**Objective:** To examine the effect of changing age at diagnosis on the diagnosed prevalence of autism among different birth cohorts.

**Design:** Population-based cohort study.

**Setting:** Children were identified in the Danish Medical Birth Registry and psychiatric outcomes were obtained via linkage with the Danish National Psychiatric Register.

**Participants:** All children born in Denmark from January 1, 1994, through December 31, 1999 (N=407,458).

**Main Outcome Measures:** The age-specific prevalence, hazard ratio, and relative risk by age.

**Results:** Statistically significant shifts in age at diagnosis were observed for autism spectrum disorder; children diagnosed before age 9 years in the cohorts born between January 1, 1994, and December 31, 1995, between January 1, 1996, and December 31, 1997, and between January 1, 1998, and December 31, 1999, were on average diagnosed at ages 5.9 (95% confidence interval [CI], 5.8-6.0), 5.8 (95% CI, 5.7-5.9), and 5.3 (95% CI, 5.2-5.4) years, respectively. The relative risk comparing the 1996-1997 birth cohort with the 1994-1995 birth cohort at age 3 years was 1.20 (95% CI, 0.86-1.67), which decreased to 1.10 (95% CI, 1.00-1.20) at age 11 years. Similarly, the relative risk comparing the 1998-1999 birth cohort with the 1994-1995 birth cohort at age 3 years was 1.69 (95% CI, 1.24-2.31), which decreased to 1.23 (95% CI, 1.11-1.37) at age 11 years. Similar results were observed for childhood autism.

**Conclusions:** Shifts in age at diagnosis inflated the observed prevalence of autism in young children in the more recent cohorts compared with the oldest cohort. This study supports the argument that the apparent increase in autism in recent years is at least in part attributable to decreases in the age at diagnosis over time.

**ARCH Pediatr Adolesc Med. 2008;162(12):1150-1156**

**RECENT REVIEW OF THE EPIDEMIOLOGY OF AUTISM DOCUMENTED THE LARGE NUMBER OF STUDIES THAT HAVE SHOWN AN INCREASE IN THE AGE-SPECIFIC PREVALENCE OF REPORTED AUTISM CASES IN THE LAST 2 DECADES.** Once considered rare, the current prevalence estimates for all autism spectrum disorders of about 6 cases per 1000 children indicate that autism spectrum disorder may be the second most common serious developmental disability after mental retardation.2-4 Recent studies have also shown that an upward trend in prevalence is not unique to autism but is also the case for other childhood neuropsychiatric disorders such as attention-deficit/hyperactivity disorder and Tourette syndrome.5-6 The increase in the reported prevalence of autism has raised the concerns that the incidence of autism is increasing and that the increase may be due to adverse exposures such as childhood vaccines.7 The increase in the prevalence of reported cases may be caused by many factors such as heightened public awareness, changes in referral pattern, changes in diagnostic criteria, case identification, or reporting methods. In the few studies that have investigated the effect of these potential confounders, the main focus has been on diagnostic substitution in which a child who might have received a disability label such as learning disability or mental retardation 15 to 20 years ago may now be diagnosed with autism because of shifting diagnostic practices.6,9 These studies suggest that diagnostic substitution may explain part of the increase in the prevalence of autism. Correct interpretation of changes in autism prevalence is impor-
tant in the public health setting for services, planning, and organization of institutions and also in etiological research when searching for risk factors associated with autism. In etiological research, special attention has been on risk factors that show an increase in prevalence similar to the increase in autism prevalence.

A limited number of studies have investigated the effect of changing age at diagnosis on the prevalence of autism. Lingam et al\textsuperscript{10} presented estimates of the change in age at diagnosis and the increase in final prevalence of autism by making specific assumptions about the diagnostic rate as a function of age and changes in the age at diagnosis. These assumptions, however, cannot be validated from data. Mandell et al\textsuperscript{11} presented the average age at diagnosis in different birth cohorts, but the difference in age at diagnosis may also reflect differences in follow-up time in the birth cohorts. Wazana et al\textsuperscript{12} performed a simulation study showing that changes in the age at diagnosis may confound the observed increase in prevalence.

Changes in the age at diagnosis may confound the observed increase in prevalence if there is insufficient follow-up to estimate the final prevalence. Figure 1 shows this problem for a hypothetical disorder where diagnosis of all affected persons is achieved before age 20 years. The reference cohort represents a birth cohort of the oldest children, and cohorts 1 and 2 represent more recent cohorts under 2 different scenarios. In cohort 1, the distribution of age at diagnosis is identical to the reference cohort, but there are 10\% more cases at each year of age; at age 20 years, the prevalence is 10\% greater than in the reference cohort. For cohort 2, there is a shorter time to diagnosis in that the diagnoses in cohort 2 are on average given 10\% earlier compared with the reference cohort, but the final prevalence at age 20 years is the same for cohort 2 and the reference cohort. With complete follow-up, the prevalence curves for each cohort reach a plateau by age 20 years, indicating that no additional cases are diagnosed after that age (Figure 1A). In the case of complete follow-up, it is straightforward to estimate the increase in final prevalence between the reference cohort and cohort 1 as the relative difference between the prevalence proportions at age 20 years. If there is not sufficient follow-up to estimate the final prevalence, we can only estimate the age-specific prevalence (Figure 1B). In this example with incomplete follow-up, the curves for cohorts 1 and 2 seem to converge and are shifted away from the reference cohort—showing the potential difficulty in distinguishing the effects of an earlier age at diagnosis from the effects of an increase in prevalence.

The aims of this study were to examine whether there is evidence for changes in the age at diagnosis and an effect on the reported prevalence of autism in Denmark and to estimate the amount of bias when using age-specific rela-
tive risk to estimate the final relative risk that is caused by changes in the age at diagnosis.

## METHODS

### STUDY DESIGN

We designed a cohort study of all children born in Denmark from January 1, 1994, to December 31, 1999. The cohort was identified in the Danish Medical Birth Registry and consisted of 407,458 children. The Danish Medical Birth Registry comprises data on all live births and stillbirths by women with permanent residence in Denmark. All live-born children in Denmark are assigned a Central Population Registry number, a unique 10-digit number used for all official personal registrations in Denmark since 1968. On the basis of the Central Population Registry number, the data from the Danish Medical Birth Registry were then linked to the Danish National Psychiatric Registry (DNPR) to obtain neuropsychiatric outcomes. The DNPR includes all inpatient admissions and from January 1, 1995, also includes all outpatient contact to psychiatric hospitals, wards, and clinics in Denmark. For children, inpatient admissions correspond to overnight hospital stays or daily hospital visits over an extended period for diagnostic evaluation and treatment, whereas outpatient admissions correspond to clinic visits on a less regular basis. Children suspected to have autism are referred by general practitioners or school psychologists to a child psychiatric ward, where they are diagnosed and treated by a psychiatrist. In Denmark, a specialized diagnostic assessment of children suspected to have autism is generally necessary to be enrolled in special services, and the diagnostic evaluations and treatment are free of charge. The DNPR includes data on clinical diagnoses, dates of admission and discharge, and terms of admission, and the International Statistical Classification of Diseases, 10th Revision (ICD-10) diagnostic code criteria have been used since 1994. The age at first admission and/or contact with the health care system is used as a proxy for the age at diagnosis, and age at first contact in the diagnostic process may be a more accurate description because the timing of diagnosis once the child is admitted into the process may vary across facilities.

Follow-up for the diagnosis of autism spectrum disorder (ICD-10 codes: F84.0, childhood autism; F84.1, atypical autism; F84.5, Asperger syndrome; F84.8, other pervasive developmental disorders; and F84.9, pervasive developmental disorders unspecified) or childhood autism (ICD-10 code F84.0) began for all children from birth and continued until the diagnosis of autism, death, or the end of follow-up on December 31, 2006, whichever occurred first. All of the analyses were made separately for autism spectrum disorder and childhood autism. The children were divided into 2-year birth cohorts, born between January 1, 1994, and December 31, 1995, between January 1, 1996, and December 31, 1997, and between January 1, 1998, and December 31, 1999 (to enhance the statistical precision compared with 1-year birth cohorts), where the 1994-1995 cohort represents the reference cohort.

The study was approved by the Danish National Board of Health and the Danish Data Protection Agency.

### STATISTICAL ANALYSIS

Previous studies on autism time trends that provide data on the prevalence by age or equivalently the rate by age, including this study, do not seem to have sufficient follow-up to estimate the final prevalence of autism. Specifically, the prevalence by age curve does not reach a plateau, or the rate by age does not converge to 0, in these studies. Because childhood mor-
specific prevalence in the most recent birth cohort (1998-1999) compared with the 1994-1995 reference cohort (Figure 2) \((P < .001\) for both autism spectrum disorder and childhood autism); the 1996-1997 cohort also had a significant increase in autism spectrum disorder compared with the reference cohort \((P = .04\) for autism spectrum disorder and \(P = .22\) for childhood autism). The tests for trend were statistically significant for both autism spectrum disorder and childhood autism \((P < .001\) in both cases).

For both autism spectrum disorder and childhood autism there was evidence for hazard ratios that are not constant as a function of age and hence indicate changes in the age at diagnosis in the more recent cohorts (Figure 3). The earlier diagnosis is reflected in decreases in the average age at diagnosis: children diagnosed with an autism spectrum disorder before age 9 years in the 1994-1995, 1996-1997, and 1998-1999 cohorts were on average diagnosed at ages 5.9 (95% confidence interval [CI], 5.8-6.0), 5.8 (95% CI, 5.7-5.9), and 5.3 (95% CI, 5.2-5.4) years, respectively. For a diagnosis of childhood autism specifically, the corresponding average ages at diagnosis were 5.1 (95% CI, 4.9-5.4), 5.0 (95% CI, 4.8-5.2), and 4.7 (95% CI, 4.6-4.9) years, respectively. There were 69% (95% CI, 24%-131%) more cases of autism spectrum disorder and 87% (95% CI, 21%-187%) more cases of childhood autism reported at age 3 years in children in the 1998-1999 birth cohort relative to children in the 1994-1995 birth cohort (Figure 3).

**BIAS CAUSED BY CHANGES IN AGE AT DIAGNOSIS**

The level of bias in reported prevalence caused by changes in age at diagnosis is shown by a graph of the age-

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**Table 1. ICD-10 Diagnostic Codes, Birth Cohorts, Live Births per Cohort, Autism Cases, and Prevalence in Each Cohort Reported to the Danish National Psychiatric Registry by December 31, 2006**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ICD-10 Code</th>
<th>Birth Cohort</th>
<th>Follow-up, y</th>
<th>Cases, No.</th>
<th>Births, No.</th>
<th>Prevalence, Cases/10,000 Individuals (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism spectrum disorder</td>
<td>F84.0, F84.1, F84.5, F84.8, F84.9</td>
<td>1994-1995</td>
<td>13</td>
<td>1046</td>
<td>139,438</td>
<td>82.0 (76.5-87.8)</td>
</tr>
<tr>
<td>Childhood autism</td>
<td>F84.0</td>
<td>1994-1995</td>
<td>13</td>
<td>282</td>
<td>139,438</td>
<td>20.7 (18.4-23.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1996-1997</td>
<td>11</td>
<td>278</td>
<td>135,413</td>
<td>21.2 (18.8-23.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1998-1999</td>
<td>9</td>
<td>321</td>
<td>132,607</td>
<td>26.4 (23.5-29.8)</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; ICD-10, International Statistical Classification of Diseases, 10th Revision.

**Figure 2.** Age-specific prevalence of autism spectrum disorder (A) and childhood autism (B) for each 2-year birth cohort (1 minus the Kaplan-Meier curve).

**Figure 3.**
specific relative risks for varying lengths of follow-up (Figure 4). The estimated age-specific relative risks for both autism spectrum disorder and childhood autism decreased with age as the follow-up of the children was increased.

Follow-up only to age 3 years resulted in an estimated relative risk of 1.20 (95% CI, 0.86-1.67) for autism spectrum disorder comparing the 1996-1997 birth cohort with the 1994-1995 birth cohort and a relative risk of 1.69 (95% CI, 1.24-2.31) comparing the 1998-1999 birth cohort with the 1994-1995 birth cohort (Figure 4). Increasing the follow-up to age 11 years resulted in an estimated relative risk of 1.10 (95% CI, 1.00-1.20) comparing the 1994-1995 and 1996-1997 birth cohorts, indicating that 52% of the estimated increase in prevalence at age 3 years could be explained by the longer follow-up to age 11 years. Similarly, increasing the follow-up from age 3 years to age 9 years resulted in an estimated relative risk of 1.23 (95% CI, 1.11-1.37) when comparing the 1994-1995 and 1998-1999 birth cohorts, indicating that at least 66% of the apparent increase in prevalence at age 3 years could be explained by the longer follow-up to age 11 years. The final relative risk for a given cohort compared with the reference cohort will be the limit of the age-specific relative risk as the follow-up increases, eventually reaching a plateau as the length of follow-up increases to the oldest age at diagnosis (ie, at complete follow-up). Further, when there is a decrease in age at diagnosis, the final relative risk can be no larger than the age-specific relative risk at the end of follow-up. In these data, compared with the reference cohort, the final relative risk for autism spectrum disorder at the end of follow-up was 1.10 (95% CI, 1.00-1.20) in the 1996-1997 cohort and 1.23 (95% CI, 1.11-1.37) in the 1998-1999 cohort, indicating an increase in the final prevalence for autism spectrum disorder in the youngest cohort at least. For childhood autism, the relative risk of 1.50 (95% CI, 1.25-1.75) based on follow-up to age 9 years in the 1998-1999 cohort compared with the reference cohort is also statistically significant.

Based on data from a cohort of children born in Denmark since the mid-1990s, the study provides quantitative evidence for a change in the age at diagnosis of autism over time and the potential effect of that change on the observed risk for a reported diagnosis of autism at different ages. Statistically significant shifts in age at diagnosis were observed for both autism spectrum disor-
der and childhood autism. The important conclusion to be made is that the shifts in age at diagnosis—especially the earlier diagnosis at younger ages—artificially inflated the differences in the observed prevalence of autism in young children in the more recent cohorts compared with the cohort of the oldest children. With a greater length of follow-up, the differences in prevalence between the cohorts decreased. It appears that in our data, however, the length of follow-up was insufficient to observe a plateau in the autism prevalence in the more recent cohorts. With longer follow-up, the relative risks of the 1996-1997 cohort and the 1998-1999 cohort compared with the 1994-1995 cohort at the end of follow-up could potentially change. Furthermore, it remains to be determined whether the statistically significant increased prevalence at the end of follow-up could be further accounted for by other factors or is reflective of a true increase in the incidence of reported autism diagnoses.

The strengths of this study include a population-based birth cohort approach, a large cohort size, and all diagnostic data having been obtained from a nationwide register based on standardized diagnostic reporting procedures and using a common diagnostic coding system (ICD-10). The ICD-10 classification system has been used in Denmark since 1994 and both inpatient and outpatient data have been included in the DNPR since 1995. Hence, selection of the study cohort was made explicitly to ensure that administrative reporting of autism to the DNPR was stable throughout the study follow-up period between 1995 and 2006. However, the findings could also reflect better diagnostic acumen of the ICD-10 di-

![Table 2. Age-Specific Relative Risk in Each 2-Year Birth Cohort Relative to the Reference Cohort](image)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Birth Cohort</th>
<th>Age 3 y RR (95% CI)</th>
<th>Age 9 or 11 y RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1996-1997</td>
<td>1.20 (0.86-1.67)</td>
<td>1.10 (1.00-1.20)</td>
</tr>
<tr>
<td></td>
<td>1998-1999</td>
<td>1.69 (1.24-2.31)</td>
<td>1.23 (1.11-1.37)</td>
</tr>
<tr>
<td></td>
<td>1996-1997</td>
<td>1.53 (0.98-2.40)</td>
<td>1.11 (0.94-1.31)</td>
</tr>
<tr>
<td></td>
<td>1998-1999</td>
<td>1.87 (1.21-2.87)</td>
<td>1.50 (1.25-1.75)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.

*Age at the end of follow-up was 11 years for the 1996-1997 cohort and 9 years for the 1998-1999 cohort.
agnostic system from the 1994-1995 cohort to the later 1996-1997 and 1998-1999 cohorts. The study is based on clinical diagnosis as a case identification strategy, and the effect of age at diagnosis may be different if other case identification strategies are used. However, clinical diagnoses are used to estimate autism prevalence, and this study highlights the difficulty in interpretation of such prevalence data.

Completeness of the DNPR for autism is believed to be high. In other studies, the prevalence of autism spectrum disorder has generally been reported to range from 33 to 106 cases per 10 000 individuals.2,10,14,16,17,21,22 Childhood autism is most commonly reported to have a prevalence of approximately 20 cases per 10 000 individuals.6,8,18,21,23 The age-specific prevalences observed in this study in the oldest cohort (Figure 2) (1994-1995 cohort, aged 13 years: 82 cases per 10 000 individuals for autism spectrum disorder and 21 cases per 10 000 individuals for childhood autism) are comparable. No validations of accuracy have been made for autism spectrum disorder diagnoses in the DNPR in general. An assessment based on expert review of diagnostic records of 499 children born in the 1990s with a reported DNPR diagnosis of childhood autism found that 94% met criteria for a correct diagnosis based on a coding scheme developed by the Centers for Disease Control and Prevention for autism surveillance in the United States (Marlene B. Lauritsen, MD, Meta Jørgensen, MD, Sanne Lemcke, RN, Kresten M. Madsen, PhD, Susanne Toft, RN, Jakob Grove, PhD, D.E.S., and P.T., unpublished data, June 2008).

The decrease in age at diagnosis may be due to better diagnostic abilities of doctors, an earlier onset of autism symptoms in new cases of autism, or an earlier onset of autism symptoms that would have otherwise appeared at an older age.

In conclusion, this study supports the argument that the apparent increase in autism in recent years is at least in part attributable to a decrease in the age at diagnosis over time. The empirical evidence for a decrease in the age at diagnosis of autism in more recent years is important as it is well known that the long-term prognosis for children with autism is enhanced by early identification and treatment.23 This study also provides an approach for quantifying the proportion of the increase in autism prevalence observed at specific ages that is attributable to changes in age-specific hazard rates of diagnosis. The results demonstrate the effect of incomplete follow-up on the potential for misinterpretation of autism trends.

Accepted for Publication: May 8, 2008.

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Author Contributions: Dr Parner had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Parner, Schendel, and Thorsen. Acquisition of data: Parner. Analysis and interpretation of data: Parner, Schendel, and Thorsen. Drafting of the manuscript: Parner. Critical revision of the manuscript for important intellectual content: Parner, Schendel, and Thorsen. Statistical analysis: Parner. Obtained funding: Schendel and Thorsen. Administrative, technical, and material support: Schendel and Thorsen.

Financial Disclosure: None reported.

Disclaimer: The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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