
Sociological Environmental Causes are Insufficient to Explain Autism Changepoints of Incidence

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ABSTRACT: The Environmental Protection Agency (EPA) recently published a study analyzing time trends in the cumulative incidence of autistic disorder (AD) in the U.S., Denmark, and worldwide. A birth year changepoint (CP) around 1988 was identified. It has been argued that the epidemic rise in autism over the past three decades is partly due to a combination of sociologic factors along with the potential contribution of thimerosal containing vaccines. Our work conducted an expanded analysis of AD changepoints in CA and U.S., and determined whether changepoints in time trends of AD rates temporally coincide with changepoints for the proposed causative sociologic and environmental factors. Birth year changepoints were identified for 1980.9 [95% CI, 1978.6-1983.1], 1988.4 [95% CI, 1987.8-1989.0] and 1995.6 [95% CI, 1994.6-1996.6] for CA and U.S. data, confirming and expanding the EPA results. AD birth year changepoints significantly precede the changepoints calculated for indicators of increased social awareness of AD. Furthermore, the 1981 and 1996 AD birth year changepoints don't coincide with any predicted changepoints based on altered thimerosal content in vaccines nor on revised editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM).

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Keywords: autistic disorder, changepoint, environmental cause

In the U.S. and many other countries, autism spectrum disorder prevalence has been increasing over the past three decades.^[1,2,3,4,5,6,7,8,9,10] Recent publications suggest that some portion of the rise is due to sociologic factors (improved detection, increased awareness, increased services and funding), while another portion must be explained by biologic factors.^[1,2,4,11,12] Recently, the Environmental Protection Agency (EPA) published a study that calculated changepoint years in the cumulative incidence of autistic disorder (AD), a more diagnostically stable subset of autism spectrum disorders.^[13]

Changepoint analysis assumes that time series data can be fit with multiple lines with significantly different slopes; the “changepoint” is the point where the slope changes from one value to another value. Changepoint analyses have been used to detect ecosystem response to environmental changes, and resulting estimated thresholds have been used as basis for setting environmental policy.^[14] For example, changepoint analysis led to the measurement of the phosphorus threshold from agricultural runoff that resulted in ecological imbalances in the Everglades.^[15] These types of analyses are instrumental in setting the EPA’s national nutrient policy.^[14] The EPA’s autism study concluded that for California, Denmark, and combined worldwide autistic disorder data, there is a changepoint near birth year 1988. Their analysis demonstrates that AD was diagnosed at a higher rate in children born after 1988. Their analysis also indicates that there should be a universal environmental, sociologic or physiologic factor (prenatal or postnatal), whose introduction or change significantly affected children born in 1988 or later.

Many studies have been published that have tried to measure the effects of sociologic factors on autism rates. The impact of diagnostic substitution has been measured using California data,^[9] selected U.S. data,^[16] as well as Canadian data.^[17] However, there has been no consensus among these studies about the effect of diagnostic substitution. None of these studies has attempted to calculate changepoints for these sociologic factors. Other sociologic factors that have been considered include age at diagnosis,^[11,12,18] proximity to other autistic children,^[19] and legislative approval of special autism services.^[4] One study, using CA data, has suggested that as much as 12% of the CA autism rate could be due to earlier age of diagnosis.^[11] Another study, using CA data for birth cohorts born after 2000, recently concluded that 4% of autism diagnoses may be linked to physical proximity to another family whose child has been diagnosed with autism.^[19] Regrettably, this study did not distinguish between purely social effects, such as communication, or the presence of some shared environmental factor due to physical proximity. A different study, using West Australian data, published that increased autism diagnosis rates in younger children can be correlated to the approval of special services for younger autistic children, as well as to the occasion of a meeting of professionals that discussed various criteria to be used for autism diagnosis.^[12] Unfortunately, this publication did not mention timing of the actual disbursement of newly approved services nor did the authors include information about when the agreed upon autism diagnostic criteria was published or disseminated.

Based on the 2010 EPA changepoint publication, we have examined the potential impact of various sociologic and environmental factors proposed to be responsible for the current autism rates. Because of the known difficulties with autism ascertainment,^[20,21] no attempt is made in this work to quantify these sociologic factors relative to autism trends. Rather, we have focused on the question of whether changepoints can be identified for these sociologic factors and whether any identifiable changepoints can be temporally associated with autism disorder changepoints. Sociologic factors are represented by quantitative data such as the number of Yahoo chat groups discussing autism, the number of scientific publications referring to autism, and the number of professionals qualified to diagnose autism. Without debating whether diagnostic substitution or relaxation have or have not occurred, autism birth year changepoints can be predicted based on revisions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) using printing dates for these revisions. Finally, we have predicted autism birth year changepoints based on changes in thimerosal content of childhood vaccines. Our work has identified two additional autism disorder birth year changepoints, 1981 and 1996, that must be considered along with the EPA published 1988 changepoint. Comparison of sociologic changepoints or thimerosal-predicted birth year changepoints to actual autism disorder changepoints demonstrates that further research is needed to identify environmental factors that are temporally and physiologically relevant to the 1981, 1988 and 1996 autism disorder changepoints.

Methods

Previously published autistic disorder (AD) data obtained from large populations and having a time span adequate for changepoint analyses were used. Sociologic factors were quantified in the following manner : 1) “increased professional awareness” was quantified by the number of autism related publications counted using the PubMed database, and by U.S. Census numbers of those professionals qualified to diagnose autism; and 2) ‘increased parental awareness’ was quantified as the number of messages found in Yahoo internet chat groups that mention autism. For vaccine thimerosal content and DSM revisions, changepoints are predicted based on the year of FDA approval of the vaccine and the month/year of publication of the DSM revision, respectively, as changepoints cannot be reliably calculated for these data.

Autism Rates

Autistic disorder data for California originally came from the California Department of Developmental Services^[22] and are used because they have been previously published. Other CA data for similar years are available, but the data are caseload numbers, not prevalence data.^[23] The actual data for 1970 through 1997 used in our changepoint analysis was obtained from the EPA publication^[13] and the data for 1991 through 2002 from Schechter and Grether.^[24] For the CA 4-yr olds data,^[24] attempts were made to obtain original data from the authors; however, only the CA Department of Developmental Services (DDS) can supply original data. Communications to the CA

DDS were not answered, most likely due to California state budget cuts (personal communication). Hence, the data were obtained from the PDF image file of the published paper. United States national prevalence data were downloaded from the Department of Education (<https://www.ideadata.org/default.asp>) and from <http://www.fightingautism.org/idea/>. Some pre-computed prevalence data were verified by comparison with Newschaffer study in 2005^[25] and with direct downloads from the Department of Education IDEA program^[26] and prevalence was obtained by normalizing to birth year data as obtained from the U.S. Census.^[27]

Autism Professionals

According to California Department of Development Services, the professionals that are qualified to diagnose ASD are psychiatrists, pediatricians, neurologists and clinical psychologists. The numbers of psychiatrists, pediatricians and neurologists practicing in the United States for various years were obtained from editions of the U.S. Statistical Abstracts,^[27] published by the U.S. Census Bureau. The numbers are given for office-based practices only. Total U.S. population for corresponding years was obtained from the same source. The numbers of clinical psychologists were obtained from the American Psychological Association.^[28] The document lists the numbers of members of various divisions of the APA. Since a member can be listed in multiple divisions, we avoided redundancy by counting only the numbers listed under “Clinical Psychology” which is the largest division. The annual numbers of all professionals qualified to diagnose autism were then added and normalized to the annual U.S. population (Table I).

Extraction of Autism Related Publications in PubMed

The list of publications in PubMed^[29] that contained “autism” or “autistic” in the title or abstract was downloaded on July 21, 2009. (Total N=12614, Table I). The annual number of autism related publications was normalized to the annual number of total PubMed articles written in the English language.

Extraction of Autism Related Messages in Yahoo Chat Groups

The websites of 4,087 Yahoo groups were found by using the search term “autism” in the Yahoo! group search box. The addresses of these sites were collected and the webpages were downloaded between September and November 2009. The number of messages for groups containing two or more members was extracted and totaled for each year. For a background count, the list of all websites listed under the “Health and Wellness” and “Children’s” categories was obtained and downloaded during the same time period. Websites that were already in the autism list were removed. The numbers of messages in the remaining webpages were counted in the same way as for the autism set (Table I). Although Yahoo was started in early 1994,^[30] the database nevertheless contains messages dated back to 1990; however, no attempt was made to verify the questionable early 1990 dated messages due to privacy restrictions, as well as due to the fact that the numbers prior to 1998 were very small compared to the total.

Table 1: Input data used for sociologic analyses

Data Source	Total Counts
U.S. Census, American Psychological Association	70,000 average total of psychiatrists, pediatricians, neurologists, and psychologists
PubMed	10,132 “autism OR autistic” articles (1977-2008); 10,689 for 1923-2008 14,288,181 total PubMed articles for 1977-2008
Yahoo (1990-2008)	3,298 autism sites; 7,160,441 total messages 3,025 non-autism children’s health sites; 3,126,315 total messages

Federal Funding for Special Education

Appropriations for IDEA Part B grants were obtained from Newschaffer et al. (2005)^[25] as retrieved from <http://www.newamerica.net/files/CRS%20IDEA%20Funding%20Memo.pdf>. The number of children ages 3-21 served by IDEA funding was obtained from <http://nces.ed.gov/programs/coe/2009/section1/table-cwd-1.asp>. The number of funded autistic children was obtained from http://nces.ed.gov/programs/digest/d05/tables/dt05_050.asp?referrer=report. Federal funding for general education was obtained from U.S. Department of Education, National Center for Education Statistics, Common Core of Data (CCD), “National Public Education Financial Survey,” 1993–94 through 2005–06; National Elementary and Secondary Average Daily Attendance Model, 1993–94 through 2005–06; and Elementary and Secondary Education Current Expenditures Model, 1969–70 through 2005–06. Documents were downloaded on August 24, 2009.

Changepoint Analysis

Changepoint analyses are piecewise linear regression fits to data. Line segments are fit to the data and t-tests are conducted to check if the differences in the slopes are statistically significant. The intersections of the line segments are called changepoints. The analyses are usually conducted to determine if the introduction or onset of some unknown factor results in a trend change for a measurable quantity. Changepoints and 95% confidence intervals, as well as other fit parameters, were initially calculated for all data sets assuming only one changepoint; the “hockey-stick algorithm” was used which is an iterative piecewise linear modeling algorithm as described in Qian,^[14] similar to the method used by McDonald and Paul.^[13] However, identification of a 1981 changepoint for the DOE IDEA data spurred subsequent visual examination of the CA DDS data from 1970-1997 and suggested two distinct changepoints within this dataset. Therefore, further analysis was performed using a segmented line fit algorithm which can detect multiple changepoints.

Qian's hockey-stick algorithm fits two lines connected at the changepoint by a quadratic curve; the reported fit parameters using this model are 1) the y-intercept, 2) the slope of the pre-changepoint line, 3) the change in slope, and 4) the changepoint year. Our modeling was conducted using the R statistical software^[31] implementation of the Qian algorithm.^[14] Our results using Qian's algorithm for 1970-1997 data were compared against the EPA results to check our software implementation. Our calculated changepoint and 95% confidence intervals were identical to the EPA data to the nearest tenth of decimal place.

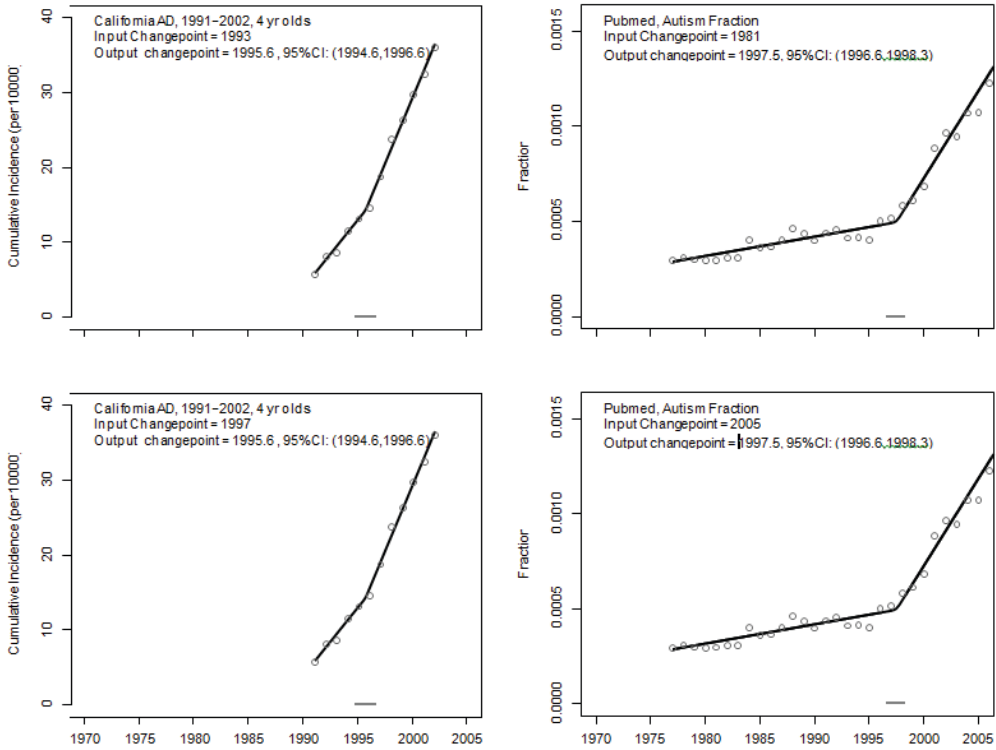
The hockey-stick method requires initial input estimates in order to run the algorithm. To reduce operator bias we objectively determined our initial input parameters as follows: 1) the y-intercept input used was the earliest value of the y-axis data (e.g., prevalence at the earliest year); 2) the pre-changepoint slope input used was the calculated slope from the earliest year of data to the mid-point year of data of the entire dataset; 3) the change in slope input used was the pre-changepoint slope input times 1000; and 4) the changepoint year input was the mid-point year for each dataset.

To establish the robustness of the Qian algorithm and its independence from the input parameters, we also ran the algorithm using deliberately chosen poor initial inputs. The fit results were robust to a wide variation of input parameters as long as the changepoint year input was more than three years away from the earliest or the latest year in the dataset. For the CA data used by McDonald and Paul,^[13] variation of changepoint year inputs from 1974-1993 still allowed the other input parameters to vary by 8-14 orders of magnitude without impacting the algorithm's calculated output parameters (fit not shown). Figure 1 illustrates the robustness of the hockey-stick method using worst case changepoint year inputs for the Schechter and Grether CA DDS data^[24] and for the autism publication data extracted from PubMed, chosen because they contain the smallest and the largest number of dependent variable data, respectively. For these two datasets, the other inputs can vary by 9-28 and 10-23 orders of magnitude, respectively, without impacting the algorithm's calculated output parameters.

Since the CA 1970-1997 data were suggestive of having two changepoints, further testing was conducted to check if the data could be better fit better by two changepoints. The "segmented" line fit algorithm^[32] allows for an arbitrary number of changepoints to be calculated. Each line segment is parameterized similarly as for the "hockey-stick" algorithm. Different pairs of input changepoint years were tried and the Akaike Information Criterion (AIC)^[33] and the Bayesian Information Criterion (BIC),^[34] methods for finding the model that best fits data with the least number of parameters, were used to compare the different results. The R statistical software was used to run the "segmented" and AIC algorithms.

For the data presented, all possible pairs of input changepoint years were tried. All other input parameters were set to default values. Not all pairs of input years led to convergence; what are presented here are results from fits that converged and had the lowest AIC and BIC scores.

Figure 1: Illustration of robustness of the fitting algorithm – the panels show that the same final change-points are calculated by the fitting program for extreme values of initial changepoints: Birth years (1993, 1997) for the CA 4 yr old data and calendar years (1980, 2006) for the PubMed autism publication data. See text for more discussion.



DSM Publication Counts

Diagnostic and Statistical Manual (DSM) editions were checked for printing dates, found on the copyright page. This information was used as an indication of the rapidity with which changes in diagnostic criteria were embraced by the professional community. To determine whether DSM revisions might be related to changes in AD diagnosis rates, we predicted a range of AD changepoint birth years based on the printing dates for the various DSM revisions. Our assumptions were that the earliest age of autism diagnosis is three years and that by eight years of age diagnosis is stable,^[35,36] therefore, a DSM revision would be predicted to induce a changepoint between eight years prior to the earliest print date and three years prior to the latest print date. We compared these predicted changepoint ranges to the calculated changepoints for autistic disorder.

Thimerosal Containing Vaccines (TCVs)

A historical analysis of TCVs was conducted to determine the years in which changes to the thimerosal load received by vaccinated children occurred. Assuming that increased thimerosal load is related to AD we predicted AD changepoints based on

FDA approval of new vaccines or new dosing schedules of TCVs and compared these predicted changepoint ranges to the actual calculated changepoints for autistic disorder.

Results

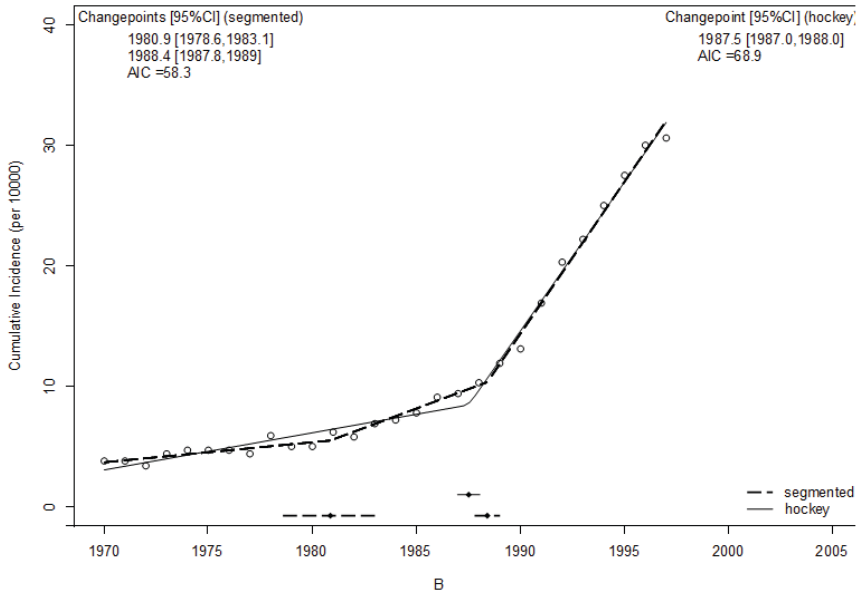
Changepoint Analysis

Visual assessment of CA DDS AD data for birth years 1970-1997 suggested an earlier changepoint, in addition to the 1987.5 changepoint identified by McDonald and Paul [13] using hockey-stick analysis. Furthermore, hockey-stick analysis of DOE AD data for 19 year olds born between 1973 and 1987 identified an AD changepoint (CP) for birth year (BYr) 1980.8, confirming the visual observations of the CA DDS AD data. We therefore compared segmented analysis (2 changepoints) to hockey-stick analysis (1 changepoint) of the CA DDS AD data (Figure 2). Based on the Akaike Information Criterion (AIC) [33] and Bayesian Information Criterion (BIC), [34] the “segmented” algorithm with 2 changepoints (1980.9, 1988.4) resulted in a better fit of the data versus the single changepoint in 1987.5. Figure 3 illustrates changepoints calculated using the hockey-stick method for DOE 1973-1987 data, BYr CP 1980.8 (A), CA DDS AD data for 4 year olds born between 1991 and 2002, BYr CP 1995.6 (C), numbers of professionals qualified to diagnose AD from 1970 to 2005, CP 1997.4 (D), autism related publications in the PubMed database, CP 1997.5 (E), and the number of autism messages posted on Yahoo chat groups between 1990 and 2005, CP 1998.0 (F). Figure 3 (B) illustrates the changepoint for the CA DDS AD data from 1970 to 1997 using the segmented (2 changepoints) fit algorithm, BYr CP 1980.9 and BYr CP 1988.4.

As shown in Table 2, all data except for the number of “Autism Diagnosing Professionals” have positive slope changes after the identified changepoint. The “Autism Diagnosing Professionals” data actually shows a slight dip after the calculated changepoint year. Changepoint analysis demonstrates that measured increases in sociologic factors proposed to be responsible for increased rates of AD diagnosis trail AD changepoints by as much as 16 years and therefore cannot be drivers for the rise in AD prevalence. The temporal relationship among these CPs is more clearly shown in Figure 4 for AD data and for sociologic data with positive post-CP slope changes. All calculated AD BYr CPs (1980.8, 1980.9/1988.4, 1995.6) precede the sociologic data CPs (1997.5, 1998.0). This analysis demonstrates that while sociologic factors such as awareness of autism disorder among parents and professionals have increased, the increased prevalence of AD is most likely responsible for those increases, and not the other way around as has been widely suggested.

Another sociologic factor believed to drive autism diagnoses is an increase in federal funding for special education. Autistic Disorder was not added as a separate disability type under the Individuals with Disabilities Education Act (IDEA) until 1992,^[37] well after the increase in AD prevalence identified by the 1980.9 and 1988.4 changepoints. Additionally, the amount of Special Education Funding to state programs is not tracked or allocated per disability type, so funding is not affected by an increase or decrease from year to year in the number of pupils in the autism category (personal communica-

Figure 2: Comparison of “hockey” and “segmented” fits for California AD 1970-1997 data. Both analyses yield changepoints with overlapping confidence intervals near 1988. However, “segmented” analysis reveals a second changepoint near 1981. The lower AIC (Akaike Information Criterion) value for the “segmented” analysis shows that 2-changepoint model gives a better fit than the single changepoint (hockey) model.



tion Department of Education, 12/10/2010). Objective changepoint analysis identifies 1998.7 as the CP for federal funding, again demonstrating that increases in sociologic factors cannot have driven autism prevalence.

Purported Effect of DSM Changes on Autistic Disorder Prevalence

The first *Diagnostic and Statistical Manual of Mental Disorders*, *DSM I*, was published by the American Psychiatric Association in 1952. Since then there have been five major revisions: *DSM II* (1968); *DSM III* (1980); *DSM III – R* (1987); *DSM IV* (1994) and *DSM IV – TR* (2000). The impact of DSM revisions on the diagnosis of autism depends on the significance of changes to diagnostic criteria and on the rapidity with which the DSM revisions are disseminated and applied. Table 3 compares diagnostic criteria for autistic disorder, not autism spectrum disorder, across DSM revisions. As the table demonstrates, DSM revisions differ primarily in that more examples of behaviors typical of autism disorder are listed with each revision. However, the required number of behaviors for an autism diagnosis remains the same or actually increases with the revisions, rather than becoming less stringent as has been commonly suggested. Furthermore, if relaxed diagnosis were to lead to an increase in AD prevalence then one would expect a decrease in the number of Symptom Categories required for diagnosis, however, these Symptom Categories are consistent across DSM revisions.

The DSM printing record (Table 4) suggests that the dissemination and application of the DSM revisions is quite rapid after the date of DSM publication, and therefore,

Figure 3: Change-point analysis results and fits to autism rates and sociologic trends. Panels display data, “hockey-stick” or “segmented” fits and associated change-points as described in the text. Note that all data except for Autism Diagnosing Professionals have statistically significant slope increases after the change-point year. The slope for the number of Autism Diagnosing Professionals actually decreased slightly after the change-point year.

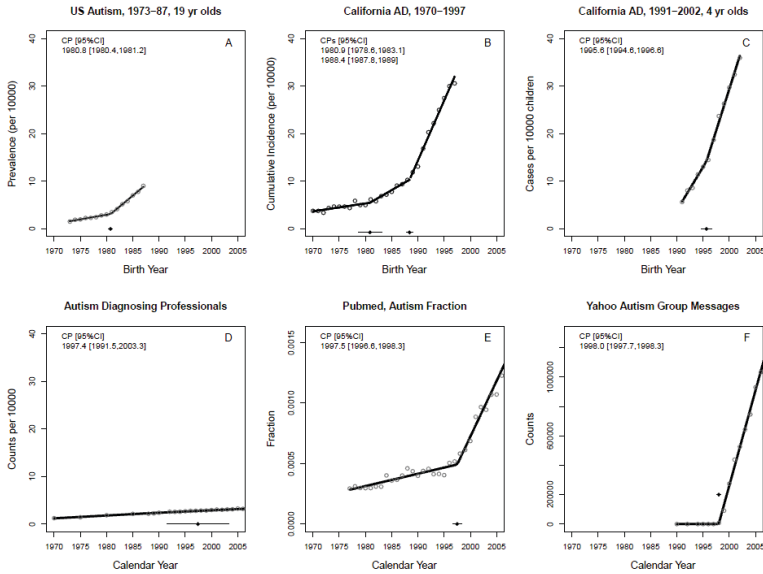


Figure 4: Timeline of autism rate birth year change-points and sociologic calendar year change-points. Only data with slope increases after the change-point are included in this graph. Raw data are displayed as normalized relative counts ($y = (y_{max} - y_{min})/y_{max}$). Note that all autism rate change-points temporally precede all sociologic change-points. (CA = California data, BY= Birth Year, CY = Calendar Year, AD)

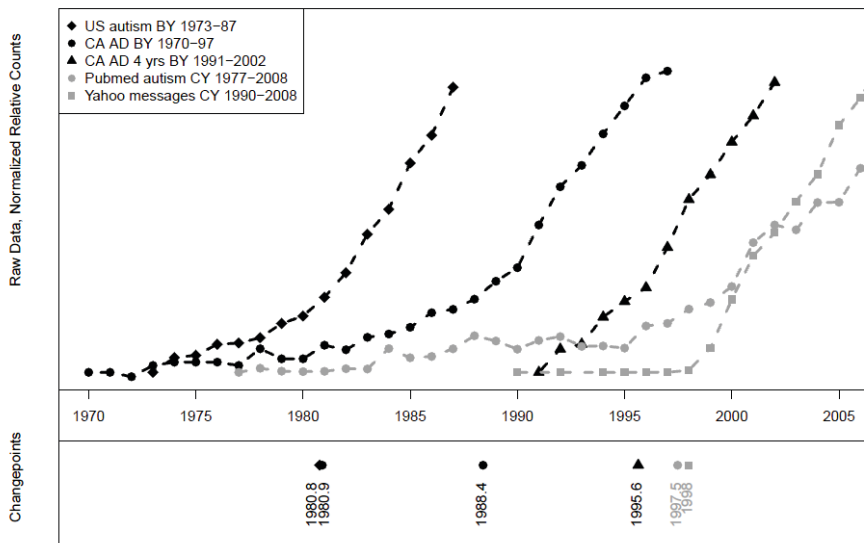


Table 2: Results of changepoint analyses for autistic disorder and sociologic data

	Pre-Change- point Slope	Changepoint (95% CI)	%Slope Change	Slope change Pr(>t-value)
AUTISTIC DISORDER				
U.S. autism, 19 yr olds, 1973-87 (H)	1.93E-01	1980.8 (1980.4-1981.2)	374.0	3.69E-10
CA AD BYr 1970-97 (S)	1.66E-01	1980.9 (1978.6-1983.1)	285.6	<0.05
	6.42E-01	1988.4 (1987.8-1989.0)	293.2	<0.05
CA AD, 4yr olds, 1991-2002 (H)	1.81E+00	1995.6 (1994.6-1996.6)	92.6	2.27E-04
SOCIOLOGIC FACTORS				
Autism-diagnosing professionals (H)	5.90E-02	1997.4 (1991.5-2003.3)	-23.8	3.75E-02
PubMed autism fraction (H)	1.02E-05	1997.5 (1996.6-1998.3)	805.2	3.95E-16
Yahoo autism groups messages (H)	4.84E+01	1998.0 (1997.7-1998.3)	268139.8	6.56E-14

Changepoints were originally calculated using the hockey-stick algorithm "H" (see text) for all data sets. For CA AD BYr 1970-97, the 'segmented' algorithm gave a better fit and results are displayed in the table. CA = California; AD = autistic disorder; BYr = Birth Year; H=hockey-stick algorithm; S=segmented algorithm

the printing dates can be used to predict expected BYr CPs if DSM revisions affect AD diagnosis rates. Predicted expected BYr CP ranges are found in Table 4. CP ranges are predicted to be eight years prior to the earliest printing date and three years prior to the latest printing date for each revision based on first diagnosis of AD occurring after three years of age and firm diagnosis by eight years of age.^[35,36] Assuming that the DSMs are strictly followed, the latest predicted BYr CPs as a result of DSM changes are 1978, 1984, and 1992 for DSM-III, III-R, and IV, respectively. There is no corresponding calculated AD CPs associated with those years (Table 4).

Thimerosal Containing Vaccines (TCVs)

Thimerosal has been used as a preservative in vaccines since the 1940s. Similar to DSM revisions, additional Thimerosal Containing Vaccines (TCVs) introduced into the childhood vaccination schedule can be used to predict expected AD BYr CPs. Table 5 reflects the history of TCVs used in the U.S. and changes in the amount of thimerosal that would be contained in vaccines administered to children 0-18 months as a result of changes in the childhood vaccination schedule published by the CDC. From 1948 to 1988, only one TCV, the DTP vaccine was routinely used. Per the CDC's recommended childhood immunization schedule, the DTP vaccine was administered in a series of four doses at 2, 4, 6 months and 15 to 18 months. The total amount of mercury per dose is 25ug; therefore the total amount of mercury injected from birth to 18 months is 100ug. Because this amount remained constant for 40 years, there is no predicted thimerosal changepoint prior to 1988. However, the first measurable AD changepoint occurs in 1980.8, irrespective of any change in the amount of mercury present in childhood vaccines.

Beginning in mid-1989, a single dose Hib vaccine, administered at 15-18 months, was added to the CDC's recommended vaccination schedule. There were two manufacturers of the vaccine, containing 25 or 50ug, respectively. This increased the total amount of mercury a fully vaccinated 0-18 month old child would have received from 100ug to 150ug, and predicts an expected BYr CP sometime on or before 1989, depending on catch-up vaccination programs, and roughly corresponds to the calculated 1988.4 AD BYr CP.

In 1991 the Hib vaccine was approved to be administered in a four dose schedule at 2, 4, 6 and 12-14 months. The predicted BYr CP based on this change in TCVs would be 1991; however, no calculated AD BYr CP corresponds to this date. In 1994 the Hep B vaccine, which contained 12.5ug of thimerosal, was approved in a three dose schedule at birth, 2 and 6 months. The predicted BYr CP based on this change in TCVs would be 1994; however the calculated AD BYr CP is 1995.6.

Discussion

Many publications have tried to address the suggestion that sociologic factors, particularly diagnostic practices, may be responsible for an apparent rise in autism prevalence, with inconsistent conclusions.^[9,16,17,38] Rather than debating or modeling the

Table 3: Comparison of diagnostic criteria for autistic disorder (AD) across DSM revisions

Autistic Disorder Symptom Category	DSM II (1968) Schizophrenia, childhood type	DSM III (1980) Infantile Autism	DSM III R (1987) Autistic Disorder	DSM IV (1994) and DSM IV R (2000) Autistic Disorder
Number of symptom examples listed / Number of examples required for diagnosis				
Impaired Social Interaction e.g. Pervasive lack of responsiveness to other people listed	3 examples/ Requirement not listed	1 example/ 1 required	5 examples/ 2 required	4 examples/ 2 required
Impaired Communication E.g. Marked abnormalities in the production of speech, including volume, pitch, stress, rate, rhythm, and intonation; stereotyped and repetitive use of language or idiosyncratic language.	1 example/ 1 required	4 examples/ Requirement not listed	6 examples/ 1 required	4 examples/ 1 required
Atypical or withdrawn behavior e.g. Stereotyped body movements (for example, hand flicking or twisting, spinning, head-banging, complex whole-body movements)	1 example/ 1 required	2 examples/ Requirement not listed	5 examples/ 1 required	4 examples/ 1 required
Age of onset	Before puberty	Before 30 months	Before 36 months unless specified	Before 36 months
Alternative diagnosis that must be excluded:	Schizophrenia symptoms	None listed	None listed	Rett's disorder* or childhood disintegrative disorder

Table 4: Printing schedules for DSM revisions/editions

	Date of printing	Number printed	Predicted BYr CP range by DSM printings	Calculated BYr CP
DSM III	Feb-80	40,000		
	May-80	25,000		
	Sep-80	25,000		
	Nov-80	30,000		
	Jan-81	30,000		
	Mar-81	35,000		
	Sep-81	25,000	Feb 1972-Sep 1978	1980.85*
DSM IIIR	May-87	75,000		
	Jun-87	80,000		
	Nov-87	75,000	May 1979 –Nov 1984	1988.4
DSM IV	May-94	not given		
	Jul-94	not given		
	Aug-94	not given		
	Jan-95	not given	May 1986- Jan 1992	1995.6

BYr = Birth Year; CP = changepoint; DSM = Diagnostic and Statistical Manual;

*Average of CPs from CA 1970-97 and U.S. autism (19 yr olds) data sets;

Predicted birth year changepoints in column 4 are placed 8 years prior to the earliest printing date and 3 years prior to the last printing date because tools for autism diagnosis before the age of 3 were not previously available and autism diagnosis has been found to be final and permanent by the age of 8 ((Luyster R 2009) (Lord 2006)).

Table 5: Thimerosal containing vaccines and national vaccination schedule from 0-18 months

Time Period	Age / Thimerosal Containing Vaccine(mcgs)	12-14 mos	15-18 mos	Range of Potential thimerosal amount (µggs) introduction	Predicted BYr CP based on thimerosal introduction	Calculated BYr CP
At Birth						
1948-1988	2 mos DTP (25)	4mos DTP (25)	6 mos DTP (25)	15-18 mos DTP (25)	100	
Total					100	1980.85
1989-1990	DTP (25)	DTP (25)	DTP (25)	DTP (25) Hib (12.5-25)*	100	
Total					112.5-125	1988.4
1991-1993	DTP (25) Hib (12.5-25)	DTP (25) Hib (12.5-25)	DTP (25) Hib (12.5-25)	DTP (25) Hib (12.5-25)	100	
Total					150-200	1988.4
1994 - 1999	DTP (25) Hib (0-25) Hep B (12.5)	DTP (25) Hib (0-25) Hep B (12.5)	DTP (25) Hib (0-25) Hep B (12.5)	DTP/DTaP (25) Hib (0-25)	100	
Total					137.5-237.5	1995.6

BYr=Birth Year; CP=change point; mcgs=micrograms

Note that thimerosal has been in DTP since 1948

*HiB was not licensed for less than 18 months of age until 1991;

** 2 versions of HiB on market contained 12.5 and 25mcgs;

***3 versions of HiB contained 0, 12.5, 25mcgs

magnitude of changes in sociologic or environmental factors proposed to have contributed to increased AD prevalence, we chose to evaluate the significance of those changes based on calculated or predicted changepoints, and how these changepoints correspond to changepoints in autistic disorder prevalence rates. Our work has confirmed, and expanded on, the 1987.5 AD BYr CP published by McDonald and Paul^[13]. AD BYr CPs are evident in the U.S., particularly California, in about 1981, 1988 and 1996.

To calculate changepoints for the proposed sociologic factors involved in autistic disorder prevalence, we have utilized objective data to represent sociologic factors. For instance, the quantity of publications devoted to autism relative to the total number of scientific publications contained in PubMed each year is an objective number indicative of professional awareness of AD. Parental and professional awareness about AD has certainly increased; however, changepoint analysis suggests that previously elevated AD prevalence was responsible for increased awareness, rather than the suggested awareness driving autism diagnoses. All of the sociologic changepoints that we were able to calculate occur at least two and as many as 16 years after changepoints in AD prevalence.

We further asked the question whether information about diagnostic criteria and thimerosal vaccine load would predict AD changepoints consistent with our calculated AD changepoints. Similar to the sociologic factors examined, changes in diagnostic criteria have clearly occurred, however, examination of DSM revisions suggests that autism disorder diagnosis (excluding autism spectrum disorders) has not been relaxed. DSM IV introduced a requirement to exclude Rett's Disorder, implying that DSM-IV may be more restrictive than DSM-III or IIIR. Furthermore a 2005 study by the Centers for Disease Control (CDC) of 115 Atlanta area patients^[39] concluded that "most practitioners (70%) did not use a diagnostic instrument when assigning the first ASD diagnosis." The remaining 30% who did use a diagnostic tool for initial diagnosis used autism-specific diagnostic tools such as the Childhood Autism Rating Scale (CARS) and the Autism Behavior Checklist (ABC). The DSM manual was not listed among the diagnostic tools used by any of the practitioners when making their initial diagnosis of either Autism Disorder or Autism Spectrum Disorder. Both CARS^[40] and ABC^[41] were developed in the 1970s, prior to the earliest calculated AD changepoint year. Interestingly, Rellini et al studied 65 AD subjects and concluded that CARS and DSM-IV are actually in agreement.^[42] More importantly, we analyzed only autistic disorder data; excluding datasets that contained ASD diagnoses, and as the CDC authors state, a child with autistic disorder "can be less complicated to diagnose than other spectrum disorders." Regardless of whether AD diagnostic relaxation has or has not occurred, and regardless of whether DSM is used as a tool for initial AD diagnosis or not, predicted AD birth year changepoints based on DSM revision printing schedules do not correlate with calculated AD changepoints.

While several studies have suggested that thimerosal may pose potential dangers to the developing brain,^[43,44] our consideration of thimerosal is not to evaluate either the safety or potential danger of this adjuvant. Rather, like our approach to sociologic factors,

we are concerned only with changepoints predicted by the introduction of thimerosal containing vaccines (TCVs) and any temporal association of those changes with calculated AD BYr CPs. One could point to the calculated 1988.4 AD BYr CP and conclude that introduction of the thimerosal containing Hib vaccine in 1989 was associated with and might be responsible for this changepoint. However, per the CDC data on vaccine coverage levels,^[45] coverage levels for the Hib vaccine were less than 29% in 1992, and no TCVs can be associated with either the 1981 or the 1995.6 calculated AD BYr CPs. This inconsistency calls into question a relationship between TCVs and AD prevalence increases. The fact that somewhat high levels of thimerosal have been used in vaccines since 1948, without an associated AD epidemic, further challenges the significance of thimerosal in vaccines and AD rates. Additionally, over the past decade Thimerosal levels in childhood vaccines have been reduced yet AD rates have continued to increase.^[46]

Several studies have concluded that sociological factors have led to an artificial perception that AD/ASD has increased over the past decades. Although evidence of sociologic effects have been published in studies examining reduced age of diagnosis,^[11,12] residential proximity to other autistic children,^[19] and co-morbid mental retardation,^[47] no changepoints have been calculated in those publications, leaving the question of whether these particular factors are causative, or merely associative, unanswered. Wazana et al. have performed hypothetical modeling to predict the impact that earlier age at diagnosis, broadened diagnostic criteria and improved ascertainment efficiency would have on AD frequency.^[20] Their analysis predicts an AD changepoint in calendar years 1974 and 1994, as shown in Figure 1 of their paper. These might correspond to birth years 1966 to 1971 and 1986 to 1991, assuming earliest diagnosis at age three and latest diagnosis at age eight. While their modeling predicted a changepoint in 1994 which they suggest is associated with the introduction of DSM IV, the calendar year CPs predicted by the hypothetical modeling of Wazana et al., even when translated into BYr CPs, do not explain the actual calculated AD BYr CPs of 1981, 1988^[13] and 1996.

Data Advantages/Limitations

The California DDS AD datasets used in this study are the same data analyzed in many autism and sociologic papers. This data has the advantage of containing only children with AD diagnoses, but not Asperger Syndrome for which diagnostic criteria do appear to have been added and broadened. Although only AD data are theoretically contained in the CA DDS dataset, the possibility of non-uniform implementation of CDER status criteria cannot be ruled out. However, it may be assumed that large numbers of cases sufficiently reduces the impact of random errors caused by non-uniform CDER status implementation.

The main shortcoming of our analysis stems from the original autism prevalence or incidence data: the diagnosis of autism is behaviorally based and there are currently no biomarkers available to validate diagnosis. To address this shortcoming, only autistic disorder (AD) data have been used, as diagnostic criteria for AD have been stable (Table 4) and AD diagnoses have been demonstrated to be stable and permanent compared

to ASD diagnoses.^[35] Caution should be also used in extrapolating these conclusions to other states or countries, as there may well be additional sociologic factors involved that have not been considered in our study; for example, immigration effects, increases in the number of two-career households, and increases in availability of group day care, among others.

The data we used in our analysis to numerically represent sociological factors are objective and publicly accessible, therefore, the same data are available to others for further analysis and modeling. While the internal content of Yahoo messages cannot be individually checked due to privacy concerns, it is assumed that the large number of these messages minimizes random error or false positives, i.e., messages that are not actually autism-related. It is also implicitly assumed that parents who read these messages use the information towards evaluating their children. Other modes of parental communication are not easily quantifiable, for example, communication with relatives or the pediatrician, without undertaking large surveys that rely on recall and therefore somewhat subjective data. Our emphasis has been to obtain and analyze large unbiased datasets of independent indicators of various sociologic factors.

In conclusion, a great deal of attention has been focused on the possibility that sociologic factors account for a significant fraction of the rise in autism. Our work demonstrates that the temporal changes in the rise of autistic disorder do not correspond to temporal changes in sociologic factors such as increased parental and professional awareness, or federal special education funding. Our study does not rule out the possibility of sociologic effects artificially elevating AD prevalence after 1996, the latest AD BYr changepoint detected from our datasets. However, our results support and expand the recommendation in the EPA changepoint publication,^[13] to place emphasis on identifying environmental or other factors that are temporally associated with specific AD BYr CPs of 1981, 1988 and 1996. Further research on other environmental factors is clearly warranted.

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