Prevalence of Autism Spectrum Disorder in Adolescents Born Weighing <2000 Grams

AUTHORS: Jennifer A. Pinto-Martin, PhD, MPH,[a] Susan E. Levy, MD,[b] Judith F. Feldman, PhD,[c] John M. Lorenz, MD,[d] Nigel Paneth, MD, MPH,[e] and Agnes H. Whitaker, MD[c]

[a]University of Pennsylvania School of Nursing and School of Medicine, Philadelphia, Pennsylvania; [b]Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; [c]Division of Child and Adolescent Psychiatry, Department of Psychiatry, Columbia University Medical Center, New York State Psychiatric Institute, New York, New York; [d]Department of Pediatrics, College of Physicians and Surgeons, Columbia University, New York, New York; and Departments of [e]Epidemiology and Pediatrics and Human Development, College of Human Medicine, Michigan State University, East Lansing, Michigan

KEY WORDS
low birth weight, preterm, autism spectrum, screening, diagnosis, outcome

ABBREVIATIONS
LBW—low birth weight
ASD—autism spectrum disorder
DAWBA—Development and Well-being Assessment
NBHS—Neonatal Brain Hemorrhage Study
SCQ—Social Communication Questionnaire
ASSQ—Autism Spectrum Screening Questionnaire
ADI-R—Autism Diagnostic Interview–Revised
ADOS—Autism Diagnostic Observation Schedule

Dr Pinto-Martin (the principal investigator) had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Pinto-Martin, Paneth, Levy, Whitaker, and Feldman were responsible for study concept and design; Drs Pinto-Martin, Paneth, Levy, and Whitaker performed the acquisition of data; Drs Feldman and Paneth conducted the statistical analysis; Drs Pinto-Martin, Paneth, and Whitaker obtained funding; and all authors were responsible for analysis and interpretation of data, drafting of the manuscript, and critical revision of manuscript for important intellectual content.

www.pediatrics.org/cgi/doi/10.1542/peds.2010-2846

doi:10.1542/peds.2010-2846

Accepted for publication Jul 20, 2011

Address correspondence to Jennifer A. Pinto-Martin, PhD, MPH, University of Pennsylvania School of Nursing and School of Medicine, ClaireM. Fagin Hall, 418 Curie Blvd, Philadelphia, PA 19104-4217. E-mail: pinto@nursing.upenn.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

Funded by the National Institutes of Health (NIH).

WHAT'S KNOWN ON THIS SUBJECT: Low birth weight and/or prematurity are considered to be risk factors for autism spectrum disorders, largely on the basis of retrospective studies or prospective studies that have used screening rather than diagnostic instruments.

WHAT THIS STUDY ADDS: This is the first study of the prevalence of autism spectrum disorders in a prospectively followed low birth weight population using validated diagnostic instruments. The 5% estimated prevalence rate found was ~5 times the rate reported in the general population.

abstract

OBJECTIVE: To estimate the diagnostic prevalence of autism spectrum disorders (ASDs) in a low birth weight (LBW) cohort.

METHODS: Participants belonged to a regional birth cohort of infants ($N = 1105$) born weighing <2000 g between October 1, 1984, and July 3, 1989, and followed up by periodic assessments to 21 years of age. At 16 years ($n = 623$), adolescents were screened for ASD using a wide net (previous professional diagnosis of an ASD or a score above a liberal cutoff on the Social Communication Questionnaire or the Autism Spectrum Symptoms Questionnaire). At 21 years ($n = 189$), 60% of screen positives and 24% of screen negatives were assessed for diagnoses of ASD by the Autism Diagnostic Observation Schedule or the Autism Diagnostic Interview–Revised.

RESULTS: Samples retained at ages 16 and 21 years were representative of samples assessed at earlier ages except for lower levels of social risk. Of positive screens, 11 of 70 had ASD; of negative screens, 3 of 119 had ASD. The fractions of the 2 screening groups with ASD (14.3% in screen-positives and 2.5% in screen negatives) were weighted by fractions of screen-positives and screen-negatives among the adolescents (18.8% and 81.2%, respectively). This calculation produced an estimated prevalence rate of ASD in the entire cohort of 5% (31 of 623).

CONCLUSIONS: The diagnostic prevalence of ASD in this LBW preterm cohort was higher than that reported by the Centers for Disease Control and Prevention for 8-year-olds in the general US population in 2006. *Pediatrics* 2011;128:883–891

Low birth weight (LBW) and prematurity are established risk factors for cognitive and motor disability.[1,2] The prevalence of neurodevelopmental impairment increases with diminishing birth weight and gestational age.[3] As survival of the smallest and most immature infants improves, impaired survivors represent an increasing public health challenge.

Emerging evidence suggests that LBW may also be a risk factor for autism spectrum disorders (ASDs). Retrospective studies have suggested an association between LBW and/or preterm birth and risk for ASD.[4–10] Prospective studies in children[11–13] and adolescents[3,14–16] have supported this suggestion. Most prospective studies, however, have determined risk for ASD on the basis of screening instruments rather than a definitive diagnosis. Only 1 prospective study to date has assessed the actual diagnostic prevalence of ASD in children born prematurely.[17,18] In that study, 219 parents of 11-year-olds born at the extremely low gestational age of <26 weeks in the United Kingdom and Ireland were interviewed by telephone or responded to an online survey of a multipurpose structured psychiatric interview, the Development and Well-being Assessment (DAWBA).[19] Using this instrument, the prevalence of ASD in births <26 weeks was reported to be 8%. Such extreme prematurity, however, affects <0.25% of all US births.[20]

This report presents the screening and diagnostic prevalence of ASD in a large population-representative cohort of adolescents born weighing between 500 and 2000 g, a weight interval that represents ~3% of US births.[21]

METHODS

Neonatal Brain Hemorrhage Study Cohort

The study sample was drawn from the Neonatal Brain Hemorrhage Study (NBHS) cohort, consisting of all infants admitted to 3 hospitals that together cared for 85% of births <2000 g in 3 central New Jersey counties from October 1, 1984, to July 30, 1987.[22] At that time, these 3 counties were demographically comparable to the nation as a whole, except for having a slightly higher per capita income and slightly lower proportion of minorities.[22] This cohort was prospectively enrolled at birth and reassessed at ages 2,[23,24] 6,[25,26] 9,[27,28] 16,[29,30] and 21 years. All enrolled families spoke English.

Two-Stage Design and Sampling Methods

The prevalence of ASD in the NBHS cohort was estimated by using a 2-stage design. In the first stage, a screening for ASD using parent questionnaires was conducted at the 16-year follow-up. In the second stage, at the 21-year follow-up, a diagnostic assessment for ASD was conducted with young adults recruited from all those who screened positive in the first stage and from a systematically obtained sample of those who screened negative in the first stage. Lists of screened negative potential recruits were initially selected at random in batches on the basis of year of birth (to ensure minimum appropriate age of participants), stratified according to gender to match the male:female ratio of screen-positives for that birth year. When numbers of screen-negative recruits fell short for a given birth year, additional recruits were drawn from all remaining screen-negatives of the appropriate gender without respect to birth year.

First Stage: Screening Procedure for ASD (at 16 Years of Age)

As part of a larger psychiatric follow-up,[29] adolescents were assessed for symptoms of ASD by using the Social Communication Questionnaire (SCQ), previously known as the Autism Screening Questionnaire,[31] and the Autism Spectrum Screening Questionnaire (ASSQ).[32] Adolescents' parents were also asked whether a professional had ever diagnosed their child with an ASD (autism, Asperger syndrome, or pervasive developmental disorder [not otherwise specified]). Screening data were obtained primarily by questionnaires collected at a home visit (499 [80%]) and the remainder by mail and/or telephone (127 [20%]).

A participant in the 16-year follow-up was considered "screen-positive" if he or she met any of the following criteria: (1) a score of ≥9 on the SCQ; (2) a score of ≥12 on the ASSQ; or (3) a history of professional diagnosis of ASD. The screen was designed to cast as wide a net as possible, so the cutoff points used were lower than the customary cutoff points of 15 for the SCQ[31] and 22 for the ASSQ.[32]

Second Stage: Recruitment and Diagnostic Procedure

Young adults were located by using tracking information available from earlier follow-ups; when necessary, Accurint, a national tracking system, was used. In some cases, parents facilitated contact.

The diagnostic instruments used were: (1) the Autism Diagnostic Interview–Revised (ADI-R)[33] (administered to parents); and (2) the Autism Diagnostic Observation Schedule (ADOS, module 4) (administered to the young adults).[34] Both the ADIR and the ADOS are well-validated instruments widely used in research. The validity of these tools may be compromised in the circumstance of severe to profound disability (eg, mental age < 2 years).[35,36] In this circumstance, additional information obtained from clinical history can be combined with information from the ADI-R and/or ADOS to inform a best-estimate diagnosis using the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*

criteria.[37] Two research associates, who were blind to screening status and research reliable in the administration and scoring of the diagnostic instruments, completed the assessments under the supervision of the director of the Regional Autism Center (Dr Levy). In-person assessments took place at the Children's Hospital of Philadelphia or at the Children's Hospital of Philadelphia Specialty Care Center in Princeton, New Jersey. For the ADIR, scores needed to be above published threshold scores on each of 4 domains: (1) reciprocal social interaction; (2) communication; (3) restricted, repetitive, stereotyped patterns of behavior; and (4) abnormality of development evident at or before 36 months.[38] For the ADOS, the total score on the communication and social domains needed to be above the published threshold for an ASD.[39]

Of the total 189 patients evaluated at 21 years of age, data were available from both the ADOS and the ADI-R on 144 (76%). An additional 75 had data from either the ADOS alone ($n = 10$) or the ADI-R alone ($n = 65$). Most of those evaluated with the ADIR alone ($n = 62$) had distance or scheduling issues that precluded an in-person ADOS evaluation; the remaining 3 patients were evaluated only by parental interview using the ADI-R because they were severely disabled.

Human Subjects Consideration

This study was approved by the institutional review board of the Children's Hospital of Philadelphia and the New York State Psychiatric Institute. Consent was obtained from the participating young adults (or their legal guardians, as applicable) and their families.

Statistical Analysis

Two sets of analyses addressed attrition issues. The first set compared those who were screened as adolescents to the remaining eligible adolescents on basic sample characteristics shown in Table 1 using t tests for continuous measures and χ^2 tests for categorical ones. The second set determined whether sample loss between adolescence and young adulthood was conditional on ASD screening status. These analyses were conducted using 2 (positive versus negative screen status) by 2 (retained in sample versus not retained) analysis of variances (for continuous dependent measures), logistic regressions (for dichotomies), and multinomial regressions (for categorical variables having >2 categories). Significant interactions and main effects are reported; consistent with general statistical practice, follow-up comparisons between retention groups within screen status strata were only undertaken where there were significant interactions.

Prevalence in the entire cohort was calculated by weighting the proportions of screen-positives and screen-negatives found to have ASD as young adults by the proportion of screen-positives and screen-negatives in the adolescent sample.

The relation of the ASD diagnosis to basic sample characteristics was examined by using χ^2 statistics. SPSS software[40] was used for all analyses; the criterion for statistical significance was set at a 2-tailed α value of 0.05.

TABLE 1 Sample Characteristics: LBW Adolescents Screened for ASD at 16 Years of Age and Others Eligible but Not Screened for ASD at 16 Years of Age

	16-y-Old Sample Screened for ASD ($n = 623$)	Others Eligible at 16 y of Age ($n = 239$)[a]
Maternal social risk, %[b,c]	43.9	65.1
Minority status, %[b]	27.0	40.6
Less than high school education, %[b,d]	12.0	33.5
Age younger than 19 y, %[b,e]	5.6	16.0
Unmarried, %[b,f]	22.9	46.4
Receiving public assistance, %[b,g]	21.6	41.7
Male gender, %	49.3	52.3
Birth weight, mean ± SD, g	1475.3 ± 353.3	1492.7 ± 377.9
≥1500 , %	52.5	54.4
1000–1499, %	35.3	32.2
<1000, %	12.2	13.4
Gestational age, mean ± SD, completed wk	31.2 ± 3.1	31.3 ± 3.3
>36 wk, %	3.7	4.2
34–36 wk, %	19.3	18.9
32–33 wk, %	22.3	24.4
28–31 wk, %	42.1	40.3
<28 wk, %	12.7	13.2
Small for gestational age, %[h]	32.3	34.7
Bronchopulmonary dysplasia, %[i]	5.3	4.2

[a] Surviving and nonadopted LBW cohort members at age 16 years who were lost to follow-up ($n = 151$), who refused participation ($n = 83$), or who were assessed at age 16 years but were missing all 3 components of the ASD screen ($n = 5$). Of these last 5 patients, 3 were disabled mentally (IQ < 55) and/or could not walk without assistance. Thirty-one survivors were not eligible to be seen at age 16 years because they had been adopted.

[b] Age 16 years sample screened for ASD versus others eligible at age 16 years: $P \leq .001$, unadjusted for multiple tests.

[c] Mother's social risk at time of participant's birth. One or more of the components listed in the 5 successive rows.[47] When ≥1 components of risk were missing, the total was pro-rated by multiplying 5 by the proportion of nonmissing risk factors that were positive for risk.

[d] Not present for all cases; column n values are 559 and 182, respectively.

[e] Not present for all cases; column n values are 622 and 238, respectively.

[f] Not present for all cases; column n values are 538 and 168, respectively.

[g] Not present for all cases; column n values are 509 and 168, respectively.

[h] Lowest 10th percentile of weight for weeks of postconception age, using norms of Yudkin et al.[48]

[i] Defined as the need for oxygen and/or ventilatory support at 36 weeks' postmenstrual age. Not present for all cases; column n values are 620 and 238, respectively.

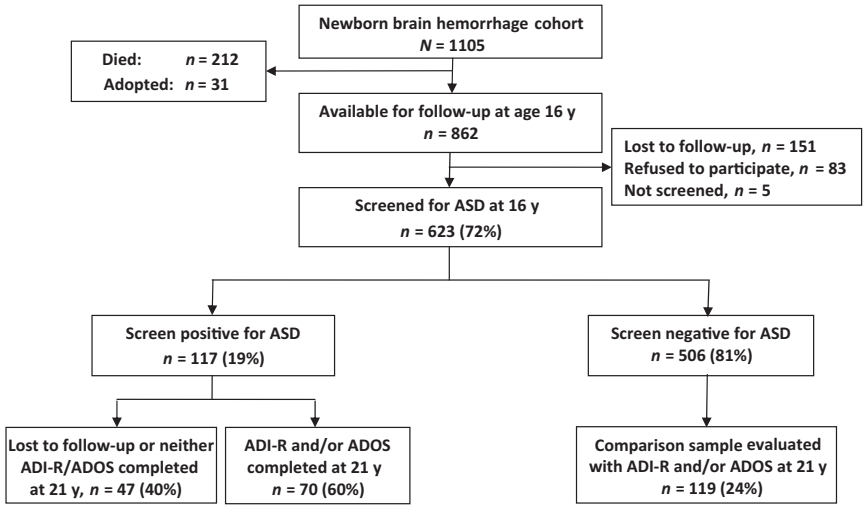

FIGURE 1
Sample attrition.

RESULTS

Sample Attrition

Figure 1 shows the attrition of the sample from birth to young adulthood. By 16 years of age, 862 adolescents were considered eligible for follow-up; of these, 628 participated. All but 5 participating families completed the autism screening instruments at that time, leaving a final sample of 623 (72%; Fig 1). Of these, 80.7% completed all 3 parts of the screen and very few (8.0%) completed only 1 part. At 21 years of age, 60% of the screen-positive group ($n = 70$) was evaluated for an ASD diagnosis at 21 years of age (Fig 1), whereas 40% ($n = 47$) were lost to follow-up because of inability to contact ($n = 11$), inability to schedule because of time/distance constraints ($n = 27$), or refusal ($n = 9$).

Table 1 shows the characteristics of adolescents screened for ASD and those eligible but not screened at 16 years of age. The 2 groups differed significantly only with respect to lower maternal social risk at birth in those screened.

Table 2 shows the characteristics of those who were and were not retained in the sample from 16 to 21 years of age according to screen status. These data address the possibility that characteristics of those retained (versus not retained) were dependent on screen status. With the exception of 1 component of maternal birth social risk (ie, receipt of public assistance), this was not the case. For this 1 variable, there was a significant interaction between screen status and sample retention (Wald $\chi^2_1 = 4.92$, $P = .027$) such that there was a greater discrepancy between retained and not-retained among the screen-positives, although those retained had lower percentages of those receiving public assistance in both groups (Table 2 legend).

Significant main effects of retention, irrespective of screen status, were all in the expected direction, namely that those not retained in the sample at 21 years of age ($n = 434$) were more likely than those retained in the sample ($n = 189$) to be at greater risk for suboptimal neurodevelopmental outcomes (Table 2 legend).

Significant main effects of screen status, irrespective of sample retention, were similarly all in the same direction. Those who screened positive at 16 years of age ($n = 117$) compared with those who screened negative ($n = 506$) were more likely to be at greater risk for suboptimal neurodevelopmental outcomes (Table 2 legend). Notably, however, boys were only marginally more common among the screen-positives (56.4%) than among the screen-negatives (47.6%; $P < .10$), indicating that the gender matching of screen-negatives to screen-positives was fairly successful. Another important characteristic of the screen positive and screen-negative samples (data not shown in Table 2)—namely, the percentage of families in each group who were interviewed by telephone because of scheduling and distance issues—also did not differ across the groups (32.9% and 34.5%, respectively).

Screening Prevalence at 16 Years of Age

Of the 623 adolescents screened for ASD, 117 (18.8%) were screen-positive by 1 or more of the 3 screening criteria. Of the 117 screen-positives, 62 were positive on the SCQ alone, 26 were positive on the ASSQ alone, and 6 were positive solely by parent report of a professional diagnosis. Sixteen were positive on 2 parts, and 7 were positive on all 3 parts of the screen.

Diagnostic Prevalence of ASD

Of the 70 young adults examined who were screen-positive as adolescents, 11 were found to have ASD (Table 3). Of the 119 screen-negatives, 3 were found to have ASD.

To estimate the prevalence of ASD cases in the original sample of 623 adolescents, the numbers of young adults found to have ASD in the 2 screening groups (14.3% among the screen-positives and 2.5% among the screen-negatives) were weighted by the fractions of screen-positives and negatives among the adolescents (18.8% and 81.2%, respectively) as shown in Table 3. Thus, the best estimate of the prevalence of ASD in the entire adolescent LBW cohort is 5.0% (31 of 623).

TABLE 2 Birth Risk Factors and 16-Year Neurodevelopmental Status in Screen-Positives and Screen-Negatives According to Sample Retention From 16 to 21 Years

	Screened Positive at 16 y of Age		Screened Negative at 16 y of Age	
	Retained in Sample ($n = 70$)	Not Retained in Sample ($n = 47$)	Retained in Sample ($n = 119$)	Not Retained in Sample ($n = 387$)
Perinatal risk factors				
HUS status				
NA, % (reference category)	58.6	66.0	84.0	81.1
Germinal matrix and/or intraventricular hemorrhage, %	18.6	14.9	14.3	14.0
Parenchymal lesion and/or ventricular enlargement, %	22.9	19.1	1.7	4.9
Birth social risk: ≥1 of 5 risk conditions, %[a]	38.6	73.9	26.1	46.8
Minority status, %	18.6	53.2	11.8	30.0
Less than high school education, %[b]	11.9	26.2	6.5	12.0
Age < 19 y, %	2.9	10.9	1.7	6.7
Unmarried, %[c]	15.4	42.5	8.2	26.3
Receiving public assistance, %[d]	16.1	51.3	14.7	21.1
Male gender, %	54.3	59.6	56.3	45.0
Birth weight, mean ± SD, g	1420 ± 395	1404 ± 370	1507 ± 348	1484 ± 344
≥1500 g, % (reference category)	50.0	44.7	55.5	53.0
1000–1499 g, %	30.0	40.4	33.6	36.2
<1000 g, %	20.0	14.9	10.9	10.9
Gestational age, mean ± SD, completed wk	31 ± 3	31 ± 3	31 ± 3	31 ± 3
>36 wk, % (reference category)	5.7	0.0	1.7	4.4
34–36 wk, %	20.0	17.0	21.0	18.9
28–31 wk, %	48.6	38.3	42.0	41.3
<28 wk, %	15.7	14.9	16.0	10.9
Small for gestational age, %[e]	34.3	31.9	22.7	34.9
Bronchopulmonary dysplasia (%)[f]	11.6	6.4	5.0	4.2
Neurodevelopment at age 16 y				
Disabled cognitively or motorically, %[g]	18.6	23.4	0.8	1.3
Inability to walk without assistance, %[h]	12.9	12.8	0.8	1.3
Severe intellectual impairment, %[i]	14.3	23.4	0.0	0.8

Significant interaction between screen status and retention status. The only significant interaction involved a greater disparity between retained and not retained in the percentage of mothers who received public assistance at the time of their child's birth among the screen-positives than among the screen-negatives (Wald $\chi^2_1 = 4.92$, $P = .027$). In the screen-positives, the percentage of mothers receiving assistance in those retained was 35.2 percentage points lower than in those not retained ($\chi^2_1 = 14.17$, $P < .001$), whereas among the screen-negatives this percentage was 6.4 percentage points lower in those retained than in those not retained ($\chi^2_1 = 1.86$, $P = .172$).

Significant main effects for retention in sample, irrespective of screen status. Those not retained ($n = 434$) compared with those retained ($n = 189$) were more likely to be male and small for gestational age (55.6% vs 46.5%, and 34.6% vs 27.0%, respectively; both $P < .05$). They were also more likely to have ≥1 social risk factors (49.7% vs 30.7%; $P < .001$). Of the social risk factors, those not retained were more likely to be of minority status (32.5% vs 14.3%; $P < .01$) and to be unmarried (28.0% vs 11.0%; $P < .001$).

Significant main effects for screen status, irrespective of retention in sample. Those who screened positive at age 16 years ($n = 117$) compared with those who screened negative ($n = 506$) had slightly lower mean birth weights (1413.6 vs 1489.6 g; $P < .05$) and were more likely to have parenchymal lesions or ventricular enlargement as determined by neonatal head ultrasound (21.4% vs 4.2%; $P < .001$). At the time of the adolescents' birth, the mothers of those who screened positive were more likely than the mothers of those who screened negative to have ≥1 social risk factors (52.6% vs 41.9%; $P < .001$). They were more likely to be a member of a minority (32.5% vs 25.7%; $P < .01$), to have less than a high school education (17.4% vs 10.7%; $P < .05$), to be unmarried (25.7% vs 22.2%; $P < .05$), and to be receiving public assistance (29.7% vs 19.6%; $P < .001$). The adolescents were also more likely to be disabled (either cognitively or motorically) and more likely to be nonambulatory and severely mentally disabled (20.5% vs 1.2%, 12.8% vs 1.2%, and 18.8% vs 0.6%, respectively; all, $P < 0.001$) at age 16 years. Males were only marginally more common among the screen-positives (56.4%) than among the screen-negatives (47.6%) ($P < .10$).

NA indicates not available.

[a] Components are listed in the 5 succeeding rows. When ≥1 components of risk were missing, the total was pro-rated by multiplying 5 by the proportion of nonmissing risk factors that were positive for risk.

[b] Not present for all cases; column *n* values are 67, 42, 107, and 343, respectively.

[c] Not present for all cases; column *n* values are 65, 40, 93, and 335, respectively.

[d] Not present for all cases; column *n* values are 62, 39, 95, and 313, respectively

[e] In the lowest decile of the distribution of weight for gestational age using the gender-specific norms of Yudkin et al.[48]

[f] Defined as the need for oxygen and/or ventilatory support at 36 weeks postmenstrual age. Not present for all cases; column *n* values are 69, 47, 119, and 385, respectively.

[g] Severe intellectual impairment or inability to walk without assistance.

[h] Item 5 of the Activities Limitations Questionnaire.[49]

[i] For those seen in person at age 16 years, Wechsler Abbreviated Scale of Intelligence, Full-Scale IQ (FSIQ)[50] <55 or untestable and ≥2 domains of the Vineland Adaptive Behavior Scale (VABS)[51] scored as low or moderately low; for those assessed by telephone interview at that age, average of FSIQ scores from testing at 6 and/or 9 years <55 and ≥2 subdomains of the VABS scored as low or moderately low, or when FSIQ data were unavailable from earlier waves of testing, a composite score of the VABS from the telephone interview <55.

Characteristics of the Cases

Of the 14 cases, 3 were screen-negative as adolescents and 11 were screen-positive (Table 4). All 14 cases had an ADI-R completed by a parent. Six did not have ADOS scores; 5 of these could only be interviewed by telephone, precluding an ADOS assessment, and 1 was assessed using the ADOS, but the results were considered invalid because of physical disability. Of the 8 cases with a completed ADOS, 2 met the threshold on both the ADI-R and ADOS, 1 on only the ADI-R, and the rest on only the ADOS.

TABLE 3 Estimated Prevalence of ASD in Total Cohort ($N = 623$) Based on Findings in 198 Participants With Diagnostic Assessment at 21 Years of Age

	ASD Prevalence in Young Adults by Screening Status, % (*n*/*N*)	Screening Status Prevalence in Total Cohort, % (*n*/*N*)	Estimated *n* and Prevalence of ASD in Total Cohort
Screen-positive	15.7 (11/70)	18.8 (117/623)	18 (15.7% × 117)
Screen-negative	2.5 (3/119)	81.2 (506/623)	13 (2.5% × 506)
Total	7.0 (14/189)	—	5.0% (31/623)

TABLE 4 Characteristics of the ASD Cases

Case No.	21-y Assessment				Gender	16-y Assessment			
	ADI-R	ADOS	Age, mo[a]			FSIQ	VABSC	Riley Score[b]	Other DSM-IV Diagnoses[c]
			First Word	First Phrase					
Screen-negatives									
1	No diagnosis	ASD	<24	<33	Male	118	92	0	None
2	No diagnosis	ASD	21	21	Male	115	85	8	ODD
3	No diagnosis	ASD	17	19	Male	127	95	2	None
Screen-positives									
4	ASD	No dx	<24	Unknown	Female	112	65	11	None
5	No diagnosis	Autism	18	24	Female	99	81	12	Motor-vocal tics
6	ASD	Autism	30	45	Male	97	64	9	Tourette's syndrome
7	ASD	Not tested[d]	36	60	Male	77	45	7	Transient tic disorder; specific phobia
8	ASD	Not tested[d]	≥24	36	Male	76	56	7	ADHD; ODD; CD; social phobia
9	ASD	ASD	15	36	Female	72	64	7	ADHD
10	No diagnosis	ASD	36	48	Male	68	74	6	none
11	ASD	Not tested[d,e]	60	60	Male	Not tested[d,e]	39	—[d,e]	Not assessed[d,e]
12	ASD	Not tested[e]	36	36	Male	Not tested[e]	32	—[e]	Not assessed[e]
13	ASD	Not tested[d]	18	30	Male	Not tested[e]	54	—[d]	Not assessed[d]
14	ASD	Not tested[d]	36	45	Male	Not tested[e]	50	—[d]	Not assessed[d]

FSIQ indicates full-scale IQ (from the WASI); VABSC, Vineland Adaptive Behavior Scale Composite[51]; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; ODD, oppositional/defiant disorder; ADHD, attention deficit hyperactivity disorder; CD, conduct disorder.

[a] Based on ADIR scoring for items 9 (first word) and 10 (first phrase) where "normal" is <24 and <33 months, respectively.

[b] Scores ≥5 are in the top 10% of the Riley Motor Problems[52] distribution; they indicate some motor impairment.

[c] Ascertained at age 16 years with the Diagnostic Interview Schedule for Children/Parent Version–IV, using the threshold algorithm,[30]

[d] Assessed by telephone; no in-person assessments at this age.

[e] Severe motor impairment; nonambulatory.

The overall male to female gender ratio was 3.7:1 (11 boys, 3 girls). Sixty-four percent (9 of 14) were relatively high functioning and verbal (ie, phrase speech and IQ ≥70). Of the 11 cases who were screen-positive in adolescence, 6 were reported to have been diagnosed with ASD by a professional and 5 had not. For these 11 subjects, scores on the Weschler Abbreviated Scale of Intelligence at 16 years of age ranged widely, from 50 (the default score for those too cognitively impaired to be tested) to 112; their Vineland scores also varied widely, ranging from 32 to 81. By contrast, of the 3 cases who screened negative in adolescence, all IQ scores were at least 1 SD above the mean (≥115), whereas Vineland composite scores ranged from 85 to 95. None of these 3 cases met threshold on the ADI-R. Six of the 14 cases (42.9%) met criteria for at least 1 other psychiatric disorder at 16 years of age on the basis of a validated psychiatric interview.[30]

None of the basic sample characteristics in Table 1 were significantly related to a diagnosis of ASD, although there were marginal relations for gender and birth weight ($P < .10$). The percentage of boys having a diagnosis of ASD (9.9%) was larger than that of girls having a diagnosis (3.3%; $\chi^2_1 = 3.32$, $P = .07$). In addition,10.6% of those born weighing <1500 g had an ASD diagnosis compared with only 3.7% of those born weighing between 1500 and 2000 g ($\chi^2_1 = 3.68$, $P = .055$).

DISCUSSION

This is the first study to have estimated the prevalence of ASD in a prospectively followed LBW population using research-validated diagnostic instruments. ASD prevalence in this US population-representative cohort of LBW (<2000 g) adolescents was estimated to be 5%, a fivefold increase over that reported by the Centers for Disease Control and Pre-

vention for 8-year-olds in the US general population in 2006 (0.9%).[41] In addition, we found that 18.8% of the adolescents screened positive for ASD. Screening criteria were designed to maximize sensitivity, contributing to the high false-positive rate encountered. Nonetheless, 2.5% of those with ASD, notably high-functioning boys, were not picked up on screening.

As a group, the 14 subjects with ASD diagnosed in young adulthood seemed to be relatively high functioning in terms of IQ and spoken language. The proportion (63%) with an IQ of ≥70 (at least borderline intelligence) was higher than that of a recent population estimate of 45% for school-aged cases of ASD.[42] All of the cases here had developed phrase speech, which has recently been reported as absent in 10% to 20% of persons with ASD.[43] One possible reason for these apparent differences is that ASD associated with prematurity has a distinctive neurodevelopmental profile. Alternatively, a number of additional low-functioning ASD cases might have been diagnosed had the retention rate in the screen-positive group been greater. The greater retention of those with less overall social risk is consistent with this possibility. Addressing these alternative possibilities is beyond the scope of this report.

Prospective studies have reported high screening prevalence in LBW and/or premature toddlers ranging from 21%[13,44] to 37%[12] using the Modified Checklist for Autism in Toddlers. In prospective cohorts of older children (11 and 14–15 years), the screening prevalence was not quite so high (<1% to 3.7%), but some studies did not use autism-specific screens.[16,45,46] Johnson et al[17] recently reported screening and diagnostic prevalence of ASD of their prospective cohort of all births <26 weeks in 1995 in the United Kingdom and Ireland. Of the survivors, 71% were assessed at 11 years using the SCQ screening instrument and a clinical best estimate diagnostic package, the DAWBA. Screening prevalence was 15.8%, comparable to that found in our study. Diagnostic prevalence was 8%. It is not clear whether restriction of the Johnson et al sample to extremely low gestational age survivors and/or features of the DAWBA account for the higher diagnostic prevalence rate in their study.

To date, the only epidemiologic study to estimate prevalence rates of ASD in adults born prematurely is that of Moster et al.[2] Using linked compulsory national registries in Norway, they found that the rates of disability payments for ASD among adults 20 to 36 years old in 2003 (born between 1967 and 1983) rose significantly as gestational ages declined. Rates in that study rose from 0.05% among those born at term (gestational age ≥ 37 weeks) to 0.6% among those born at gestational ages of 23 to 27 weeks. Although these rates were considerably lower than the 5% found here, the inverse relation of gestational age to ASD of sufficient severity to warrant disability payments in adulthood highlights the long-term public health impact of prematurity on ASD-associated disability.

Strengths

In this study, rigorous diagnostic procedures were used to estimate the diagnostic prevalence of ASD in AN LBW population. Given that the present cohort was not restricted to those at the lower extremes of birth weight and gestational age, generalizability of our findings is broader than is often the case in LBW/preterm follow-up studies. Moreover, because this cohort is population based, findings are likely to have greater generalizability than those from hospital-based cohorts.

Limitations

The proportion lost to follow-up over the 5-year period between the adolescent and young-adult follow-up was relatively high. However, the differences in characteristics between those retained in the young adult sample versus those not retained were, for the most part, the same among those who screened positively and negatively in adolescence. Some adolescents did not receive all parts of the 3-part screen. In addition, not all young adults were assessed using both the ADIR and ADOS. ASD diagnosis at an earlier follow-up age might have increased participant availability for the in-person ADOS evaluations. Finally, the lack of a normal birth weight control group allowed comparison only with general population estimates of ASD prevalence.

CONCLUSIONS

The estimated prevalence of ASD diagnoses in this LBW cohort was 5 times the prevalence reported by the Centers for Disease Control and Prevention for 8-year-olds in the general US population in 2006. This prospective study, using rigorous diagnostic procedures, confirms that the rate of ASD is elevated among LBW/preterm survivors.

ACKNOWLEDGMENTS

Funding for this study was provided by National Institutes of Health grant R01MH073807 (to Dr Pinto-Martin, primary investigator) (March 1, 2009, to February 28, 2010, to Drs Pinto-Martin and Levy; subcontract to Dr Whitaker, primary investigator, at Columbia University; to Drs Lorenz and Feldman; and to Dr Paneth, primary investigator, at Michigan State).

Administrative, technical, and material support was provided by Catherine Christman. Research clinical evaluations of the young adult participants were conducted by Michelle Petrongolo, MS, and Megan Carolan Tomkinson, MEd, from the Children's Hospital of Philadelphia. They received no compensation other than salary support through the grant.

REFERENCES

1. Boulet SL, Schieve LA, Boyle CA. Birth weight and health and developmental outcomes in US children, 1997-2005. *Matern Child Health J*. 2011;15(7):836–844
2. Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. *N Engl J Med*. 2008;359(3):262–273
3. Hack M, Taylor HG, Schluchter M, Andreias L, Drotar D, Klein N. Behavioral outcomes of extremely low birth weight children at age 8 years. *J Dev Behav Pediatr*. 2009;30(2):122–130
4. 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(4):514–519
5. Glasson EJ, Bower C, Petterson B, de Klerk N, Chaney G, Hallmayer JF. Perinatal factors and the development of autism: a population study. *Arch Gen Psychiatry*. 2004;61(6):618–627
6. Hultman C, Sparen P, Cnattingius S. Perinatal risk factors for infantile autism. *Epidemiology*. 2002;13(4):417–423
7. Bryson SE, Smith IM, Eastwood D. Obstetrical suboptimality in autistic children. *J Am Acad Child Adolesc Psychiatry*. 1988;27(4):418–422
8. Levy S, Zoltak B, Saelens T. A comparison of obstetrical records of autistic and nonautistic referrals for psychoeducational evaluations. *J Autism Dev Disord*. 1988;18(4):573–581
9. Wilkerson DS, Volpe AG, Dean RS, Titus JB. Perinatal complications as predictors of infantile autism. *Int J Neurosci*. 2002;112(9):1085–1098
10. Deykin EY, MacMahon B. Pregnancy, delivery, and neonatal complications among autistic children. *Am J Dis Child*. 1980;134(9):860–864
11. Limperopoulos C, Bassan H, Sullivan NR, et al. Positive screening for autism in expreterm infants: prevalence and risk factors. *Pediatrics*. 2008;121(4):758–765
12. Limperopoulos C, Bassan H, Gauvreau K, et al. Does cerebellar injury in premature infants contribute to the high prevalence of long-term cognitive, learning, and behavioral disability in survivors? *Pediatrics*. 2007;120(3):584–593
13. Kuban KC, O'Shea TM, Allred EN, Tager-Flusberg H, Goldstein DJ, Leviton A. Positive screening on the Modified Checklist for Autism in Toddlers (M-CHAT) in extremely low gestational age newborns. *J Pediatr*. 2009;154(4):535–540
14. Maimburg RD, Vaeth M. Perinatal risk factors and infantile autism. *Acta Psychiatr Scand*. 2006;114(4):257–264
15. Indredavik MS, Vik T, Heyerdahl S, Kulseng S, Fayers P, Brubakk AM. Psychiatric symptoms and disorders in adolescents with low birth weight. *Arch Dis Child Fetal Neonatal Ed*. 2004;89(5):F445–F450
16. Indredavik MS, Vik T, Skranes J, Brubakk AM. Positive screening results for autism in ex-preterm infants. *Pediatrics*. 2008;122(1):222; author reply 222–223
17. Johnson S, Hollis C, Kochhar P, Hennessy E, Wolke D, Marlow N. Autism spectrum disorders in extremely preterm children. *J Pediatr*. 2010;154(4):525–531.e2
18. Johnson S, Hollis C, Kochhar P, Hennessy E, Wolke D, Marlow N. Psychiatric disorders in extremely preterm children: longitudinal finding at age 11 years in the EPICure study. *J Am Acad Child Adolesc Psychiatry*. 2010;49(5):453–463
19. Goodman R, Ford T, Richards H, Gatward R, Meltzer H. The Development and Well-being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. *J Child Psychol Psychiatry*. 2000;41(5):645–655
20. O'Shea TM, Allred EN, Dammann O, et al. The ELGAN study of the brain and related disorders in extremely low gestational age newborns. *Early Hum Dev*. 2009;85(11):719–725
21. Martin JA, Hamilton BE, Sutton PD, et al. Births: final data for 2007. *Natl Vital Stat Rep*. 2010;58(24):1–86
22. Paneth N, Rudelli R, Kazam E, Monte WA. *Brain Damage in the Preterm Infant*. London, United Kingdom: MacKeith Press; 1994
23. Pinto-Martin JA, Riolo S, Cnaan A, Holzman C, Susser MW, Paneth N. Cranial ultrasound prediction of disabling and non-disabling cerebral palsy at age two in a low birthweight population. *Pediatrics*. 1995;95(2):249–254
24. Pinto-Martin JA, Dobson V, Cnaan A, Zhao H, Paneth NS. Vision outcome at age 2 years in a low birth weight population. *Pediatr Neurol*. 1996;14(4):281–287
25. Whitaker AH, Van Rossem R, Feldman JF, et al. Psychiatric outcomes in low birthweight children at age six: Relation to neonatal cranial ultrasound abnormalities. *Arch Gen Psychiatry*. 1997;54(9):847–856
26. Whitaker AH, Feldman JF, Van Rossem R, et al. Neonatal cranial ultrasound abnormalities in LBW infants: relation to cognitive outcomes at age six. *Pediatrics*. 1996;98(4 pt 1):719–729
27. Pinto-Martin JA, Whitaker AH, Feldman JF, Van Rossem R, Paneth N. Relation of cranial ultrasound abnormalities in low-birthweight infants to motor or cognitive performance at ages 2, 6, and 9 years. *Dev Med Child Neurol*. 1999;41(12):826–833
28. Pinto-Martin J, Whitaker A, Feldman J, et al. Special education services and school performance in a regional cohort of low-birthweight infants at age nine. *Paediatr Perinatal Epidemiol*. 2004;18(2):120–129
29. Whitaker AH, Feldman JF, Lorenz JM, et al. Motor and cognitive outcomes in nondisabled low-birth-weight adolescents. *Arch Pediatr Adolesc Med*. 2006;160(10):1040–1046
30. Whitaker A, Feldman JF, Lorenz JM, et al. Neonatal head ultrasound abnormalities in preterms and adolescent psychiatric disorders. *Arch Gen Psychiatry*. In press
31. Berument S, Rutter M, Lord C, Pickles A, Bailey A. Autism screening questionnaire: diagnostic validity. *Br J Psychiatry*. 1999;175:444–451
32. Ehlers S, Gillberg C, Wing L. A screening questionnaire for Asperger syndrome and other high-functioning autism spectrum disorders in school age children. *J Autism Dev Disord*. 1999;29(2):129–141
33. 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(5):659–685
34. Lord C, Risi S, Lambrecht L, et al. The autism diagnostic observation schedule-generic: a standard measure of social-communication deficits associated with autism spectrum disorders. *J Autism Dev Dis*. 2000;30(3):205–223
35. Saemundsen E, Juliusson H, Hjaltested S, et al. Prevalence of autism in an urban population of adults with severe intellectual disabilities: a preliminary study. *J Intellect Disabil Res*. 2010;54(8):727–735
36. Papanikolaou K, Paliokosta E, Houliaras G, et al. Using the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule-Generic for the diagnosis of autism spectrum disorders in a Greek sample with a wide range of intellectual abilities. *J Autism Dev Disord*. 2009;39(3):414–420
37. de Bildt A, Sytema S, Ketelaars C, et al. Interrelationship between Autism Diagnostic Observation Schedule-Generic (ADOS-G), Au-

tism Diagnostic Interview-Revised (ADI-R), and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) classification in children and adolescents with mental retardation. *J Autism Dev Disord*. 2004;34(2):129–137

38. Rutter M, Le Couteur A, Lord C. *ADIR: Autism Diagnostic Interview Revised Manual*. Los Angeles, CA: Western Psychological Services; 2003
39. Lord C, Rutter M, DiLavore P, Risi S. *Autism Diagnostic Observation Schedule Manual*. Los Angeles, CA: Western Psychological Services; 2002
40. SPSS I. *SPSS for Windows* [computer program]. Chicago, IL: SPSS, Inc; 2009
41. Autism and Developmental Disabilities Monitoring Network Surveillance Year 2006 Principal Investigators; Centers for Disease Control and Prevention (CDC). Prevalence of autism spectrum disorders—Autism and Developmental Disabilities Monitoring Network, United States 2006. *MMWR Surveill Summ*. 2009;58(10):1–20
42. Charman T, Pickles A, Simonoff E, Chandler S, Loucas T, Baird G. IQ in children with autism spectrum disorders: data from the Special Needs and Autism Project (SNAP). *Psychol Med*. 2011;41(3):619–627
43. Lord C, Risi S, Pickles A. Trajectory of language development in autistic spectrum disorders. In: Rice M, Warren S *Developmental Language Disorders: From Phenotypes to Etiologies*. Mahwah, NJ: Lawrence Erlbaum Associates; 2004:7–29
44. Johnson S, Marlow N. Positive screening results on the modified checklist for autism in toddlers: implications for very preterm populations. *J Pediatr*. 2009;154(4):478–480
45. Hack M. Adult outcomes of preterm children. *J Dev Behav Pediatr*. 2009;30(5):460–470
46. Elgen I, Sommerfelt K, Markestad T. Population based, controlled study of behavioural problems and psychiatric disorders in low birthweight children at 11 years of age. *Arch Dis Child Fetal Neonatal Ed*. 2002;87(2):F128–F132
47. Hack M, Taylor G, Klein N, Eiben R, Schatschneider C, Mercuri-Minich N. School-age outcomes in children with birth weights under 750 grams. *N Engl J Med*. 1994;331(12):753–759
48. Yudkin PL, Aboualfa M, Eyre JA, Redman CW, Wilkinson AR. New birthweight and head circumference centiles for gestation ages 24 to 42 weeks. *Early Hum Dev*. 1987;15(1):45–52
49. Cadman D, Boyle MH, Offord DR, et al. Chronic illness and functional limitation in Ontario children: Findings of the Ontario Child Health Study. *CMAJ*. 1986;135(7):761–767
50. Wechsler D. *Wechsler Abbreviated Scale of Intelligence (WASI)*. San Antonio, TX: Pearson Publishing; 1999
51. Sparrow SS, Cicchetti DV, Balla DA. *Vineland Adaptive Behavior Scales, 2nd ed. (Vineland-II)*. San Antonio, TX: PsychCorp; 2005
52. Riley GD. *Riley Motor Problems Inventory: Manual*. Los Angeles, CA: Western Psychological Services; 1976

ARTHRITIS AND EXERCISE: *My father has osteoarthritis and my mother rheumatoid arthritis. I call them frequently and ask what they have been doing. Almost invariably they report that they have not done much at all. Their approach to managing joint pain is to sleep in, rest, and avoid exercise. I am pretty sure that is not the regimen their physicians have recommended. I remind them that physical activity is good for joints. Unfortunately, they don't really believe that is true. My parents are not the only adults with arthritis who are not exercising. As reported in the* Los Angeles Times *(Health: August 31, 2011), in a study of 1,000 adults aged 49–84 with knee osteoarthritis, "only 13 percent of men and 8 percent of women met federal guidelines of 2.5 hours of moderate-intensity, low-impact activity each week." Something as simple as walking a dog can be beneficial. Part of the problem may be that initially, exercise can be a bit painful. The longer individuals put off exercising, the more likely it is they will experience some pain at the start of their exercise program. This leads to a vicious negative cycle. Exercise is not only good for joints but contributes to overall fitness and weight loss—both of which are beneficial. The best way to get adults such as my parents exercising again is not known. One approach might be to encourage them at the onset of their disease so that exercise becomes part of their daily routine. My own approach has been to remind my parents that their dog is obese and going stir-crazy. While they may not exercise for their own health, they love their dog and want to ensure her continued good health. So, after such a reminder, my mother will often take the dog for a walk. They both seem happier afterwards.*

Noted by WVR, MD