Pervasive Developmental Disorders in Preschool Children

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UTISM IS A SEVERE DEVELOPMENTAL DISORDER INVOLVING DEVIANCE AND OFTEN DELAY IN THE DEVELOPMENT OF LANGUAGE OR COMMUNICATION SKILLS; SOCIAL INTERACTIONS AND RECIPROCITY; AND IMAGINATION, PLAY, AND INTERESTS. Since the first epidemiological survey of autism was conducted in the mid 1960s in England, more than 30 surveys have been performed worldwide. Rates of autism typically have been reported in the range of 4 to 6 per 10000 although these figures increased in surveys conducted in the last 15 years. These estimates do not account for a large group of children falling short of strict diagnostic criteria for autism (pervasive developmental disorders [PDDs]) and whose development poses similar assessment and educational challenges.

Although the apparent increased prevalence of autism may reflect improved detection and recognition of autism and its variants, it might also index a secular change in the incidence of the disorder. The role of genetic factors in the origin of autism does not favor such a hypothesis; however. Moreover, no survey has thus far concentrated specifically on preschool children. Obtaining a reliable estimate in this age group is particularly important since early intensive preschool education might improve the outcome in autism. Accordingly, the goals of this study were to estimate the prevalence of PDDs in preschool children in a geographically defined population.

For editorial comment see p 3141.

Context Prevalence rates of autism-spectrum disorders are uncertain, and speculation that their incidence is increasing continues to cause concern.

Objective To estimate the prevalence of pervasive developmental disorders (PDDs) in a geographically defined population of preschool children.

Design, Setting, and Participants Survey conducted July 1998 to June 1999 in Staffordshire, England. The area’s 15500 children aged 2.5 to 6.5 years were screened for developmental problems. Children with symptoms suggestive of a PDD were intensively assessed by a multidisciplinary team, which conducted standardized diagnostic interviews and administered psychometric tests.

Main Outcome Measure Prevalence estimates for subtypes of PDDs.

Results A total of 97 children (79.4% male) were confirmed to have a PDD. The prevalence of PDDs was estimated to be 62.6 (95% confidence interval, 50.8-76.3) per 10000 children. Prevalences were 16.8 per 10000 for autistic disorder and 45.8 per 10000 for other PDDs. The mean age at diagnosis was 41 months, and 81% were originally referred by health visitors (nurse specialists). Of the 97 children with a PDD, 25.8% had some degree of mental retardation and 9.3% had an associated medical condition.

Conclusions Our results suggest that rates of PDD are higher than previously reported. Methodological limitations in existing epidemiological investigations preclude interpretation of recent high rates as indicative of increased incidence of these disorders although this hypothesis requires further rigorous testing. Attention is nevertheless drawn to the important needs of a substantial minority of preschool children.

METHODS

Site and Target Population
The study was conducted at the child development centers in Stafford, Cannock, and Wightwick in the Midlands, England, and it received approval from the South Staffordshire Health Authority local ethics committee. These child development centers serve the entire preschool and early school population of one National Health Service Trust. The survey was conducted from July 1998 to June 1999 although some initial clinical assessments were performed from 1994 onward. The area is a mixture of urban, rural, and semi-industrial areas. There is a stable population of indigenous British people with a small (1.4%), mostly Asian, immigrant population. The total population living in the area covered by the National Health Service Trust was 320000 people in June 1998. The target population included all children (N=15500) born between January 1, 1992, and December 31, 1993, living within the target area on June 6, 1998.

Case Identification and Definition: 4 Stages
Stage 1. The national framework of Child Health Surveillance recommendations

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mends the screening by health professionals of all UK children at birth; at age 6 weeks; between ages 6 and 9 months, 18 and 24 months, and 31/2 and 31/2 years. In the study population, all the neonatal and 6-week screenings were performed by pediatricians or general practitioners and the 7-month screening by health visitors, who are nurse specialists experienced in working with children and families. Health visitors or physicians performed the 18- to 24-month and 31/4- to 31/2-year screening. Screening was conducted in accordance with the guidelines of the “Health for All Children” report, which emphasizes continuity of care, making observations, checking history, eliciting parental concerns, offering health advice and guidance, and moving away from prescriptive tests. The primary care worker may also have had the opportunity to listen to and discuss any concerns about the child’s progress during the immunization visits at 2, 3, 4, and 13 months. Besides health visitors, speech and language therapists, pediatricians, general practitioners, and other professionals contributed to the referral process, especially for children older than 3 years. The study was coordinated through the child development centers that processed all the referrals of preschool children.

The participating professionals underwent training sessions on early identification of developmental problems and received written guidelines for referral of children with developmental or behavioral problems. The guidance to those making referrals for the initial screenings was left purposefully general to include children with any likely serious developmental, behavioral, or physical problems. This procedure also ensured maximal sensitivity for PDD case finding. The guidelines for the initial screen were to refer all children with more than mild or transient problems in one or more areas of development, including personal-social, fine or gross motor, speech and language, play skills and attention, concentration, and behavioral difficulties. Referrals were sought as soon as any problem was identified, usually by the age of 2 to 21/2 years or earlier.

Stage 2. Children referred at this initial stage underwent a second screening carried out by a developmental pediatrician (S.C.) or by the child development team, consisting of a pediatrician, a specialist health visitor, and speech and language, physical, occupational, and play therapists. Parents or main caretakers were involved in each stage of the screening. Any urgent referrals were fast-tracked to the developmental pediatrician or a multidisciplinary team.

Stage 3. Children who failed the second screening were selected for a 2-week assessment conducted by a multidisciplinary team. During these assessments, a play therapist led a group of 4 children with their participating parents in 2-hour sessions of structured activities as well as free play. A developmental pediatrician (S.C.) took a detailed developmental history and conducted a comprehensive medical and neurological examination. Children were assessed by a speech and language therapist, a pediatric physical therapist, an occupational therapist, a dental nurse, a dietitian, and a nurse specialist trained in behavioral intervention for children with PDDs and other learning problems. Hearing was assessed by an audiological physician, and vision was screened by an orthoptist. At the end of this assessment, a clinical diagnostic formulation was made by the lead pediatrician.

All screening and evaluation steps undertaken at stages 1, 2, and 3 were part of a normal screening procedure implemented by the local service. Permission for extra data collection associated with research was sought either at the end of stage 3 or shortly after entering stage 4. About 75% of parents provided written informed consent. The rest provided oral informed consent.

Stage 4. Children strongly suspected of having a PDD diagnosis were further assessed with standardized diagnostic measures and psychometric assessments. The Autism Diagnostic Interview-Revised (ADI-R) is a semistructured diagnostic interview for use with caregivers of children with a possible PDD diagnosis. The ADI-R was administered by the developmental pediatrician (S.C.), who has been trained in its use. The ADI-R algorithm generates scores for the areas of social interaction, communication (verbal and nonverbal), repetitive behaviors, and age of recognition of first abnormalities for which appropriate cutoff points are available. The ADI-R algorithm is compatible with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic criteria. A total ADI-R score is obtained by summing the scores in the 3 domains of developmental deviance.

Children diagnosed as having a PDD subsequently underwent a formal psychometric assessment by a senior educational psychologist. All tests were performed in 1999 and early 2000. The tests used were the Wechsler Preschool and Primary Scale of Intelligence and the Merrill-Palmer tests. Intellectual functioning was estimated according to performances on the nonverbal scales of the Wechsler Preschool and Primary Scale of Intelligence or with the quotient derived from the Merrill-Palmer test. Mental retardation was defined according to conventional levels of severity (ie, mild, moderate, severe, profound, <20). The final diagnostic determination was derived from a review of all existing data by the pediatrician who knew all children well. Diagnosis was made with DSM-IV diagnostic criteria for PDD including autistic disorder (AD), Asperger syndrome, Rett syndrome, childhood disintegrative disorder, and pervasive developmental disorder—otherwise specified (PDD-NOS).

Reliability Study
All ADI-R interviews were videotaped or audiotaped. A subset of 38 ADI-R videotapes was selected at random and blindly rated by 3 trained raters (including E.F.). Interrater reliability for domain scores as measured by the intraclass correlation coefficient was 0.82 for social interactions, 0.87 for nonverbal communication, 0.85 for verbal com-
munication (based on a subset of 28 children with a sufficient language level), 0.59 for repetitive behaviors, and 0.86 for the total ADI-R score. Agreement on the proportion of subjects scoring higher than each of the predetermined cutoffs was high for all domains (social interactions, 92.1%; nonverbal communication, 90.0%; verbal communication, 85.7%; repetitive behavior, 81.6%; and onset before age 3 years, 97.4%). Blinded raters were also asked to provide an independent global diagnostic judgment about the presence or absence of a PDD based on the parental interview. Independent raters confirmed the presence of a PDD in all 38 children, yielding a 100% agreement with the original pediatrician’s diagnoses.

Biological Investigations
Following the 2-week assessment, systematic laboratory investigations were performed, which included full blood cell count; plasma chemistry; serum calcium, thyrotropin and thyroxine, and creatine kinase levels; plasma and urine amino acid chromatogram; urine organic acids; chromosomes; fragile X testing; and electroencephalogram. The skin of children with suggestive birthmarks was examined with UV light to detect markers of tuberous sclerosis. In a small number of cases, brain imaging using computed tomographic or magnetic resonance imaging scans was performed on clinical suspicion of a possible neurological problem.

Statistical Analyses
Between-group comparisons for continuous variables were performed with both nonparametric (Kruskal-Wallis) and parametric 1-way analyses of variance followed by post hoc Scheffé pairwise comparisons. Because P values were almost identical, the results of parametric analyses are subsequently presented. χ² tests were used for categorical variables. Throughout, a conventional P value of .05 was retained as the level of statistical significance. Asymptotic 95% confidence intervals (CIs) for prevalence estimates were obtained with STATA software version 6.16

RESULTS
Prevalence
The details of case ascertainment in this investigation are summarized in the Figure. Of the 576 children referred to a child development center for a stage 1 assessment, 103 children were clinically diagnosed as having PDD at the stage 3 assessment. Of these 103 children, 99 parents agreed to take part in the ADI-R interview and 4 parents refused. One interview was deferred indefinitely for external circumstances, and 98 interviews were finally carried out (95 videotaped, 3 audiotaped).

Of the 5 children who did not receive an ADI-R interview, a final PDD diagnosis was subsequently confirmed by an independent educational psychologist or child psychiatrist (2, AD; 3, PDD-NOS). Of the 98 children with ADI-R data, 6 children did not fulfill strict ADI-R diagnostic criteria for a PDD at stage 4. Thus, at the completion of stage 4, 97 children were diagnosed as having PDD, resulting in a prevalence estimate of 62.6 (95% CI, 50.8-76.3) per 10000 children for all PDDs. Further analysis by PDD subtype led to the following estimates: for 26 children with AD, the prevalence was 16.8 (95% CI, 11.0-24.6) per 10000; for 13 with Asperger syndrome, 8.4 (95% CI, 4.5-14.3) per 10000; for 1 girl with Rett syndrome, 0.6 (95% CI, 0.02-3.6) per 10000; for 1 boy with childhood disintegrative disorder, 0.6 (95% CI, 0.02-3.6) per 10000; and for 56 with PDD-NOS, 36.1 (95% CI, 27.3-46.9) per 10000. For the 71 children with a PDD diagnosis other than AD, the prevalence was 45.8 (95% CI, 35.8-57.7) per 10000 children.

ADI-R Mean Scores
The mean (SD) age of 92 children with available ADI data was 58.1 (13.0) months at interview. Excluding the boy

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with childhood disintegrative disorder and the girl with Rett syndrome, comparison of scores across the 3 remaining diagnostic subgroups yielded significant differences in all domains except for the repetitive behaviors domain (Table 1). Post hoc tests showed that children with AD had consistently higher scores than the 2 other groups, which in turn did not differ from each other. All children met the requirement of an onset before age 3 years.

### Referral Source and Age at Diagnosis

Thirty-four percent of the 97 referrals came from pediatricians, 32.9% from speech and language therapists, 21.6% from health visitors, 5.1% from general practitioners, and 6.2% from miscellaneous sources. However, a closer look at referral patterns showed that most of the referrals to pediatricians and speech therapists were initiated by health visitors; thus, taking these data in combination, 79 (81%) of the 97 children were originally identified by the health visitor as having a problem requiring further assessment. The average age of children at referral was 35.7 months (range, 11-63 months), and the average age at initial clinical diagnosis was 41 months (range, 21-78 months).

Analyses of variance were performed to test for differences in age at referral and age at diagnosis in the 95 children with AD, Asperger syndrome, or PDD-NOS diagnoses. A significant effect of diagnosis was found for age at referral ($F_{2,92}=11.3; P<.001$). Pairwise comparisons showed that mean age at referral for children with AD (30.0 months) was significantly lower than for children with PDD-NOS (37.2 months; $P=.03$) or with Asperger syndrome (47.5 months; $P<.001$). Age at referral of children with PDD-NOS was also significantly lower than in those children with Asperger syndrome ($P=.01$). For age at diagnosis, a significant effect of diagnostic subgroup was also found ($F_{2,92}=12.0; P<.001$). Post hoc Scheffé tests similarly indicated significantly lower mean age at diagnosis for children with AD (34.6 months) vs children with PDD-NOS (43.1 months; $P=.005$) and lower age at diagnosis for children with Asperger syndrome (51.8 months; $P<.001$), whereas children with PDD-NOS had significantly lower mean age at diagnosis than those with Asperger syndrome ($P=.04$).

### Clinical Correlates

The sample included 77 boys (79.4%) with no significant difference ($\chi^2=0.33; P=.85$) in the proportion of boys in the AD (76.9%), Asperger syndrome (84.6%), and PDD-NOS (80.4%) groups. Of the 97 children, 29 (29.9%) had no functional use of language defined as the daily spontaneous use of 3-word phrases. The proportion of children without functional language was however strongly associated with diagnostic subtype (AD, 69.2%; Asperger syndrome, 0%; PDD-NOS, 16.1%; $\chi^2=30.6; P<.001$).

Of the 97 children, 37 children underwent Merrill-Palmer testing and 56, Wechsler Preschool and Primary Scale of Intelligence testing. Four children could not be tested for practical reasons. Overall, 24 (25.8%) of 93 children had some degree of mental retardation. The 2 children with childhood disintegrative disorder and Rett syndrome scored in the moderate range of mental retardation. However, patterns of cognitive functioning varied according to diagnosis (Table 2) and, combining together all levels of mental retardation, a significant difference was found for the presence or absence of mental retardation between the 3 PDD subtypes ($\chi^2=40.6; P<.001$), the AD group having more frequent and severe cognitive delays than the Asperger syndrome and PDD-NOS groups.

In the sample, 5 children had a sibling with another PDD (including 1 twin pair). Four of the sibling pairs were in the age range of this study and were included in the prevalence pool. Of the sibling pairs, 3 sets were diagnosed with both pairs having PDD-NOS, 1 set with AD and PDD-NOS, and 1 set with Asperger syndrome and AD. Based on the total number of siblings across all 93

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**Table 1. Mean Autism Diagnostic Interview-Revised (ADI-R) Scores by Diagnostic Subgroup**

<table>
<thead>
<tr>
<th>Diagnostic Subgroup</th>
<th>AD (n = 24)</th>
<th>PDD-NOS (n = 53)</th>
<th>Asperger Syndrome (n = 13)</th>
<th>Fisher Statistic</th>
<th>P Value†</th>
<th>AD vs PDD-NOS P Value‡</th>
<th>AD vs Asperger Syndrome P Value‡</th>
<th>PDD-NOS vs Asperger Syndrome P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social interaction</td>
<td>22.3 (4.9)</td>
<td>13.6 (5.2)</td>
<td>13.4 (3.3)</td>
<td>28.2</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.99</td>
</tr>
<tr>
<td>Communication</td>
<td>11.5 (2.2)</td>
<td>6.4 (3.5)</td>
<td>7.3 (2.8)</td>
<td>23.2</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.001</td>
<td>.62</td>
</tr>
<tr>
<td>Repetitive behavior</td>
<td>5.3 (2.1)</td>
<td>5.3 (2.5)</td>
<td>6.0 (2.3)</td>
<td>0.5</td>
<td>.63</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Total ADI-R score</td>
<td>42.1 (5.8)</td>
<td>30.6 (8.9)</td>
<td>31.9 (5.6)</td>
<td>17.9</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.001</td>
<td>.85</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SD) unless otherwise indicated. AD indicates autistic disorder; PDD-NOS, pervasive developmental disorder—not otherwise specified. Ellipses indicate that Fisher statistic was not significant. The 2 children with a diagnosis of either childhood disintegrative disorder or Rett syndrome and the 5 children without ADI-R views were not included in the analysis. The range of ADI-R scores for social interaction was 2 to 30; communication (nonverbal), 0 to 14; repetitive behaviors, 1-12; and total scores, 18 to 54.

†Fisher statistic from analysis of variance and P value.

‡Results of post hoc Scheffé tests.

**Table 2. Intellectual Functioning by Diagnostic Subgroup**

<table>
<thead>
<tr>
<th>Diagnostic Subgroup</th>
<th>AD (n = 26)</th>
<th>PDD-NOS (n = 53)</th>
<th>Asperger Syndrome (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal range</td>
<td>8 (30.8)</td>
<td>49 (92.4)</td>
<td>12 (100)</td>
</tr>
<tr>
<td>Mild to moderate retardation</td>
<td>13 (50.0)</td>
<td>4 (7.6)</td>
<td>0</td>
</tr>
<tr>
<td>Severe to profound retardation</td>
<td>5 (19.2)</td>
<td>0 (0.0)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data are presented as number (percentage). AD indicates autistic disorder; PDD-NOS, pervasive developmental disorder—not otherwise specified. The 2 subjects with either childhood disintegrative disorder or Rett syndrome and the 4 children who could not be tested are not included in this analysis.
families (n=220, including the 97 participating children), the sibling risk is estimated at 3.94% (5/127) in this study.

**Associated Medical Conditions**

The results of medical investigations in this sample are summarized in **Table 3**. There was no case of deafness, blindness, or fragile X disorder, and only 1 child had tuberous sclerosis. Six of 8 children with an abnormal medical result had mental retardation. Overall, the proportion of children with any abnormal medical result was 9.3%.

**COMMENT**

Most other surveys estimated the prevalence of children with PDD to be nearer to 20 per 10000 children than the 62.6 per 10000 prevalence in our study. This rate is, however, consistent with the 57.9 and 67.4 per 10000 estimates reported in 2 recent investigations. These 3 surveys have all used intensive screening procedures, focused on children younger than 10 years, and used modern standardized diagnostic measures such as the ADI-R10-12 or the Autism Diagnostic Observation Schedule-Generic. The somewhat lower estimate of 26.1 per 10000 (and 30.1 per 10000 among children aged 5 to 9 years) obtained in another UK survey probably reflects methodological differences in an investigation that was focusing primarily on common childhood psychiatric disorders. Thus, the latter survey did not rely on screening procedures and diagnostic measures specific to PDDs. It is worth noting that 4 UK surveys of children in the same age groups conducted at the same time and in the same country showed a 6-fold variation in prevalence rates, emphasizing how powerfully various methods used in a survey affect prevalence estimates. The findings also point to the probable lack of sensitivity of case finding procedures in earlier surveys resulting in underestimation of rates. Therefore, the prevalence of PDDs seems to be about 60 per 10000 children, an estimate that draws attention to the needs of a substantial minority of children.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Diagnosis</th>
<th>Age at Diagnosis, mo</th>
<th>IQ</th>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Autism</td>
<td>44</td>
<td>31</td>
<td>Tuberosclerosis</td>
</tr>
<tr>
<td>Female</td>
<td>PDD-NOS</td>
<td>49</td>
<td>83</td>
<td>Hydrocephalus with premature thelarche</td>
</tr>
<tr>
<td>Male</td>
<td>PDD-NOS</td>
<td>39</td>
<td>100</td>
<td>Hydrocephalus with aqueduct stenosis and vermian hypoplasia</td>
</tr>
<tr>
<td>Male</td>
<td>Autism</td>
<td>42</td>
<td>65</td>
<td>XYY Karyotype</td>
</tr>
<tr>
<td>Female</td>
<td>PDD-NOS</td>
<td>39</td>
<td>44</td>
<td>XXX Karyotype</td>
</tr>
<tr>
<td>Male</td>
<td>Autism</td>
<td>57</td>
<td>44</td>
<td>Cerebral palsy, abnormal EEG results, no overt seizures</td>
</tr>
<tr>
<td>Female</td>
<td>PDD-NOS</td>
<td>50</td>
<td>85</td>
<td>Cerebral palsy</td>
</tr>
<tr>
<td>Female</td>
<td>PDD-NOS</td>
<td>56</td>
<td>68</td>
<td>Bardet-Biedl syndrome, sleep disturbance with parasomnia-like events</td>
</tr>
<tr>
<td>Male</td>
<td>Childhood disintegrative disorder</td>
<td>78</td>
<td>38</td>
<td>Left monoplegia, epilepsy with continuous EEG disturbance from right hemisphere, small infarct in right parietal area</td>
</tr>
</tbody>
</table>

*PDD-NOS indicates pervasive developmental disorder—not otherwise specified; EEG, electroencephalogram.*
rowly defined as autism (ie, 50% in the Brick Township study among 3- to 10-year-olds and 25% among 3- to 5-year-olds in a Finnish survey). This shift has important implications for intervention since the majority of these children will require education in mainstream schools with provision of individual support. In addition, it is possible that very early intervention in autism and PDD might be associated with a much better cognitive outcome in the short term. Evidence of the beneficial impact of intensive educational programs between the ages of 2 and 4 years has accumulated recently, and the notion of a critical period for a maximal effect of intensive educational interventions clearly requires further examination. Parents recognize the first developmental abnormalities before the second birthday in the majority of cases, and one encouraging result from this survey was that four fifths of PDD cases were identified at a very early age by trained health visitors, indicating that early population screening programs could detect a high proportion of children with PDDs before the age of 2 years. Instruments with adequate levels of sensitivity and specificity are currently being developed, which may make that goal attainable. Such screening must be supported with appropriate assessment services combining special expertise in autism and multidisciplinary skills, as was the case in our population.

Consistent with a major role of genetic factors in PDD, identified medical abnormalities were found in less than 10% of our sample. Moreover, the abnormalities reported in this sample might not be causally implicated in the development of PDD and might have occurred simply as random findings in a population submitted to intensive medical work-up. Nevertheless, the rate of 10% for medical abnormalities of potential etiological significance is consistent with prior findings deriving from both clinical and epidemiological surveys. The rate of sibling recurrence obtained in this study is also consistent with figures of 3% to 7% reported by other investigators, and although the absolute magnitude of the risk remains small, a comparison with the population prevalence points toward a large increase in the risk of autism or PDD in families with an already affected child.

Some limitations of this study must be mentioned. First, clinical assessment of children was not performed with standardized diagnostic techniques although such instruments were available for parental interviews and cognitive testing. It is unlikely that this would affect the prevalence estimates obtained in this study since experienced clinicians agreed 100% on the presence of a PDD in the whole sample. Availability of these assessments might nevertheless have provided a different breakdown of the diagnosis into various diagnostic subcategories. Assessing young children with PDDs is a complex task and guidelines to draw the line between high-functioning autism, Asperger syndrome, and PDD-NOS remain to be firmly established. Second, there is a possibility that some children might have been missed despite the intensive screening efforts used in the survey. This might particularly apply to some cases of Asperger syndrome who are sometimes not detected before school age and might have led to some underestimation of the prevalence. Conversely, some children diagnosed as having mild forms of PDD-NOS may turn out on follow-up assessments to have more transient developmental problems. This might have produced an inflation of the prevalence estimate. Whether these 2 problems might cancel each other remains to be seen, but we are committed to reassess this sample at age 8 to 10 years to address these issues and to obtain a more stable estimate.

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