Variation in Incidence of Neurodevelopmental Disorders With Season of Birth

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Background: The etiologies of autism spectrum disorder and many neurodevelopmental disorders are largely unknown. The detection of a seasonal variation of birth of children diagnosed with a certain disorder could suggest etiological factors that follow a seasonal pattern. We examined the seasonal variation of births of children diagnosed with any of 4 common childhood neuropsychiatric disorders: autism spectrum disorder, hyperkinetic disorder, Tourette syndrome, and obsessive-compulsive disorder.

Methods: The study cohort consisted of all children born in Denmark from 1990 through 1999 identified in the Danish Medical Birth Register (n = 669,995). Outcome data consisted of both inpatient and outpatient diagnoses reported to the Danish National Psychiatric Registry from 1995 through 2004 using the International Classification of Diseases, 10th edition, diagnostic coding system. Logistic regression combined with spline (a smoothing method) was used to estimate the variation with season of birth for each disorder. Estimates of risk of each disorder with season of birth were adjusted for differences in follow-up time and change in incidence over time.

Results: No convincing variations in season of birth were observed for any of the 4 disorders, or for the autism-spectrum-disorder subtypes.

Conclusion: Although we cannot rule out the possibility of seasonal variation of birth for a range of childhood neurodevelopmental disorders, we find little evidence that seasonal environmental factors are related to these disorders.

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The detection of seasonal variation in the birth of children with neuropsychiatric disorders could provide clues to etiological factors that follow a similar seasonal pattern. An excess of winter–spring births has consistently been reported in schizophrenia, leading to speculations of an association between schizophrenia and factors following a seasonal pattern.[1] Such factors could include the mother's nutritional condition during pregnancy, her exposure to influenza or other infections, maternal hormones, or meteorological factors, such as humidity or temperature. These risk factors could possibly affect the development of other neuropsychiatric disorders.

In this study, we examined the seasonal variation of birth of children diagnosed with any of 4 common neuropsychiatric developmental disorders that emerge in childhood: hyperkinetic disorder, obsessive-compulsive disorder, Tourette syndrome, or autism spectrum disorder. All 4 disorders have specific diagnostic criteria and high comorbidity.[2,3]

In ICD-10 (International Classification of Diseases, 10th Edition[4]), autism spectrum disorder includes a group of disorders characterized by qualitative abnormalities in reciprocal social interactions; patterns of communication; or a restricted, stereotyped, repetitive repertoire of interests and activities; or a combination thereof. Hyperkinetic disorder is characterized by lack of persistence in activities that require cognitive involvement and a tendency to move from one activity to another without completing any one, together with disorganized, ill-regulated, and excessive activity. The essential feature of obsessive-compulsive disorder is recurrent obsessive thoughts or compulsive acts. Tourette syndrome is a form of tic disorder in which there are multiple motor tics and one or more vocal tics. We studied the seasonal variation of birth of children diagnosed with one or more of these psychiatric disorders.

METHODS

Study Design

This was a population-based cohort study that included all children born in Denmark from 1 January 1990 through 31 December 1999. The cohort was identified using the Danish Medical Birth Registry. The Registry was established in 1968 and 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, which is a unique 10-digit number used for all official personal registrations in Denmark since 1968.[5]

Data on outcome were from the Danish National Psychiatric Registry. All inpatient admissions to psychiatric hospitals and psychiatric wards in general hospitals in Den-

TABLE 1. A Description of the Birth Cohort Used for Each Disorder

	ICD-10 Code	Birth Cohort	No. Cases	Children Born at ≥37 Weeks No. (%)	No. Births
Hyperkinetic disorder	F90	1992–1999	2033	1722 (85)	542,213
Obsessive-compulsive disorder	F42	1990–1995	485	431 (89)	402,315
Tourette syndrome	F95.2	1990–1995	259	235 (91)	402,315
Autism spectrum disorder	F84.0, F84.1, F84.5, F84.8, F84.9	1994–1999	1860	1669 (90)	407,118
Childhood autism	F84.0	1994–1999	714	630 (88)	407,118
Atypical autism	F84.1	1994–1999	145	130 (90)	407,118
Asperger syndrome	F84.5	1994–1999	350	325 (93)	407,118
Pervasive developmental disorder–not otherwise specified	F84.8, F84.9	1994–1999	651	582 (90)	407,118

mark have been registered since 1969. Psychiatric outpatient contact has been reported since 1 January 1995. The Psychiatric Registry includes data on clinical diagnoses, dates of admission and discharge, and terms of admission.[6] All diagnoses are made by psychiatrists, and the ICD-10 diagnostic coding criteria have been used since 1994. The specific diagnostic codes used for this study are provided in Table 1. For autism spectrum disorder, analyses were performed for the disorder as a whole, as well as for each subdiagnosis.

Data from the Birth Registry were linked to the Psychiatric Registry using the Central Population Registry number. For this study, follow-up time for a reported diagnosis was restricted to the time period after inclusion of both inpatient and outpatient registration and adoption of ICD-10 in the Psychiatric Registry (1 January 1995 through 31 December 2004). The youngest age of reported diagnosis was 3 years for hyperkinetic disorder, 1 year for autism spectrum disorder and subgroups, and 5 years for obsessive compulsive disorder or Tourette syndrome. To insure that no children included in the analyses for a particular disorder received a diagnosis before 1 January 1995, different birth cohorts within the larger study cohort were used for the analysis of each disorder. Table 1 displays the different analytic birth cohorts for each disorder.

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

Analytic Approach

The effect of any changes in incidence of reported diagnoses over time needed to be removed to estimate the actual seasonal variation. For example, increased rates of autism and attention deficit hyperactive disorder have been reported in recent years.[7,8] Such increases can impose a crude seasonal variation when data are pooled across years. This effect of the time trend on seasonal variation is shown in Figure 1, in which the risk of being diagnosed with hyperkinetic disorder for children born in December is increased compared with children who are born in January. Consequently, we adjusted for time trends in the analysis as described below.

Each disorder was analyzed separately. Children with more than one autism spectrum disorder subdiagnosis were included in the analysis for the most severe autism spectrum disorder subdiagnosis (defined as the diagnosis with the lowest extension number on the F84.x code), as well as in the analysis for the combined group of autism spectrum disorder. Some children had 2 or more different diagnoses, such as Tourette syndrome and hyperkinetic disorder; in those cases, the child was included as an outcome in the analysis for each separate condition. With this approach, the analysis of each condition could include children with only one diagnosis and children with 2 or more different diagnoses. The association with seasonal variation could differ for children with single and multiple conditions. However we could not distinguish these because of the small numbers of eligible cases. However, we did perform a sensitivity analysis by excluding children with multiple diagnoses and reestimating the seasonal variation effect for each condition based only on children with a single diagnosis.

The follow-up time began for all children at birth and continued until the date of a relevant diagnosis or death or until the end of follow-up time on 31 December 2004. No
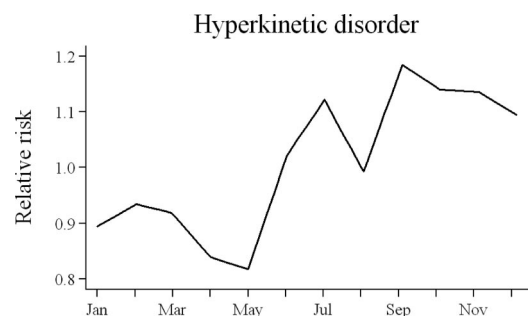

FIGURE 1. The seasonal variation of birth for Danish children born 1992–1999 and diagnosed with hyperkinetic disorder, with no adjustments made for the general trend for increased incidence of reported diagnoses over time.

attempts were made to adjust for out-migration; Denmark has a low rate of out-migration.[9]

When working with right-censored data, the appropriate analytic method is usually Cox regression which accounts for incomplete follow-up time. However, Cox regression assumes proportionality of the hazards, and our data did not meet this assumption. When we compared our cruder adjustment for right-censored data with Cox regression analyses, we found there was no major difference in the results.

Seasonal variation in the birth of diagnosed children was estimated by logistic regression, using STATA version 8.0 (StataCorp, College Station, TX). The risk of being diagnosed depended on the length of the follow-up time, possible increase in risk over time (time trends), and possible seasonal variation of births. These 3 factors were described in a model using the cubic spline method.[10] Splines are a smoothing technique, and the cubic spline is a variant that consists of piecewise cubic polynomials. The spline is modeled as a set of explanatory variables (the spline variables) in a regression analysis. The spline function allowed the assumption of a periodic season. A periodic season involved 2 restrictions: (1) the risk estimates at the end of December were restricted to be equal to the risk estimates at the beginning of January and (2) the slope of the curve at the end of the year was restricted to be equal to the slope of the curve at the start of the year. Because of these 2 restrictions, the number of parameters (spline variables) included in the seasonal spline function was reduced by two. The number of knots was, however, unchanged. The validity of the assumption of a periodic season was confirmed using a likelihood ratio test.

The present analysis included 2 spline functions. The first spline function described the seasonal variation using 6 spline variables, corresponding to 3 knots, equally spaced. More than 4 variables are seldom required in a restricted cubic spline analysis,[11] but because the present study included a large sample size the seasonal variation was fitted using 6 variables. The assumption of a periodic season reduced the number of spline variables to four. Thus only 4 degrees of freedom were used in estimating the seasonal variation and in testing the statistical significance of the seasonal variation; hence, increased statistical power was obtained. The second spline adjusted for the time trend and difference in follow-up time, ie, the second spline described calendar time. This second spline function was fitted using 3 spline variables. The reason for using a relatively low number of spline variables in the second spline was to obtain a rather smooth spline function and thus to avoid coincidently adjusting for a part of the seasonal variation. The final analysis was performed using logistic regression on 7 spline variables. The test for a seasonal variation of birth was performed by testing the statistical significance of the seasonal spline function (the 4 seasonal spline variables), ie, hypothesizing no seasonal variation of birth.

The use of the spline variables in the analysis allowed a day-by-day analysis of the seasonal variation of birth and thereby avoided grouping the year into months, quarters, or other arbitrary time intervals within the year, as has been done in previous studies. The relative risk (RR) curves compared the risk of a particular day to the average risk over the whole year. The 95% confidence interval (CI) was calculated according to the fit of the spline model, ie, the confidence interval corresponded to the fit evaluated for each individual day. To demonstrate the adequacy of the fit of the smoothed seasonal-spline function, we display in Figure 2 the point estimates obtained by grouping the season into months, while still adjusting for the time trend and differences in follow-up time using the second spline.

Seasonal variation could be associated with risk factors arising at different times in pregnancy, such as during the first or second trimester, and not just around the date of delivery. If variation in length of pregnancy was not considered, then seasonal variation in pregnancy exposures arising at times other than delivery might be missed. Alternatively, variation in gestational length might be on the causal pathway in the association between season of birth and outcome, such as if seasonal variation in infectious exposures leads to preterm births, which in turn could lead to one of the studied neurodevelopmental outcomes. Although it was desirable to explore the relation between season of birth and outcome by gestational age, the numbers of preterm (≤37 weeks' gestation) children for obsessive-compulsive disorder, Tourette syndrome, or the autism spectrum disorder subdiagnoses were generally too small for reliable estimates; subanalyses of preterm children were performed only for children with hyperkinetic disorder or autism spectrum disorder as a whole. For all diagnoses, to control for differences in length of gestation, we performed subanalyses of the relation between season of birth and outcome that included only term (>37 weeks' gestation). For each disorder, the number of children born at term is displayed in Table 1.

Risk factors arising at the exact time of conception could be of great importance. Data included information on gestational age, and so we were able to estimate date of conception. Therefore, we additionally performed the analyses based on estimates of the season of conception, rather than season of birth.

RESULTS

A total of 4376 children were diagnosed with a total of 4637 disorders. The numbers of children diagnosed with each disorder are shown in Table 1.

Figure 2 shows the adjusted seasonal variation in birth for the various subdiagnoses. The figure displays the seasonal variation from the smoothing function, with 95% CI and the adequacy of the fit of the smoothing function, by demonstrating risk estimates after grouping the birth year into months. For each of the disorders, the relative risk estimates for birth at different dates during the year ranged from slightly under 1.0 to slightly over 1.0. The CIs were calculated separately for each day; CIs can be used only to estimate the uncertainty of the measurement of each day, not to compare 2 separate days. Atypical autism had the greatest variation in relative risk estimates, ranging from the lowest risk estimate of 0.71 (95% CI = 0.49–1.02) for children born in September, to the highest risk estimate of 1.29 (0.90–1.85) for children born in
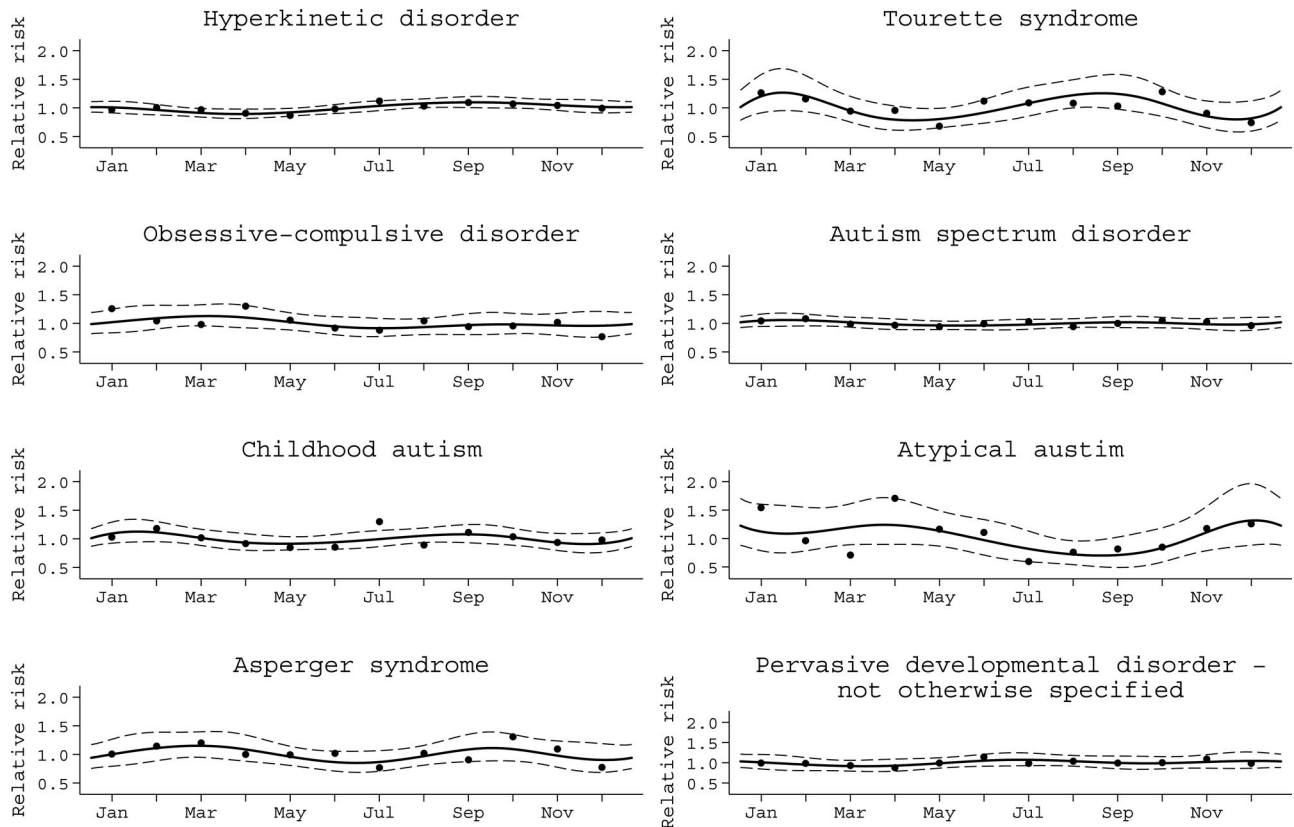
FIGURE 2. The estimated adjusted seasonal variation of birth (solid line), with 95% CIs (dashed line) and the point values, after grouping the season into months, for Danish children diagnosed with various conditions by 31 December 2004. Children born 1990–1995 were included in the analyses of Tourette syndrome or obsessive-compulsive disorder. Children born 1992–1999 were included in the analysis of hyperkinetic disorder. Children born 1994–1999 were included in the analyses of autism spectrum disorder or the autism spectrum disorder subdiagnoses.

December. Autism spectrum disorder overall had the least variation in risk estimates, ranging from 0.96 (0.89–1.04) for children born in May to 1.06 (0.95–1.18) for children born in February. Disorders with a relatively low case count, such as atypical autism and Tourette syndrome, displayed a great variation in the range of risk estimates within a year, while disorders with a high case count, such as hyperkinetic disorder or the autism spectrum disorder overall, displayed only minor variation in risk estimates within the year.

No convincing evidence for variation in season of birth was observed for any of the 4 disorders, or the autism spectrum disorder subdiagnoses (hyperkinetic disorder: $P = 0.06$; Tourette syndrome: $P = 0.14$; obsessive compulsive disorder: $P = 0.71$; autism spectrum disorder: $P = 0.83$; childhood autism: $P = 0.52$; atypical autism: $P = 0.27$; Asperger syndrome: $P = 0.55$; and pervasive developmental disorder-not otherwise specified: $P = 0.83$). There was no change in these results based on the subanalyses of term children alone, the subanalyses of children born preterm with hyperkinetic disorder or autism spectrum disorder, or the sensitivity analyses of children with a single diagnosis. When analyzing data by season of conception, the association of season with hyperkinetic disorder became slightly stronger ($P = 0.04$).

DISCUSSION

This study found no substantial seasonal variation in birth for hyperkinetic disorder, obsessive-compulsive disorder, Tourette syndrome, autism spectrum disorder, or for any one of the autism spectrum disorder subdiagnoses. There was some evidence of a seasonal effect for hyperkinetic disorder, with higher rates in autumn and lower in spring.

Many previous studies have looked at seasonal variation in the birth of children with autism, with inconsistent results. Earlier studies, many with small sample sizes, found an increased risk of developing autism among births in certain months,[12–17] while more recent and often larger studies have reported no consistent seasonal variation.[18–20] No studies have explored seasonal variations in birth for children diagnosed with hyperkinetic disorder, although a report[21] on attention-deficit/hyperactivity disorder (ADHD) found that certain small subgroups of children with ADHD had an increased risk of being diagnosed with ADHD if they were born in September. Diagnostically, ADHD (based on the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition) overlaps hyperkinetic disorder (based on the ICD-10) regarding symptoms of hyperactivity,

but, unlike hyperkinetic disorder, ADHD also permits symptoms of inattention in the absence of hyperactivity.[22] Greenberg[23] found no seasonal variation of birth for obsessive compulsive disorder in 1981. No studies have been published on seasonal variation of birth of children with Tourette syndrome.

Previous studies have had a number of limitations which are addressed in the present study. Unlike prior studies, we applied a day-by-day analysis. This approach is preferred, compared with arbitrarily dividing the year into months or quarters.[17,20] Dividing the year into months causes the loss of statistical power, either by multiple testing in which 12 separate significance tests are performed[13] or by the use of a single test with 12 categories resulting in a test with 11 degrees of freedom.[12,17,20] It is not known if the time of birth or the time of different prenatal periods is of importance when studying seasonal variation. Thus, the crude and arbitrary classification of season of birth into months or yearly quarters gives limited information on both the exact time of birth and the time of different periods within the pregnancy. This study tested for seasonal variation of birth using 4 degrees of freedom and no categorization of the season of birth.

Bolton et al[18] emphasized the necessity of adjusting for the general time trend when studying the seasonal variation of birth of children with disorders that have a change in incidence by year of birth. In the present study, the increase in incidence of reported diagnoses by year of birth affected the seasonal variation. The chance of being diagnosed increased continuously from January through December each year. This created an artifact when many continuous years were combined, causing a dramatic decrease in risk for select disorders between births at the end of December (highest risk) and the beginning of January (lowest risk). This risk difference was unlikely to have been associated with etiologic mechanisms linked to seasonal variation because living conditions (eg, weather, diet, or infection rates) among these 2 consecutive months were similar. Adjusting for time trends in incidence of reported diagnosis removed this artifact, and the true seasonal variation could then be estimated.

This study involved large cohorts of children based on data from a nationwide psychiatric register in which diagnostic information for all conditions were uniformly reported using the same diagnostic coding system (ICD-10). Nevertheless, a limitation of the present study was that, while all diagnoses in the Psychiatric Registry are reported by psychiatrists, generally the diagnoses have not been validated by external review. A small pilot validation of the childhood autism diagnosis verified the validity of 40 infantile autism diagnoses recorded in the Psychiatric Registry[24]; 92% met the criteria for autistic disorder, based on a coding scheme developed by the Centers for Disease Control and Prevention.[25] An unofficial validation of 171 hyperkinetic disorder diagnoses was performed by Linnet[26] in 2004; the agreement percentage on a full diagnosis of ADHD was 89%, while the remaining 11% lacked only one symptom to fulfill this diagnosis. While not comprehensive or definitive, these stud-ies suggest that, in general, the validity of the reported diagnoses in the Psychiatric Registry is acceptable.

Although our putative marker for exposure was date of birth, there could have been other time points in pregnancy at which the true seasonal exposure of risk occurred. We attempted to control for this possibility by limiting our subanalysis to full-term children, so that season of birth also served as a proxy measure for season of conception, first trimester, second trimester, etc. We also attempted to perform the analysis for preterm children because of the possible link between premature birth and infection during pregnancy. Due to the limited number of preterm births, this analysis was possible only for hyperkinetic disorder and autism spectrum disorder overall (Table 1). For all disorders, no significant seasonal variation was observed for the subgroups of children born at term, nor was there seasonal variation observed for children diagnosed with autism spectrum disorder or hyperkinetic disorder and born preterm. We combined all preterm births into a single category, although the association between season of birth and outcome could have varied by gestational age within this heterogeneous group. The inability to perform analyses with more narrowly defined ranges of gestational age might have reduced our ability to detect a seasonal variation effect on autism spectrum disorder overall or hyperkinetic disorder among the preterm children. When analyzing data by season of conception, only one disorder (hyperkinetic disorder) reached statistical significance ($P = 0.04$). We believe that caution is required when interpreting this finding. Although this result might represent a true variation in season of conception, it may also represent the result of multiple testing—a mere chance finding. Replication in other data sets would be needed before this single finding could be given more weight.

Seasonal variation of birth is a fairly crude proxy measure for more specific exposures that vary seasonally and may be linked etiologically with one of these disorders. In fact, seasonal exposures that vary in the time of year might counterbalance each other and be undetectable in a general analysis of season of birth. Thus, the lack of a seasonal variation of birth does not exclude the possibility that one or more environmental factors, such as infection, could be related to these disorders.

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