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ORIGINAL ARTICLE

A Qualitative and Quantitative Review of Obstetric Complications and Autistic Disorder

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Abstract To investigate the possible association of obstetric complications and autistic disorder, we performed a review of case-control studies of any obstetric complication in autistic disorder. If the odds ratio = {(Number of cases with autistic disorder with any obstetric complication) / (Number of cases with autistic disorder without any obstetric complication)}/{(Number of controls without autistic disorder with any obstetric complication) / (Number of controls without autistic disorder without any obstetric complication)} <1, then there are more complications in controls; =1, then complications are equal in cases and controls; and >1, then there are more complications in cases. Most publications do not provide the raw data to calculate the odds ratio. Many calculated odds ratios support the hypothesis that cases with autism have more obstetric complications. Further investigation is warranted to clarify the relationships between obstetric complications and autism and related conditions in the general population worldwide.

Keywords Case-control study · Infant low birth weight · Labor complications · Pervasive child developmental disorders · Pregnancy complications

The multiple publications investigating possible relationships between obstetric complications and autistic disorder are confusing and contradictory. Ineffective experimental designs, meager sample sizes, and variable diagnostic criteria for

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autistic and obstetric disorders (Cochran 1977) hinder interpretation of many published articles. In particular, conflicting definitions of both autistic disorder and obstetric complications impede comparisons and contrasts among published reports. The dearth of specific raw data in published articles prevents secondary analyses of the results. Innovative strategies to identify the relationships between obstetric events and developmental disabilities will likely facilitate the investigation of the role of obstetric complications in the pathogenesis of autism and related conditions.

Obstetric Complications and Schizophrenia

Obstetric complications have long been identified in the case histories of some individuals with schizophrenia (Buckley 1998). However, conflicting and contradictory reports have hindered identification of associations between obstetric events and schizophrenia. A series of investigations has utilized meta-analytic strategies to clarify whether or not obstetric complications play a role in schizophrenia (Cannon *et al.* 2002). Geddes and Lawrie (1995) identified published articles about obstetric complications and schizophrenia with the assistance of colleagues and other researchers. The authors included only studies with a control group without schizophrenia and with diagnostic criteria for schizophrenia and obstetric complications. Rather than employing one of the many procedures to score obstetric complications, the authors simply dichotomously categorized obstetric complications as present or absent. This strategy yielded twenty case-control studies, one prospective cohort study, and two historical cohort studies. Heterogeneity of effect was absent between studies. The pooled odds ratio for presence of obstetric complications on the later development of schizophrenia was 2.0. There was significant heterogeneity between pooled estimates of case-control and historical cohort studies. Selection bias (Greenland 1987) likely was present since there was a dearth of small studies reporting no effect. This meta-analysis concluded that people with obstetric complications were twice as likely to develop schizophrenia as those without obstetric complications (Cannon *et al.* 2002; Geddes and Lawrie 1995).

Verdoux *et al.* (1997) took the meta-analysis of schizophrenia a step further by specifically investigating the possible relationship between obstetric complications and family history, age of onset, and gender. The authors hypothesized that obstetric complications are more likely in: (1) individuals with sporadic schizophrenia than individuals with familial schizophrenia, (2) males with schizophrenia than females with schizophrenia, and (3) people who develop schizophrenia early in life than those who develop schizophrenia later in life. After obtaining the written informed consents of all participants, the authors obtained the raw data from researchers in order to categorize individuals utilizing a detailed protocol. The authors scored all obstetric complications as definite or probable obstetric complications according to the Obstetric Complication Scale (Lewis *et al.* 1989). Logistic regression analyses were performed to check for relationships of obstetric complications to family history, age of onset, and gender. Age of onset of schizophrenia before 22 years was significantly associated with definite obstetric complications. A significant linear

trend associated definite obstetric complications with age of onset of schizophrenia partitioned into quartiles (<19, 19–21, 22–25, and >25 years). However, obstetric complications were not associated with family history and gender. These results suggest that obstetric complications may affect the developing brain to result in the development of schizophrenia in vulnerable individuals (Verdoux *et al.* 1997).

Insults to the brain in the prenatal, natal, and postnatal periods may impede the cortical migrations of neurons in the developing brain resulting in the development of schizophrenia (Lafargue and Brasic 2000). Verdoux *et al.* (1997) note that both age of onset of schizophrenia and the presence of definite obstetric complications may be caused by another unidentified influence. However, the authors conclude that "environmental factors such as obstetric complications play a role in the pathophysiology of early-onset schizophrenia, either alone or by interacting with other factors" (Verdoux *et al.* 1997, p. 1226). The authors advanced the field by identifying a possible interaction between environmental influences and a vulnerable subgroup of people with schizophrenia, such as people with schizophrenia with a particular gene (Cannon *et al.* 2002).

Cannon *et al.* (2002) further advanced the study of obstetric complications and schizophrenia by providing a historical review and a meta-analysis (Fleiss 1993) of prospective population-based studies. Only eight studies met the rigorous inclusion criteria they required. The three groups of problems identified were complications of pregnancy and delivery and fetal developmental abnormalities. The authors identified pre-eclampsia, bleeding during pregnancy, maternal diabetes mellitus, and rhesus incompatibility as complications of pregnancy significantly associated with schizophrenia. They identified asphyxia, uterine atony, and emergency Caesarean section as complications of delivery significantly associated with schizophrenia. They also identified low birth weight, congenital malformations, and small head circumference as fetal developmental abnormalities significantly associated with schizophrenia. Cannon *et al.* (2002) suggest that more precise indicators of obstetric complications, including quantitative measurements and exposures during pregnancy, such as infection, malnutrition, and stress, are needed to advance the study of obstetric complications and schizophrenia.

Obstetric Complications and Autism

The technique of meta-analysis has established an association between obstetric complications and schizophrenia (Fleiss 1993; Geddes and Lawrie 1995; Verdoux *et al.* 1997; Cannon *et al.* 2002) and is a promising tool to investigate a possible association between obstetric complications and autistic disorder. Therefore, we seek to apply the methodology of meta-analysis to case-control studies of autistic disorder and obstetric complications (Fleiss 1993). We developed a reliable procedure to identify a database of case-control reports of obstetric complications and autistic disorder published in the past century (Brašić and Holland 2006). We seek now to apply the technique of meta-analysis to the reliable case-control studies of obstetric complications in autistic disorder and to disprove the null hypothesis that there is no association between obstetric complications and autism. Specifically we seek to determine if there exists an association between any complication and autism.

Materials and Methods

Identification of a Comprehensive Database of All Potential Case-control Studies of Autistic Disorder and Obstetric Complications

Literature Searches

On October 7, 1997, we performed a literature search at the Ehrman Medical Library of the New York University School of Medicine for all citations combining "autistic disorder" *or* "autism" *or* "child developmental disorders, pervasive," *and* "infant low birth weight" *or* "labor complications" *or* "pregnancy complications" utilizing databases as follows: Aidsline 1980 to September 1997, CancerLit 1983 to September 1997, CINAHL 1982 to August 1997, HealthSTAR 1975 to October 1997, Medline 1966 to October 1997, and PsychINFO 1984 to October 1997. We then included articles cited in the published reference lists possibly containing information about case-control studies of obstetric complications in autistic disorder and relevant articles from the indices of journals reviewed for this study and other apparently appropriate articles (Brašić and Holland 2006). We subsequently performed a literature search via PubMed from 1995 to 2005 on October 10, 2005, for all citations combining "autistic disorder" *or* "autism" *or* "child developmental disorders, pervasive," *and* "infant low birth weight" *or* "labor complications" *or* "pregnancy complications."

Of these additional articles, we excluded several classes of articles from analysis for this current review of any overall obstetric complication and autism. We excluded studies of specific conditions, fetal valproate syndrome (Bescoby-Chambers *et al.* 2001; Williams *et al.* 2001), low birth weight (Halsey *et al.* 1996), and tuberous sclerosis (Park and Bolton 2001 (Table 3)), including only cases with autism spectrum disorders with the specific condition without any cases with autism spectrum disorders without the specific condition. We excluded a study of the pregnancies of women with cerebrospinal fluid shunts (Liakos *et al.* 2000). We also excluded reviews (Blaxill 2004; Buckley 1998; Hultman and Sparén 2004; Jick and Kaye 2004; Lawler *et al.* 2004; Newschaffer and Cole 2005; Rutter 2005; Simon 1999; Susser and Bresnahan 2002; Szatmari *et al.* 1998; Verdoux 2004), articles without raw data about obstetric complications (Barbaresi *et al*. 2005; Wilkerson *et al.* 2002; Zwaigenbaum *et al.* 2002 (Table 1)), articles with data about only specific obstetric complications, but not any obstetric complication (Cederlund and Gillberg 2004; Croen *et al.* 2005; Glasson *et al.* 2004 (Tables 1 and 3); Hultman *et al.* 2002 (Table 1); Jick and Kaye 2003 (Table 1); Juul-Dam *et al.* 2001 (Table 1); Larsson *et al.* 2005 (Table 1); Pickles *et al.* 2000 (Table 1)), studies without differentiation of autism from other pervasive developmental disorders (Glasson *et al.* 2004 (Tables 1 and 3)), articles without controls (Cederlund and Gillberg 2004; Gillberg and Cederlund 2005; Hippler and Klicpera 2003; McInnes *et al.* 2005 (Table 1)), and articles about animals (Boksa *et al.* 2002; Fatemi *et al.* 2002).

Definitions of Classification Categories

We defined (1) an autistic disorder case-control study as a report in which there is at least one case with autistic disorder and at least one control without autistic disorder, and (2)

Table 1 Characteristics of 56 articles reporting potential case control studies of autism and obstetric complications including 44 articles classified by at least one of two psychiatric raters as case-control studies of autistic disorder and obstetric complications (Brašić and Holland 2006), and other articles identified through literature searches and reference lists

Reference	Type of study	Source of obstetric complications	Method of measurement of obstetric complications	Cases	Controls	Diagnosis	Presence of data to calculate overall odds ratio for any obstetric complication in case-control study of autistic disorder with normal control subjects
Allen *et al.* 1971[b]	Case-control	Parental recall	Individual obstetric complications	Children with autism (*N*=26) and children with early childhood schizophrenia who had gone through an autistic period (*N*=7)	Normal children matched for age, ordinal position in sibline, number of sibs, sex of sibs, race, sex, socioeconomic status, and religion (*N*=33) Brain-damaged children with behavioral disturbances (*N*=30)	DeMyer-Churchill diagnostic criteria for infantile autism and for early childhood schizophrenia (DeMyer *et al.* 1971)	No
Annell 1963[b]	Case reports	Hospital records	Individual obstetric complications	All children with a psychotic syndrome admitted to an inpatient child psychiatric hospital	None	Clinical diagnosis	No
Bolton *et al.* 1994[d]	Case-control	Maternal interview	Weighted scale	Sample of probands with autism	Sample of probands with Down syndrome	ADI, ADOS, DSM-III-R, and ICD-10	No

Table 1 (continued)

Reference	Type of study	Source of obstetric complications	Method of measurement of obstetric complications	Cases	Controls	Diagnosis	Presence of data to calculate overall odds ratio for any obstetric complication in case-control study of autistic disorder with normal control subjects
Bolton *et al.* 1997[d]	Case-control	Maternal interview and obstetric records when available	Weighted scale	Sample of probands with autism	Sample of probands with Down syndrome	ADI, ADOS, DSM-III-R, and ICD-10	No
Bryson *et al.* 1988[d]	Case-control	Obstetric records	Weighted scale	Cases identified through an epidemiological sample of a geographical region	Siblings of cases Sample of children of comparable chronological and mental ages Sample of normal children	DSM-III-R	No
Campbell *et al.* 1978a[d]	Case-control	Obstetric and medical records	Weighted scale	A sample of inpatients on a child psychiatric unit	Siblings of cases Sample of children attending a day-care center for normal preschool children Sample of children of colleagues of the authors	Clinical diagnosis	No
Campbell *et al.* 1978b[d]	Case-control	Obstetric records	Weighted scale	A sample of inpatients on a child psychiatric unit	Siblings of cases	DSM-II and DSM-III	No
Christianson *et al.* 1994[d]	Case-control	Parental recall	Individual obstetric	A case of autism exposed to valproic acid during	Sibling of case and other patients	DSM-III-R	No

			complications	pregnancy in a developmental disabilities clinic	exposed to valproic acid during pregnancy in a developmental disabilities clinic		
Cryan *et al.* 1996[a,c]	Case-control	Obstetric records	Weighted scale	A sample of patients with autism in a region	Live birth of the same sex preceding the proband at the hospital of birth of the proband	DSM-III-R	Yes (Table 2)
Deb *et al.* 1997[d]	Case-control	Obstetric records	Weighted scale	Sample of children in a population study of mental retardation	Siblings of probands	DSM-III-R	No
DeMyer 1979[d]	Case-control study	Parental interview	Individual obstetric complications	Sample of children with autism	Sample of children who were physically and behaviorally normal Sample of children who were mentally retarded but not psychotic	DeMyer-Churchill diagnostic criteria for infantile autism and for early childhood schizophrenia (DeMyer *et al.* 1971)	No
Deykin and MacMahon 1980[d] cited in Tsai 1987[b]	Case-control study	Maternal interview and available obstetric records	Individual obstetric complications	Sample of children with autism	Unaffected siblings of probands	Clinical diagnosis	No
Finegan and Quarrington 1979[d] cited in Tsai 1987[b]	Case-control study	Obstetric records	Individual obstetric complications	Sample of children with autism	Siblings of cases	Clinical diagnosis	No
Funderburk *et al.* 1983[b]	Historical cohort study	Parental interview confirmed by obstetric	Individual obstetric complications	Sample of children with autism	Samples of normal infants born in comparable metropolitan or state	DSM-III	No

Table 1 (continued)

Reference	Type of study	Source of obstetric complications	Method of measurement of obstetric complications	Cases	Controls	Diagnosis	Presence of data to calculate overall odds ratio for any obstetric complication in case-control study of autistic disorder with normal control subjects
		records when possible			areas in previously published surveys		
Ghaziuddin *et al.* 1995[d]	Case-control study	Parental interview and obstetric records	Weighted scale	Sample of children with high-functioning autism	Sample of children with Asperger syndrome	DSM-III-R and ICD-10D	No (Table 3)
Gillberg and Gillberg 1983[a,d] cited in Tsai 1987[b]	Case-control study	Obstetric records	Weighted scale	Sample of children with autism born in a geographical region	Children of same sex as proband born as close as possible in the same obstetric department	Clinical diagnosis	Yes (Table 2)
Gillberg and Gillberg 1991[d]	Case-control study	Obstetric records	Weighted scale	Sample of children with autism born in a geographical region	Matched normal children	Clinical diagnosis	No
Gillberg *et al.* 1990[b]	Case series of twin pairs with only one twin with autism	Obstetric records	Individual obstetric complications	Sample of twins discordant for autism	None	Clinical diagnosis	No
Glasson *et al.* 2004	Case-control study	Data recorded on a regional registry	Individual obstetric complications	Sample of children with autism, Asperger syndrome, and pervasive developmental disorder not otherwise specified	Sample of normal children matched for sex with probands born in the same geographical region	DSM	No. Children with autism are not differentiated from children with other pervasive

				born in a geographical region	in the same year		developmental disorders for report of any obstetric complication (Table 3)
Goodman 1990[b]	Technical note on a case series of twin pairs with only one twin with autism (Gillberg *et al.* 1990)[b]	Obstetric records	Individual obstetric complications	Sample of twins discordant for autism	None	Clinical diagnosis	No
Goodwin and Goodwin 1969[c]	Case series	Maternal interview	Individual obstetric complications	Sample of children referred to a pediatric clinic	None	Kanner's criteria for the diagnosis of childhood autism	No
Green *et al.* 1984[b]	Case series of children with autism	Parent interview confirmed by obstetric records when possible	Weighted scale	Sample of inpatients with infantile autism	Sample of inpatients with schizophrenic disorder Sample of inpatients with conduct disorder, undersocialized, aggressive	DSM-III	No
Harper and Williams 1974[d]	Retrospective historical cohort study in a geographical region	Hospital records	Individual obstetric complications	Sample of inpatients with autism referred for evaluation in a geographical region	Sample of emotionally disturbed inpatients in the same geographical region Sample of inpatients admitted to a pediatric department for upper respiratory and urinary tract infections in the same geographical region	Clinical diagnosis	No

Table 1 (continued)

Reference	Type of study	Source of obstetric complications	Method of measurement of obstetric complications	Cases	Controls	Diagnosis	Presence of data to calculate overall odds ratio for any obstetric complication in case-control study of autistic disorder with normal control subjects
Hinton 1963, cited in Pollack and Woerner 1966[b]	Case-control study	Hospital records	Individual obstetric complications	Sample of children admitted for psychosis	Sample of children admitted for tonsillectomy and adenoidectomy	Clinical diagnosis	No
Hultman *et al.* 2002	Prospective case-control in a geographical region	Prenatal, birth, and neonatal records	Individual obstetric complications	All children hospitalized for infantile autism from a geographical region during the study period	Sample of children without infantile autism matched by year of birth, sex, and hospital of birth of probands	ICD-9 Code 299A	No
Jick and Kaye 2003	Case-control	Physician records	Individual obstetric complications	Sample of cases with autism	Random sample of up to five control boys matched for age	Clinical diagnosis	No
Juul-Dam *et al.* 2001	Case-control	Obstetric and neonatal records and parental interview	Individual obstetric complications	Sample of children with autism from a developmental disabilities clinic	Sample of children with pervasive developmental disorder not otherwise specified from a developmental disabilities clinic Various published control groups	DSM-IV, ADI-R, ADOS, and CARS	No
Kanner and Lesser 1958[b]	Case series	Clinical records	Individual obstetric	Sample of children with autism referred to a child	Nonautistic children	Clinical diagnosis	No

			complications	psychiatric clinic			
Knobloch and Pasamanick (1975)[d] This is the published article of the data of Knobloch and Pasamanick (1962) cited in Pollack and Woerner 1966[b].	Case series of children seen in a developmental service in a children's hospital	Clinical records	Individual obstetric complications	The 64 children with autism excluding 14 children with phenyketonuria (50 children) in the first 1,900 patients seen in the developmental service	The next 50 children who were abnormal without symptoms of autism The next 50 children without neuropsychiatric disorders	Clinical diagnoses	No Published data are apparently erroneous (Knobloch and Pasamanick 1975[d], Table 1, page 185).
Kolvin *et al.* 1971[c]	Case series of children with psychosis admitted to child psychiatric inpatient units	Maternal interview and clinical record	Individual obstetric complications	Sample of children with infantile psychosis	Sample of children with psychosis of later onset	Clinical diagnosis	No (Table 3)
Larsson *et al.* 2005	Case-control study	Danish Medical Birth Register	Individual obstetric complications	Children in the Danish Psychiatric Central Register born between 1973 and 1994, and discharged from a Danish psychiatric hospital with infantile or atypical autism	Controls matched by gender, birth year, and age in days	ICD-8 diagnosis codes 299.00–299.01, and ICD-10 diagnosis codes F84.0–F84.1x	No
Laxer *et al.* 1988[b]	Retrospective case-control study	Parental responses on questionnaires	Individual obstetric complications	Sample of children with autism	Samples of children with multiple physical handicaps Sample of children with Down's syndrome	Retrospective diagnosis from parental reports	No
Levy *et al.* 1988[d]	Case-control	Delivery records	Weighted scale	Sample of children with autism referred to a psychoeducational clinic	Sample of children without autism referred to the study psychoeducational clinic	Clinical diagnosis	No

Table 1 (continued)

Reference	Type of study	Source of obstetric complications	Method of measurement of obstetric complications	Cases	Controls	Diagnosis	Presence of data to calculate overall odds ratio for any obstetric complication in case-control study of autistic disorder with normal control subjects
Links *et al.* 1980[d]	Case-control	Birth and pregnancy records and maternal history if available	Weighted scale	Sample of children with autism surveyed in a geographical region	Siblings of probands	Clinical diagnosis	No (Table 3)
Lobascher *et al.* 1970[d]	Case-control	Case records	Individual obstetric complications	Sample of children with autism	Sample of matched normal children without a history of a neurological disorder	Clinical diagnosis	No
Lord *et al.* 1989a[b]	Case-control	Medical records	Individual obstetric complications	Sample of people with mild mental retardation and autism	Sample of people with mild mental retardation but without autism	Clinical diagnosis	No
Lord *et al.* 1991[d]	Case-control	Medical records and maternal interview	Weighted scale	Samples of people with autism	Normal siblings of probands	ADI-R and DSM-III-R	No
Lotter 1967	Case-control	Medical records and maternal interview	Weighted scale	Sample of people with autism	Siblings of probands	Clinical diagnosis	No
Mason-Brothers *et al.* 1990[d]	Case-control	Medical records	Individual obstetric complications	Sample of people with autism	Normal siblings of probands	DSM-III	No

McInnes *et al.* 2005	Case series	Medical records and parental interview	Individual obstetric complications	Sample of people with autism	None	ADI-R and ADOS	No
Park and Bolton 2001	Case-control	Maternal interview	Weighted scale	Sample of children and adolescents with tuberous sclerosis recruited for a research study	Unaffected siblings of probands	ADI-R, ADOS, and ICD-10	No (Table 3)
Pasamanick *et al.* 1956[b]	Children referred for behavioral disturbances	Hospital records	Individual obstetric complications	Children referred for behavioral disturbances	Children matched for sex and class	Clinical diagnosis	No
Pickles *et al.* 2000	Sample of patients with autism	Maternal interview	Weighted scale	Sample of patients with autism	Samples of patients with Down syndrome matched to probands	ADI, ADOS, ICD-10, PL-ADOS	No
Piven *et al.* 1993[d]	Sample of probands with autism	Informant interview and hospital records when available	Weighted scale	Sample of probands with autism	Sample siblings of the probands with autism	ADI, ADOS, ICD-10	No
Roboz and Pitt 1971[b]	Cases series of admissions to an institution for people with mental retardation	Clinical charts	Individual obstetric complications	Sample of children with childhood psychosis admitted to an institution for people with mental retardation	Sample of children with undifferentiated mental deficiency admitted to an institution for people with mental retardation	Clinical diagnosis	No
Rutter and Lockyer 1967[c]	Retrospective case-control	Clinical charts	Individual obstetric complications	Sample of prepubertal children with psychosis	Sample of prepubertal children without psychosis	Clinical diagnosis	No
Steg and Rapoport 1975[d]	Case-control	Clinical charts	Individual obstetric complications	Sample of children in residential care with psychosis	Sample of inpatient children with pediatric conditions	Clinical diagnosis	No

Table 1 (continued)

Reference	Type of study	Source of obstetric complications	Method of measurement of obstetric complications	Cases	Controls	Diagnosis	Presence of data to calculate overall odds ratio for any obstetric complication in case-control study of autistic disorder with normal control subjects
				Sample of children in residential care with severe behavioral disorders	Sample of outpatient children in a child guidance clinic Sample of boys in a school for learning disabilities		
Taft and Goldfarb 1964 cited in Pollack and Woerner 1966[b]	Case-control	Hospital charts and interviews of mothers and physicians	Weighted scale	Sample of children with schizophrenia	Samples of normal children	Clinical diagnosis	No
Tanoue and Oda 1989[d]	Case-control	Clinical charts	Individual obstetric complications	Sample of outpatients with infantile autism at a child guidance clinic	Sample of normal children in same region as probands	DSM-III	No
Tanoue *et al.* 1988[b]	Outpatients with infantile autism at a child guidance clinic	Hospital and vital statistics records	Individual obstetric complications	Sample of outpatients with infantile autism at a child guidance clinic	None	DSM-III	No
Terris *et al.* 1964 cited in Pollack and Woerner 1966[b]	Case-control study	Hospital records	Individual obstetric complications	Sample of children with schizophrenia	Sample of healthy children	Clinical diagnosis	No
Torrey *et al.* 1975[d]	Case-control	Prospective records	Individual obstetric complications	Sample of children with autism	Sample of neurologically and behaviorally normal children with and	Clinical diagnosis	No

					without mental retardation		
Vorster 1960 cited in Pollack and Woerner 1966[b]	Case-control	Maternal interview and hospital records when possible	Individual obstetric complications	Sample of children with schizophrenia	Siblings of probands	Clinical diagnosis	No
Wing *et al.* 1967[b]	Survey of children with autism in a total population	Medical records when available	Individual obstetric complications	Children with autism in a total population	Siblings of probands	Clinical diagnosis	No (Table 3)
Zambrino *et al.* 1995[d]	Survey of children with pervasive developmental disorder	Unknown clinical charts	Weighted scale	Children with pervasive developmental disorder with and without damage of the central nervous system	Sample of normal subjects Sample of subjects with mental retardation	DSM-III-R	No
Zwaigenbaum *et al.* 2002	Case-control study	Parental interview	Weighted scale	Sample of children with autism	Unaffected siblings of probands	ADI-R, ADOS, and DSM-IV	No

ADI Autism Diagnostic Interview (Le Couteur *et al.* 1989), *ADI-R* Autism Diagnostic Interview—Revised (Lord *et al.* 1994), *ADOS* Autism Diagnostic Observation Schedule (Lord *et al.* 1989b), *CARS* Childhood Autism Rating Scale (Schopler *et al.* 1980), *DSM-II* Diagnostic and statistical manual of mental disorders (2nd edn.) (American Psychiatric Association 1968), *DSM-III* Diagnostic and statistical manual of mental disorders (3rd edn.) (American Psychiatric Association 1980), *DSM-III-R* Diagnostic and statistical manual of mental disorders (3rd edn.—revised) (American Psychiatric Association 1987), *DSM-IV* Diagnostic and statistical manual of mental disorders (4th edn.) (American Psychiatric Association 1994), *ICD-8* International Classification of Diseases, Eighth Revision (Cited in Larsson *et al.* 2005), *ICD-9* International Classification of Diseases, Ninth Revision (Cited in Hultman *et al.* 2002), *ICD-10* International Classification of Diseases, Tenth Revision (World Health Organization 1992), *ICD-10D* International Classification of Disease, Tenth Edition [sic], Draft Version (World Health Organization 1990) (Cited in Ghaziuddin *et al.* 1995[d]), *PL-ADOS* Pre-Lingual Autism Diagnostic Observation Schedule (PL-ADOS) (DiLavore *et al.* 1995)

[a] Indicates the two articles fulfilling the criteria for any obstetric complication and providing data for case-control studies of autistic disorder and any obstetric complications (Table 2).

[b] Indicates the 15 articles identified as case-control studies of autistic disorder and obstetric complications by a blind rater, but not a nonblind rater (Brašić and Holland 2006).

[c] Indicates the four articles identified as case-control studies of autistic disorder and obstetric complications by a nonblind rater, but not a blind rater (Brašić and Holland 2006).

[d] Indicates the 25 articles identified as case-control studies of autistic disorder and obstetric complications by both blind and nonblind raters (Brašić and Holland 2006).

an obstetric rating scale as the recording of the presence or absence of obstetric, pregnancy, or labor complications. Two board-certified psychiatrists independently rated all articles on presence or absence of cases of autistic disorder, controls without autistic disorder, and obstetric complications. The unblind rater blinded all 156 articles so that all identifying information concerning the date of publication, the name of the journal, the ethnicity of the subjects, the location of the study site, and the identity of the authors and all other people mentioned in the paper was removed. The methods section of the articles presented to the blind reviewer were cut from photocopied articles. Both blind and nonblind raters independently classified all 156 papers as autistic case-control studies with or without obstetric complications rating scales, autistic case reports without controls with or without obstetric complications rating scales, and other articles (Brašić and Holland 2006). We classified obstetric complications as present or absent. We interpreted any report of any obstetric complications as the presence of obstetric complications (Brašić and Holland 2006; Geddes and Lawrie 1995).

Overall for the 150 articles rated by both blind and nonblind raters, percent agreement between raters was 61.3% and the κ (kappa) statistic was 0.480 (Fleiss 1981; Shrout *et al.* 1994). We accepted ratings of strength of agreement of $\kappa>0.40$ as representing adequate reliability (Fleiss 1981). We then examined interrater reliability for the two independent variables, the presence of case-control studies of autistic disorder and the presence of obstetric complications. We obtained good interrater reliability for the classification of case-control studies of autistic disorder with 74.6% agreement and $\kappa=0.451$, and for the classification of obstetric complications with 84.0% agreement and $\kappa=0.658$ (Brašić and Holland 2006).

Definition of Odds Ratio

A relevant statistic to analyze the possible association of autistic disorder and obstetric complications is the odds ratio, as follows:

$$Odds\ ratio = \frac{\frac{(Number\ of\ cases\ of\ autistic\ disorder\ with\ any\ obstetric\ complication)}{(Number\ of\ cases\ of\ autistic\ disorder\ without\ any\ obstetric\ complication)}}{\frac{(Number\ of\ normal\ controls\ without\ autistic\ disorder\ with\ any\ obstetric\ complication)}{(Number\ of\ normal\ controls\ without\ autistic\ disorder\ without\ any\ obstetric\ complication)}} \quad (1)$$

(Brašić *et al.* 2003).

Characterization of Published Case-control Studies of Autistic Disorder and Obstetric Complications

In order to facilitate future research on the topic of obstetric complications and autism, we have summarized the salient characteristics of the 44 studies rated by at least one rater as a case-control study of autistic disorder and obstetric complications (Brašić and Holland 2006). Both the blind and the nonblind raters classified 25 studies as case-control studies of autistic disorder and obstetric complications (Bolton *et al.* 1994; Bolton *et al.* 1997; Bryson *et al.* 1988; Campbell *et al.* 1978a and b; Christianson *et al.* 1994; Deb *et al.* 1997; DeMyer 1979; Deykin and MacMahon 1980; Finegan and Quarrington 1979; Ghaziuddin *et al.* 1995; Gillberg and Gillberg 1983, 1991; Harper and Williams 1974; Knobloch and Pasamanick 1975; Levy *et al.*

1988; Links *et al.* 1980; Lobascher *et al.* 1970; Lord *et al.* 1991; Mason-Brothers *et al.* 1990; Piven *et al.* 1993; Steg and Rapoport 1975; Tanoue and Oda 1989; Torrey *et al.* 1975; Zambrino *et al.* 1995; Brašić and Holland 2006). The blind rater only classified fifteen studies as case-control studies of autistic disorder and obstetric complications (Allen *et al.* 1971; Annell 1963; Funderburk *et al.* 1983; Gillberg *et al.* 1990; Goodman 1990; Green *et al.* 1984; Kanner and Lesser 1958; Laxer *et al.* 1988; Lord *et al.* 1989a; Pasamanick *et al.* 1956; Pollack and Woerner 1966; Roboz and Pitt 1971; Tanoue *et al.* 1988; Tsai 1987; Wing *et al.* 1967; Brašić and Holland 2006). The nonblind rater only classified four studies as case-control studies of autistic disorder and obstetric complications (Cryan *et al.* 1996; Goodwin and Goodwin 1969; Kolvin *et al.* 1971; Rutter and Lockyer 1967; Brašić and Holland 2006).

We summarized each of 56 potential case-control studies of autism and obstetric complications including 44 studies rated as a case-control study of autistic disorder and obstetric complications by at least one rater (Brašić and Holland 2006) and other relevant articles identified through literature searches and reference lists in order to facilitate further qualitative and quantitative analyses (Table 1).

Results

The characteristics of 56 potential case-control studies of autism and obstetric complications identified for this study are summarized in Table 1. Of these studies only two meet our criteria of cases with autistic disorder, normal controls without autistic disorder, and any obstetric complication (Cryan *et al.* 1996; Gillberg and Gillberg 1983). Since we have so few studies, further steps in a meta-analysis of any obstetric complication in case-control studies of autism would likely be misleading. Rather than dredging data to apply the procedures of a meta-analysis to extremely limited data, we present the extant data for individual case-control studies with normal controls of autism and any obstetric complication (Cryan *et al.* 1996; Gillberg and Gillberg 1983) with odds ratios and 95% confidence intervals (Stata Corporation 2003) (Table 2). Of the two studies meeting the criteria, the results are discordant. One study suggests that people with autism have fewer obstetric complications than the general population (Cryan *et al.* 1996). The other study shows a striking effect such that all people with autism had obstetric complications (Gillberg and Gillberg 1983). However, in the study with the marked effect, all subjects with autism had obstetric complication leading to an odds ratio with division by zero, an undefined operation (Gillberg and Gillberg 1983). Performing a meta-analysis with these two studies pooled may be misleading.

Discussion

We performed qualitative and quantitative reviews of obstetric complications and autism. Two board-certified psychiatrists independently and reliably rated 156 publications about obstetric complications and autism for presence or absence of cases of autistic disorder, controls without autistic disorder, and obstetric complications (Brašić and Holland 2006). Table 1 summarizes the salient traits of the 44 articles rated as case-control studies by at least one rater supplemented by 12

additional articles identified through literature searches and reference lists. We then identified the publications with cases of autistic disorder, normal controls without autistic disorder, and any obstetric complication for a planned meta-analyis. In order to be selected for the proposed meta-analysis, articles must include the raw data to compute the odds ratio (Eq. 1), at least one case of autistic disorder, at least one normal control without autistic disorder, and any rating of any obstetric complication. Many studies could not be included in the planned review due to the absence of at least one of these requirements, (1) the necessary raw data, (2) cases of autistic disorder, (3) normal controls without autistic disorder, and (4) any obstetric complication.

First, raw data is needed to compute the odds ratio (Eq. 1). Over the past century several studies have been performed including assessments of obstetric complications in cases of autism and controls without autism. Since raw data was not published in the final report, we cannot calculate the odds ratio (Eq. 1) necessary for quantitative analyses including meta-analyses. While some editors restrict the length

Table 2 Data from case-control studies of any obstetric complication in autistic disorder with normal control subjects (See Table 1)

Reference	Number of persons with autistic disorder with obstetric complications	Number of persons with autistic disorder without obstetric complications	Number of normal controls without autistic disorder with obstetric complications	Number of normal controls without autistic disorder without obstetric complications	Odds ratio Point estimate (Stata Corporation 2003)	95% confidence interval, exact (Stata Corporation 2003)
Cryan *et al.* 1996[a,b]	9	40	17	32	0.4235294 (0.42 was the rounded value originally published (Cryan *et al.* 1996).)	(0.1467591, 1.174373) The published interval (0.167–1.1) (Cryan *et al.* 1996) is apparently erroneous.
Gillberg and Gillberg 1983[a,c]	25	0	19	6	undefined	(1.896442, undefined)

Odds ratio point estimates and exact 95% confidence intervals were computed utilizing case-control immediate (cci) (Stata Corporation 2003).

[a] Indicates the two articles fulfilling the criteria for any obstetric complication and providing data for case-control studies of autistic disorder and any obstetric complications (Table 1).

[b] Indicates the four articles identified as case-control studies of autistic disorder and obstetric complications by a nonblind rater, but not a blind rater (Brašić and Holland 2006).

[c] Indicates the 25 articles identified as case-control studies of autistic disorder and obstetric complications by both blind and nonblind raters (Brašić and Holland 2006).

Table 3 Data from case-control studies of obstetric complications in autistic disorder failing to meet criteria for inclusion in overall review of a case-control study of autistic disorder with a normal control group and any overall obstetric complication (Tables 1 and 2)

Reference	Number of persons with autistic disorder with obstetric complications	Number of persons with autistic disorder without obstetric complications	Number of controls without autistic disorder with obstetric complications	Number of controls without autistic disorder without obstetric complications	Odds ratio Point estimate (Stata Corporation 2003)	95% confidence interval, exact (Stata Corporation 2003)
Ghaziuddin *et al.* 1995[c]	9 Cases with high-functioning autism	1 Case with high-functioning autism	8 Controls with Asperger syndrome	2 Controls with Asperger syndrome	2.25	(0.0951194, 147.2381)
Glasson *et al.* 2004	175 Includes persons with Asperger syndrome and pervasive developmental disorders not otherwise specified	290 Includes persons with Asperger syndrome and pervasive developmental disorders not otherwise specified	426	887	1.256476	(1.000988, 1.574706)
Kolvin *et al.* 1971[b]	21	25	5 Children with late-onset psychosis	27 Children with late-onset psychosis	4.536	(1.358476, 17.45143)
Links *et al.* 1980[c]	39	5	37 Siblings of probands	15 Siblings of probands	3.162162	(0.9569747, 12.1201)
Park and Bolton 2001	12 Patients with tuberous sclerosis and autism spectrum disorders	2 Patients with tuberous sclerosis and autism spectrum disorders	29 Siblings of probands with tuberous sclerosis	11 Siblings of probands with tuberous sclerosis	2.275862	(0.3935977, 23.87451)
Park and Bolton 2001	12 Patients with tuberous sclerosis and autism spectrum disorders	2 Patients with tuberous sclerosis and autism spectrum disorders	18 Patients with tuberous sclerosis and without autism spectrum disorders	2 Patients with tuberous sclerosis and without autism spectrum disorders	0.6666667	(0.0443141, 10.49928)
Wing *et al.* 1967[a]	6	22	3 Siblings of probands	41 Siblings of probands	3.727273	(0.6998791, 24.78951)

Odds ratio point estimates and exact 95% confidence intervals were computed utilizing case-control immediate (cci) (Stata Corporation 2003).

[a] Indicates the 15 articles identified as case-control studies of autistic disorder and obstetric complications by a blind rater, but not a nonblind rater (Brašić and Holland 2006).

[b] Indicates the four articles identified as case-control studies of autistic disorder and obstetric complications by a nonblind rater, but not a blind rater (Brašić and Holland 2006).

[c] Indicates the 25 articles identified as case-control studies of autistic disorder and obstetric complications by both raters (Table 1) (Brašić and Holland 2006).

of original articles, the publication of the raw data is crucial for readers, both to check the original interpretations and for future secondary analyses. Publication of full original data is a critical step in the dissemination of knowledge advanced by case-control studies. This problem may be addressed by contacting authors of published studies to obtain the raw data needed for to calculate the odds ratio (Eq. 1) and other parameters for secondary analyses and meta-analyses. International collaboration among researchers is needed to obtain a complete data set of the raw data of case-control studies worldwide. Thus, many fine studies could not be included in a quantitative review due to the absence of the needed raw data.

Second, cases of autistic disorder are needed to compute the odds ratio (Eq. 1). For this reason, cases of behavioral disturbances, psychosis, and schizophrenia were not included in our quantitative review. We further seek to differentiate the autistic disorder from other pervasive developmental disorders. Therefore, we excluded from our proposed meta-analysis, articles without cases of autistic disorder. Tools to reliably identify cases of autistic disorder (Lord *et al.* 2000; Lord *et al.* 1989b; Lord *et al.* 1994; Schopler *et al.* 1980) can be utilized for future research to verify the presence of cases of autistic disorder. Cases of autistic disorder are a key requirement for a quantitative study of case-control studies of obstetric complications and autism.

Third, controls without autistic disorder are needed to compute the odds ratio (Eq. 1). In order to differentiate between cases of autistic disorder and controls without autistic disorder, we seek normal control subjects. While there are sound strategies to compare cases of autistic disorder with subjects with other developmental disabilities, those are not normal control subjects. Additionally since families of a proband with autistic disorder are likely to exhibit traits of developmental disabilities, siblings of probands are not normal control subjects. Comparisons of cases of autistic disorder and siblings and groups of people with developmental disabilities merit review (Table 3), but not as case-control studies of autistic disorder and normal control subjects (Table 2). Thus, normal control subjects are needed to for case-control studies of autistic disorder.

Fourth, a rating of any obstetric complication is needed for the odds ratio (Eq. 1). Many fine studies did not publish the raw data for the presence of any obstetric complication. Studies with data about specific obstetric complications can be utilized for future analyses of specific obstetric complications. Several studies used weighted scales for obstetric complications without raw data on obstetric complications. Those studies may be included in future studies of weighted scales to assess obstetric complications in autistic disorder and related conditions. Many different scales were used by various investigators. Since the obstetric complication scales vary widely, secondary analyses of publications of weighted scales will be impeded by the absence of uniformity among the different measurements. Many studies were excluded from analysis in the current study due to the absence of raw data about the presence of any obstetric complication in cases and controls.

Thus, many studies were excluded from our quantitative analysis of case-control studies of autistic disorder and obstetric complications due to the absence of raw data, the absence of cases of autistic disorder the absence of normal controls without autistic disorder, and the absence of an overall rating of the presence of any obstetric complication.

Strategies for Comprehensive Meta-analyses of Obstetric Complications and Autism

We can learn from the advances obtained through meta-analyses of obstetric complications and schizophrenia. In particular future quantitative analysis of specific obstetric complications and autism is needed. Additional studies to include the gradations reflected by some weighted scales of obstetric complications are needed. Analyses are needed to reflect the scaled severity, e.g., mild, moderate, and severe, of obstetric complications. Ultimately an international collaborative meta-analysis of the individual patient data of all researchers with raw data on obstetric complications diagnosed with established measures and autism diagnosed with optimal instruments (Lord *et al.* 2000; Lord *et al.* 1994) will facilitate a data base with an adequate sample size to tease out evidence to determine whether or not the pathophysiology of autism involves neurodevelopmental impairments. Written informed consent from each patient will be needed to undertake this project (Verdoux *et al.* 1997).

Limitations of this Study

There are several limitations to this study. Many articles published over the past century were reviewed in an attempt to locate all case-control studies of autistic disorder and obstetric complications (Brašić and Holland 2006). Thus, we undertook a comprehensive review of the topic of obstetric complications in autism. Undoubtedly, we have overlooked some studies. We ask our colleagues to inform us of other studies to include in future meta-analyses of obstetric complications in autistic disorder. Reviewing the articles led to a profound appreciation of the extensive work performed by researchers on obstetric complications in autism in the past century. While terminology has evolved over the past century, we used our best clinical judgment about including data from articles in quantitative reviews. In general we interpret "childhood schizophrenia" to indicate a condition different from autistic disorder. Therefore, we excluded reports of schizophrenia from these reviews about autistic disorder. Nevertheless, our inclusion of studies may be broad. We have not restricted analyses to those few studies using contemporary diagnostic instruments because we sought to utilize as much genuine data about obstetric complications in autistic disorder as possible. Future studies may reasonably require contemporary valid and reliable instruments for autistic disorder and obstetric complications.

Choice of appropriate control groups is critical for the interpretation of the results. Incomplete records hinder analyses of studies. For example, Levy *et al.* (1988) omitted three cases of autism from analysis of their case-control study because the records were illegible. This may introduce a bias to their study. Levy *et al.* (1988) utilized children without autism referred to their developmental disabilities clinic as the control group. Thus, their control group included children with Down syndrome, De Lange syndrome, Lowe syndrome, seizure disorders, spastic quadriplegia, and deafness/blindness. They conclude that there are more obstetric complications in this control group. Clearly the control group included children with genetic and medical conditions presenting early in gestation. Many of these children were apparently markedly damaged since early in gestation. Obstetric complications are likely in this

control group of children with severe genetic (Brašić *et al.* 2003) and medical disorders. Since Levy *et al.* (1988) did not publish the raw data for their study, we lacked the needed numerical data to include this data set for further analysis.

This study demonstrates the need for publication of full data sets by researchers. As demonstrated by the reviews of obstetric complications and schizophrenia (Geddes and Lawrie 1995; Verdoux *et al.* 1997) and autism (Brašić and Holland 2006), published studies frequently lack the data needed for further analyses. Some editors and publishers discourage the publication of complete data sets. However, the practice of publishing only the summary statistics of scientific studies limits the usefulness of the research. Although investigation of relationships between obstetric complications and schizophrenia or autism was not a goal of some research studies reviewed for the current project (Brašić and Holland 2006), valuable data to investigate the relationship between obstetric complications and autism was obtained during those studies. Unfortunately much valuable data cannot now be used because it is unavailable. We encountered many studies in our review (Brašić and Holland 2006) without publication of the needed data. We encourage authors, editors, and publishers to publish complete data sets to facilitate the work of future investigators. Some studies cannot be repeated. Other scientists may be able to utilize data from completed studies. Prompt publication of the complete data set may facilitate the identification and correction of errors in the final publication. Unfortunately, final publications of well-conducted studies contain apparently erroneous tabulation of obstetric complications (Knobloch and Pasamanick 1962, 1975). For example, Knobloch and Pasamanick (1975) report odd numbers of percentages of obstetric complications in groups of 50 each. In fact, percentages of conditions in 50 subjects are always even. This published data cannot be included in further analyses since there are apparent errors (Knobloch and Pasamanick 1975, Table 1, page 185). Therefore, we beseech our colleagues, their editors, and their publishers, to publish full data sets. The publication of data sets will facilitate further investigation by future researchers. While collaboration among researchers is a desirable practice, it is a challenge to accomplish. If researchers publish complete data sets, then future researchers will have access to data that may be impossible to obtain.

Future Research on Obstetric Complications and Autism

Advances in the elucidation of the relationship between obstetric complications and schizophrenia (Geddes and Lawrie 1995; Verdoux *et al.* 1997; Cannon *et al.* 2002) provide clues about research strategies to apply to obstetric complications and autism and other developmental disabilities. Specifically qualitative and quantitative reviews of autism and both (1) specific obstetric complications and (2) weighted scales of obstetric complications will likely be productive. International collaborations between investigators to share raw data likely will help to increase the sample size to allow refinements in study questions including the use of logistic regression (Verdoux *et al.* 1997). Limiting studies to those meeting refined inclusion criteria, including controlled prospective population-based cohorts, will likely improve the quality of the data (Cannon *et al.* 2002). Future studies may expand prenatal obstetric complications to include maternal exposures, including maternal phenylketonuria (Szatmari *et al.* 1998). Several hypotheses have been proposed to explain

possible roles between obstetric complications and autism (Szatmari *et al.* 1998). (1) Autism may cause physiological changes in the fetus to result in the obstetric mishaps (Szatmari *et al.* 1998). (2) Other genetic or environmental influences may result in obstetric complications (Szatmari *et al.* 1998). (3) Obstetric complications may directly affect the fetus to result in autism and other pervasive developmental disorders (Szatmari *et al.* 1998). Future studies may tease out the data to determine the appropriate theory. The use of qualitative and quantitative reviews offers promise to clarify the relationship between autism and obstetric complications.

Future research is needed to clarify the association of obstetric complications with other pervasive developmental disorders, such as Asperger and Rett syndromes, and with other developmental disorders, such as Down, Lesch-Nyhan, and Tourette syndromes. A clinical study of a hundred males with Asperger syndrome found that almost a third had pregnancy complications and almost two thirds had perinatal complications (Cederlund and Gillberg 2004). These observations suggest obstetric complications are an important event in many individuals with Asperger syndrome. Qualitative and quantitative reviews of obstetric complications and Asperger syndrome will likely elucidate gender and other effects. Qualitative and quantitative reviews of obstetric complications and other developmental disorders will likely demonstrate associations. Thus, this form of secondary analyses of studies about obstetric complications and anomalies of development will likely advance the knowledge about developmental disorders.

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