iceland, Norway, and Sweden. J Child Psychol Psychiat, 30 (1989) 405

[38] Tsai L: Pre-, peri-, and neonatal factors in autism. Neurobiological issues in autism. Plenum Press, New York 1987, p 179

[39] Wakschlag IS, BB Lahey, R Loeber, SM Green, RA Gordon, BL Leventhal: Maternal smoking during pregnancy and the risk of conduct disorder in boys. Arch Gen Psychiat 54 (1997) 670

Received September 13, 1999. Accepted September 19, 1999.

Larry Burd, Ph.D.
Child Evaluation and Treatment Program
1300 S. Columbia Rd.
Grand Forks, ND 58202 U.S.A.
Phone: +1(701)780-2477
FAX: +1(701)780-2440
e-mail: laburd@mail.med.und.nodak.edu