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Timing of Increased Autistic Disorder Cumulative Incidence

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Autistic disorder (AD) is a severe neurodevelopmental disorder typically identified in early childhood. Both genetic and environmental factors are implicated in its etiology. The number of individuals identified as having autism has increased dramatically in recent years, but whether some proportion of this increase is real is unknown. If real, susceptible populations may have exposure to controllable exogenous stressors. Using literature AD data from long-term (~10-year) studies, we determined cumulative incidence of AD for each cohort within each study. These data for each study were examined for a changepoint year in which the AD cumulative incidence first increased. We used data sets from Denmark, California, Japan, and a worldwide composite of studies. In the Danish, California, and worldwide data sets, we found that an increase in AD cumulative incidence began about 1988−1989. The Japanese study (1988−1996) had AD cumulative incidence increasing continuously, and no changepoint year could be calculated. Although the debate about the nature of increasing autism continues, the potential for this increase to be real and involve exogenous environmental stressors exists. The timing of an increase in autism incidence may help in screening for potential candidate environmental stressors.

Introduction

Autism is considered a common, serious neurodevelopmental disability (*1*). It is a pervasive disorder that often results in severe morbidity but has no specific diagnostic biomarkers and an uncertain etiology. It is a heterogeneous, behaviorally defined spectrum of related disorders typically diagnosed in early childhood and varying in pervasiveness, severity, and onset (*2*). There are five core subtypes of autism; each is defined by the presence of abnormal behaviors involving language, social interaction, and repetitive or ritualistic patterns of activities or interests and by the age of onset (*3, 4*). As a group, these subtypes are referred to as "pervasive developmental disorders" (PDDs) in the most recent diagnostic systems (*3, 4*). Autistic spectrum disorder (ASD) is a subset of this, composed of autistic disorder (AD), Asperger syndrome, and PDD not otherwise specified (*5*). AD or classic or infantile autism of earlier classifications (*6*) is one of the most severe forms of autism and is diagnosable by age 3 (*4*).

Autism limits the functioning of the affected individual (*7*), increases parental stress, and places a heavy burden on their families (*5*). The care for an autistic individual over a lifetime has been estimated to be between $3.2 M (*8*) and $4.7 M (*9*). With many recent studies finding an increasing trend in the number of autistic individuals identified (*1, 6, 10*−*22*), the total health care costs continue to increase. Thus, the proportions of these cases that may represent a real increase or be caused by changes in diagnostic criteria, reporting, or available services remain important research (*23*) and societal questions.

The genetic contribution to the etiology of autism is based on results from twin and family studies, as well as on co-occurring genetic disorders (*24*). For the most part, the genetic component of autism does not follow a simple model of inheritance (*25*), and more than 29 genes currently are implicated (*26*). Environmental exposure to exogenous environmental factors (intrauterine rubella, thalidomide, and valproate) also has been linked to the development of autism in some individuals, but none of these exposures are invariably associated with autism (*27*). Thus, it may be a complex interaction between exposure to environmental stressors and genetic susceptibility that leads to the phenotypic expression of autism (*23, 24, 28*).

If some portion of the observed increases in autism cases in recent studies is not due to various artifacts, then such rapid increases would be unlikely to result from genetic mechanisms alone. This suggests that such an increase might be due to an increasing exposure to exogenous environmental factors (*27, 29, 30*) affecting susceptible individuals during vulnerable periods of their development (*28*). Some research has examined possible contributing environmental factors, including measles, mumps, and rubella (MMR) vaccine (*31*), thimerosal-containing vaccines (*32*), tetrachloroethylene, trichloroethylene, and trihalomethanes in drinking water (*33*), and certain metals (e.g., mercury, cadmium, nickel) and chemicals (trichloroethylene and vinyl chloride) in the ambient air around birth sites (*34*). Subsequent studies on MMR vaccine (*16, 18, 35, 36*) and thimerosal-containing vaccines (see review (*37*), *13, 18, 20, 38, 39*) did not support a relationship with autism. In a 2004 report, the Immunization Safety Committee of the Institute of Medicine determined that the body of epidemiological evidence favors rejection of a causal relationship between either MMR or thimerosal-containing vaccines and autism (*40*). Work on tetrachloroethylene, trichloroethylene, and trihalomethanes in drinking water (*33*) also has not supported a relationship with autism. Certain airborne metals and solvents still require confirmation of any relationship to autism (*34*). New research studies are continuing to evaluate other possible environmental factors (*24, 41*).

There are numerous candidate exogenous factors that could be associated with autism. A means to reduce the number of potential candidate substances is highly desirable. The recent increase in reported cases of autism in the literature presents an opportunity to examine for changepoints associated with the beginning of the increases in the different populations. The occurrence of changepoints would narrow the time frame to be examined for a possible change in exogenous exposures or new exposures and, in this way, could reduce the list of candidate substances. Also, if subsequent studies found no relevant, common, or increasing exposures during the different time periods associated with the changepoints within the different populations, then, perhaps, the increases should be considered artifacts, at least until such time as it can be demonstrated otherwise.

We identified studies from the literature that enabled us to determine AD cumulative incidence (the sum of all AD cases determined for a specific birth cohort up to a given age

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(*16*)). We then attempted to estimate the existence of a statistically significant changepoint associated with the increase in AD cumulative incidence for each of those studies.

Materials and Methods

The broadening and changing of diagnostic criteria for the spectrum of autistic disorders over time have complicated interpretation of increasing cases of autism (*26*). To reduce the impact of this in our analysis, we chose to focus on AD, one of the most severe and potentially recognizable forms of autism. We examined studies in recent reviews (*6, 42*) and those from more recent literature for which AD cumulative incidence data were available (identified as birth year given in Table S1, Supporting Information). In some studies, a mean cumulative incidence was given for a range of age groups of children (e.g., 5−7 year olds). In cases like this, we used the birth year of the calculated mean age cohort in the group (e.g., 6 in the above example), and this was the birth year cohort associated with the mean cumulative incidence (identified as calculated birth year in Table S1, Supporting Information). All data were taken from the publications with no attempt to access the original data.

From these studies, we selected individual studies that met our additional criteria of being relatively recent, long term, and having cumulative incidence determined when cohorts were age 5 or more. Studies with AD cumulative incidence data on about 10 cohorts or more were selected to provide sufficient record length for changepoint analysis and to eliminate the need to combine different studies and their associated methodological differences (*43*). The children in a birth cohort in a selected study had to have been followed until at least age 5 for an AD cumulative incidence estimate as AD will be underestimated for children younger than age 5 (*11, 16*) and may be underestimated until age 10 (*22*). Lastly, the selected studies had to have collected data between the late 1980s and mid-1990s as previous estimates for the timing of increases in autism range from the mid-1980s to the early 1990s (*13, 15, 17*).

Three studies met our criteria: (1) Honda and coinvestigators for Kohoku Ward, Yokohama, Japan (*16*); (2) Lauritsen and others for Denmark (*14*); and (3) the California Health and Human Services Agency, Department of Developmental Services (CDDS) for California (*11*). In the Honda study (*16*), the birth year for cohorts was given and cumulative AD incidence was determined after 7 years of age for each cohort. For the Lauritsen study (*14*), we estimated birth year cohorts from AD cumulative incidence in 5 and 6 year olds. The CDDS study (*11*) provided cohorts' birth years, and AD cumulative incidence for a cohort was determined after the children were age 5.

We also used our entire assembled AD data set (Table S1, Supporting Information, including the three long-term studies) to assess whether a changepoint for increased AD cumulative incidence could be detected from the worldwide studies. These studies provided more data and an enhanced geographic scope but were also far more temporally and methodologically variable.

We examined each of the three studies and the assembled worldwide data set for a changepoint in the time sequence of AD cumulative incidence by birth year cohorts in each study by fitting a hockey-stick model (*44*) to the data in each case. This approach uses ordered data and piecewise linear regression to split the response variable into two groups, generating a linear regression for each group. The point of intersection for these regression lines and the residual sum of squares for the two regression lines are determined. This process is repeated until an intersection point is found that minimizes the residual sum of squares value; this is the changepoint. We considered the changepoint to be significant

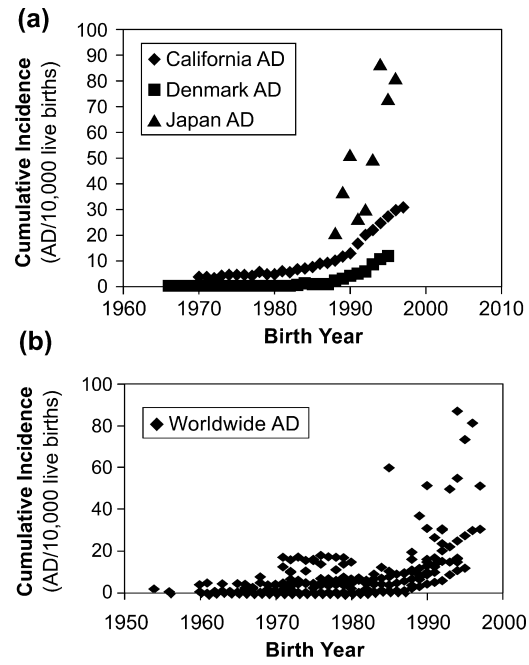

FIGURE 1. Autistic disorder (AD) cumulative incidence time series by cohort birth year from the literature for (a) Denmark ((*14*)), California ((*11*)), and Kohoku Ward, Japan ((*16*)) and (b) worldwide AD cumulative incidence.

if the 95% confidence interval for the slope of the linear regression for AD cumulative incidence in the prechangepoint years did not overlap with the 95% confidence interval for the slope of the linear regression for AD cumulative incidence in the postchangepoint years (a conservative test for differences (*45*)). When a significant changepoint was found, the 95% confidence interval around the changepoint was calculated using bootstrap resampling for 1000 samples (*46*). The mean AD cumulative incidence was calculated for the pre- and postchangepoint years for these studies. Statistical analyses were conducted with S-PLUS software (*47*).

Results

Cumulative AD incidence for birth cohorts was estimated from the literature for those studies with sufficient information (Table S1, Supporting Information). AD cumulative incidence appeared to increase in all three of our selected long-term studies, California (*11*), Denmark (*14*), and Kohoku Ward, Japan (*16*) (Figure 1a), as well as in the worldwide data set (Figure 1b).

For both California and Denmark a changepoint for increasing AD cumulative incidence was calculated; it was 1987.5 in both cases (Table 1). For the worldwide data set, a changepoint also was calculated and it was 1988.7 (Table 1). No changepoint year could be calculated for the Kohoku Ward, Japan, data set (Table 1), as AD cumulative incidence increased continuously over the entire period of study (1988−1996) (Figure 1a). In the California study, the Danish study, and the worldwide data set, the calculated changepoint year was determined to be significant because the prechangepoint regression slope in each case was significantly different from its respective postchangepoint regression slope (Table 1). Pre- and postchangepoint means of AD cumulative incidence per 10 000 live births were calculated to be 5.7 and 20.8, respectively, for California, 0.6 and 6.6, respectively, for Denmark, and 6.0 and 24.2, respectively, for the worldwide data set (Table 1).

Discussion

Many recent studies suggest that cases of autism have been increasing (*1, 6, 10−22*). Charman (*48*) suggested three

TABLE 1. Changepoint Year When Autistic Disorder (AD) Cumulative Incidence Increased for Each Study[a]

assembled data sets	changepoint year	95% confidence range for changepoint year	95% confidence range for slope	mean AD cumulative incidence per 10 000 live births
California AD	1987.5*	1987.0−1988.0		
pre			0.24−0.37	5.7
post			2.3−2.5	20.8
Denmark AD	1987.5*	1987.0−1988.0		
pre			0.0082−0.056	0.6
post			1.3−5.4	6.6
Japan AD				
pre				
post			2.6−10.6	54.7
worldwide AD	1988.7*	1985.9−1991.8		
pre			0.12−0.42	6.0
post			1.9−7.1	24.2

[a] For a significant (*) changepoint year, mean pre- and postchangepoint cumulative AD incidences were calculated.

possible explanations for the increases: (1) recent studies include artifacts that produce a false increase, (2) the current rate is correct but does not indicate a true increase, (3) and the current increase is correct and indicates a real increase. Distinguishing between whether the observed increases are real increases in the incidence of autism or simply an increase attributable to changes in reporting, clinical definitions, or the kinds of services offered continues to be a source of controversy (*9, 23, 49, 50*). The impacts of these issues have been discussed extensively based on a number of different studies (*1, 6, 9, 11, 12, 16−19, 22, 51, 52*) but without definitive clarification of the overall reason for the increase. Thus, using extant empirical data does not allow for discrimination as to whether the observed increases are real or apparent (*48*).

The three studies that were selected for inclusion in our analysis had sufficient record length for time trend analysis because they collected administrative data for programmatic services to autistic children (*11, 14, 16*). Each of these studies, which showed cumulative incidence of autism increasing (Figure 1a), had the advantage of using the data collections from a single administrative database that covered a well-defined geographic region (*11, 14, 16*). This was not true of our worldwide data set, where differences in method of data collection, record length, and geographic area (*6, 42*, Table S1, Supporting Information) may all have contributed substantially to an increase in AD cumulative incidence (Figure 1b).

Administrative databases also have the advantage of a relatively consistent methodology over periods of time (*22*). However, all three of our selected databases have some methodological changes associated with their long-term data collections (*11, 14, 16*). A changing of the diagnostic criteria and a broadening of the definition of autism to PDD (*3, 4*) occurred during the data collection within the Danish (*14*) and California (*11*) databases, but a single diagnostic criterion was applied consistently within the Kohoku Ward study (*16*). As we were aware of the issues with broadening and changing diagnostic criteria, in our study selection criteria we chose explicitly to focus on AD, which has had relatively consistent diagnostic criteria since about 1978 (*6*). However, this does not necessarily mean that the diagnostic criteria have been consistently applied in practice over this time frame. It does appear that AD criteria have been applied fairly consistently since about 1994 in the Danish database (*14, 52*) and across the United States (*53*) with the use of ICD-10 (*3*) and DSM-IV (*4*), respectively. A recent analysis of the California database from the early 1990s through about 2006 suggests that changing diagnostic criteria may account for about a 2.2-fold higher cumulative incidence of autism, relative to the 7-fold increase observed over 11 birth cohorts (*22*). It is unknown how consistently previous AD criteria were applied or how the application of the current criteria compare with past criteria.

Administrative data may also be prone to diagnostic substitution, where children with multiple diagnoses may be identified differently over time depending on which diagnosis allows the individual to receive administrative services (*48*). In British Columbia, Canada, changes in the assignment of special education codes may account for at least one-third of the increase in autism prevalence from 1996 to 2004 (*13*). However, in the California data set, diagnostic substitution from the category of mental retardation to autism could not account for increased autism from 1987 to 1994 (*22*).

We selected studies for analysis in which the assessment for AD cumulative incidence was determined in children no younger than age 5, as AD cases appear to be underestimated for children younger than this (*11, 16*). However, AD cases may continue to be underestimated until age 10 (*22*), and this may have led to an underestimate of the AD cumulative incidence in our selected studies. For the California database, increasing the age of assessment from age 5 to 9 would result in an increase in AD cumulative incidence of about 31% in 1990 and about 24% in 1996 based on Hertz-Picciotto and Delwiche data (*22*).

Studies with AD assessment in children occurring before age 10 may show an apparent increase in autism because of earlier ages of diagnosis in recent years, relative to historic underidentification at the same assessment age (*22, 52*). In fact, Parner and coinvestigators (*52*) examined recent cohorts (1996 and 1997; 1998 and 1999) in the Danish database and found that at least some of the AD increase was attributable to earlier diagnosis. In the California database, a shift toward a younger age at diagnosis also was found and contributed to about 12% of the observed increase in autism from 1990 to 1996, based on assessment at age 10 (*22*). Thus, earlier diagnosis contributed to increases in AD cumulative incidence in at least two of our selected studies and, likely, to studies in our worldwide data set (Table S1, Supporting Information).

In addition to finding that changes in diagnostic criteria and earlier age at diagnosis do contribute to some of the observed increase in cumulative AD incidence in the California database for 1990−2006, Hertz-Picciotto and Delwiche (*22*) also found that the inclusion of milder cases of autism contributed to the increase. This contribution was not as much as that resulting from changing diagnostic criteria but was more than that contributed by earlier age at diagnosis. Differential migration of autistic children into the state also was found to play a minor role in the increase (*22*). The investigators suggest that wider awareness of autism, greater motivation of parents to seek services, and increased

funding for services also may contribute to increasing cumulative AD incidence, but these factors could not be documented or quantified (*22*).

In the Danish database, confounding factors for interpreting the increase in AD cumulative incidence, other than those mentioned above, included outpatient activities being included in the Danish registry after 1994 and one Danish hospital that only began reporting autism cases to the registry in 1992 and, subsequently, accounted for about 20% of all Danish autism cases. The inclusion of outpatients (patients not requiring an overnight hospital stay or not requiring daily visits over an extended period for diagnosis and treatment (*52*)) in the registry did not appear to contribute more than about 10% to the increased AD cases, as the increase in AD cumulative incidence for the 1995 cohort (the last one included in our analysis) was 12.0 per 10 000 and for 1994 it was 10.8 per 10 000 ((*14*); Table S1, Supporting Information). However, including one hospital in the registry in 1992 that subsequently began contributing 20% of the Danish autism cases likely would result in an increase in AD cumulative incidence. To examine the impact of this on our calculated changepoint, we chose to reduce the AD cumulative incidence for the affected birth years of 1992−1995 in the data set by 20% to make them consistent with earlier birth years and then reanalyze this data set. With this adjustment, there was still a significant changepoint, but it was shifted about 1 year earlier to 1986.8 (analyses not shown).

In late 1994, during the period of study of Kohoku Ward, the ward boundaries were redrawn (*16*), potentially affecting the studies of the most recent 3 years of AD cumulative incidence estimates. However, Honda and coinvestigators (*16*) found that the redistricted Kohoku Ward was sociodemographically indistinguishable from the old ward and concluded that, as such, their estimates of cumulative AD incidence were unaffected.

There are confounding issues associated with interpreting the increased AD cumulative incidence observed in the administrative data in all three studies selected for our analyses. More recent analyses examining the California (*22*) and Danish (*52*) administrative databases found that at least some of the AD cumulative incidence was artifactual. Even after extensive examination of the recent years of the California database and evidence of at least some of the increase being due to artifacts, Hertz-Picciotto and Delwiche (*22*) found no evidence of AD cumulative incidence leveling off through 2006 and concluded that the possibility of a true increase in cumulative incidence should be considered seriously. Also, for the Danish database, cumulative AD incidence has continued to increase in recent years, and a true increase in incidence cannot be ruled out (*52*). Thus, based on extant studies, it does not seem possible to assess whether or how much of the observed increases in cumulative incidence are real.

Whether or not the increase in AD is real, there still is an increase in the number of individuals diagnosed and, with that, the subsequent public health burden associated with delivery of services to them (*8, 17*). On the basis of the lifetime care costs for an autistic individual of between $3.2 M (*8*) and $4.7 M (*17*), our estimate of the mean increase in cumulative AD incidence in California from 1988 to 1997, and mean number of live births in California for this period, we calculated the mean lifetime care cost for a cohort in California during this period to be between $2.7 B and $4.0 B. These costs likely have continued to grow in recent years, as autism in California has shown no signs of plateauing (*22*).

Because of the economic and societal costs associated with increased diagnoses of autism, it is important to determine whether a preventable exposure to an environmental factor may be associated with the increase. By determining that about 1988 was the changepoint year for increased AD cumulative incidence for California and Denmark and that about 1989 was the changepoint year for the worldwide data set (Table 1), we attempted to narrow the time frame within which exposure to possible candidate environmental factors likely would have had to occur. Although we found the similarity in these changepoint years surprising, they are consistent with increasing AD incidence in cohorts born after 1987 in a Minnesota county (*15*), with increasing AD incidence in Sweden beginning in the mid- to late 1980s (*13*) and with the greatest increase in ASD prevalence occurring in cohorts born between 1987 and 1992 across the United States (*17*).

Future studies should examine for novel or increasing exposures to environmental factors from gestation to at least age 3 for our calculated 1988−1989 birth cohorts. Assuming a dose−response relationship, a candidate factor would have continued to increase in the environment from the late 1980s through at least the mid-1990s in California, Denmark, and possibly Japan and other developed countries (Figure 1); increased exposure may have continued into recent years, as AD cumulative incidence has continued to increase in California (*21, 23*) and Denmark (*52, 54*). Not much is known about autism across birth years in emerging countries, but a recent study of ASD in Hong Kong (*55*) is suggestive of a rise in autism but beginning more recently than our calculated changepoints. If an increase does exist and continues with additional data on new cohorts in Hong Kong, a changepoint (albeit for ASDs) also could be calculated. This would provide an additional exposure test for candidate environmental factors in a different country and time frame.

Any candidate environmental factor also should be examined for differences in the level of exposure among the different study areas used in our analyses. Using our postchangepoint means in AD cumulative incidence for each of the studies, it appears that exposure was higher in California and potentially in other developed countries than it was in Denmark (Table 1). However, Kohoku Ward may have experienced the highest exposure of all (Table 1). It should be noted that exposure levels need not be substantially different among our study areas, as these increases could result from populations with very different genetic susceptibilities responding to a similar level of exposure. The possibility of exposure to several environmental factors acting synergistically on susceptible populations also cannot be ruled out.

Toxicological examination of any candidate environmental factor also would need to be conducted. Candidate factors would need to be disruptive to early human neural development, routes of exposure would need to be consistent with bioavailability to fetuses and infants, and the timing of increases in the production, use, or disposal of a factor resulting in human exposure would have to be consistent with our calculated changepoints and exposure gradients. An initial toxicological screening could be conducted using Agency for Toxic Substances and Disease Registry toxicological profiles (http://www.atsdr.cdc.gov/) or similar data sets. However, if no suitable candidates or combinations of candidates meeting these criteria can be found, then, perhaps, most of the observed increases are not caused by an environmental factor but result from study artifacts that produce false increases or from the current levels being correct but not a true increase.

The incidence of autistic individuals appears to be continuing to increase, and the societal and economic costs associated with this increase are substantial. Although artifacts associated with observed increases in various studies cannot be ruled out, from a precautionary standpoint, it seems prudent to assume that at least some portion of this increase in incidence is real and results from environmental

factors interacting with susceptible populations. As such exposure is potentially preventable, identification of relevant candidate environmental factors should be a research priority. We suggest that screening for candidate substances includes the timing of the AD cumulative incidence increases, the possibility of widespread exposure in developed countries, the possibility of a dose−response relationship, bioavailability to human fetuses and infants, and examination for toxic mechanisms that could affect early human neurodevelopment. If a weight-of-evidence identification of an environmental factor or a mixture of factors can be made and the level(s) in the environment reduced, profound worldwide economic and societal effects could result from the real reduction in the number of new individuals affected by autism.

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Appendix A

ABBREVIATIONS

AD	autistic disorder
ASD	autistic spectrum disorder
CDDS	California Department of Developmental Services
MMR	measles, mumps, and rubella
PDD	pervasive developmental disorder

Supporting Information Available

Table S1 shows the studies from the literature that enabled estimates of autistic disorder (AD) cumulative incidence to be made; these studies were used in the worldwide composite data set. This material is available free of charge via the Internet at http://pubs.acs.org.

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