Prenatal, Perinatal, and Neonatal Factors in Autism, Pervasive Developmental Disorder-Not Otherwise Specified, and the General Population

Naya Juul-Dam, MD*‡; Jeanne Townsend, PhD‡§; and Eric Courchesne, PhD‡§

ABSTRACT. *Objectives.* **To examine various pre-, peri-, and neonatal factors in autistic participants and in pervasive developmental disorder-not otherwise specified (PDD-NOS) participants and to compare the incidence of each factor to that of the normal population.**

Methods. **Seventy-four participants (66 males, 8 females) were diagnosed with autism at 2.5 through 4 years of age using the most accurate and up-to-date methods, including the *Diagnostic and Statistical Manual of Mental Disorders* and the Autism Diagnostic Interview-Revised. At age 5, all participants were reevaluated using the *Diagnostic and Statistical Manual of Mental Disorders*, the Autism Diagnostic Interview-Revised, the Childhood Autism Rating Scale, and the Autism Diagnostic Observation Schedule-Revised, resulting in 61 autistic and 13 PDD-NOS participants. Twenty-eight pre-, peri-, and neonatal factors were examined in these 2 groups using both medical records and parental interviews. Incidences were compared with those of the US population as reported in the *Report of Final Natality Statistics, 1995.* This grand scale population group was used to closely approximate comparison to a normal, unbiased population. Results were analyzed using the binomial probability test, with a *P* value of <.05, constituting a significant difference in incidence. A Bonferroni correction was applied to the data to adjust for the number of factors investigated.**

Results. **Although most of the factors showed comparable incidences between the index and control groups, several factors showed statistically significant differences. Following the Bonferroni correction, the autism group was found to have a significantly higher incidence of uterine bleeding, a lower incidence of maternal vaginal infection, and less maternal use of contraceptives during conception when compared with the general population. Similarly, the PDD-NOS group showed a higher incidence of hyperbilirubinemia when compared with the general population.**

Conclusions. **The results of this study support previous findings suggesting a consistent association of unfavorable events in pregnancy, delivery, and the neonatal phase and the pervasive developmental disorders. However, interpretation of the meaningfulness of these results is difficult, as the specific complications that carried the highest risk of autism and PDD-NOS represented various forms of pathologic processes with no presently apparent unifying feature. Additional studies are needed to corroborate and strengthen these associations, as well as to determine the possibility of an underlying unifying pathological process.**

This study's analysis of obstetric and neonatal complications in combination with the use of participants diagnosed at an early age provides some interesting concepts to consider. Perhaps future research will confirm certain pre-, peri-, and neonatal associations that could be used to generate a high-risk historical profile with which to use in conjunction with currently employed diagnostic tools. This may, in turn, help to determine the reliability of a diagnosis of autism in younger children, leading to earlier intervention and assistance for an improved outcome in long-term functionality and quality of life. *Pediatrics* **2001;107(4). URL: http://www.pediatrics.org/cgi/content/full/107/4/e63; *autism, pervasive developmental disorder, pregnancy, delivery, risk factors, neonatal.***

ABBREVIATIONS. PDD, pervasive developmental disorder; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, IV*; ADI-R, Autism Diagnostic Interview-Revised; PDD-NOS, pervasive developmental disorder-not otherwise specified.

Autism is a behavioral syndrome with a reported prevalence of ~10 per 10 000 and an approximate 4:1 ratio of affected males to females.[1] It is classified under the category of pervasive developmental disorder (PDD) and results from a neurologic disorder affecting various functions of the brain. Autism is characterized by impairments in reciprocal social interaction, impairments in verbal and nonverbal communication, lack of imaginative play, and a pattern of repetitive, stereotypical behaviors and interests. Like most other behavioral syndromes, it seems to be a causally heterogeneous disorder. In the literature there is varying support for a wide spectrum of hypotheses regarding the cause of autism: from genetic studies showing a high concordance rate in monozygotic twins[2] to the relationship between environmental events and the development of autism.[1]

A number of studies have investigated the association between particular pre-, peri-, and neonatal factors and autism.[3–5] A summary of their findings is shown in Table 1. Nevertheless, no consistently identified factors have been shown. Other approaches, such as comparing composite scales, have been used with the argument that detection of liability is not dependent on specific items and that factors associ-

From the *School of Medicine, University of California, San Diego; ‡Laboratory for Research on the Neuroscience of Autism, Children's Hospital Research Center; and the §Department of Neurosciences, School of Medicine, University of California, San Diego, La Jolla, California.

Received for publication Oct 18, 2000; accepted Jan 12, 2001.

Reprint requests to (E.C.) Laboratory for Research on the Neuroscience of Autism, 8110 La Jolla Shores Dr, Suite 201, La Jolla, CA 92037. E-mail: ecourchesne@ucsd.edu

TABLE 1. A Three-Study Comparison of Autistic Children and Controls for Frequency of Pre-, Peri-, and Neonatal Problems: Percentage of Affected Children

Factor	Authors and Groups Studied					
	Study 1 (Finegan and Quarrington[3])		Study 2 (Deykin and MacMahon[4])		Study 3 (Gillberg and Gillberg[5])	
	Autistic (n = 15)	Siblings (n = 15)	Autistic (n = 118)	Siblings (n = 246)	Autistic (n = 25)	Controls (n = 25)
Prenatal						
Bleeding	20	7	13	9	44	8
Infection/illness	7	0	16	15	27	8
Edema			18	18	48	24
Preeclampsia			3	4	12	12
Accident/injury	7	0	4	1		
Use of medication	20	0	44	37	40	16
Weeks' gestation <37 wk	20	13				
<36 wk					48	12
>42 wk					12	0
Perinatal						
Malposition	13	0	13	9	4	8
General anesthesia	67	40				
Forceps/vacuum extraction	40	53	60	59	12	16
Cesarean section	7	7	8	2		
Cord complications	7	7	18	14	12	16
Amniotic fluid (clear)	27	0			24	4
Prolonged labor	7	0	15	9		
Neonatal						
Low birth weight/small for gestational age	20	7	7	3	12	0
Respiratory distress	20	0			4	4
Oxygen treatment	13	0	20	15	4	0
Low Apgar score/poor condition	20	7	14	8	24	4
Jaundice	20	0	8	9	4	0
Clinical dysmaturity					50	2

ated with autism may be nonspecific.[6] However, composite scales are unweighted, leading to the possibility that rare but highly significant events may be underemphasized.[7] Although some studies using one form of composite scales, "the optimality score," have shown significant differences between autism and controls, reanalysis of this data indicated that when results were adjusted for birth order, there was no longer any association between optimality and autism.[6]

The present study examined various pre-, peri-, and neonatal factors similar to those in previous studies with several modifications. Although most of the earlier studies (before 1980) lacked standardized diagnostic criteria, this study used the most recent and accepted diagnostic criteria for the identification of autistic participants, including the *Diagnostic and Statistical Manual of Mental Disorders, IV* (DSM-IV)[8] and the Autism Diagnostic Interview-Revised (ADI-R).[9] The DSM-IV, in conjunction with the ADI-R, was shown to be more selective for autism than the previously used DSM-III criteria, resulting in fewer false-positives when distinguishing between autistic patients and other patients with developmental impairments.[10] Furthermore, although previous studies have relied solely on parental reports for data collection, this study incorporates obstetrical and neonatal medical records to corroborate information supplied by the parents. Finally, even the most recent studies have compared the autism group with their own similarly sized control group (matched controls, unaffected siblings, etc), the latter of which have shown sizable variations in results between studies. This study used reports of large population samples as its control group in an attempt to maximize the comparison of autistic participants to the normal population.

The participants in this study all carried a preliminary diagnosis of PDD (which encompasses both autism and pervasive developmental disorder-not otherwise specified [PDD-NOS]) when diagnosed at 2 through 4 years old. Because testing at this age does not give a definite diagnosis because of incomplete cognitive development, these cases were reevaluated 3 years later. At this point, some members of the group no longer met the complete criteria for autism and were rediagnosed with PDD-NOS. In addition to comparing the autism group and normal population, the PDD-NOS group was also compared with the normal population to assess for any statistically significant differences.

METHODS

Participants and Diagnosis

Seventy-four participants (66 males and 8 females) who were enrolled in an ongoing study of autism at the University of California, San Diego, Laboratory for Research on the Neuroscience of Autism were entered into the present study. All of these participants were diagnosed with PDD at 2.5 through 4 years old using DSM-IV and ADI-R criteria. Other disorders thought to be associated with autism (fragile X syndrome, Asperger's syndrome, cerebral palsy, tuberous sclerosis, and neurofibromatosis) were excluded. At 5 years old, all participants were reevaluated using the DSM-IV, ADI-R, Childhood Autism Rating Scale,[11] and the Autism Diagnostic Observation Schedule-Revised.[12] This information was analyzed by Dr Catherine Lord, who made the subsequent final diagnosis. At this point, 61 participants maintained the diagnosis of autism and 13 were diagnosed with PDD-NOS.

Incidences of various factors for the control group were primarily taken from the *Report of Final Natality Statistics, 1995*.[13] This publication presents compiled data from the entire population of the United States. For the factors not included in this source, several other sources were used, all with control samples ranging from ~8000 to >40 000.[14–18]

Data Collection

Data on 28 pre-, peri-, and neonatal risk factors were obtained on each participant from parental interviews and a review of all available obstetric and neonatal records. A list of these variables appears in Table 2. Parents of the participants were interviewed regarding the pregnancy and birth history of their children using 2 questionnaires (available from author by request). Completed questionnaires were available for 51 autism (84%) and 13 PDD-NOS participants (100%). Obstetrical and neonatal records were requested on all participants. They were obtained on 45 autism (74%) and 12 PDD-NOS participants (92%). Whenever specific obstetric or neonatal information was lacking in the hospital notes, it was assumed that there was no adversity.

Analysis

Incidence of each factor was reported and tabulated for the autism, PDD-NOS, and general population groups. Incidences for the control group were primarily taken from the *Report of Final Natality Statistics, 1995*[13] as well as several other sources.[14–18] Comparison of each variable was performed using the binomial probability test for categorically defined data. Analysis was performed comparing the index and control groups, where a P value $<.05$ was considered statistically significant. Additionally, a Bonferroni correction was performed for the number of tests in each group.

RESULTS

In total there were 74 participants (61 autism and 13 PDD-NOS), of which complete records were obtained for 64 participants (51 autism and 13 PDD-NOS).

Table 3 lists maternal age (mean and percentage >30 years old) and parity of the autism, PDD-NOS, and general population groups. Mean maternal age was not available for the general population group used in this comparison, but the mean maternal ages for the autism and PDD-NOS groups are similar to that published in other reports.[19] Autistic participants were less commonly first- and fourth-born compared with the general population.

TABLE 2. Pre-, Peri-, and Neonatal Factors Examined in This Study

Prenatal factors
Maternal age
Parity
Number of previous abortions/miscarriage
Gestational age (<37 wk)
Bleeding in pregnancy (T2, T3)
Vaginal infections
Fever
Preeclampsia
Gestational diabetes
Rhesus incompatibility
Smoking during pregnancy
Use of contraception at conception
Perinatal factors
Induced labor
Cesarean section
Nonvertex presentation
Forcep extraction
Vacuum extraction
Prolonged labor (>20 h)
Precipitous labor (<3 h)
Multiple gestation
Cord complication (prolapse/around neck/knot)
Trauma on delivery
Neonatal factors
Low birth weight (<2500 g)
Low Apgar score (<7 at 5 min)
Respiratory distress syndrome
Oxygen treatment
Hyperbilirubinemia (>10 mg/dL)
Seizures
Birth defect

TABLE 3. Maternal Age and Birth Order in the Autism, PDD-NOS, and General Population Groups*

	Autism (n = 51)	PDD-NOS (n = 13)	General Population†
Maternal age: mean	30.25	30.77	
Maternal age >30 y	45%	54%	35%
Parity: 1	31%	39%	42%
2–3	65%	62%	48%
4+	4%	0%	10%

* Numbers represent either means or percentages as indicated.
† General population values from Ventura et al.[13]

Table 4 summarizes the findings of the factors examined in the autism, PDD-NOS, and general population groups. Incidence of second- or third-trimester uterine bleeding and rhesus incompatibility both occurred at significantly higher rates in autistic participants compared with the general population ($P <$ .05). However, incidence of vaginal infection, smoking, and contraceptive use during conception was significantly lower in the autistic group than in the general population. Among the perinatal factors, significantly higher incidences in the autistic group were found in induction of labor and prolonged and precipitous labor. The neonatal factors with statistically significant higher rates included oxygen requirement at birth and presence of hyperbilirubinemia.

When the Bonferroni correction was performed for the number of tests in each group, the following factors remained significant: increased uterine bleeding, less vaginal infection, and less contraceptive use during conception.

The PDD-NOS group showed results similar to those of the autism group, with significantly lower incidence in vaginal infection but higher incidence of induced and precipitous labor, oxygen requirement at birth, and hyperbilirubinemia. After the Bonferroni correction, only increased incidence of hyperbilirubinemia remained statistically significant.

Table 5 shows the demographic characteristics of the autism, PDD-NOS, and general population groups. These include ethnicity (based on race of mother) and education level reported as number of years of completed education by the mother.

DISCUSSION

Significance of Birth Order Differences in Autism

Several studies have found that autistic individuals tend to be first- or fourth-born more commonly than controls.[4,20,21] Rather than having a role in the cause of autism, this phenomenon is most widely believed to be a result of alterations in the reproductive behavior of parents in response to the birth of a

TABLE 4. Incidence of Pre-, Peri-, and Neonatal Factors in the Autism, PDD-NOS, and General Population Groups: Percentage of Affected Children

Factor	Autism (n = 51)	PDD-NOS (n = 13)	General Population*
Prenatal			
Previous abortions >2	4	8	
Gestational age <37 wk	10	8	11
Uterine bleed	14‡	0	1
Vaginal infection	10§	8§	22[14]
Fever	26	31	17[14]
Preeclampsia	8	2	3[15]
Gestational diabetes	6	17	3
Rh incompatibility	12‡	10	3
Smoking	6§	8	14
Contraceptive use	12§	0	48[16]
Perinatal			
Induced labor	29‡	46‡	16
Cesarean section	24	15	21
Nonvertex presentation	4	8	4
Forcep extraction†	8	9	4
Vacuum extraction†	5	0	6
Prolonged labor	12‡	8	1
Precipitous labor	10‡	23‡	2
Multiple gestation	0	8	2
Cord complication	18	25	26[17]
Birth injury	4	8	0.3
Neonatal			
Low birth weight	4	0	7
Low Apgar score	0	11	1
Respiratory distress syndrome	4	0	1
Oxygen requirement	12‡	23‡	3
Hyperbilirubinemia	22‡	54‡	12[18]
Seizures	0	0	0.09
Birth defect	2	23	3

* All general population values from Ventura et al[13] unless indicated by a reference number.
† Percentage of vaginal deliveries only (autism, n = 39; PDD-NOS, n = 11).
‡ $z > 1.65$ ($P < .05$).
§ $z < -1.65$ ($P < .05$).

TABLE 5. Demographic Characteristics of the Autism, PDD-NOS, and General Population Groups*

	Autism (%)	PDD-NOS (%)	General Population (%)
Ethnicity†			
White	92	92	62
Hispanic	6	0	17
Black	0	0	15
Asian/Pacific islander	2	1	4
American Indian	0	0	1
Years of school completed‡			
<12	2	0	23
12	14	0	34
13–15	37	23	22
≥16	47	77	21

* General population values from Ventura et al.[13]
† Based on race of mother.
‡ By mother.

handicapped child, also known as the "reproductive stoppage rules."[22]

The association between parity and autism is additionally complicated by the difficulty in separating parity effects from the possible effects of maternal age. Increased maternal age has been associated with autism in some studies[5,21] but not in others.[23] Although in this study there was a higher percentage of mothers over 30 years old in the autism and PDD-NOS groups than in the general population, the difference was not statistically significant. Likewise, this study did not show a higher incidence of first- or fourth-born individuals in the autistic and PDD-NOS groups compared with the general population.

Individual Pre-, Peri-, and Neonatal Complications

This study supported previous publications indicating an association between several pre-, peri-, and neonatal complications and autism. A higher incidence of uterine bleeding found in this study was also reported in all 3 studies displayed in Table 1 (study 1: Finegan and Quarrington[3]; study 2: Deykin and MacMahon[4]; and study 3: Gillberg and Gillberg[5]). Prolonged labor also occurred at a higher rate in studies 1 and 2, and an increased incidence of oxygen requirement was reported in studies 1, 2, and 3. Hyperbilirubinemia occurred at a higher rate in this study as well as in studies 1 and 3. The remaining factors found to be significant in this study (rhesus incompatibility, smoking, contraceptive use during conception, induced labor, and precipitous labor) were not investigated in those studies.

Although the sample size of the autism and PDD-NOS groups was not significantly larger than most other similar studies, this study had the benefit of using large-size populations as the control group. Most general population values were taken from the *Report of Final Natality Statistics, 1995*, which presents compiled data from the entire United States.[13] For the factors not included in this source, several other sources were used, all with control samples ranging

from ~8000 to >40 000.[14–18] These large-size samples were used to represent as much of an unbiased, normal population as possible. Previous studies have used similar sized control groups in the form of siblings or matched pairs, often with results that are statistically higher than these general population groups and differ widely between studies.[5,6]

The use of a large-size population offers the benefit of approximating as close to an unbiased control group as possible. Nevertheless, there are drawbacks to using such a control group. These include differences in the demographic characteristics (such as ethnicity and educational attainment) between the control and participant groups. The large-size population included participants from all ethnicities and levels of education, whereas the autism and PDD-NOS groups consisted of participants from predominantly white, more educated families. In an ideal setting with an index group mirroring the demographic distribution of the general population, this method would legitimize any statistically significant differences in incidence of complications observed.

It is important to consider the difference in population characteristics between the index and control groups in the discussion of the results of this study. Different ethnicities show variable incidences of medical conditions: Hispanics and American Indians have a higher incidence of diabetes, whereas blacks have a lower incidence of multiple births.[13] The educational attainment of women who give birth is important because higher education level is associated with more timely receipt of prenatal care and fewer lifestyle and health behaviors during pregnancy that are detrimental to birth outcome. In addition, higher educational attainment has been linked to delayed childbearing and ultimately smaller family sizes.[24] In general, whites acquire more education than do other ethnicities, and the index groups in this study consisted of a much larger proportion of this ethnicity than the general US population.

The differences in education attainment may account for the statistically significantly lower incidence prenatal factors within the autism and PDD-NOS groups. Increased education regarding health issues and subsequent healthier behavior would explain the lower incidence of vaginal infections, smoking during pregnancy, and contraceptive use at time of conception in the autism group. Incidence of vaginal infection increases with multiple partners, partners with sexually transmitted diseases, and poor hygiene—all of which occur at a higher incidence in lower socioeconomic populations. Similarly, there is a higher incidence of smoking in these same populations. The last item, contraceptive use during conception, may be explained by the idea that parents with a higher level of education will use better family-planning methods (use of more reliable contraceptive methods or multiple contraceptives simultaneously), and have a decreased incidence of becoming pregnant while on contraceptives.

The remaining statistically significant factors (uterine bleeding, rhesus incompatibility, induced labor, prolonged or precipitous labor, oxygen requirement at birth, and hyperbilirubinemia) are all examples of a potential compromise in the environment of the child during pregnancy and delivery.

Bleeding in the second half of pregnancy may be caused by benign events, such as tears in the vulva or vagina, or those with more severe consequences like placenta previa (attributable to abnormal location of the placenta over the internal cervical opening) and abruptio placentae (premature separation of the normally implanted placenta). The family questionnaire did not ask parents to specify the cause of uterine bleeding (if known) and none of the collected obstetrical records specifically noted a history of either of these severe conditions. Rhesus incompatibility involves maternal antibodies that develop against the red blood cells of the fetus, which may then pass through the placenta and lead to hematologic destruction within the fetus.

Labor may be induced by the obstetrician as a result of fetal compromise attributable to any number of reasons. The data from the index group did not specify the exact reason for induction of labor; thus, it is difficult to assess the relevance of this result without additional investigation as to the reasons for induction. A prolonged labor may be caused by fetal malposition, fetopelvic disproportion, excess sedation, inadequate contractions, and rupture of the fetal membranes before the onset of active labor. Risks associated with this include increased rates of operative vaginal deliveries or emergent cesarean section, an increased risk of intrauterine infection, and an associated increased risk of fetal compromise. Fetal compromise may take the form of asphyxia, infection, or head trauma from prolonged pressure—all of which may have lasting neurologic consequences. Precipitous labor may be caused by decreased resistance of the birth canal or abnormally strong contractions, the effects of which have not been studied as extensively as other pregnancy and delivery complications. Severe uterine contractions with reduced intervals of relaxation may prevent appropriate uterine blood flow and fetal oxygenation. Resistance of the birth canal to expulsion of the head may cause intracranial trauma, although this is very rare.[25]

Oxygen requirement at birth is an indication of inadequate respiratory capability in the newborn, which is critical in ensuring suitable oxygen delivery to all organs of the child, including the brain. Asphyxia, at the extreme level, may cause irreparable damage to the brain resulting in cerebral palsy, mental retardation, and other scenarios of abnormal brain development. Hyperbilirubinemia may cause neurologic damage and residual deficits if it is severe enough, although none of the index cases provided a history of blood transfusion at birth (which is the standard treatment for severe jaundice). Nevertheless, there are no conclusive data as to whether mild to moderate levels of bilirubin in the blood may cause less obvious neurologic deficits that may have a delayed onset consistent with the features of the PDDs.

Bolton et al[7] suggested additional differentiation between complications based on their severity, as determined by the selection of obstetric complica-

tions known to be associated with a high risk of developmental disorder. These include: prematurity (<36 weeks), low birth weight (<2500 g), respiratory distress syndrome, rhesus incompatibility, emergency cesarean section, resuscitation, severe fetal/neonatal infection, hemolytic anemia, transfusion for anemia, gross physical abnormality in the fetus, and severe trauma during birth. This study did not evaluate for all these factors, and of the ones included, only rhesus incompatibility was shown to have a statistically higher rate in the autism group versus the general population.

The results of this study support previous findings suggesting that there is a consistent association of unfavorable events in pregnancy, delivery, and the neonatal phase and autism. However, the interpretation of these results is difficult, because the specific complications that carried the highest risk of autism represented various forms of pathologic processes with no apparent unifying feature. This lack of specificity may indicate that various types of physical damage may underlie some features of autistic symptomatology, but that no single complication or cluster of complications is responsible for the development of autism. Furthermore, this may indirectly support the hypothesis that autism has a genetic cause determining a particular pathologic development that may even cause these complications to occur.[2,7]

Analysis of possible obstetric complications with the use of participants diagnosed with autism at a young age, then reevaluated at a later age, provides some interesting possibilities for the future. Perhaps additional research will confirm certain pre-, peri-, and neonatal associations that could be used to generate a high-risk historical profile with which to use in conjunction with diagnostic tools currently used. This may help to determine the reliability of a diagnosis of autism in younger children, leading to earlier intervention and assistance for an improved outcome in long-term functionality and quality of life.

ACKNOWLEDGMENTS

This work was supported by funds from the National Institute of Neurological Disorders and Stroke (2-RO1-NS-19855) awarded to Dr Eric Courchesne and a National Institutes of Health Summer Research Training Grant to Dr Naya Juul-Dam.

REFERENCES

1. Fombonne E. The epidemiology of autism: a review. *Psychol Med*. 1999; 29:769–786
2. Szatmari P, Jones MB, Zwaigenbaum L, MacLean JE. Genetics of autism: overview and new directions. *J Autism Dev Disord*. 1998;28:351–368
3. Finegan JA, Quarrington B. Pre-, peri- and neonatal factors and infantile autism. *J Child Psychol Psychiatry*. 1979;20:119–128
4. Deykin EY, MacMahon B. Pregnancy, delivery, and neonatal complications among autistic children. *Am J Disabled Child*. 1980;134:860–864
5. Gillberg C, Gillberg IC. Infantile autism: a total population study of reduced optimality in the pre-, peri- and neonatal period. *J Autism Dev Disord*. 1983;13:153–166
6. Piven J, Simon J, Chase G, et al. The etiology of autism: pre-, peri- and neonatal factors. *J Am Acad Child Adolesc Psychiatry*. 1993;32:1256–1263
7. Bolton PF, Murphy M, MacDonald H, et al. Obstetric complications in autism: consequences or causes of the condition? *J Am Acad Child Adolesc Psychiatry*. 1997;36:272–281
8. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. 4th ed. Washington, DC: American Psychiatric Association; 1994
9. Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord*. 1994;24:659–856
10. Fombonne E. Diagnostic assessment in a sample of autistic and developmentally impaired adolescents. *J Autism Dev Disord*. 1992;22:563–581
11. Schopler E, Reichler RJ, DeVellis RF, Daly K. Toward objective classification of childhood autism: Childhood Autism Rating Scale (CARS). *J Autism Dev Disord*. 1980;10:91–103
12. Lord C, Rutter M, Goode S, et al. Autism diagnostic observation schedule: a standardized observation of communication and social behavior. *J Autism Dev Disord*. 1989;19:185–212
13. Ventura SJ, Martin JA, Curtin SC, Mathews TJ. Report of final natality statistics, 1995. *Monthly Vital Stat Rep*. 1997;45(suppl):1–80
14. Xu B, Pekkanen J, Järvelin MR, Olsen P, Hartikainen AL. Maternal infections in pregnancy and the development of asthma among offspring. *Int J Epidemiol*. 1999;28:723–727
15. Saftlas AF, Olson DR, Franks AL, Atrash HK, Pokras R. Epidemiology of preeclampsia and eclampsia in US, 1979–1986. *Am J Obstet Gynecol*. 1990;163:460–465
16. Xu B, Järvelin MR, Pekkanen J. Prenatal factors and occurrence of rhinitis and eczema among offspring. *Allergy*. 1999;54:829–836
17. Spellacy WN, Gravem H, Fisch RO. The umbilical cord complications of true knots, nuchal cords, and cords around the body: report from the collaborative study of cerebral palsy. *Am J Obstet Gynecol*. 1966;94: 1136–1142
18. Newman TB, Klebanoff MA. Neonatal hyperbilirubinemia and long-term outcome: another look at the collaborative perinatal project. *Pediatrics*. 1993;92:651–657
19. Fretts RC, Schmittdiel J, McLean FH, Usher RH, Goldman MB. Increased maternal age and the risk of fetal death. *N Engl J Med*. 1995; 333:953–957
20. Lord C, Mulloy C, Wendelboe M, Schopler E. Pre- and perinatal factors in high-functioning females and males with autism. *J Autism Dev Disord*. 1991;21:197–209
21. Tsai LY, Stewart MA. Etiological implication of maternal age and birth order in infantile autism. *J Autism Dev Disord*. 1983;13:57–65
22. Jones MB, Szatmari P. Stoppage rules and genetic studies of autism. *J Autism Dev Disord*. 1988;18:31–40
23. Mason-Brothers A, Ritvo ER, Pingree C, et al. The UCLA-University of Utah epidemiologic survey of autism: prenatal, perinatal, and postnatal factors. *Pediatrics*. 1990;86:514–519
24. Mathews T, Ventura S. Birth and fertility rates by educational attainment: United States, 1994. *Monthly Vital Stat Rep*. 1997;45(suppl): 1–20
25. Cunningham F, MacDonald P, Gant N, et al, eds. *Williams Obstetric*. 20th ed. Stamford, CT: Appleton & Lange; 1997:431

Prenatal, Perinatal, and Neonatal Factors in Autism, Pervasive Developmental Disorder-Not Otherwise Specified, and the General Population

Naya Juul-Dam, Jeanne Townsend and Eric Courchesne

Pediatrics 2001;107;e63
DOI: 10.1542/peds.107.4.e63

Prenatal, Perinatal, and Neonatal Factors in Autism, Pervasive Developmental Disorder-Not Otherwise Specified, and the General Population

Naya Juul-Dam, Jeanne Townsend and Eric Courchesne

Pediatrics 2001;107;e63
DOI: 10.1542/peds.107.4.e63