Letters

RESEARCH LETTER

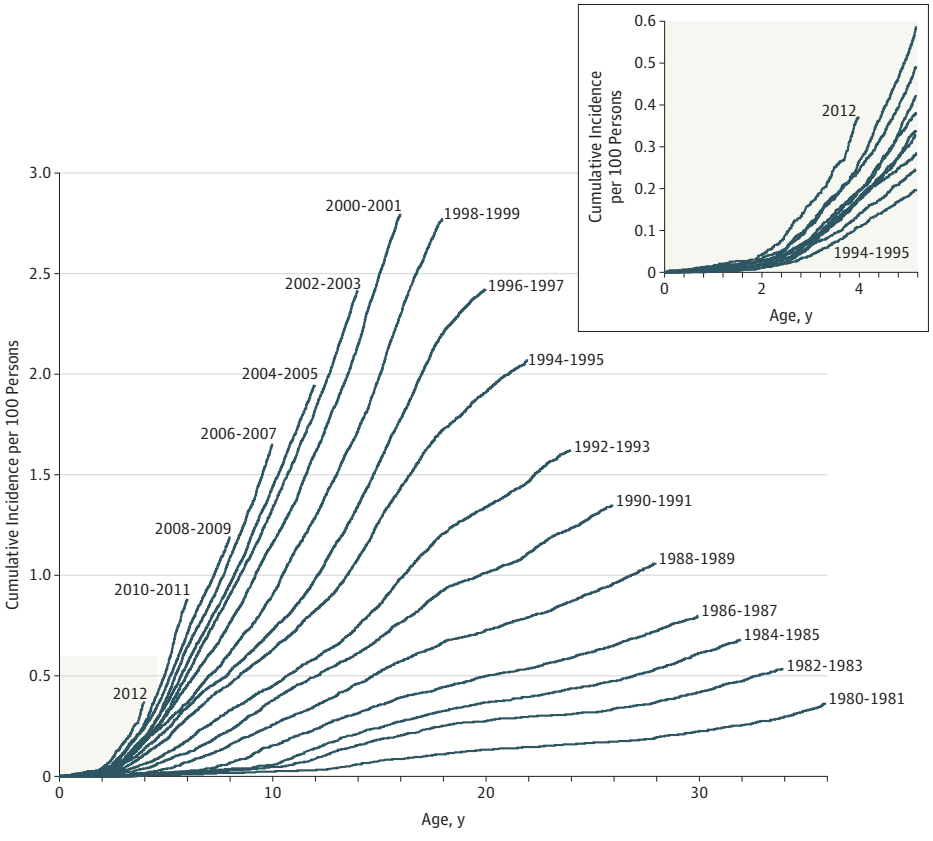
Cumulative Incidence of Autism Into Adulthood for Birth Cohorts in Denmark, 1980-2012

The Centers for Disease Control and Prevention recently reported an autism prevalence of 1.68% among 8-year-old children in the United States in 2014,[1] which is 14% higher than the reported rate for 8-year-old children in 2012 and 2010.[2,3] Autism prevalence rates of 2% and 2.47% in school-aged children were previously estimated from parent report data in US national health surveys.[4,5] These cross-sectional data may suggest that autism spectrum disorder (ASD) prevalence is reaching a peak. However, longitudinal data with follow-up into adulthood are needed to truly determine whether the prevalence has stabilized.

Methods | All live births in Denmark between 1980 and 2012 were identified in the Central Person Register and followed through 2016 for an ASD diagnosis (*International Classification of Diseases, Eighth Revision* codes 299.00, 299.01, 299.02, and 299.03; *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes F84.0, F84.1, F84.5, F84.8, and F84.9) via linkage with the Psychiatric Central Research and National Patient Registers containing diagnoses recorded by medical specialists (only inpatient contacts before 1995). Persons with suspected ASD receive a multidisciplinary evaluation at a psychiatric department and the final diagnosis is reported by a psychiatrist who has received mandatory registry-reporting training. Persons receiving the ASD subdiagnosis of pervasive development disorder, unspecified (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* code F84.9) may be advised to return for re-evaluation.

We used competing-risks survival analysis[6] to estimate ASD age-specific cumulative incidence in 2-year birth cohorts using age as the underlying time scale; persons were followed up until ASD diagnosis, death, emigration, or December 31, 2016, whichever came first (SAS version 9.4; SAS Institute Inc). In sensitivity analysis, we recalculated cumulative incidence based on the second ASD diagnosis for all persons with an ini-

Figure. Cumulative Incidence of Autism Spectrum Disorder by Age Through 2016 in Denmark Among 1980-2012 Birth Cohorts



Each curve in the main body of the Figure corresponds to the autism spectrum disorder cumulative incidence through 2016 among persons in a 2-year birth cohort (beginning 1980-1981, bottom curve), except for the left-most curve that corresponds to the last cohort composed of a single birth year, 2012. The inset is a close-up view of the autism spectrum disorder cumulative incidence through age 5 years for each birth cohort, 1994-2012 (corresponding to births after the adoption of *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* autism spectrum disorder diagnostic criteria).

Table. Cumulative Incidence of Autism Spectrum Disorder Through 2016 for Persons Born Between 1980 and 2012 in Denmark

Birth Year	Autism Spectrum Disorder Cumulative Incidence by Age per 100 Persons, % (95% CI)[a]				*ICD* System
	Age 4 y	Age 10 y	Age 16 y	Age 22 y	
1980-1981	0 (0-0)[b]	0.03 (0.02-0.04)			
1982-1983	0 (0-0)[b]	0.05 (0.02-0.11)			
1984-1985	0 (0-0)[b]				*ICD-8* only[c]
1986-1987	0 (0-0)[b]				
1988-1989	0 (0-0)[b]				
1980-1981			0.09 (0.07-0.11)	0.15 (0.13-0.17)	
1982-1983			0.20 (0.16-0.26)	0.30 (0.25-0.35)	
1984-1985		0.06 (0.02-0.17)	0.27 (0.21-0.35)	0.40 (0.33-0.48)	
1986-1987		0.15 (0.09-0.26)	0.39 (0.31-0.49)	0.54 (0.45-0.64)	*ICD-8* + *ICD-10*[d]
1988-1989		0.26 (0.17-0.39)	0.57 (0.47-0.69)	0.79 (0.68-0.91)	
1990-1991	0 (0-0)[b]	0.38 (0.27-0.52)	0.76 (0.64-0.90)	1.11 (0.98-1.25)	
1992-1993	0.01 (0.0-0.0)	0.45 (0.32-0.61)	0.98 (0.84-1.14)	1.47 (1.32-1.62)	
1994-1995	0.11 (0.02-0.40)	0.63 (0.48.0.81)	1.43 (1.27-1.61)	2.07 (1.90-2.25)	
1996-1997	0.14 (0.03-0.45)	0.73 (0.56-0.93)	1.78 (1.59-1.97)		
1998-1999	0.17 (0.05-0.50)	0.90 (0.72-1.12)	2.30 (2.09-2.51)		
2000-2001	0.18 (0.05-0.55)	1.16 (0.95-1.40)	2.80 (2.57-3.04)		
2002-2003	0.18 (0.04-0.64)	1.33 (1.09-1.61)			*ICD-10* only[e]
2004-2005	0.20 (0.04-0.70)	1.44 (1.18-1.74)			
2006-2007	0.20 (0.04-0.75)	1.65 (1.38-1.97)			
2008-2009	0.24 (0.06-0.76)				
2010-2011	0.27 (0.07-0.79)				
2012	0.37 (0.13-0.88)				

Abbreviation: *ICD*, *International Statistical Classification of Diseases and Related Health Problems*.

[a] Total *ICD-8*–diagnosed autism spectrum disorder cases: n = 184; total *ICD-10*–diagnosed autism spectrum disorder cases: n = 31 777.

[b] Too few cases to calculate cumulative incidence.

[c] Cumulative incidence based on *ICD-8* diagnoses only (reported before 1994).

[d] Cumulative incidence based on *ICD-8* diagnoses (reported before 1994) and *ICD-10* diagnoses (reported from 1994 onward).

[e] Cumulative incidence based on *ICD-10* diagnoses only (reported from 1994 onward).

tial diagnosis of pervasive development disorder, unspecified. The study was approved by the Scientific Ethics Committees of the Central Denmark Region and according to guidelines from the Danish Data Protection Agency. Under Danish law, register-based projects are exempt from obtaining informed consent.

Results | Autism spectrum disorder was reported for 31 961 persons among 2 055 928 live births. Each birth cohort cumulative incidence curve followed its own trajectory, with new case ascertainment into adulthood for older cohorts, and reaching a higher cumulative incidence with age than any of the earlier cohorts (**Figure**). The maximum value was 2.80% (95% CI, 2.57%-3.04%) at age 16 years for persons born in 2000-2001 (**Table**); it was 3.89% (95% CI, 3.52%-4.28%) in boys and 1.66% (95% CI, 1.41%-1.94%) in girls. The curves for persons born after 2001 indicate increasing cumulative incidence at younger ages (at age 10 years, 1.16% [95% CI, 0.95%-1.40%] in persons born in 2000-2001 vs 1.65% [95% CI, 1.38%-1.97%] for persons born in 2006-2007) (Table). The Figure inset for 1994-2012 births reveals shifts in the age and rate at which the curve for a given birth cohort begins to ascend more steeply than previous cohorts, yielding a cumulative incidence at age 4 of 0.11% (95% CI, 0.02%-0.40%) in persons born in 1994-1995 vs 0.37% (95% CI, 0.13%-0.88%) for persons born in 2012 (Table). In sensitivity analysis, the overall cumulative incidence pattern was unchanged but the maximum value declined (2.50% [95% CI, 2.29%-2.73%] at age 16 for persons born in 2000-2001).

Discussion | The Danish ASD trends are consistent with US cross-sectional data for similar birth cohorts.[1-5] These population-wide data with follow-up into adulthood revealed no plateau in curves in more recent birth years, suggesting that ASD cumulative incidence has not stabilized. The ongoing increases at young ages in more recent cohorts suggest that future cumulative incidence could exceed 2.8%.

The age shifts at which the curve for a given birth cohort ascended more steeply than previous cohorts and the associated increases in cumulative incidence at young ages suggest that the services that support early detection of ASD expanded during this study's observation period. However, new case ascertainment also continued well into adulthood in older cohorts. This ascertainment pattern likely reflects the complexity of the ASD phenotype, diverse age course of individual behavioral development, and family and community differences over time in ASD detection that can delay diagnosis into adulthood.

This study cannot delineate causes of the observed ASD trends or provide results by ASD characteristics that might aid services planning. Nevertheless, the results highlight the substantial public health challenges that lie ahead to meet the diverse support needs of persons with ASD across the life span.

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Accepted for Publication: July 17, 2018.

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Author Contributions: Dr Schendel and Ms Thorsteinsson had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Obtained funding: Schendel.
Administrative, technical, or material support: Schendel.
Supervision: Schendel.

Conflict of Interest Disclosures: Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Funding/Support: This study was supported in part by a contract from the European Commission Directorate-General for Health and Consumers Protection (SANCO/2014/C2/035) and an unrestricted grant from the Lundbeck Foundation (iPSYCH).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Betina B. Trabjerg, MS, Aarhus University, and Carsten Bøcker Pedersen, PhD, Aarhus University, provided guidance on some elements of the computer programming syntax that were used in analysis; they were not compensated for their role.

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Evaluation of Lowering the *P* Value Threshold for Statistical Significance From .05 to .005 in Previously Published Randomized Clinical Trials in Major Medical Journals

Lowering the threshold for statistical significance in medical research from a *P* value of .05 to .005 was recently proposed to reduce misinterpretation of study results.[1,2] *P* values less than .05 but greater than .005 would be reclassified as "suggestive." What effect this proposal would have on the medical literature is unclear. We evaluated primary end points in randomized clinical trials (RCTs) published in 3 major general medical journals with high impact factors to determine how the new threshold could affect the interpretation of previously published RCTs.

Table 1. Characteristics of Included Clinical Trials or End Points

Characteristics	No. (%) of Articles (N=203)
Journal	
JAMA	69 (34.0)
Lancet	31 (15.3)
NEJM	103 (50.7)
Intervention	
Drug	124 (61.1)
Procedure	41 (20.2)
Device	9 (4.4)
Vaccine	2 (1.0)
Other	21 (10.3)
Mixed	6 (3.0)
Funding source	
Industry	76 (37.4)
Public	81 (39.9)
Private	6 (3.0)
Hospital	17 (8.4)
Mixed (no industry)	11 (5.4)
Mixed (with industry)	10 (4.9)
Not mentioned	2 (1.0)
No. of trial centers	
Multicenter	181 (89.2)
Single center	22 (10.8)
Location	
Multinational	105 (51.7)
Single country	98 (48.3)
Type of end point, No.	272
Mortality	27 (9.9)
Other	245 (90.1)
Sample size, median (IQR)	565 (290-1215)

Abbreviations: IQR, interquartile range; *NEJM*, *New England Journal of Medicine*.

Methods | We searched PubMed from January 1, 2017, to December 31, 2017, for phase 3 RCTs published in *JAMA*, *Lancet*, and *New England Journal of Medicine* (*NEJM*). We excluded single-group trials, pooled analyses, RCTs without *P* values, and RCTs that used Bayesian or noninferiority analyses. Two authors (C. W., J. S.) screened all trials.

We extracted data for primary end points because RCTs are most often powered for these end points. The following data were extracted from each trial: *P* values for primary end points (excluding subgroups), study title, journal name, funding source, sample size, type of intervention, whether the end point was mortality, whether the trial was multicentered, and whether the trial was multinational. Data were extracted blinded and in duplicate. Discrepancies were resolved by consensus.

We first determined the proportion of end points that would maintain statistical significance with a threshold of *P* less than .005 and that would be reclassified as suggestive