Original Investigation

Explaining the Increase in the Prevalence of Autism Spectrum Disorders

The Proportion Attributable to Changes in Reporting Practices

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IMPORTANCE The prevalence of autism spectrum disorders (ASDs) has increased markedly in recent decades, which researchers have suggested could be caused in part by nonetiologic factors such as changes in diagnosis reporting practices. To our knowledge, no study has quantified the degree to which changes in reporting practices might explain this increase. Danish national health registries have undergone a change in diagnostic criteria in 1994 and the inclusion of outpatient contacts to health registries in 1995.

OBJECTIVE To quantify the effect of changes in reporting practices in Denmark on reported ASD prevalence.

DESIGN, SETTING, AND PARTICIPANTS We used a population-based birth cohort approach that includes information on all individuals with permanent residence in Denmark. We assessed all children born alive from January 1, 1980, through December 31, 1991, in Denmark (n = 677 915). The children were followed up from birth until ASD diagnosis, death, emigration, or the end of follow-up on December 31, 2011, whichever occurred first. The analysis uses a stratified Cox proportional hazards regression model with the changes in reporting practices modeled as time-dependent covariates.

EXPOSURES The change in diagnostic criteria in 1994 and the inclusion of outpatient diagnoses in 1995.

MAIN OUTCOMES AND MEASURES Autism spectrum disorders.

RESULTS For Danish children born during the study period, 33% (95% CI, 0%-70%) of the increase in reported ASD prevalence could be explained by the change in diagnostic criteria alone; 42% (95% CI, 14%-69%), by the inclusion of outpatient contacts alone; and 60% (95% CI, 33%-87%), by the change in diagnostic criteria and the inclusion of outpatient contacts.

CONCLUSIONS AND RELEVANCE Changes in reporting practices can account for most (60%) of the increase in the observed prevalence of ASDs in children born from 1980 through 1991 in Denmark. Hence, the study supports the argument that the apparent increase in ASDs in recent years is in large part attributable to changes in reporting practices.

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Autism spectrum disorders (ASDs) are child neurodevelopmental disorders characterized by impairments in social interaction and communication and by repetitive behavior. The reported prevalence of ASDs has increased markedly during the past 3 decades.[1-5] The current ASD prevalence in children is estimated to be approximately 1%[4] but has been reported to be as high as 2.6%.[6] The apparent increase in ASD prevalence has led to much debate about how much can be attributed to a real increase in incidence owing to etiologic factors compared with the effects of nonetiologic factors, such as changes in reporting practices, greater public awareness, changes in referral patterns, and a decreasing age at diagnosis.[7] The unexplained increase in ASD prevalence has raised considerable public concern, with a possible effect on some parents' health care decisions for their children. For example, the claimed connection between the measles, mumps, and rubella vaccine and autism[8] may have had a negative effect on some parents' decisions regarding vaccination of their children. In fact, vaccination rates have declined in Denmark and other countries after the vaccine-autism connection was claimed,[9,10] followed by a significant increase in measles and mumps cases.[10,11]

Few studies have attempted to quantify the contribution of specific factors to changes in ASD prevalence. A number of investigations have looked at the effect of parental age changes and of certain perinatal risk factors on ASD prevalence under the hypothesis of a causal pathway.[12-14] Studies focusing on nonetiologic factors mainly have considered the contribution of an earlier age at diagnosis and diagnostic substitution.[15-18] Two studies noted a sharp increase in ASD prevalence coincident with a change in diagnostic criteria in Western Australia[19] and Denmark,[20] although the authors did not quantify this. Another study[21] used an age-period-cohort model[22,23] to disentangle prevalence trends into parts attributable to age, period, and cohort. However, the age-period-cohort model has identifiability issues[22]; hence, certain model constraints that may be difficult or impossible to validate must be imposed. To our knowledge, no study has quantified the effect on ASD prevalence of changes in reporting practices.

The Danish national health registries have undergone 2 major changes in reporting practices during the past 3 decades.[24] First, the mandatory diagnostic criteria for reporting to the Danish Psychiatric Register (DPR) changed in 1994 from the *International Classification of Diseases, Eighth Revision* (*ICD-8*), to the *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*). The introduction of the *ICD-10* meant the recognition of autism as a whole spectrum of disorders and a change in the specific symptoms needed to be met for an ASD diagnosis to be eligible. Changes in autism diagnostic criteria were not limited to the *ICD-10* but also were instituted in the same period in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) versions used primarily in the United States. Second, the DPR began to include discharge diagnoses from outpatient admissions in 1995, whereas only diagnoses from inpatient admissions had been reported historically. Thus, psychiatric diagnoses derived from a more diverse array of medical contacts from 1995 and since. Similar changes in national health registries occurred in other Nordic countries during the 1990s. In this population-based cohort study of all children born from January 1, 1980, through December 31, 1991, in Denmark, the aim was to quantify the effect on reported ASD prevalence of the diagnostic criteria change in 1994 and the inclusion of outpatient data to the DPR in 1995.

Methods

Study Population and ASD Outcome Information

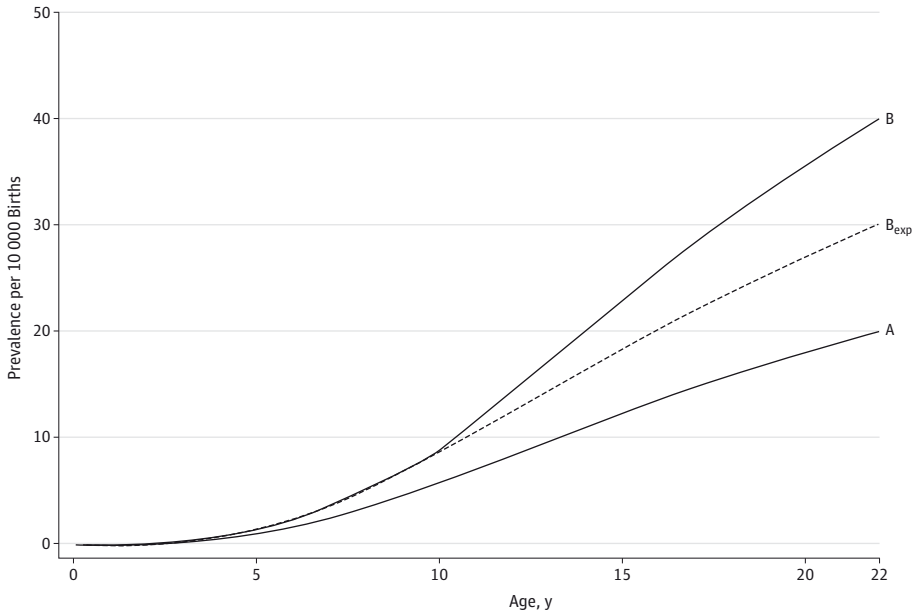
This study was approved by the Danish National Board of Health and the Danish Data Protection Agency. Consent from individuals for this register-based study was not required. The study cohort consisted of all children born alive from January 1, 1980, through December 31, 1991, in Denmark (n = 677 915). We limited ourselves to births before 1992 to ensure that ASD diagnoses were given before the change in diagnostic criteria in 1994. The births were identified through the Danish Medical Birth Registry, which consists of information on all births by women with permanent residence in Denmark.[25] Since 1968, all live-born children have been assigned a unique personal identification number[26] through which we linked birth data with ASD outcome and information on death and emigration.

Children in Denmark who are suspected of having an ASD are referred by general practitioners or school psychologists to a child psychiatric ward, where they undergo evaluation by a multidisciplinary team and are assigned a final diagnosis by a child psychiatrist; Danish health care is universal and free of charge. All cases of ASDs are registered in the DPR by psychiatrists once a formal diagnosis is established and without regard for the need for treatment or educational provisions. The DPR holds information on all inpatient admissions to psychiatric hospitals and wards since 1969 and, since January 1, 1995, it also includes information on outpatient admissions. The *ICD-8* was used as the diagnostic classification tool for reporting to the DPR from 1969 through 1993. On January 1, 1994, the *ICD-8* was replaced by the *ICD-10*, which is still used today.[24] We used the following ASD diagnosis codes: 299.00, 299.01, 299.02, and 299.03 from the *ICD-8* and F84.0, F84.1, F84.5, F84.8, and F84.9 from the *ICD-10*. The children in the study cohort were followed up from birth until they received an ASD diagnosis, died, or emigrated or until the end of follow-up on December 31, 2011, whichever occurred first. That is, death, emigration, and end of follow-up were treated as censoring events.

Statistical Analysis

How changes in reporting practices influence ASD prevalence can be estimated from age-specific prevalence curves when clinical diagnoses are collected continuously over time. The term *influence* refers to the change in prevalence estimated by comparing diagnosis rates before and after the time of a change in reporting practices. **Figure 1** illustrates this principle for a hypothetical disorder in hypothetical birth cohorts A and B. Cohort A is a reference birth cohort in which we assume that no changes in reporting practices have occurred during follow-up. Cohort B is a more recent birth cohort experiencing an increase in age-specific prevalence due to a calendar

Figure 1. Age-Specific Prevalence of a Hypothetical Disorder in Hypothetical Birth Cohorts A and B



Cohort A is a reference cohort in which we, for simplicity, assume that no changes in reporting practices occur; increases in prevalence are observed by age (prevalence estimate at 22 years of age, 20). Cohort B is a later cohort in which a change in reporting practices was implemented at 10 years of age (prevalence estimate at 22 years of age, 40). An expected prevalence curve (B_{exp}) for cohort B is computed under the scenario of an increase in prevalence of the disorder over calendar time (calendar effect) but assumes that no change in reporting practices took place (prevalence estimate at 22 years of age, 30).

effect (an effect connected to the time of birth) and a change in reporting practices at 10 years of age. The age at diagnosis distribution is assumed to be the same in both cohorts, that is, diagnoses are not given at an earlier or a later age in one cohort compared with the other. This assumption ensures proportional rates between the cohorts.[15] A Cox proportional hazards regression model can then be fitted to estimate the relative risk for a calendar time effect by comparing diagnosis rates in cohort B with those in cohort A to 10 years of age. The estimated relative risk for a calendar time effect may then be used to compute an expected age-specific prevalence curve for cohort B under the assumption of an increase in prevalence due to a calendar effect only (B_{exp} in Figure 1).

The total increase in prevalence between cohorts A and B at the end of follow-up is the difference between the 2 observed prevalence curves at 22 years of age (40 − 20 per 10 000). The increase in prevalence associated with the change in reporting practices is the difference in cohort B at 22 years of age between the observed and expected prevalence curves with no change in reporting practices (40 − 30 per 10 000). The proportion of the total increase in the observed prevalence between cohorts A and B at 22 years of age that is explained by the change in reporting practices is thus (40 − 30)/(40 − 20) = 50%.

For our analysis, the ASD prevalence curves against calendar time and age were estimated for each 1-year birth cohort using the Kaplan-Meier estimator. The calendar years (1994 and 1995) or corresponding ages of cohort members (3-15 years) at which the changes in reporting practices occurred are marked in the respective graphs. For the rest of the statistical analyses, we divided the study cohort into 2-year birth subcohorts (1980-1981, 1982-1983, 1984-1985, 1986-1987, 1988-1989, and 1990-1991) and we fixed the time scale to be age. This method ensured that the age at diagnosis distribution is constant within each subcohort; larger subcohorts could invalidate this assumption. We checked the assumption by inspecting whether the diagnosis rates were proportional within each subcohort by log-minus-log plots; we further validated the assumption by comparing observed Kaplan-Meier curves with estimated prevalence curves under the model.

The analysis was slightly more complicated than described by Figure 1 because all individuals experienced 2 changes in reporting practices occurring at different times. Moreover, the prevalence curve for the reference birth cohort in our study is also under the effect of changes in reporting practices that have to be removed to replicate the cohort A scenario of Figure 1. This removal was performed using the same technique that we used to remove the effect of a change in reporting practices for cohort B in the example of Figure 1. A mathematical description of the analytic approach appears in the eAppendix in the Supplement.

Overall effects of the 2 changes in reporting practices were estimated by fitting a Cox proportional hazards regression model stratified on the subcohorts. That is, we allowed separate baseline rates and separate linear calendar effects in each subcohort to allow for variability in calendar effect between the subcohorts. The change in diagnostic criteria and inclusion of outpatient data were both modeled as time-dependent covariates in the same stratified Cox model. In this connection, a child became at risk for an *ICD-10* diagnosis on January 1, 1994, and at risk for an outpatient diagnosis on January 1, 1995. We also investigated time trends in the effects and computed sex-specific overall effects by stratification.

The proportions of the observed increase in ASD prevalence that can be explained by the 2 changes in reporting practices were computed as follows. For every individual in the study, we computed his or her expected prevalence curves by age in each of the following scenarios: (1) no changes in re-

Table 1. Numbers of Live Births and Reported ASD Diagnoses Before, Between, and After the Diagnostic Change and Inclusion of Outpatient Data

	No. of Births	No. of Reported ASD Diagnoses		
		1980-1993	1994-1995	1996-2011
Overall	**677 915**	**192**	**100**	**3664**
Sex				
Male	347 955	154	85	2865
Female	329 960	38	15	799
2-y Birth cohort				
1980-1981	110 170	37	9	179
1982-1983	103 335	46	21	311
1984-1985	105 404	38	6	452
1986-1987	111 362	30	15	599
1988-1989	120 003	28	32	870
1990-1991	127 641	13	17	1253

Abbreviation: ASD, autism spectrum disorder.

porting practices and no calendar effect (baseline prevalence); (2) only a calendar effect; (3) a calendar effect and a diagnostic change; (4) a calendar effect and the inclusion of outpatients; and (5) a calendar effect, a diagnostic change, and the inclusion of outpatients. By calculating mean individual-specific expected prevalence curves in each of the 5 scenarios, we present expected prevalence curves for the whole study population in the 5 scenarios. Based on the expected prevalence estimates at 22 years of age (the end of follow-up for the latest subcohort), we calculated the proportion of the prevalence increase that can be explained by the changes in reporting practices. To obtain 95% CIs for the proportions and prevalence estimates at 22 years of age in the 5 scenarios, we used the bootstrap method with 1000 replications. We used commercially available statistical software (STATA/SE, version 13.1; StataCorp) in all calculations.

Sensitivity Analyses

In the main analysis, 2-year subcohorts were chosen such that model assumptions were satisfied while having a parsimonious model to estimate the changes in reporting practices. Larger subcohorts would likely invalidate the model assumption that the age at diagnosis would be constant within subcohorts, whereas smaller subcohorts would yield more imprecise estimates. To assess how the parameter estimates depend on the size of the subcohorts, we analyzed the data using 1- and 3-year subcohorts.

The proportion of the prevalence increase explained by the changes in reporting practices were calculated based on mean expected prevalence estimates at 22 years of age corresponding to the end of follow-up for the latest subcohort (1990-1991). We performed the same calculation based on the mean prevalence estimates at the end of follow-up for each subcohort specifically (22-32 years of age).

One of the main psychiatric hospitals in Denmark did not report diagnoses to the DPR until 1992.[20] In a sensitivity analysis, we assessed whether adjusting for this feature made any impression on the effects of the diagnostic change and the inclusion of outpatient data.

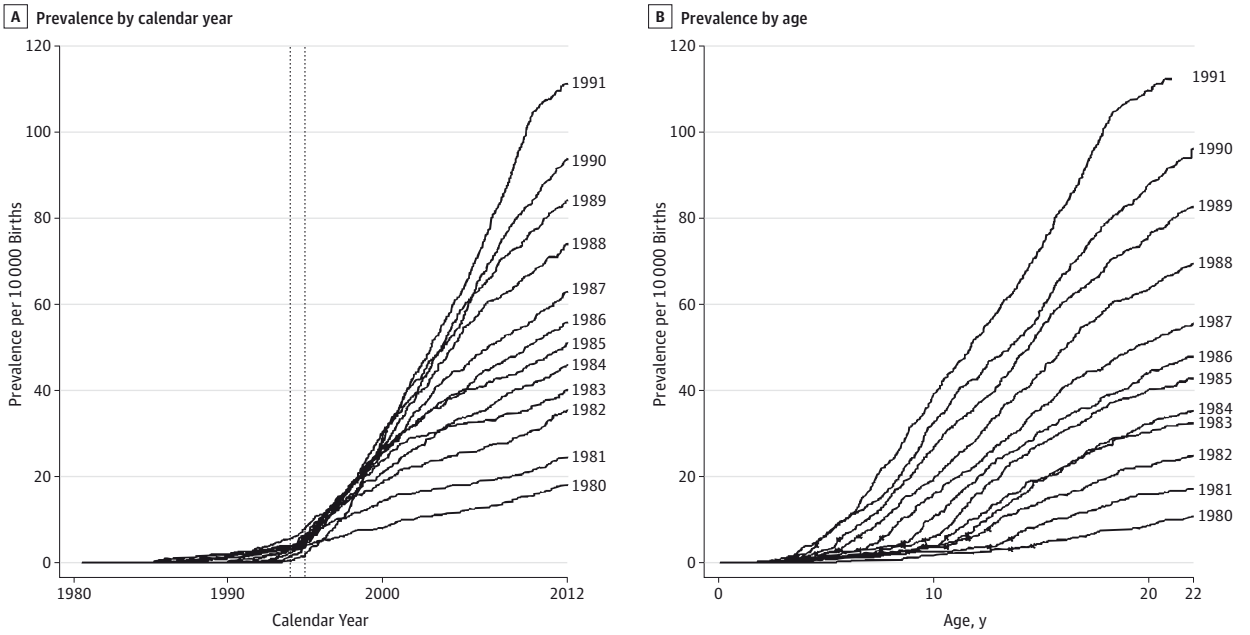
Results

Of the 667 915 children born from 1980 through 1991 in Denmark, a total of 3956 received an ASD diagnosis before the end of follow-up (**Table 1**). Of these, 192 diagnoses were reported before 1994; 100, from 1994 through 1995; and 3664, after 1995. Kaplan-Meier plots of observed ASD prevalence in 1-year birth cohorts against calendar time and age showed a sharp increase around the calendar years and cohort ages corresponding to the diagnostic change (1994; 3-14 years of age) and inclusion of outpatient data (1995; 4-15 years of age) (**Figure 2**).

The overall diagnostic change effect was estimated as a hazard ratio (HR) of 1.42 (95% CI, 0.99-2.04; $P = .06$). The overall outpatient effect was estimated as an HR of 1.62 (95% CI, 1.24-2.12; $P < .001$). For male participants, the diagnostic change and outpatient effects were estimated as HRs of 1.84 (95% CI, 1.20-2.80) and 1.73 (95% CI, 1.28-2.35), respectively, with both being statistically significant ($P < .001$). For female participants, the 2 effects were estimated as HRs of 0.58 (95% CI, 0.27-1.23) and 1.33 (95% CI, 0.74-2.37), respectively, and neither was statistically significant ($P = .15$ and $P = .34$, respectively). The diagnostic change effect differed significantly by sex ($P = .01$), whereas the outpatient effect did not ($P = .42$). No time trends were observed in either of the 2 effects ($P = .10$ and $P = .07$, respectively) (**Table 2**).

Figure 3 shows the mean expected prevalence curves in the 5 scenarios. The prevalence estimates at 22 years of age in the 5 scenarios are 9.4 (95% CI, 3.5-24.7), 41.7 (95% CI, 16.3-106.3), 57.9 (95% CI, 25.1-132.9), 64.7 (95% CI, 27.7-150.4), and 90.5 (95% CI, 44.5-182.9) per 10 000 for scenarios 1 through 5, respectively. The increase in prevalence owing to calendar effect and the diagnostic change is the difference in prevalence of scenarios 3 and 1, that is, 57.9 and 9.4 per 10 000. The increase in prevalence due only to the diagnostic change is the difference in prevalence of scenarios 3 and 2, that is, 57.9 and 41.7 per 10 000. Thus, 33% (95% CI, 0%-70%) of the total increase in observed prevalence ([57.9 − 41.7]/[57.9 − 9.4]) can be explained by the change in diagnostic criteria alone. Simi-

Figure 2. Prevalence Estimates per 10 000 of Autism Spectrum Disorders by Calendar Time and Age for Each 1-Year Birth Cohort



A, Prevalence estimates by calendar year. The years of changes in reporting practices are marked as dotted vertical lines. B, Prevalence estimates by age. The ages of changes in reporting practices are marked as crosses on each cohort curve. Birth cohorts are labeled at the end of each curve.

Table 2. HRs of the Diagnostic Change and Outpatient Effect on ASD Prevalence Using 1980-1991 Births in Denmark

	Diagnostic Change Effect			Outpatient Effect		
	HR (95% CI)	*P* Value for No Effect	*P* Value for Homogeneity	HR (95% CI)	*P* Value for No Effect	*P* Value for Homogeneity
Overall	1.42 (0.99-2.04)	.06	NA	1.62 (1.24-2.12)	<.001	NA
Sex						
Male	1.84 (1.20-2.80)	<.001	.01	1.73 (1.28-2.35)	<.001	.42
Female	0.58 (0.27-1.23)	.15		1.33 (0.74-2.37)	.34	
2-y Birth cohort						
1980-1981	1.74 (0.55-5.52)	.35	.10	2.27 (0.91-5.66)	.08	.07
1982-1983	2.36 (0.99-5.59)	.05		1.52 (0.79-2.90)	.21	
1984-1985	0.89 (0.29-2.70)	.83		3.26 (1.39-7.69)	.007	
1986-1987	2.08 (0.80-5.42)	.13		2.86 (1.46-5.59)	.002	
1988-1989	1.46 (0.74-2.88)	.28		0.94 (0.55-1.62)	.82	
1990-1991	0.66 (0.29-1.52)	.33		1.26 (0.69-2.29)	.46	

Abbreviations: ASD, autism spectrum disorder; HR, hazard ratio; NA, not applicable.

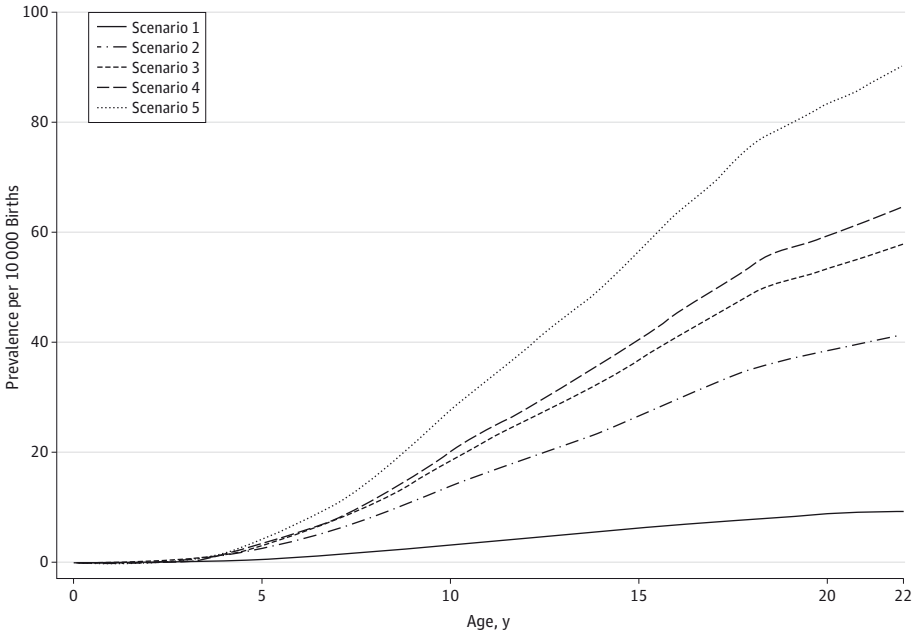
lar calculations show that 42% (95% CI, 14%-69%) of the total increase in observed prevalence ([64.7 − 41.7]/[64.7 − 9.4]) can be explained by the inclusion of outpatient data alone, and 60% (95% CI, 33%-87%) of the increase in observed prevalence ([90.5 − 41.7]/[90.5 − 9.4]) can be explained by the change in diagnostic criteria and inclusion of outpatient data.

Using 1- or 3-year subcohorts did not alter the outpatient effect significantly. On the other hand, the effect of diagnostic change was estimated to be somewhat larger when using 3-year subcohorts and somewhat smaller when using 1-year subcohorts. In the latter case, the estimated diagnostic change effect was associated with a much larger 95% CI than in the original analysis. Calculating the explained increase in prevalence based on prevalence estimates at the cohort-specific end of follow-up rather than at 22 years of age yielded very similar results, as did adjusting for the addition of diagnoses from a main psychiatric hospital in 1992.

Discussion

This study is, to our knowledge, the first to quantify the direct effect of 2 types of changes in reporting practices on ASD prevalence. The study demonstrated that most (60%) of the increase in ASD prevalence in children born from 1980 through 1991 in Denmark based on registry-reported diagnoses can be

Figure 3. Mean Expected Prevalence Curves to 22 Years of Age for 5 Scenarios



Scenario 1 indicates no changes in reporting practices and no calendar effect (baseline prevalence); 2, only a calendar effect; 3, a calendar effect and a diagnostic change; 4, a calendar effect and the inclusion of outpatients; and 5, a calendar effect, a diagnostic change, and the inclusion of outpatients (total observed prevalence). Prevalence estimates at 22 years of age are 9.4, 41.7, 57.9, 64.7, and 90.5, respectively.

explained by the change in diagnostic criteria in 1994 and the inclusion of outpatient data to the DPR in 1995. We found a larger effect on ASD prevalence in male than in female participants owing to the change in the diagnostic criteria, and we found no sex difference owing to the inclusion of outpatient data.

The change in diagnostic criteria may have had broader effects on ASD prevalence than can be captured by comparing diagnosis rates before and after the change in diagnostic criteria in 1994. The diagnostic change might have led to a gradual increase in prevalence caused by, for example, a growing awareness among clinicians of the ASD features after the change that could have gradually altered the clinical perception of ASD. This effect would not be captured in our single-point-in-time estimate of the diagnostic change effect but would instead be captured in the calendar effect and thus possibly underestimate the diagnostic change effect. On the other hand, increases in autism awareness around 1994 and 1995 not caused by the changes in reporting practices would likely be part of the estimated effects, resulting in overestimation. We observed a larger effect of changing the diagnostic criteria on ASD prevalence in male compared with female participants, suggesting that the relatively larger ASD prevalence increase observed in male compared with female patients over time[27] may be more attributable to changes in diagnostic criteria than in other types of reporting practices. In our study, the inclusion of outpatient data seemed to affect ASD prevalence rates in Danish boys and girls fairly equally.

Among the strengths of this study is that we used a population-based birth cohort approach with large sample sizes. The psychiatric diagnoses are collected continuously over time and are thought to be very complete because of the universal health care access in Denmark and prospective reporting to the registers. The reported diagnoses of childhood autism to the DPR have been validated,[28] with 94% meeting the criteria for a correct diagnosis among 499 medical records evaluated. The quality of ASD diagnoses has not been validated but generally is believed to be high.[29] We observed an ASD prevalence of 24 per 10 000 in children 8 years of age born in 1991, an estimate comparable to the prevalence of 34 per 10 000 in children aged 3 to 10 years born from 1987 through 1993 in the United States[30] but below the estimate of 67 per 10 000 in children 8 years of age born in 1992 that is based on the Autism and Developmental Disabilities Monitoring Network.[31]

Among the limitations of the study is that our conclusions apply to ASDs in Denmark only. The study exploits the fact that the change in diagnostic criteria and the inclusion of outpatients occurred in different years. The disentanglement of the 2 effects thus relies on the number of cases between the 2 changes. Consequently, the 2 individual effects, although estimated jointly, may not be as reliable as the combined effect because part of the effects of one may have been carried over to the other.

Conclusions

This study supports the argument that the apparent increase in ASD prevalence in Denmark in recent years is in large part attributable to changes in reporting practices over time. However, a considerable part of the increase in ASD prevalence is not explained by the 2 changes in reporting practices. Thus, the search for etiologic factors that may explain part of the remaining increase remains important.

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Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Hansen, Parner.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Hansen, Parner.
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