

U.S. Autistic Disorder (1970-2002) Changepoints Do Not Coincide With Changepoints For Suspected Sociologic And Environmental Causes

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Introduction

Recently, the Environmental Protection Agency (EPA) published a study that analyzed time trends in the cumulative incidence of autistic disorder (AD) in the US, Denmark, and worldwide. A birth year changepoint around 1988 was identified. It has been argued that the epidemic rise in autism over the past 3 decades is partly due to a combination of sociologic factors – changes in diagnostic rules, improved detection, and availability of special education resources. Additionally, the potential contribution of thimerosal containing vaccines continues to concern many parents and autism associations. In this work, we conducted an expanded analysis of autistic disorder changepoints in the US (California), and determined whether changepoints in time trends of autism disorder 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 California data, both 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 do not 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).

Figure 1: Changepoint analysis results and fits to autism rates and sociologic trends. Panels display data, 'hockey-stick' or 'segmented' fits and associated changepoints as described in the text. Note that all data except for Autism Diagnosing Professionals have statistically significant slope increases after the changepoint year.

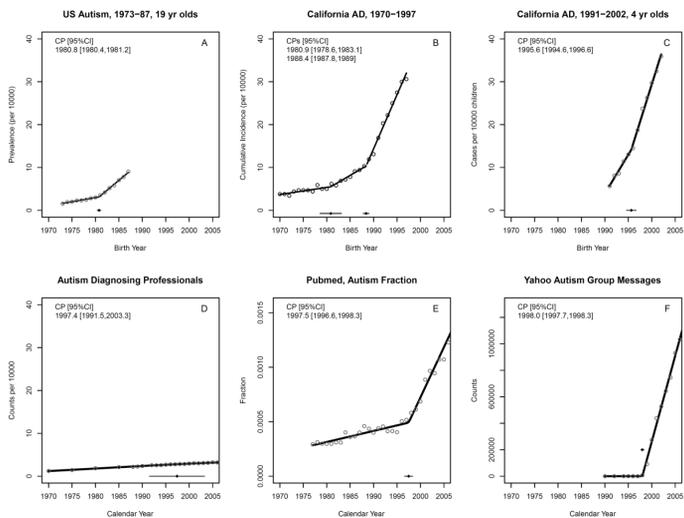


Table 1: Results of changepoint analyses for autistic disorder and sociologic data.

	Pre-Changepoint Slope	Changepoint (95% CI)	% Slope Change	Slopechange p-value
AUTISTIC DISORDER				
US 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. [Slopechange "p-value" = Pr(-t-value) = probability that the slope change is a false positive; CA = California; AD = autistic disorder; BYr = Birth Year; H=hockey-stick algorithm; S=segmented algorithm

Methods and Results

Changepoint Analysis

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 US 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. The usage history of a proposed environmental cause, thimerosal in vaccines, was reviewed. When enough data were available, changepoints are defined to be the year when a slope change occurs; piecewise linear regression fits (2 lines or 3 lines) were used to calculate these changepoints. Otherwise, changepoints were predicted based on the birthyears first potentially impacted by a specific DSM or vaccine event.

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.

Figure 2: Timeline of autism rate birthyear changepoints and sociologic calendar year changepoints. Only data with slope increases after the changepoint 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 changepoints temporally precede all sociologic changepoints. (CA = California data, BYr= Birth Year, CY = Calendar Year, AD = autistic disorder)

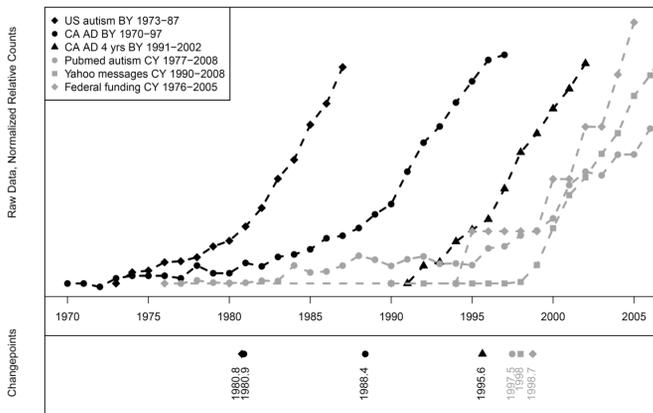


Table 2: Thimerosal containing vaccines in national vaccination schedule from 0-18 months.

Time Period	Age / Thimerosal Containing Vaccine(µg)					Range of Potential thimerosal amount (µg)	Predicted BYr CP based on thimerosal introduction	Calculated BYr CP
1948-1988	At Birth	2 mos	4mos	6 mos	12-14 mos	15-18 mos	100	1980.85
	DTP (25)	DTP (25)	DTP (25)	DTP (25)	DTP (25)	100		
1989-1990	Total					100	none	1980.85
	DTP (25)	DTP (25)	DTP (25)	DTP (25)	DTP (25)	100		
1991-1993	Total					112.5-125	1988-1990	1988.4
	DTP (25)	DTP (25)	DTP (25)	DTP (25)	DTP (25)	100		
1994 - 1999	Total					50-100**	1990-1993	1988.4
	DTP (25)	DTP (25)	DTP (25)	DTP (25)	DTP (25)	100		
1994 - 1999	Total					137.5-237.5	1994	1995.6
	Hep B (12.5)	Hib (0-25)	Hib (0-25)	Hib (0-25)	Hib (0-25)	0-100***		

BYr=Birth Year; CP=changepoint; µg=micrograms. Note that thimerosal has been in DTP since 1948
*Hib was not licensed for under 18 months of age until 1991; ** 2 versions of Hib on market contained 12.5 and 25µg; ***3 versions of Hib contained 0, 12.5, 25µg

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. Additional birthyear changepoints were identified from AD data: 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], confirming and expanding the EPA work for US data. AD birthyear changepoints significantly precede the changepoints calculated for indicators of increased social awareness of AD (1997-1999). Only the 1988 changepoint can be associated with a thimerosal vaccine event, however, low compliance may lessen the importance of that association.

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) (37); *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.

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

Autistic Disorder Symptom Category	DSM II (1968)	DSM III (1980)	DSM III R (1987)	DSM IV (1994) and DSM IV R (2000)
	Schizophrenia, childhood type	Infantile Autism	Autistic Disorder	Autistic Disorder
Impaired Social Interaction	Number of symptom examples listed / Number of examples required for diagnosis			
e.g. Pervasive lack of responsiveness to other people	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				
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	Feb 1972-Sep 1978	1980.85*
	May-80	25,000		
	Sep-80	25,000		
	Nov-80	30,000		
	Jan-81	30,000		
	Mar-81	35,000		
	Sep-81	25,000		
	May-87	75,000		
DSM IIIR	Jun-87	80,000	May 1979 -Nov 1984	1988.4
	Nov-87	75,000		
DSM IV	May-94	not given	May 1986- Jan 1992	1995.6
	Jul-94	not given		
	Aug-94	not given		
	Jan-95	not given		

BYr = Birth Year; CP = changepoint; DSM = Diagnostic and Statistical Manual; *Average of CPs from CA 1970-97 and US autism (19 yr olds) data sets; Predicted birthyear 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.

Discussion

Our work has confirmed, and expanded on, the 1987.5 AD BYr CP published by McDonald and Paul (McDonald & Paul, 2010). AD BYr CPs are evident in the US, 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 2 and as many as 16 years after changepoints in AD prevalence.

Similar to the sociologic factors examined, objective measurement of the rapidity of dissemination of DSM revisions, based on printing schedules, demonstrates that even if diagnostic criteria for autism disorder or autism spectrum disorder have been relaxed, these changes do not yield predicted birthyear changepoints that coincide with calculated, actual autism disorder birthyear changepoints. Based on the rapidity with which new DSM revisions are distributed, the DSM predicted changepoints precede all of the calculated AD BYr changepoints by several years. Furthermore a 2005 study by the Centers for Disease Control (CDC) of 115 Atlanta area patients (Wiggins et al., 2006) concluded that "most practitioners (70%) did not use a diagnostic instrument when assigning the first ASD diagnosis" anyway.

Summary

This study confirms the 1988 changepoint detected by EPA and adds 1981 and 1996 as additional changepoints. AD birthyear changepoints, particularly 1981 and 1996, cannot be explained by predicted birthyear changepoints based on altered thimerosal content in vaccines nor on revised editions of the DSM. Based on changepoint analyses, environmental factors introduced universally to children in the US according to the schedule in the table below should be investigated. A prime environmental suspect is the introduction of human DNA contaminants in vaccines introduced to the US in 1979-1983, 1989 and 1995.

	Changepoint	Changepoint	Changepoint
	1980.9	1988.4	1995.6
In utero exposure	1979-1980	1987-1988	1994-1995
Birth to 3 years of age	1980.9-1983.9	1988.4-1991.4	1995.6-1998.6

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Conflict of Interest: None
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