Prevalence and incidence rates of autism in the United Kingdom: time trend from 2004-2010 in children aged 8 years

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Prevalence and incidence rates of autism in the United Kingdom: time trend from 2004-2010 in children aged 8 years.

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Running head: Autism in the UK 2004-2010

Key words: Autism, Prevalence, Incidence.

Word Count: 2,974

Abstract (248 words)

Background

Autism was infrequently diagnosed prior to 1990. A dramatic increase in children diagnosed as autistic occurred in the 1990s in the United States (US) and United Kingdom (UK). In March 2012, in a press release widely covered by the media, the Centre for Disease Control (CDC) reported that the autism prevalence rate in 2008 in 8 year-old US children was 1 in 88, a 78% increase from a CDC estimate in 2004. The report prompted us to update UK studies begun in the early 1990s on the annual prevalence and incidence rates of autism in children aged 8 from 2004 – 2010.

Methods

Annual autism prevalence rates were estimated for children aged 8 in 2004-2010 by dividing the number diagnosed as autistic in that or any prior year by the number of children active in the study population that year. We also calculated annual incidence rates for children aged 2-8, by dividing the number newly diagnosed in 2004 -2010 by the same denominators.

Results

Annual prevalence rates for each year were steady at approximately 3.8/1000 boys and 0.8/1000 girls. Annual incidence rates each year were also steady at about 1.2/1000 boys and 0.2/1000 girls.

Conclusions

Following a five fold increase in the annual incidence rates of autism during the 1990s in the UK, the incidence and prevalence rates in 8 year-old children reached a plateau in the early 2000s and remained steady through 2008. Whether prevalence rates have increased after early 2000 in the US remains uncertain.

Summary

Article focus

- The documented prevalence of autism rose dramatically from the mid 1980s; the most recent figure from the USA was 1 in 88 eight year-old children; changes in diagnostic criteria and societal changes have contributed, but the rise has been described as a false epidemic of autism.
- Some studies in UK children suggested that the rise was levelling off in children born in the mid-to-late 1990s.
- This investigation of annual prevalence and incidence rates extends earlier work on the same database, using the same age criteria as the recent US study.

Key messages

- The prevalence and incidence of autism in 8-year old UK children was level from 2004 to 2010, with rates much lower than reported in the USA.
- The cause of the rise in the 1980s-1990s and the subsequent levelling of prevalence and incidence in the UK is incompletely understood. It is not known if the rise in recorded prevalence in the USA has continued.

Strengths and limitations of this study

This was a population study, fully representative of the UK. Cases were recorded in the GP clinical records but all were diagnosed by specialists. The diagnosis of autism recorded in the General Practice Research Database (GPRD) has been confirmed as

highly sensitive. The GPRD is a uniquely constructed resource of clinical medical information that has succeeded in providing a reliable continuous standardized accounting of demographics, medical diagnoses and prescribed medicines over more than 20 years.

There may have been unidentified cases (false negatives) in the study population. However this was a real-life clinically-based study with no attempt to screen the child population for autism. Such screening may have contributed to the diagnosis being made too frequently.

Background

In March 2012, the US Centre for Disease Control (CDC) issued a press release[1] that described the results of a long term study on the annual prevalence rate of autism in 8 year old children[2]. They reported that 1 of 88 children aged 8 years had been diagnosed as autistic in or prior to 2008. This represented a 78% increase from the estimate in 2004. The press release received wide media attention and prompted us to review and update the information accrued in the United Kingdom (UK) General Practice Research Database (GPRD) over the last 20 years to derive annual prevalence rate estimates in children in the UK for the years 2004 -2010. For direct comparison with the CDC study, we restricted our results to 8 year old children.

Methods

The GPRD is a unique longitudinal electronic medical database constructed and implemented in 1990 through a combined effort of the Boston Collaborative Drug Surveilance Program (BCDSP), a UK general practitioner (GP) who spent five years creating a comprehensive electronic GP office medical record system to replace preexisting paper records, and a private company, Vamp Health. The GPs who participated used identical software and were trained to enter medical information according to a formal protocol. Some 1000 general practitioners in over 300 general practices - about 5% of the UK population - were enrolled by 1996. The distribution of practices was designed to be representative of the UK population. Our programmer constructed a unique comprehensive computer file structure that integrated all the information into a unified resource that allowed for rapid access to the full dataset, updated annually. Early validation studies found an 87% correlation between the diagnoses in consultant's letters and those in the GPRD record.[3] The high quality, stability and consistency of the recorded information over time has been repeatedly demonstrated in more than 150 publications.[4-11]

Autism is a developmental disorder manifested early in childhood and characterized by a spectrum of abnormal social and communication skills and unusual behaviour. The condition was infrequently diagnosed prior to 1990. However, an awareness of a gradual increase in the frequency of diagnosed autism was anecdotally noted during the early 1990s. The validity of the autism diagnosis recorded by GPs in this study was

derived from review of the extensive specialist referral reports.[5] The quality and specificity of the diagnosis of autism in the GPRD were subsequently confirmed by an independent research group based on DSM4 criteria.[12-13]

Annual prevalence rates were calculated by dividing the number of children aged 8 years diagnosed as autistic and recorded in the continuous medical record by the GP at any prior time, by the number of 8 year olds active in the database that year. For example, prevalence rates for 2004 were based on the number of children who were aged 8 in 2004 and had been diagnosed as autistic during the 8 prior years 1996-2004. Continuous prevalence rates were similarly estimated for each subsequent calendar year.

We also calculated annual incidence rates by dividing the annual number of children aged 2-8 newly diagnosed with autism in each year (2004 – 2010), by the number of children aged 2-8 active in the practices in that year. Practices enrolled in the GPRD only after 1996 were excluded from the study.

The study protocol was approved by the MHRA's Independent Scientific Advisory Committee (ISAC) . All data were anonymised. The GPRD data source was constructed by Hershel Jick and Dean MacLaughlin. The study was designed by Hershel Jick and Brent Taylor. The database access was created by Dean MacLaughlin. Data analysis was done by Hershel Jick and Brent Taylor. The manuscript was written by Brent

Taylor and Hershel Jick. All the authors vouch for the accuracy and completeness of the data and the analyses as presented. They also vouch for the fidelity of the final report. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Results

Table 1 shows the annual number of boys aged 8 years who had been diagnosed as autistic in each or any prior year i.e., prevalent cases. The annual number of prevalent cases (a reflection of the cumulative incidence) is remarkably similar over calendar time, as is the number of boys active in the population from 2004 -2010. The resulting annual prevalence rate estimates of about 3.8/1000 boys are steady over time. The 95% confidence limits widely overlapped in each year.

Table 1 also shows the annual number of boys aged 2-8 diagnosed as autistic for the first time (incident) in each year from 2004-2010. The annual number of incident cases is again remarkably similar over time as is the number of boys active in the practices each year, resulting in annual incidence estimates of about 1.2/1000 boys over the years. The total number of boys was 1190.

The number of girls initially diagnosed as autistic from 2004-2010 was 217. Table 2 provides the annual prevalence and incidence rate estimates over time for girls. Girls were about one fifth as likely to be diagnosed with autism as boys.

Discussion

For many years the terms incidence and prevalence were applied in medicine primarily to describe acute outbreaks of infectious diseases such as influenza, measles and mumps. Since the mid 1950s, these terms have also been applied to chronic diseases such as diabetes, cancer and more recently autism. Even a superficial consideration of the use of these general terms will reveal the complexity and subtlety of their application in quantitative observational time trend studies in clinical medicine.

The term "prevalence"alone is used widely to describe a general property possessed by an indefinite quantity of a condition e.g., the prevalence of conservative voters is higher in rural compared to urban areas. It is also used in public health as a general frequency or quantity, e.g., the prevalence of flu is higher in the winter than in the summer .

By contrast, in formal epidemiological research, reliable quantitative estimates of incidence and prevalence "rates" require accurate identification of the number of newly diagnosed cases in a defined population from which the cases were derived, at a given age during a given time period. Valid comparisons of annual rate estimates over many years are dependent on the stability of the base population and the ascertainment of the condition under study.

In 1996, the CDC conducted a study based on screening and abstraction of records in the 5 counties of Atlanta Georgia.[14] The prevalence was estimated to be 3.4 per 1000

among children aged 3 to 10. Surveys in California in 1983-85 and in 1993-95 based on birth cohorts[15-16] found that during years 1980-1994 there was a large annual secular increase in the number of cases of autism; these increases were estimated as a prevalence of 44 per 100,000 live births in the 1980 cohort and 208 in the 1994 cohort[17]. A study from Denmark estimated that the prevalence of autism rose from less than 2 per 10,000 prior to 1990 to more than 10 per 10,000 in 2000.[18] Taken together these reports provided clear evidence that there was a substantial increase in the number of young children diagnosed as autistic in the US and Europe during the decade of the 1990s.

In February 1998 Wakefield et al reported a case series of 12 autistic children with bowel disorders most of whom had recently received the MMR vaccine[19]. The authors suggested that the MMR vaccine may have been causally related to these gastro-intestinal conditions. This widely publicised paper led to subsequent studies to evaluate the proposition that the MMR vaccine might be causaly related to autism.

In the following year, Taylor et al reported results from a study based on birth cohorts from 1979-1992 in the North East Thames (UK) health region[20]. They reviewed special needs records and found that fewer than 10 children per year born from 1979 through 1986 were diagnosed as autistic. Subsequently, the number increased to almost 50 in children born in 1992. They found no correlation between MMR vaccination and the rise in the prevalence of autism.

Shortly thereafter, the BCDSP examined experience accrued in the GPRD since 1990 to estimate annual cumulative incidence rates for birth cohorts from 1988-93 for boys age 2-5 years and found that the autism cumulative incidence rates increased some 5 fold from an estimated of 6 per 10,000 in boys born in 1988 to 30 per 10,000 in those born in 1993. At the same time MMR vaccination was given to over 90% of young children ruling out an association between the vaccine and the dramatic increase in rates. [21]

Subsequent studies also found no association between MMR and autism. [17, 18, 22, 23,] Lingam et al suggested that the previously observed annual increase in prevalence may have been leveling off by the mid-1990s. [23]

The BCDSP continued to assess time trends by updating the findings recorded in the GPRD for additional birth cohorts. Results for birth cohorts from 1994 to 1995 continued to show a rise in the cumulative incidence of diagnosed autism but results for 1996-97 indicated that the rise may have reached a plateau.[24] Subsequent follow up demonstrated that rates had in fact plateaued in the 1996 cohort and remained steady for 1996 through the 2001 birth cohort[25] (See Figure 1). Children born in 2001 would have been diagnosed as autistic at aged 2-4 in 2003-2005.

Taken together the published findings conclusively demonstrated that there was a dramatic similtaneous rise in the number of children diagnosed as autistic in the US, UK, and Denmark during the 1990s. In addition, there was highly persuasive evidence

that MMR vaccine was not the cause of the rise. Despite firm evidence that a steady state occurred in children born from 1996 through 2001 in the UK, litigation continued in US courts until 2010.

The initial autism studies[5, 15-18, 20-25] were based primarily on birth cohorts usually aged 2-5 years. In this design the number of newly diagnosed (incident) cases is determined separately for each annual birth cohort. By contrast, the nature and interpretation of annual prevalence "rates" of autism are far more complex and superficially counterintuitive, particularly where the design objective is to estimate changes in yearly time trends or to compare results with other similarly designed studies.

The CDC chose to estimate annual prevalence rates for children of the same age - 8 years – in each of successive calendar years. Annual prevalence estimates apply to children who encompass a large age range e.g., 2-8 years and each of the autism cases may be included as prevalent in multiple years. For example, when examining the period 2004 to 2010, a child diagnosed at age 2 in 2004 would be included in the prevalence estimate for each of the next six years until the child reached age 9 years and no longer is a prevalent case. Children diagnosed at age 6 in 2005 would be included in the prevalence estimates for only 3 years thereafter. Year of age at first diagnosis is thus a critical variable in estimating the annual prevalence rates over many years.

The 2012 CDC report[2] was a follow up to studies of 8 year old children initiated in 2000 and repeated every two years thereafter. The results were derived from a network of 6-11 US states depending on the years, and based on school or medical records or both. Early reports estimated annual prevalence rates of 6.7 and 6.6 per 1000 children in 2000 and 2002. Starting in 2004, prevalence rate estimates rose steadily until 2008 when they reached 11.3 per 1000, a rise of 78% from 2004. The latest prevalence rate estimates varied widely from state to state – 4.1/1000 in Alabama to 21.2/1000 in Utah. A detailed commentary on the limitations of the CDC report was published shortly after it was released.[26] This commentary raised important questions related to the accuracy and specificity of the combined rate estimates over the years.

In the present paper we review and update an extraordinary 20-year exploration of the annual rates of autism in young children as recorded in real time and derived from a unique carefully designed medical database in the UK. In a formal analysis of the data recorded continuously by some 1000 GPs, we have documented that the cumulative incidence of autism in children born from 1988-1995 began to increase and continued to rise from a low level by more than five fold during these years. The annual incidence then leveled off and reached a steady state in children born from 1996-2001.

In order to compare the UK experience with that reported by the CDC, we restricted our current prevalence study to annual calendar years 2004-2010 in children 8 years of age. These children would have all been born after 1995. Combined, the results in this

20-year population-based UK resource, provide highly persuasive evidence that a major rise in GP-diagnosed incidence rates of autism occured in the decade of the 1990s but reached a plateau shortly after 2000 and remained steady through 2010. This incidence plateau was necessarily accompanied by steady prevalence rates for 8 year old children.

It is possible that at least a part of the early rise was related to changing and broadening diagnostic criteria to include a spectrum of disorders[27-28] as well as increased general medical and public awareness.[29] However, it seems unlikely that these factors materially explain the extraordinary increase in the number of children diagnosed in the 1990s; nor the steady state that followed thereafter in 2004 through 2010. While the MMR vaccine is surely not the cause of the dramatic rise in the 1990s, the actual cause remains in large part a mystery.

There are important similarities between the results found in the US and UK in the secular epidemiology of autism. Few children were diagnosed as autistic in either country prior to 1990. A continuous simultaneous extraordinary rise in the number of children diagnosed as autistic began in both countries in the early 1990s and lasted for a decade. The distribution of first time diagnosis according to age and gender was the same. These similarities between countries as well as within different locations in each country point to a common etiology for this extraordinary medical story.

By contrast, there is a large difference in the percentage of children diagnosed as autistic in the two countries. The estimated prevalence rates of autism in the UK population, about 4 per 1000 in 8 year old boys in 2008, is far lower than the more than 11 per 1000 in 8 year old boys reported by the CDC from the US for the same calendar year. This large difference between countries is closely similar to differences in rates reported in children diagnosed and treated for attention deficit hyperactivity disorder (ADHD) in the two countries. [30, 31]

There is wide-spread concern that the diagnosis of autism using the present criteria has become too broad and that the diagnosis is made too frequently. "If the *DSM-IV* criteria are taken too literally, anybody in the world could qualify for Asperger's or PDD-NOS," Catherine Lord, one of the members of the APA's *DSM*-V Development Neurodevelopmental Disorders Work Group has said. "The specificity is terrible. We need to make sure the criteria are not pulling in kids who do not have these disorders."[32] The forthcoming DSM-V criteria will considerably tighten criteria. This tightening should affect what has been described as the 'false epidemic of autism'.[33]

The GPRD is a uniquely constructed resource of clinical medical information that has succeeded in providing a reliable continuous standardized accounting of demographics, medical diagnoses and prescribed medicines over more than 20 years. The substance of its construction and implementation is highly complex. Nowhere is

this clearer than in the current findings related to the enormously complex secular epidemiology of autism.

In conclusion, the annual prevalence of clinically confirmed autism recorded by UK general practitioners remained steady for the 7-year period 2004-10. Whether it has increased in the US over these years remains uncertain.

Acknowlegements

The authors gratefully acknowledge the excellent work of the general practitioners who have contributed to the GPRD.

Figure 1*

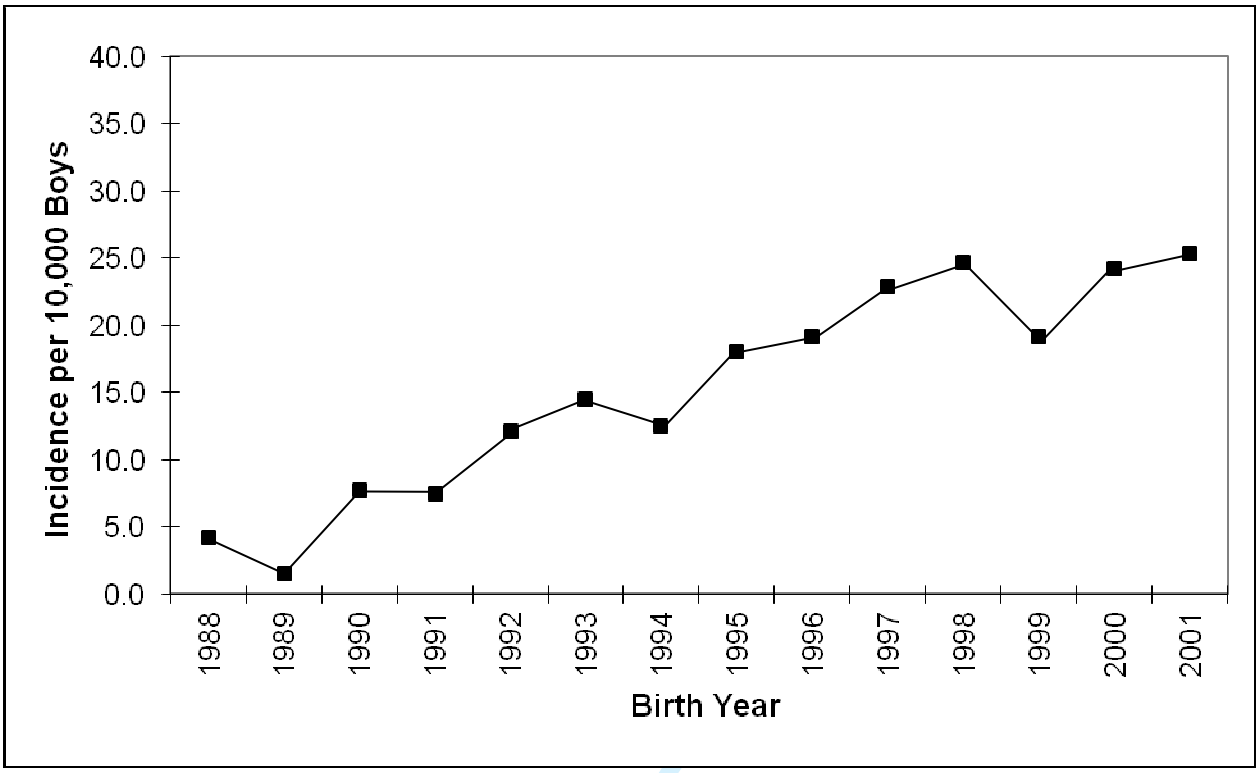

Figure. Three-year cumulative incidence of diagnosed autism among boys age 2-4 years, by year of birth.[25]

*Adapted from Hagberg KW, Jick H. "Autism in the UK for birth cohorts" 1988-2001. Epidemiology 2010;21:426-427.

Table 1. Prevalence and Incidence Rates of Boys Aged 8 for Years 2004 – 2010

Year	Number of Boys aged 8 in CPRD	Number of Prevalent Cases	Prevalence Rate per 1000	Number of Incident Cases	Incidence Rate per 1000
2004	145,483	521	3.58	172	1.18
2005	143,721	535	3.72	170	1.18
2006	147,049	568	3.86	190	1.29
2007	142,229	540	3.80	173	1.22
2008	138,847	543	3.91	170	1.22
2009	138,317	566	4.09	180	1.30
2010	132,143	515	3.90	135	1.02

Table 2. Prevalence and Incidence Rates of Girls Aged 8 for Years 2004 – 2010

Year	Number of Girls aged 8 in CPRD	Number of Prevalent Cases	Prevalence Rate per 1000	Number of Incident Cases	Incidence Rate per 1000
2004	136,752	109	0.80	27	0.20
2005	135,511	112	0.83	30	0.22
2006	138,548	112	0.81	34	0.25
2007	134,083	125	0.93	41	0.31
2008	130,876	107	0.82	29	0.22
2009	130,367	106	0.81	30	0.23
2010	124,135	101	0.81	26	0.21

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Page 1 (prevalence, incidence, time trend)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Pages 2-3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses Page 4 ('…to derive annual prevalence rate estimates for children in the UK')
Methods		
Study design	4	Present key elements of study design early in the paper Page 4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 4-5 (details of the GPRD, with references)
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Page 4-6 (details of the GPRD with references, including validity of autism diagnoses)
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page 4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page 4-6
Bias	9	Describe any efforts to address potential sources of bias N/A (population-based clinical database)
Study size	10	Explain how the study size was arrived at N/A (population-based clinical database)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why N/A
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding N/A – tabulations only – no statistical analysis
		(*b*) Describe any methods used to examine subgroups and interactions N/A
		(*c*) Explain how missing data were addressed Not addressed per se; this analysis was based on general-practitioner-recorded diagnoses
		(*d*) If applicable, explain how loss to follow-up was addressed N/A (although cases may have entered or left the individual practices over time, our analysis is based on annual figures.
		(*e*) Describe any sensitivity analyses N/A
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Page 6-7 and Tables 1 and 2
		(b) Give reasons for non-participation at each stage N/A
		(c) Consider use of a flow diagram ?
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and

		information on exposures and potential confounders Representative UK general practice population
		(b) Indicate number of participants Table 1 and 2 with missing data for each variable of interest N/A
		(c) Summarise follow-up time (eg, average and total amount) Annual numbers of children with autism diagnosed 2004-2010, as explained on page
Outcome data	15*	Report numbers of outcome events or summary measures over time Table 1 and 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included N/A
		(*b*) Report category boundaries when continuous variables were categorized N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses N/A
Discussion		
Key results	18	Summarise key results with reference to study objectives Page 14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Not really mentioned in the present discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page 12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results Page 12-14
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based No grant funding for this project.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Prevalence and incidence rates of autism in the United Kingdom: time trend from 2004-2010 in children aged 8 years

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Prevalence and incidence rates of autism in the United Kingdom: time trend from 2004-2010 in children aged 8 years.

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Running head: Autism in the UK 2004-2010

Key words: Autism, Incidence, Prevalence, UK, 2004-2010.

Word Count: 2,915

Abstract (248 words)

Background

Autism was infrequently diagnosed prior to 1990. A dramatic increase in children diagnosed as autistic occurred in the 1990s in the United States (US) and United Kingdom (UK). In March 2012, in a press release widely covered by the media, the Centre for Disease Control (CDC) reported that the autism prevalence rate in 2008 in 8 year-old US children was 1 in 88, a 78% increase from a CDC estimate in 2004. The report prompted us to update UK studies begun in the early 1990s on the annual prevalence and incidence rates of autism in children aged 8 from 2004 – 2010.

Methods

Annual autism prevalence rates were estimated for children aged 8 in 2004-2010 by dividing the number diagnosed as autistic in that or any prior year by the number of children active in the study population that year. We also calculated annual incidence rates for children aged 2-8, by dividing the number newly diagnosed in 2004 -2010 by the same denominators.

Results

Annual prevalence rates for each year were steady at approximately 3.8/1000 boys and 0.8/1000 girls. Annual incidence rates each year were also steady at about 1.2/1000 boys and 0.2/1000 girls.

Conclusions

Following a five fold increase in the annual incidence rates of autism during the 1990s in the UK, the incidence and prevalence rates in 8 year-old children reached a plateau in the early 2000s and remained steady through 2008. Whether prevalence rates have increased after early 2000 in the US remains uncertain.

Background

In March 2012, the US Centre for Disease Control (CDC) issued a press release[1] that described the results of a long term study on the annual prevalence rate of autism in 8 year old children[2]. They reported that 1 of 88 children aged 8 years had been diagnosed as autistic in or prior to 2008. This represented a 78% increase from the estimate in 2004. The press release received wide media attention and prompted us to review and update the information accrued in the United Kingdom (UK) General Practice Research Database (GPRD) over the last 20 years to derive annual prevalence rate estimates in children in the UK for the years 2004 -2010. For direct comparison with the CDC study, we restricted our results to 8 year old children.

Methods

The GPRD is a unique longitudinal electronic medical database constructed and implemented in 1990 through a combined effort of the Boston Collaborative Drug Surveilance Program (BCDSP), a UK general practitioner (GP) who spent five years creating a comprehensive electronic GP office medical record system to replace preexisting paper records, and a private company, Vamp Health. The GPs who participated used identical software and were trained to enter medical information according to a formal protocol. Some 1000 general practitioners in over 300 general practices - about 5% of the UK population - were enrolled by 1996. The distribution of practices was designed to be representative of the UK population. Our programmer

constructed a unique comprehensive computer file structure that integrated all the information into a unified resource that allowed for rapid access to the full dataset, updated annually. Early validation studies found an 87% correlation between the diagnoses in consultant's letters and those in the GPRD record.[3] The high quality, stability and consistency of the recorded information over time has been repeatedly demonstrated in more than 150 publications.[4-11]

Autism is a developmental disorder manifested early in childhood and characterized by a spectrum of abnormal social and communication skills and unusual behaviour. The condition was infrequently diagnosed prior to 1990. However, an awareness of a gradual increase in the frequency of diagnosed autism was anecdotally noted during the early 1990s. The validity of the autism diagnosis recorded by GPs in this study was derived from review of the extensive specialist referral reports.[5] The quality and specificity of the diagnosis of autism in the GPRD were subsequently confirmed by an independent research group based on DSM4 criteria.[12-13]

Annual prevalence rates were calculated by dividing the number of children aged 8 years diagnosed as autistic and recorded in the continuous medical record by the GP at any prior time, by the number of 8 year olds active in the database that year. For example, prevalence rates for 2004 were based on the number of children who were aged 8 in 2004 and had been diagnosed as autistic during the 8 prior years 1996-2004.

Continuous prevalence rates were similarly estimated for each subsequent calendar year.

We also calculated annual incidence rates by dividing the annual number of children aged 2-8 newly diagnosed with autism in each year (2004 – 2010), by the number of children aged 2-8 active in the practices in that year. Practices enrolled in the GPRD only after 1996 were excluded from the study.

The study protocol was approved by the MHRA's Independent Scientific Advisory Committee (ISAC) . All data were anonymised. The GPRD data source was constructed by Hershel Jick and Dean MacLaughlin. The study was designed by Hershel Jick and Brent Taylor. The database access was created by Dean MacLaughlin. Data analysis was done by Hershel Jick and Brent Taylor. The manuscript was written by Brent Taylor and Hershel Jick. All the authors vouch for the accuracy and completeness of the data and the analyses as presented. They also vouch for the fidelity of the final report. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Results

Table 1 shows the annual number of boys aged 8 years who had been diagnosed as autistic in each or any prior year i.e., prevalent cases. The annual number of prevalent cases (a reflection of the cumulative incidence) is remarkably similar over calendar time,

as is the number of boys active in the population from 2004 -2010. The resulting annual prevalence rate estimates of about 3.8/1000 boys are steady over time. The 95% confidence limits widely overlapped in each year.

Table 1 also shows the annual number of boys aged 2-8 diagnosed as autistic for the first time (incident) in each year from 2004-2010. The annual number of incident cases is again remarkably similar over time as is the number of boys active in the practices each year, resulting in annual incidence estimates of about 1.2/1000 boys over the years. The total number of boys was 1190.

The number of girls initially diagnosed as autistic from 2004-2010 was 217. Table 2 provides the annual prevalence and incidence rate estimates over time for girls. Girls were about one fifth as likely to be diagnosed with autism as boys.

Discussion

For many years the terms incidence and prevalence were applied in medicine primarily to describe acute outbreaks of infectious diseases such as influenza, measles and mumps. Since the mid 1950s, these terms have also been applied to chronic diseases such as diabetes, cancer and more recently autism. Even a superficial consideration of the use of these general terms will reveal the complexity and subtlety of their application in quantitative observational time trend studies in clinical medicine.

The term "prevalence"alone is used widely to describe a general property possessed by an indefinite quantity of a condition e.g., the prevalence of conservative voters is higher in rural compared to urban areas. It is also used in public health as a general frequency or quantity, e.g., the prevalence of flu is higher in the winter than in the summer .

By contrast, in formal epidemiological research, reliable quantitative estimates of incidence and prevalence "rates" require accurate identification of the number of newly diagnosed cases in a defined population from which the cases were derived, at a given age during a given time period. Valid comparisons of annual rate estimates over many years are dependent on the stability of the base population and the ascertainment of the condition under study.

In 1996, the CDC conducted a study based on screening and abstraction of records in the 5 counties of Atlanta Georgia.[14] The prevalence was estimated to be 3.4 per 1000 among children aged 3 to 10. Surveys in California in 1983-85 and in 1993-95 based on birth cohorts[15-16] found that during years 1980-1994 there was a large annual secular increase in the number of cases of autism; these increases were estimated as a prevalence of 44 per 100,000 live births in the 1980 cohort and 208 in the 1994 cohort[17]. A study from Denmark estimated that the prevalence of autism rose from less than 2 per 10,000 prior to 1990 to more than 10 per 10,000 in 2000.[18] Taken together these reports provided clear evidence that there was a substantial increase in the number of

young children diagnosed as autistic in the US and Europe during the decade of the 1990s.

In February 1998 Wakefield et al reported a case series of 12 autistic children with bowel disorders most of whom had recently received the MMR vaccine[19]. The authors suggested that the MMR vaccine may have been causally related to these gastro-intestinal conditions. This widely publicised paper led to subsequent studies to evaluate the proposition that the MMR vaccine might be causaly related to autism.

In the following year, Taylor et al reported results from a study based on birth cohorts from 1979-1992 in the North East Thames (UK) health region[20]. They reviewed special needs records and found that fewer than 10 children per year born from 1979 through 1986 were diagnosed as autistic. Subsequently, the number increased to almost 50 in children born in 1992. They found no correlation between MMR vaccination and the rise in the prevalence of autism.

Shortly thereafter, the BCDSP examined experience accrued in the GPRD since 1990 to estimate annual cumulative incidence rates for birth cohorts from 1988-93 for boys age 2-5 years and found that the autism cumulative incidence rates increased some 5 fold from an estimated of 6 per 10,000 in boys born in 1988 to 30 per 10,000 in those born in 1993. At the same time MMR vaccination was given to over 90% of young children ruling out an association between the vaccine and the dramatic increase in rates. [21]

Subsequent studies also found no association between MMR and autism. [17, 18, 22, 23,] Lingam et al suggested that the previously observed annual increase in prevalence may have been leveling off by the mid-1990s. [23]

The BCDSP continued to assess time trends by updating the findings recorded in the GPRD for additional birth cohorts. Results for birth cohorts from 1994 to 1995 continued to show a rise in the cumulative incidence of diagnosed autism but results for 1996-97 indicated that the rise may have reached a plateau.[24] Subsequent follow up demonstrated that rates had in fact plateaued in the 1996 cohort and remained steady for 1996 through the 2001 birth cohort[25] (See Figure 1). Children born in 2001 would have been diagnosed as autistic at aged 2-4 in 2003-2005.

Taken together the published findings conclusively demonstrated that there was a dramatic similtaneous rise in the number of children diagnosed as autistic in the US, UK, and Denmark during the 1990s. In addition, there was highly persuasive evidence that MMR vaccine was not the cause of the rise. Despite firm evidence that a steady state occurred in children born from 1996 through 2001 in the UK, litigation continued in US courts until 2010.

The initial autism studies[5, 15-18, 20-25] were based primarily on birth cohorts usually aged 2-5 years. In this design the number of newly diagnosed (incident) cases is determined separately for each annual birth cohort. By contrast, the nature and interpretation of

annual prevalence "rates" of autism are far more complex and superficially counterintuitive, particularly where the design objective is to estimate changes in yearly time trends or to compare results with other similarly designed studies.

The CDC chose to estimate annual prevalence rates for children of the same age - 8 years – in each of successive calendar years. Annual prevalence estimates apply to children who encompass a large age range e.g., 2-8 years and each of the autism cases may be included as prevalent in multiple years. For example, when examining the period 2004 to 2010, a child diagnosed at age 2 in 2004 would be included in the prevalence estimate for each of the next six years until the child reached age 9 years and no longer is a prevalent case. Children diagnosed at age 6 in 2005 would be included in the prevalence estimates for only 3 years thereafter. Year of age at first diagnosis, including prior to 2004, is thus a critical variable in estimating the annual prevalence rates at age 8 over many years. The full detail that yielded the annual prevalence rates could be reviewed directly for consistency.

The 2012 CDC report[2] was a follow up to studies of 8 year old children initiated in 2000 and repeated every two years thereafter. The results were derived from a network of 6-11 US states depending on the years, and based on school or medical records or both. Early reports estimated annual prevalence rates of 6.7 and 6.6 per 1000 children in 2000 and 2002. Starting in 2004, prevalence rate estimates rose steadily until 2008 when they reached 11.3 per 1000, a rise of 78% from 2004. The latest prevalence rate estimates

varied widely from state to state – 4.1/1000 in Alabama to 21.2/1000 in Utah. A detailed commentary on the limitations of the CDC report was published shortly after it was released.[26] This commentary raised important questions related to the accuracy and specificity of the combined rate estimates over the years.

In the present paper we review and update an extraordinary 20-year exploration of the annual rates of autism in young children as recorded in real time and derived from a unique carefully designed medical database in the UK. In a formal analysis of the data recorded continuously by some 1000 GPs, we have documented that the cumulative incidence of autism in children born from 1988-1995 began to increase and continued to rise from a low level by more than five fold during these years. The annual incidence then leveled off and reached a steady state in children born from 1996-2001.

In order to compare the UK experience with that reported by the CDC, we restricted our current prevalence study to annual calendar years 2004-2010 in children 8 years of age. These children would have all been born after 1995. Combined, the results in this 20-year population-based UK resource, provide highly persuasive evidence that a major rise in GP-diagnosed incidence rates of autism occured in the decade of the 1990s but reached a plateau shortly after 2000 and remained steady through 2010. This incidence plateau was necessarily accompanied by steady prevalence rates for 8 year old children.

It is possible that at least a part of the early rise was related to changing and broadening

diagnostic criteria to include a spectrum of disorders[27-28] as well as increased general medical and public awareness.[29] However, it seems unlikely that these factors materially explain the extraordinary increase in the number of children diagnosed in the 1990s; nor the steady state that followed thereafter in 2004 through 2010. While the MMR vaccine is surely not the cause of the dramatic rise in the 1990s, the actual cause remains in large part a mystery. The current study provides compelling evidence that incidence rates have remained steady in children born since the late 1990's in the UK – at least as diagnosed and recorded in general practice.

There are important similarities between the results found in the US and UK in the secular epidemiology of autism. Few children were diagnosed as autistic in either country prior to 1990. A continuous simultaneous extraordinary rise in the number of children diagnosed as autistic began in both countries in the early 1990s and lasted for a decade. The distribution of first time diagnosis according to age and gender was the same. These similarities between countries as well as within different locations in each country point to a common etiology for this extraordinary medical story.

By contrast, there is a large difference in the percentage of children diagnosed as autistic in the two countries. The estimated prevalence rates of autism in the UK population, about 4 per 1000 in 8 year old boys in 2008, is far lower than the more than 11 per 1000 in 8 year old boys reported by the CDC from the US for the same calendar year. This large difference between countries is closely similar to differences in rates reported in

children diagnosed and treated for attention deficit hyperactivity disorder (ADHD) in the two countries. [30, 31]

The GPRD is a uniquely constructed resource of clinical medical information that has succeeded in providing a reliable continuous standardized accounting of demographics, medical diagnoses and prescribed medicines over more than 20 years. The substance of its construction and implementation is highly complex. Nowhere is this clearer than in the current findings related to the enormously complex secular epidemiology of autism.

In conclusion, the annual prevalence of clinically confirmed autism recorded by UK general practitioners remained steady for the 7-year period 2004-10. Whether it has increased in the US over these years remains uncertain.

Acknowlegements

The authors gratefully acknowledge the excellent work of the general practitioners who have contributed to the GPRD.

Figure 1*

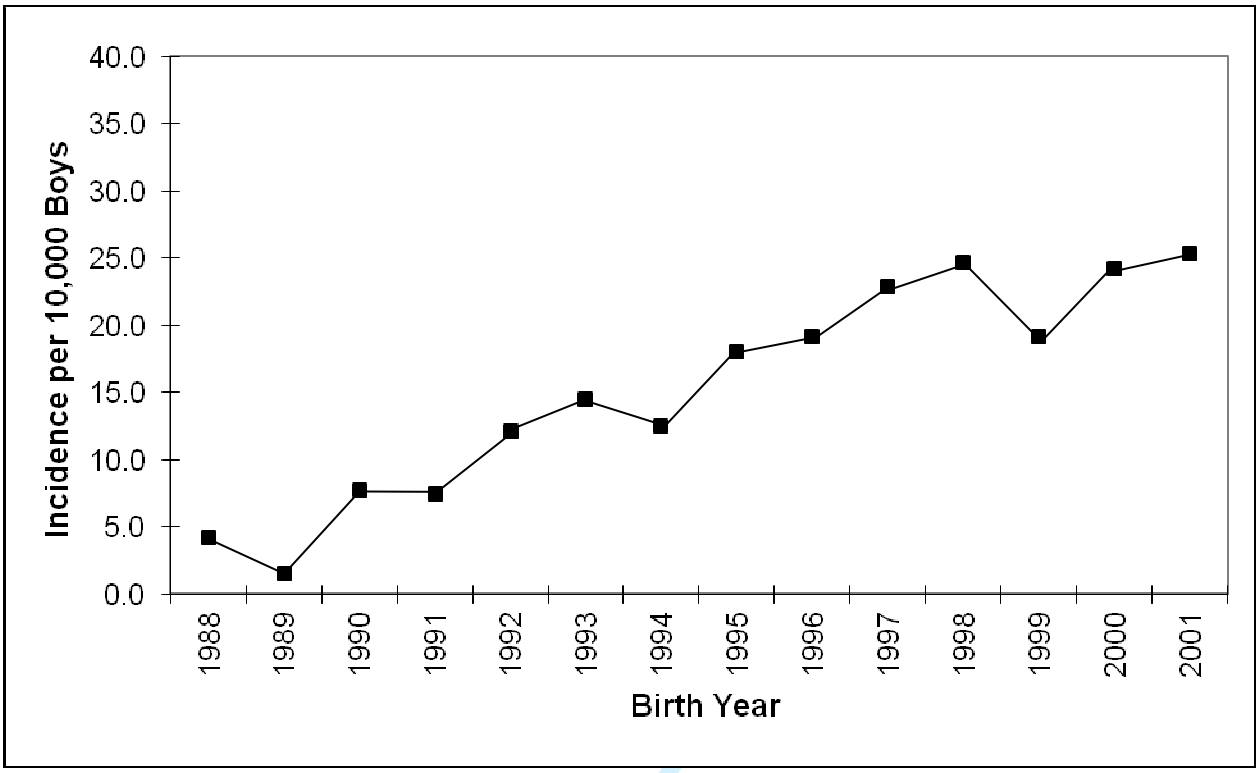

Figure. Three-year cumulative incidence of diagnosed autism among boys age 2-4 years, by year of birth.[25]

*Adapted from Hagberg KW, Jick H. "Autism in the UK for birth cohorts" 1988-2001. Epidemiology 2010;21:426-427.

Table 1. Prevalence and Incidence Rates of Boys Aged 8 for Years 2004 – 2010

Year	Number of Boys aged 8 in CPRD	Number of Prevalent Cases	Prevalence Rate per 1000	Number of Incident Cases	Incidence Rate per 1000
2004	145,483	521	3.58	172	1.18
2005	143,721	535	3.72	170	1.18
2006	147,049	568	3.86	190	1.29
2007	142,229	540	3.80	173	1.22
2008	138,847	543	3.91	170	1.22
2009	138,317	566	4.09	180	1.30
2010	132,143	515	3.90	135	1.02

Table 2. Prevalence and Incidence Rates of Girls Aged 8 for Years 2004 – 2010

Year	Number of Girls aged 8 in CPRD	Number of Prevalent Cases	Prevalence Rate per 1000	Number of Incident Cases	Incidence Rate per 1000
2004	136,752	109	0.80	27	0.20
2005	135,511	112	0.83	30	0.22
2006	138,548	112	0.81	34	0.25
2007	134,083	125	0.93	41	0.31
2008	130,876	107	0.82	29	0.22
2009	130,367	106	0.81	30	0.23
2010	124,135	101	0.81	26	0.21

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Summary

Article focus

- Prior to the middle 1980's, autism was infrequently diagnosed in children. Over the next decade, the number of children diagnosed as autistic rose more than five-fold in the US, UK, and Denmark. In 2012, a study from the CDC in the US reported that the prevalence of autism in 2008 in children age 8 was 1 in 88 children and that the 2008 prevalence rate was 78% higher than the prevalence rate in 2004.
- Earlier independent studies from the UK had reported that autism rates may have levelled off in children born in the mid to late 1990's.
- This investigation of annual prevalence and incidence rates extends earlier work on the same data source using the same age criteria as the recent US study.

Key messages

- The prevalence and incidence of autism in 8-year old UK children was level from 2004 to 2010, with rates much lower than reported in the USA.
- Whether the prevalence rate rose has increased in the U.S. in the last decade remains uncertain. Whether the rates have increased in the US remains uncertain.

Strengths and limitations of this study

This was a population study, fully representative of the UK. Cases were recorded in the GP clinical records but all were diagnosed by specialists. The diagnosis of autism recorded in the General Practice Research Database (GPRD) has been confirmed as highly sensitive. The GPRD is a uniquely constructed resource of clinical medical information that has succeeded in providing a reliable continuous standardized accounting of demographics, medical diagnoses and prescribed medicines over more than 20 years.

There may have been individual children with autism who were diagnosed elsewhere and not notified to their GP's or other autistic children who remained undiagnosed.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Page 1 (prevalence, incidence, time trend)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Pages 2-3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses Page 4 ('…to derive annual prevalence rate estimates for children in the UK')
Methods		
Study design	4	Present key elements of study design early in the paper Page 4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 4-5 (details of the GPRD, with references)
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Page 4-6 (details of the GPRD with references, including validity of autism diagnoses)
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page 4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page 4-6
Bias	9	Describe any efforts to address potential sources of bias N/A (population-based clinical database)
Study size	10	Explain how the study size was arrived at N/A (population-based clinical database)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why N/A
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding N/A – tabulations only – no statistical analysis
		(*b*) Describe any methods used to examine subgroups and interactions N/A
		(*c*) Explain how missing data were addressed Not addressed per se; this analysis was based on general-practitioner-recorded diagnoses
		(*d*) If applicable, explain how loss to follow-up was addressed N/A (although cases may have entered or left the individual practices over time, our analysis is based on annual figures.
		(*e*) Describe any sensitivity analyses N/A
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Page 6-7 and Tables 1 and 2
		(b) Give reasons for non-participation at each stage N/A
		(c) Consider use of a flow diagram ?
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and

		information on exposures and potential confounders Representative UK general practice population
		(b) Indicate number of participants Table 1 and 2 with missing data for each variable of interest N/A
		(c) Summarise follow-up time (eg, average and total amount) Annual numbers of children with autism diagnosed 2004-2010, as explained on page
Outcome data	15*	Report numbers of outcome events or summary measures over time Table 1 and 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included N/A
		(*b*) Report category boundaries when continuous variables were categorized N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses N/A
Discussion		
Key results	18	Summarise key results with reference to study objectives Page 14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Not really mentioned in the present discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page 12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results Page 12-14
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based No grant funding for this project.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Prevalence and incidence rates of autism in the United Kingdom: time trend from 2004-2010 in children aged 8 years.

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Running head: Autism in the UK 2004-2010

Key words: Autism, Incidence, Prevalence, UK, 2004-2010.

Word Count: 2,915

Abstract (248 words)

Background

Autism was infrequently diagnosed prior to 1990. A dramatic increase in children diagnosed as autistic occurred in the 1990s in the United States (US) and United Kingdom (UK). In March 2012, in a press release widely covered by the media, the Centre for Disease Control (CDC) reported that the autism prevalence rate in 2008 in 8 year-old US children was 1 in 88, a 78% increase from a CDC estimate in 2004. The report prompted us to update UK studies begun in the early 1990s on the annual prevalence and incidence rates of autism in children aged 8 from 2004 – 2010.

Methods

Annual autism prevalence rates were estimated for children aged 8 in 2004-2010 by dividing the number diagnosed as autistic in that or any prior year by the number of children active in the study population that year. We also calculated annual incidence rates for children aged 2-8, by dividing the number newly diagnosed in 2004 -2010 by the same denominators.

Results

Annual prevalence rates for each year were steady at approximately 3.8/1000 boys and 0.8/1000 girls. Annual incidence rates each year were also steady at about 1.2/1000 boys and 0.2/1000 girls.

Conclusions

Following a five fold increase in the annual incidence rates of autism during the 1990s in the UK, the incidence and prevalence rates in 8 year-old children reached a plateau in the early 2000s and remained steady through 2008. Whether prevalence rates have increased after early 2000 in the US remains uncertain.

Background

In March 2012, the US Centre for Disease Control (CDC) issued a press release[1] that described the results of a long term study on the annual prevalence rate of autism in 8 year old children[2]. They reported that 1 of 88 children aged 8 years had been diagnosed as autistic in or prior to 2008. This represented a 78% increase from the estimate in 2004. The press release received wide media attention and prompted us to review and update the information accrued in the United Kingdom (UK) General Practice Research Database (GPRD) over the last 20 years to derive annual prevalence rate estimates in children in the UK for the years 2004 -2010. For direct comparison with the CDC study, we restricted our results to 8 year old children.

Methods

The GPRD is a unique longitudinal electronic medical database constructed and implemented in 1990 through a combined effort of the Boston Collaborative Drug Surveilance Program (BCDSP), a UK general practitioner (GP) who spent five years creating a comprehensive electronic GP office medical record system to replace preexisting paper records, and a private company, Vamp Health. The GPs who participated used identical software and were trained to enter medical information according to a formal protocol. Some 1000 general practitioners in over 300 general practices - about 5% of the UK population - were enrolled by 1996. The distribution of practices was designed to be representative of the UK population. Our programmer

constructed a unique comprehensive computer file structure that integrated all the information into a unified resource that allowed for rapid access to the full dataset, updated annually. Early validation studies found an 87% correlation between the diagnoses in consultant's letters and those in the GPRD record.[3] The high quality, stability and consistency of the recorded information over time has been repeatedly demonstrated in more than 150 publications.[4-11]

Autism is a developmental disorder manifested early in childhood and characterized by a spectrum of abnormal social and communication skills and unusual behaviour. The condition was infrequently diagnosed prior to 1990. However, an awareness of a gradual increase in the frequency of diagnosed autism was anecdotally noted during the early 1990s. The validity of the autism diagnosis recorded by GPs in this study was derived from review of the extensive specialist referral reports.[5] The quality and specificity of the diagnosis of autism in the GPRD were subsequently confirmed by an independent research group based on DSM4 criteria.[12-13]

Annual prevalence rates were calculated by dividing the number of children aged 8 years diagnosed as autistic and recorded in the continuous medical record by the GP at any prior time, by the number of 8 year olds active in the database that year. For example, prevalence rates for 2004 were based on the number of children who were aged 8 in 2004 and had been diagnosed as autistic during the 8 prior years 1996-2004.

Continuous prevalence rates were similarly estimated for each subsequent calendar year.

We also calculated annual incidence rates by dividing the annual number of children aged 2-8 newly diagnosed with autism in each year (2004 – 2010), by the number of children aged 2-8 active in the practices in that year. Practices enrolled in the GPRD only after 1996 were excluded from the study.

The study protocol was approved by the MHRA's Independent Scientific Advisory Committee (ISAC) . All data were anonymised. The GPRD data source was constructed by Hershel Jick and Dean MacLaughlin. The study was designed by Hershel Jick and Brent Taylor. The database access was created by Dean MacLaughlin. Data analysis was done by Hershel Jick and Brent Taylor. The manuscript was written by Brent Taylor and Hershel Jick. All the authors vouch for the accuracy and completeness of the data and the analyses as presented. They also vouch for the fidelity of the final report. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Results

Table 1 shows the annual number of boys aged 8 years who had been diagnosed as autistic in each or any prior year i.e., prevalent cases. The annual number of prevalent cases (a reflection of the cumulative incidence) is remarkably similar over calendar time,

as is the number of boys active in the population from 2004 -2010. The resulting annual prevalence rate estimates of about 3.8/1000 boys are steady over time. The 95% confidence limits widely overlapped in each year.

Table 1 also shows the annual number of boys aged 2-8 diagnosed as autistic for the first time (incident) in each year from 2004-2010. The annual number of incident cases is again remarkably similar over time as is the number of boys active in the practices each year, resulting in annual incidence estimates of about 1.2/1000 boys over the years. The total number of boys was 1190.

The number of girls initially diagnosed as autistic from 2004-2010 was 217. Table 2 provides the annual prevalence and incidence rate estimates over time for girls. Girls were about one fifth as likely to be diagnosed with autism as boys.

Discussion

For many years the terms incidence and prevalence were applied in medicine primarily to describe acute outbreaks of infectious diseases such as influenza, measles and mumps. Since the mid 1950s, these terms have also been applied to chronic diseases such as diabetes, cancer and more recently autism. Even a superficial consideration of the use of these general terms will reveal the complexity and subtlety of their application in quantitative observational time trend studies in clinical medicine.

The term "prevalence"alone is used widely to describe a general property possessed by an indefinite quantity of a condition e.g., the prevalence of conservative voters is higher in rural compared to urban areas. It is also used in public health as a general frequency or quantity, e.g., the prevalence of flu is higher in the winter than in the summer .

By contrast, in formal epidemiological research, reliable quantitative estimates of incidence and prevalence "rates" require accurate identification of the number of newly diagnosed cases in a defined population from which the cases were derived, at a given age during a given time period. Valid comparisons of annual rate estimates over many years are dependent on the stability of the base population and the ascertainment of the condition under study.

In 1996, the CDC conducted a study based on screening and abstraction of records in the 5 counties of Atlanta Georgia.[14] The prevalence was estimated to be 3.4 per 1000 among children aged 3 to 10. Surveys in California in 1983-85 and in 1993-95 based on birth cohorts[15-16] found that during years 1980-1994 there was a large annual secular increase in the number of cases of autism; these increases were estimated as a prevalence of 44 per 100,000 live births in the 1980 cohort and 208 in the 1994 cohort[17]. A study from Denmark estimated that the prevalence of autism rose from less than 2 per 10,000 prior to 1990 to more than 10 per 10,000 in 2000.[18] Taken together these reports provided clear evidence that there was a substantial increase in the number of

young children diagnosed as autistic in the US and Europe during the decade of the 1990s.

In February 1998 Wakefield et al reported a case series of 12 autistic children with bowel disorders most of whom had recently received the MMR vaccine[19]. The authors suggested that the MMR vaccine may have been causally related to these gastro-intestinal conditions. This widely publicised paper led to subsequent studies to evaluate the proposition that the MMR vaccine might be causaly related to autism.

In the following year, Taylor et al reported results from a study based on birth cohorts from 1979-1992 in the North East Thames (UK) health region[20]. They reviewed special needs records and found that fewer than 10 children per year born from 1979 through 1986 were diagnosed as autistic. Subsequently, the number increased to almost 50 in children born in 1992. They found no correlation between MMR vaccination and the rise in the prevalence of autism.

Shortly thereafter, the BCDSP examined experience accrued in the GPRD since 1990 to estimate annual cumulative incidence rates for birth cohorts from 1988-93 for boys age 2-5 years and found that the autism cumulative incidence rates increased some 5 fold from an estimated of 6 per 10,000 in boys born in 1988 to 30 per 10,000 in those born in 1993. At the same time MMR vaccination was given to over 90% of young children ruling out an association between the vaccine and the dramatic increase in rates. [21]

Subsequent studies also found no association between MMR and autism. [17, 18, 22, 23,] Lingam et al suggested that the previously observed annual increase in prevalence may have been leveling off by the mid-1990s. [23]

The BCDSP continued to assess time trends by updating the findings recorded in the GPRD for additional birth cohorts. Results for birth cohorts from 1994 to 1995 continued to show a rise in the cumulative incidence of diagnosed autism but results for 1996-97 indicated that the rise may have reached a plateau.[24] Subsequent follow up demonstrated that rates had in fact plateaued in the 1996 cohort and remained steady for 1996 through the 2001 birth cohort[25] (See Figure 1). Children born in 2001 would have been diagnosed as autistic at aged 2-4 in 2003-2005.

Taken together the published findings conclusively demonstrated that there was a dramatic similtaneous rise in the number of children diagnosed as autistic in the US, UK, and Denmark during the 1990s. In addition, there was highly persuasive evidence that MMR vaccine was not the cause of the rise. Despite firm evidence that a steady state occurred in children born from 1996 through 2001 in the UK, litigation continued in US courts until 2010.

The initial autism studies[5, 15-18, 20-25] were based primarily on birth cohorts usually aged 2-5 years. In this design the number of newly diagnosed (incident) cases is determined separately for each annual birth cohort. By contrast, the nature and interpretation of

annual prevalence "rates" of autism are far more complex and superficially counterintuitive, particularly where the design objective is to estimate changes in yearly time trends or to compare results with other similarly designed studies.

The CDC chose to estimate annual prevalence rates for children of the same age - 8 years – in each of successive calendar years. Annual prevalence estimates apply to children who encompass a large age range e.g., 2-8 years and each of the autism cases may be included as prevalent in multiple years. For example, when examining the period 2004 to 2010, a child diagnosed at age 2 in 2004 would be included in the prevalence estimate for each of the next six years until the child reached age 9 years and no longer is a prevalent case. Children diagnosed at age 6 in 2005 would be included in the prevalence estimates for only 3 years thereafter. Year of age at first diagnosis, including prior to 2004, is thus a critical variable in estimating the annual prevalence rates at age 8 over many years. The full detail that yielded the annual prevalence rates could be reviewed directly for consistency.

The 2012 CDC report[2] was a follow up to studies of 8 year old children initiated in 2000 and repeated every two years thereafter. The results were derived from a network of 6-11 US states depending on the years, and based on school or medical records or both. Early reports estimated annual prevalence rates of 6.7 and 6.6 per 1000 children in 2000 and 2002. Starting in 2004, prevalence rate estimates rose steadily until 2008 when they reached 11.3 per 1000, a rise of 78% from 2004. The latest prevalence rate estimates

varied widely from state to state – 4.1/1000 in Alabama to 21.2/1000 in Utah. A detailed commentary on the limitations of the CDC report was published shortly after it was released.[26] This commentary raised important questions related to the accuracy and specificity of the combined rate estimates over the years.

In the present paper we review and update an extraordinary 20-year exploration of the annual rates of autism in young children as recorded in real time and derived from a unique carefully designed medical database in the UK. In a formal analysis of the data recorded continuously by some 1000 GPs, we have documented that the cumulative incidence of autism in children born from 1988-1995 began to increase and continued to rise from a low level by more than five fold during these years. The annual incidence then leveled off and reached a steady state in children born from 1996-2001.

In order to compare the UK experience with that reported by the CDC, we restricted our current prevalence study to annual calendar years 2004-2010 in children 8 years of age. These children would have all been born after 1995. Combined, the results in this 20-year population-based UK resource, provide highly persuasive evidence that a major rise in GP-diagnosed incidence rates of autism occured in the decade of the 1990s but reached a plateau shortly after 2000 and remained steady through 2010. This incidence plateau was necessarily accompanied by steady prevalence rates for 8 year old children.

It is possible that at least a part of the early rise was related to changing and broadening

diagnostic criteria to include a spectrum of disorders[27-28] as well as increased general medical and public awareness.[29] However, it seems unlikely that these factors materially explain the extraordinary increase in the number of children diagnosed in the 1990s; nor the steady state that followed thereafter in 2004 through 2010. While the MMR vaccine is surely not the cause of the dramatic rise in the 1990s, the actual cause remains in large part a mystery. The current study provides compelling evidence that incidence rates have remained steady in children born since the late 1990's in the UK – at least as diagnosed and recorded in general practice.

There are important similarities between the results found in the US and UK in the secular epidemiology of autism. Few children were diagnosed as autistic in either country prior to 1990. A continuous simultaneous extraordinary rise in the number of children diagnosed as autistic began in both countries in the early 1990s and lasted for a decade. The distribution of first time diagnosis according to age and gender was the same. These similarities between countries as well as within different locations in each country point to a common etiology for this extraordinary medical story.

By contrast, there is a large difference in the percentage of children diagnosed as autistic in the two countries. The estimated prevalence rates of autism in the UK population, about 4 per 1000 in 8 year old boys in 2008, is far lower than the more than 11 per 1000 in 8 year old boys reported by the CDC from the US for the same calendar year. This large difference between countries is closely similar to differences in rates reported in

children diagnosed and treated for attention deficit hyperactivity disorder (ADHD) in the two countries. [30, 31]

The GPRD is a uniquely constructed resource of clinical medical information that has succeeded in providing a reliable continuous standardized accounting of demographics, medical diagnoses and prescribed medicines over more than 20 years. The substance of its construction and implementation is highly complex. Nowhere is this clearer than in the current findings related to the enormously complex secular epidemiology of autism.

In conclusion, the annual prevalence of clinically confirmed autism recorded by UK general practitioners remained steady for the 7-year period 2004-10. Whether it has increased in the US over these years remains uncertain.

Acknowlegements

The authors gratefully acknowledge the excellent work of the general practitioners who have contributed to the GPRD.

Figure 1*

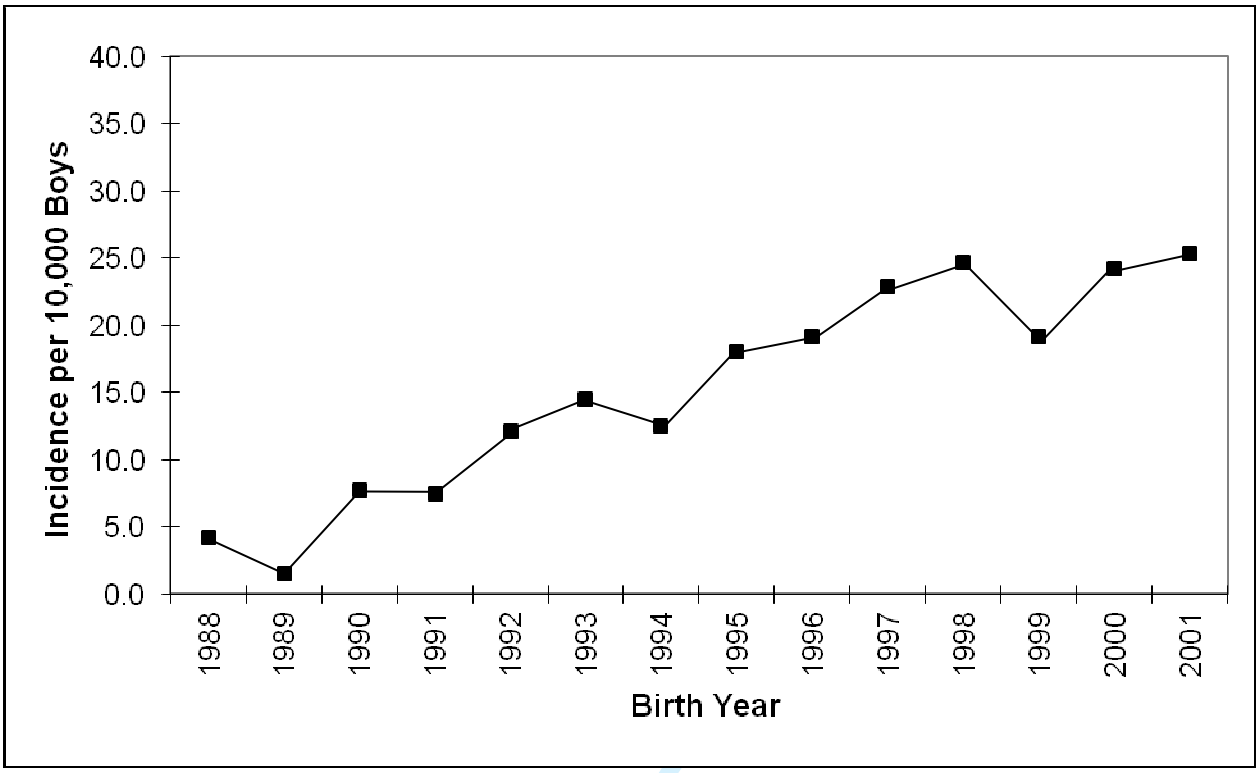

Figure. Three-year cumulative incidence of diagnosed autism among boys age 2-4 years, by year of birth.[25]

*Adapted from Hagberg KW, Jick H. "Autism in the UK for birth cohorts" 1988-2001. Epidemiology 2010;21:426-427.

Table 1. Prevalence and Incidence Rates of Boys Aged 8 for Years 2004 – 2010

Year	Number of Boys aged 8 in CPRD	Number of Prevalent Cases	Prevalence Rate per 1000	Number of Incident Cases	Incidence Rate per 1000
2004	145,483	521	3.58	172	1.18
2005	143,721	535	3.72	170	1.18
2006	147,049	568	3.86	190	1.29
2007	142,229	540	3.80	173	1.22
2008	138,847	543	3.91	170	1.22
2009	138,317	566	4.09	180	1.30
2010	132,143	515	3.90	135	1.02

Table 2. Prevalence and Incidence Rates of Girls Aged 8 for Years 2004 – 2010

Year	Number of Girls aged 8 in CPRD	Number of Prevalent Cases	Prevalence Rate per 1000	Number of Incident Cases	Incidence Rate per 1000
2004	136,752	109	0.80	27	0.20
2005	135,511	112	0.83	30	0.22
2006	138,548	112	0.81	34	0.25
2007	134,083	125	0.93	41	0.31
2008	130,876	107	0.82	29	0.22
2009	130,367	106	0.81	30	0.23
2010	124,135	101	0.81	26	0.21

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Summary

Article focus

- Prior to the middle 1980's, autism was infrequently diagnosed in children. Over the next decade, the number of children diagnosed as autistic rose more than five-fold in the US, UK, and Denmark. In 2012, a study from the CDC in the US reported that the prevalence of autism in 2008 in children age 8 was 1 in 88 children and that the 2008 prevalence rate was 78% higher than the prevalence rate in 2004.
- Earlier independent studies from the UK had reported that autism rates may have levelled off in children born in the mid to late 1990's.
- This investigation of annual prevalence and incidence rates extends earlier work on the same data source using the same age criteria as the recent US study.

Key messages

- The prevalence and incidence of autism in 8-year old UK children was level from 2004 to 2010, with rates much lower than reported in the USA.
- Whether the prevalence rate rose has increased in the U.S. in the last decade remains uncertain. Whether the rates have increased in the US remains uncertain.

Strengths and limitations of this study

This was a population study, fully representative of the UK. Cases were recorded in the GP clinical records but all were diagnosed by specialists. The diagnosis of autism recorded in the General Practice Research Database (GPRD) has been confirmed as highly sensitive. The GPRD is a uniquely constructed resource of clinical medical information that has succeeded in providing a reliable continuous standardized accounting of demographics, medical diagnoses and prescribed medicines over more than 20 years.

There may have been individual children with autism who were diagnosed elsewhere and not notified to their GP's or other autistic children who remained undiagnosed.

Prevalence and incidence rates of autism in the United Kingdom: time trend from 2004-2010 in children aged 8 years

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Evidence based practice, Paediatrics, Public health, Mental health
Keywords:	Neurogenetics < NEUROLOGY, Paediatric neurology < NEUROLOGY, Community child health < PAEDIATRICS, Paediatric neurology < PAEDIATRICS, Anxiety disorders < PSYCHIATRY, Child & adolescent psychiatry < PSYCHIATRY

Prevalence and incidence rates of autism in the United Kingdom: time trend from 2004-2010 in children aged 8 years.

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Running head: Autism in the UK 2004-2010

Key words: Autism, Incidence, Prevalence, UK, 2004-2010.

Word Count: 2,922 (excluding abstract, summary, references and acknowlegements)

Abstract

Objectives:

To update United Kingdom (UK) studies begun in the early 1990s on the annual prevalence and incidence rates of autism in children; undertaken in response to a March 2012 press release, widely covered by the media, from the United States (US) Centre for Disease Control (CDC) reporting that the autism prevalence rate in 2008 in 8 year-old US children was 1 in 88, a 78% increase from a CDC estimate in 2004. This finding suggested a continuation of the dramatic increase in children diagnosed as autistic, which occurred in the 1990s.

Design, setting Population study using the UK General Practice Research Database (GPRD)

Methods, including participants

Annual autism prevalence rates were estimated for children aged 8 in 2004-2010 by dividing the number diagnosed as autistic in each or any prior year by the number of children active in the study population that year. We also calculated annual incidence rates for children aged 2-8, by dividing the number newly diagnosed in 2004 -2010 by the same denominators.

Results

Annual prevalence rates for each year were steady at approximately 3.8/1000 boys and 0.8/1000 girls. Annual incidence rates each year were also steady at about 1.2/1000 boys and 0.2/1000 girls.

Conclusions

Following a five fold increase in the annual incidence rates of autism during the 1990s in the UK, the incidence and prevalence rates in 8 year-old children reached a plateau in the early 2000s and remained steady through 2008. Whether prevalence rates have increased from the early 2000s in the US remains uncertain.

Summary

Article focus

- The documented prevalence of autism rose dramatically from the mid 1980s; changes in diagnostic criteria and societal changes have contributed, but the rise has been described, especially in the media, as an epidemic of autism.
- Independent studies in UK children suggested that the rise was levelling off in children born in the mid-to-late 1990s.
- This investigation of annual prevalence and incidence rates, extends earlier work on the same data source, using the same age criteria and analytic methods as the recent US CDC study.

Key messages

- The prevalence and incidence of autism in 8-year old UK children was level from 2004 to 2010, with rates much lower than reported in the USA.
- The reasons for the rise in the 1980s-1990s and the subsequent levelling of prevalence and incidence in the UK are unclear. Whether the rates have continued to increase in the US remains uncertain.

Strengths and limitations of this study

- This study is fully representative of the UK general population.
- The GPRD is a uniquely constructed resource of clinical medical information that has succeeded in providing a reliable continuous standardised account of

demographics, medical diagnoses and prescribed medicines over more than 20 years. It is one of the largest sources of primary care data in the world.

- There may have been unidentified cases (false negatives) in the study population - individual children with autism who were diagnosed elsewhere and not notified to their GP's or others who remained undiagnosed.

Background

In March 2012, the US Centre for Disease Control (CDC) issued a press release[1] that described the results of a long term study on the annual prevalence rate of autism in 8 year old children[2]. They reported that 1 of 88 children aged 8 years had been diagnosed as autistic in or prior to 2008. This represented a 78% increase from the estimate in 2004. The press release received wide media attention and prompted us to review and update the information accrued in the United Kingdom (UK) General Practice Research Database (GPRD) over the last 20 years to derive annual prevalence rate estimates in children in the UK for the years 2004 -2010. For direct comparison with the CDC study, we restricted our results to 8 year old children.

Methods

The GPRD is a unique longitudinal electronic medical database constructed and implemented in 1990 through a combined effort of the Boston Collaborative Drug Surveilance Program (BCDSP), a UK general practitioner (GP) who spent five years creating a comprehensive electronic GP office medical record system to replace preexisting paper records, and a private company, Vamp Health. The GPs who participated used identical software and were trained to enter medical information according to a formal protocol. Some 1000 general practitioners in over 300 general practices - about 5% of the UK population - were enrolled by 1996. The distribution of practices was designed to be representative of the UK population. Our programmer constructed a unique comprehensive computer file structure that integrated all the

information into a unified resource that allowed for rapid access to the full dataset, updated annually. Early validation studies found an 87% correlation between the diagnoses in consultant's letters and those in the GPRD record.[3] The high quality, stability and consistency of the recorded information over time has been repeatedly demonstrated in more than 150 publications.[4-11]

Autism is a developmental disorder manifested early in childhood and characterized by a spectrum of abnormal social and communication skills and unusual behaviour. The condition was infrequently diagnosed prior to 1990. However, an awareness of a gradual increase in the frequency of diagnosed autism was anecdotally noted during the early 1990s. GPs do not themselves make the diagnosis of autism, referring children suspected of having the condition for specialist multidisciplinary assessment, which usually takes place over a period of months. Referral letters to GPRD-participating GPs from consultants and others are scanned and diagnostic information therein coded and recorded in the childs clinical record. The validity of the autism diagnosis recorded by GPs was confirmed in the earlier phases of this study by review of the extensive specialist referral reports.[5] The quality and specificity of the diagnosis of autism in the GPRD have also been validated by an independent research group based on DSM4 criteria;[12-13] in 318 cases diagnosed with autism or a related condition such as Asperger's syndrome, the researchers, using specialist reports from consultants or multidisciplinary teams in the GP record, were able to confirm the diagnosis for 294 (92.5%).

Annual prevalence rates were calculated by dividing the number of children aged 8 years diagnosed as autistic and recorded in the continuous medical record by the GP at any prior time, by the number of 8 year olds active in the database that year. For example, prevalence rates for 2004 were based on the number of children who were aged 8 in 2004 and had been diagnosed as autistic during the 8 prior years 1996-2004. Continuous prevalence rates were similarly estimated for each subsequent calendar year.

We also calculated annual incidence rates by dividing the annual number of children aged 2-8 newly diagnosed with autism in each year (2004 – 2010), by the number of children aged 2-8 active in the practices in that year. Practices enrolled in the GPRD only after 1996 were excluded from the study.

Results

Table 1 shows the annual number of boys aged 8 years who had been diagnosed as autistic in each or any prior year i.e., prevalent cases. The annual number of prevalent cases (a reflection of the cumulative incidence) is remarkably similar over calendar time, as is the number of boys active in the population from 2004 -2010. The resulting annual prevalence rate estimates of about 3.8/1000 boys are steady over time. The 95% confidence limits widely overlapped in each year.

Table 1 also shows the annual number of boys aged 2-8 diagnosed as autistic for the first time (incident) in each year from 2004-2010. The annual number of incident cases is again remarkably similar over time as is the number of boys active in the practices each year, resulting in annual incidence estimates of about 1.2/1000 boys over the years. The total number of boys was 1190.

The number of girls initially diagnosed as autistic from 2004-2010 was 217. Table 2 provides the annual prevalence and incidence rate estimates over time for girls. Girls were about one fifth as likely to be diagnosed with autism as boys.

Discussion

In the present paper we review and update an extraordinary 20-year exploration of the annual rates of autism in young children as recorded in real time and derived from a unique carefully designed medical database in the UK. In a series of formal analyses of the data recorded continuously in the GPRD by some 1000 GPs, we have documented that the cumulative incidence of autism in children born from 1988-1995 began to increase and continued to rise from a low level by more than five fold during these years.[14-16] The present study demonstrates that the annual incidence then leveled off and reached a steady state in children born from 1996-2001.

In order to compare the UK experience with that reported by the CDC, we restricted

our current prevalence study to annual calendar years 2004-2010 in children 8 years of age. These children would have all been born after 1995. Combined, the results in this 20-year population-based UK resource, provide compelling evidence that a major rise in incidence rates of autism, recorded in general practice, occured in the decade of the 1990s but reached a plateau shortly after 2000 and has remained steady through 2010. This incidence plateau was necessarily accompanied by steady prevalence rates for 8 year old children.

It is possible that at least a part of the early rise was related to changing and broadening diagnostic criteria to include a spectrum of disorders,[17-18] as well as social influences[19], including increased general medical and public awareness.[20] However, it seems unlikely that these factors materially explain the extraordinary increase in the number of children diagnosed in the 1990s; nor the steady state that followed thereafter in 2004 through 2010. While the MMR vaccine was surely not the cause of the dramatic rise in the 1990s, the actual cause remains in large part a mystery. ~~The current study provides compelling evidence that incidence rates, as recorded in general practice, have remained steady in children born since the late 1990's in the UK.~~ (omit as duplication)

For many years the terms incidence and prevalence were applied in medicine primarily to describe acute outbreaks of infectious diseases such as influenza, measles and mumps. Since the mid 1950s, these terms have also been applied to chronic diseases such as diabetes, cancer and more recently autism. Even a superficial consideration of

the use of these general terms will reveal the complexity and subtlety of their application in quantitative observational time trend studies in clinical medicine.

The term "prevalence"alone is used widely to describe a general property possessed by an indefinite quantity of a condition e.g., the prevalence of conservative voters is higher in rural compared to urban areas. It is also used in public health as a general frequency or quantity, e.g., the prevalence of influenza is higher in winter than in the summer .

By contrast, in formal epidemiological research, reliable quantitative estimates of incidence and prevalence "rates" require accurate identification of the number of newly diagnosed cases in a defined population from which the cases were derived, at a given age during a given time period. Valid comparisons of annual rate estimates over many years are dependent on the stability of the base population and the ascertainment of the condition under study.

In 1996, the CDC conducted a study based on screening and abstraction of records in the 5 counties of Atlanta Georgia.[21] The prevalence was estimated to be 3.4 per 1000 among children aged 3 to 10. Surveys in California in 1983-85 and in 1993-95 based on birth cohorts[22-23] found that during years 1980-1994 there was a large annual secular increase in the number of cases of autism; these increases were estimated as a prevalence of 44 per 100,000 live births in the 1980 cohort and 208 in the 1994 cohort[24]. A study from Denmark estimated that the prevalence of autism rose from less than 2

per 10,000 prior to 1990 to more than 10 per 10,000 in 2000.[25] Taken together these reports and others provided clear evidence that there was a substantial increase in the number of young children diagnosed as autistic in the US and Europe during the decade of the 1990s.

We could have estimated culmulative incidence and annual prevalence rates for other age ranges, e.g., for 3 or 5 year olds, from within the GPRD dataset, but there are no other published studies for comparison. Any comparisons of our results with other published studies on autism frequencies do not appear to be valid. There have been many studies investigating the prevalence of autism – in various countries across the world, assessing different ages, durations, and varying calendar times[26]. Few studies have been able to assess culmulative incidence. Prevalence estimates have varied from 2.8 to 94 for autistic disorder and 1 to 189 for "pervasive developmental disorders"[26]. Recent studies have tended to show higher prevalence rates.

Cohort effects have been identified[27] as well as marked spatial clustering[28]. Reported numbers of cases in some studies have been low and have tended to vary (e.g. 86 children with autistic spectrum disorder (ASD) at age 11 in the UK Avon study[29] and 158 from a screened population of 56,946 children age 9-10 years in the UK Special Need and Autism Project[30]), with different studies showing widely varying proportions of sub-groups of autism. Denominators have sometimes been unclear.

Some studies have based their findings on ASD screening questionnaires, which typically misidentify substantial numbers of children who have other difficulties, but not an ASD[31]. Using strict or less demanding diagnostic criteria, even within a single study where design and methodological factors are invariant, can affect prevalence estimates by up to 4.5 times[32]. There were some regional variations in rates of recorded autism in the GPRD, possibly reflecting regional variation in diagnostic practice, but rates within areas remained steady overall during the study period. This was a real-life clinically-based study, with no attempt to screen the child population for autism. Such screening may contribute to over-diagnosis[31].

In February 1998 Wakefield et al reported a case series of 12 autistic children with bowel disorders most of whom had recently received the MMR vaccine[33]. The authors suggested that the MMR vaccine may have been causally related to these gastro-intestinal conditions. This widely publicised paper led to subsequent studies to evaluate the proposition that the MMR vaccine might be causally related to autism.

In the following year, Taylor et al reported results from a study based on birth cohorts from 1979-1992 in the North East Thames (UK) health region[34]. They reviewed special needs records and found that fewer than 10 children per year born from 1979 through 1986 were diagnosed as autistic. Subsequently, the number increased to almost 50 in children born in 1992. They found no correlation between MMR vaccination and the rise in the prevalence of autism.

Shortly thereafter, the BCDSP examined experience accrued in the GPRD since 1990 to estimate annual cumulative incidence rates of autism for birth cohorts from 1988-93 for boys age 2-5 years and found that cumulative incidence rates increased some 5 fold from an estimate of 6 per 10,000 in boys born in 1988 to 30 per 10,000 in those born in 1993. At the same time MMR vaccination was given to over 90% of young children ruling out an association between the vaccine and the dramatic increase in rates. [14]

Subsequent studies also found no association between MMR and autism. [14, 24-25, 35-36,] Lingam et al suggested that the previously observed annual increase in prevalence in North-East London may have been leveling off by the mid-1990s. [36]

The BCDSP continued to assess time trends by updating the findings recorded in the GPRD for additional birth cohorts. Results for birth cohorts from 1994 to 1995 continued to show a rise in the cumulative incidence of diagnosed autism but results for 1996-97 indicated that the rise may have reached a plateau.[15] Subsequent follow up demonstrated that rates had in fact plateaued in the 1996 cohort and remained steady for 1996 through the 2001 birth cohort[16] (See Figure 1). Children born in 2001 would have been diagnosed as autistic at age 2-4 in 2003-2005.

Taken together the published findings conclusively demonstrated that there was a dramatic similtaneous rise in the number of children diagnosed as autistic in the US,

UK and Denmark during the 1990s. In addition, there was highly persuasive evidence that MMR vaccine was not the cause of the rise. Despite firm evidence that a steady state occurred in children born from 1996 through 2001 in the UK, vaccine/autism litigation continued in US courts until 2010.

The initial autism studies[5, 14-16, 34-36] were based primarily on birth cohorts usually aged 2-5 years. In that design the number of newly diagnosed (incident) cases is determined separately for each annual birth cohort. By contrast, the nature and interpretation of annual prevalence "rates" of autism, as reported in the present and the recent CDC studies, are far more complex and superficially counterintuitive, particularly where the design objective is to estimate changes in yearly time trends or to compare results with other similarly designed studies.

The CDC chose to estimate annual prevalence rates for children of the same age - 8 years – in each of successive calendar years. Annual prevalence estimates apply to children who encompass a large age range e.g., 2-8 years and each of the autism cases may be included as prevalent in multiple years. For example, when examining the period 2004 to 2010, a child diagnosed at age 2 years in 2004 would be included in the prevalence estimate for each of the next six years until the child reached age 9 years and no longer is considered a prevalent case. Children diagnosed at age 6 in 2005 would be included in the prevalence estimates for only 3 years thereafter. Year of age at first diagnosis, including prior to 2004, is thus a critical variable in estimating the

annual prevalence rates at age 8 over many years. The full detail that yielded the annual prevalence rates could be reviewed directly for consistency.

The 2012 CDC report[2] was a follow up to studies of 8 year old children initiated in 2000 and repeated every two years thereafter. The results were derived from a network of 6-11 US states depending on the years, and based on school or medical records or both. Early reports estimated annual prevalence rates of 6.7 and 6.6 per 1000 children in 2000 and 2002. Starting in 2004, prevalence rate estimates rose steadily until 2008 when they reached 11.3 per 1000, a rise of 78% from 2004. The latest prevalence rate estimates varied widely from state to state – from 4.1/1000 in Alabama to 21.2/1000 in Utah. A detailed commentary on the limitations of the CDC report was published shortly after it was released.[37] This commentary raised important questions related to the accuracy and specificity of the combined rate estimates over the years.

There are many similarities between the results found in the US and UK in the secular epidemiology of autism. Few children were diagnosed as autistic in either country prior to 1990. A continuous simultaneous extraordinary rise in the number of children diagnosed as autistic began in both countries in the early 1990s and lasted for a decade. The distribution of first time diagnosis according to age and gender was the same. These similarities between countries as well as within different locations in each country point to a common etiology for this extraordinary medical story.

By contrast, there is a large difference in the percentage of children diagnosed as autistic in the two countries. The estimated prevalence rates of autism in the UK population, about 4 per 1000 in 8 year old boys in 2008, is far lower than the more than 11 per 1000 in 8 year old boys reported by the CDC from the US for the same calendar year. This large difference between countries is closely similar to differences in rates reported for children diagnosed and treated for attention deficit hyperactivity disorder (ADHD) in the two countries.[38, 39]

The GPRD is a uniquely constructed resource of clinical medical information that has succeeded in providing a reliable continuous standardized accounting of demographics, medical diagnoses and prescribed medicines over more than 20 years. The substance of its construction and implementation is highly complex. Nowhere is this clearer than in the current findings related to the enormously complex secular epidemiology of autism.

In conclusion, the annual prevalence of clinically confirmed autism recorded by UK general practitioners remained steady for the 7-year period 2004-10. Whether it has increased in the US over these years remains uncertain.

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Contributors The GPRD data source was constructed by HJ and DM. The study was designed by HJ and BT. The database access was created by DM. Data analysis was done by HJ and BT. The manuscript was written by BT and HJ. All the authors vouch for the accuracy and completeness of the data and the analyses as presented. They also vouch for the fidelity of the final report.

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Competing interests None

Ethics The study protocol was approved by the MHRA's Independent Scientific Advisory Committee (ISAC) . All data were anonymised.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data available

Figure 1*

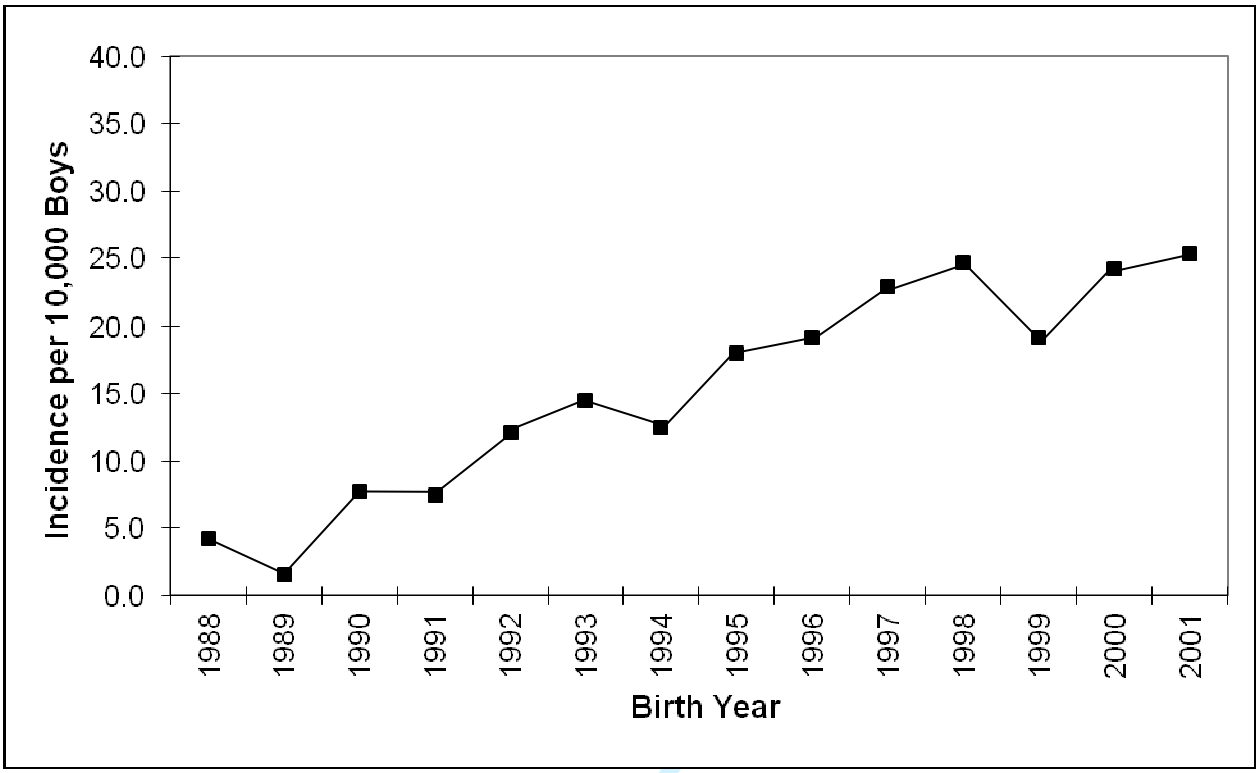

Figure. Three-year cumulative incidence of diagnosed autism among boys age 2-4 years, in birth cohorts.[16]

*Adapted from Hagberg KW, Jick H. "Autism in the UK for birth cohorts 1988-2001". Epidemiology 2010;21:426-427.

Table 1. Prevalence and Incidence Rates of Boys Aged 8 for Years 2004 – 2010

Year	Number of Boys aged 8 in GPRD	Number of Prevalent Cases	Prevalence Rate per 1000	95% Confidence Intervals	Number of Incident Cases	Incidence Rate per 1000	95% Confidence Intervals
2004	145,483	521	3.58	3.28-3.80	172	1.18	1.01-1.37
2005	143,721	535	3.72	3.41-4.05	170	1.17	1.00-1.35
2006	147,049	568	3.86	3.56-4.19	190	1.29	1.12-1.49
2007	142,229	540	3.79	3.49-4.13	173	1.21	1.05-1.41
2008	138,847	543	3.91	3.59-4.25	170	1.22	1.05-1.42
2009	138,317	566	4.09	3.77-4.40	180	1.30	1.02-1.50
2010	132,143	515	3.90	3.57-4.24	135	1.02	0.86-1.20

Table 2. Prevalence and Incidence Rates of Girls Aged 8 for Years 2004 – 2010

Year	Number of Girls aged 8 in GPRD	Number of Prevalent Cases	Prevalence Rate per 1000	95% Confidence Intervals	Number of Incident Cases	Incidence Rate per 1000	95% Confidence Intervals
2004	136,752	109	0.80	0.66-0.96	27	0.20	0.14-0.28
2005	135,511	112	0.83	0.68-0.99	30	0.22	0.15-0.31
2006	138,548	112	0.81	0.69-0.97	34	0.25	0.17-0.39
2007	134,083	125	0.93	0.78-1.11	41	0.31	0.22-0.41
2008	130,876	107	0.82	0.67-0.98	29	0.21	0.14-0.29
2009	130,367	106	0.81	0.67-0.98	30	0.23	0.16-0.32
2010	124,135	101	0.81	0.67-0.99	26	0.21	0.14-0.30

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Prevalence and incidence rates of autism in the United Kingdom: time trend from 2004-2010 in children aged 8 years.

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Running head: Autism in the UK 2004-2010

Key words: Autism, Incidence, Prevalence, UK, 2004-2010.

Word Count: 2,922 (excluding abstract, summary, references and acknowlegements)

Abstract (257 words)

Background

Autism was infrequently diagnosed prior to 1990. A dramatic increase in children diagnosed as autistic occurred in the 1990s in the United States (US) and United Kingdom (UK). In March 2012, in a press release widely covered by the media, the Centre for Disease Control (CDC) reported that the autism prevalence rate in 2008 in 8 year-old US children was 1 in 88, a 78% increase from a CDC estimate in 2004. The report prompted us to update UK studies begun in the early 1990s on the annual prevalence and incidence rates of autism in children aged 8 from 2004 – 2010, using the General Practice Research Database

Methods

Annual autism prevalence rates were estimated for children aged 8 in 2004-2010 by dividing the number diagnosed as autistic in each or any prior year by the number of children active in the study population that year. We also calculated annual incidence rates for children aged 2-8, by dividing the number newly diagnosed in 2004 -2010 by the same denominators.

Results

Annual prevalence rates for each year were steady at approximately 3.8/1000 boys and 0.8/1000 girls. Annual incidence rates each year were also steady at about 1.2/1000 boys and 0.2/1000 girls.

Conclusions

Following a five fold increase in the annual incidence rates of autism during the 1990s in the UK, the incidence and prevalence rates in 8 year-old children reached a plateau in the early 2000s and remained steady through 2008. Whether prevalence rates have increased from the early 2000s in the US remains uncertain.

Summary

Article focus

- The documented prevalence of autism rose dramatically from the mid 1980s; changes in diagnostic criteria and societal changes have contributed, but the rise has been described, especially in the media, as an epidemic of autism.
- Independent studies in UK children suggested that the rise was levelling off in children born in the mid-to-late 1990s.
- This investigation of annual prevalence and incidence rates, extends earlier work on the same data source, using the same age criteria and analytic methods as the recent US CDC study.

Key messages

- The prevalence and incidence of autism in 8-year old UK children was level from 2004 to 2010, with rates much lower than reported in the USA.
- The reasons for the rise in the 1980s-1990s and the subsequent levelling of prevalence and incidence in the UK are unclear. Whether the rates have continued to increase in the US remains uncertain.

Strengths and limitations of this study

- This study is fully representative of the UK general population.
- The GPRD is a uniquely constructed resource of clinical medical information that has succeeded in providing a reliable continuous standardised account of

demographics, medical diagnoses and prescribed medicines over more than 20 years. It is one of the largest sources of primary care data in the world.

- There may have been unidentified cases (false negatives) in the study population - individual children with autism who were diagnosed elsewhere and not notified to their GP's or others who remained undiagnosed.

Background

In March 2012, the US Centre for Disease Control (CDC) issued a press release[1] that described the results of a long term study on the annual prevalence rate of autism in 8 year old children[2]. They reported that 1 of 88 children aged 8 years had been diagnosed as autistic in or prior to 2008. This represented a 78% increase from the estimate in 2004. The press release received wide media attention and prompted us to review and update the information accrued in the United Kingdom (UK) General Practice Research Database (GPRD) over the last 20 years to derive annual prevalence rate estimates in children in the UK for the years 2004 -2010. For direct comparison with the CDC study, we restricted our results to 8 year old children.

Methods

The GPRD is a unique longitudinal electronic medical database constructed and implemented in 1990 through a combined effort of the Boston Collaborative Drug Surveilance Program (BCDSP), a UK general practitioner (GP) who spent five years creating a comprehensive electronic GP office medical record system to replace preexisting paper records, and a private company, Vamp Health. The GPs who participated used identical software and were trained to enter medical information according to a formal protocol. Some 1000 general practitioners in over 300 general practices - about 5% of the UK population - were enrolled by 1996. The distribution of practices was designed to be representative of the UK population. Our programmer constructed a unique comprehensive computer file structure that integrated all the

information into a unified resource that allowed for rapid access to the full dataset, updated annually. Early validation studies found an 87% correlation between the diagnoses in consultant's letters and those in the GPRD record.[3] The high quality, stability and consistency of the recorded information over time has been repeatedly demonstrated in more than 150 publications.[4-11]

Autism is a developmental disorder manifested early in childhood and characterized by a spectrum of abnormal social and communication skills and unusual behaviour. The condition was infrequently diagnosed prior to 1990. However, an awareness of a gradual increase in the frequency of diagnosed autism was anecdotally noted during the early 1990s. GPs do not themselves make the diagnosis of autism, referring children suspected of having the condition for specialist multidisciplinary assessment, which usually takes place over a period of months. Referral letters to GPRD-participating GPs from consultants and others are scanned and diagnostic information therein coded and recorded in the childs clinical record. The validity of the autism diagnosis recorded by GPs was confirmed in the earlier phases of this study by review of the extensive specialist referral reports.[5] The quality and specificity of the diagnosis of autism in the GPRD have also been validated by an independent research group based on DSM4 criteria;[12-13] in 318 cases diagnosed with autism or a related condition such as Asperger's syndrome, the researchers, using specialist reports from consultants or multidisciplinary teams in the GP record, were able to confirm the diagnosis for 294 (92.5%).

Annual prevalence rates were calculated by dividing the number of children aged 8 years diagnosed as autistic and recorded in the continuous medical record by the GP at any prior time, by the number of 8 year olds active in the database that year. For example, prevalence rates for 2004 were based on the number of children who were aged 8 in 2004 and had been diagnosed as autistic during the 8 prior years 1996-2004. Continuous prevalence rates were similarly estimated for each subsequent calendar year.

We also calculated annual incidence rates by dividing the annual number of children aged 2-8 newly diagnosed with autism in each year (2004 – 2010), by the number of children aged 2-8 active in the practices in that year. Practices enrolled in the GPRD only after 1996 were excluded from the study.

Results

Table 1 shows the annual number of boys aged 8 years who had been diagnosed as autistic in each or any prior year i.e., prevalent cases. The annual number of prevalent cases (a reflection of the cumulative incidence) is remarkably similar over calendar time, as is the number of boys active in the population from 2004 -2010. The resulting annual prevalence rate estimates of about 3.8/1000 boys are steady over time. The 95% confidence limits widely overlapped in each year.

Table 1 also shows the annual number of boys aged 2-8 diagnosed as autistic for the first time (incident) in each year from 2004-2010. The annual number of incident cases is again remarkably similar over time as is the number of boys active in the practices each year, resulting in annual incidence estimates of about 1.2/1000 boys over the years. The total number of boys was 1190.

The number of girls initially diagnosed as autistic from 2004-2010 was 217. Table 2 provides the annual prevalence and incidence rate estimates over time for girls. Girls were about one fifth as likely to be diagnosed with autism as boys.

Discussion

In the present paper we review and update an extraordinary 20-year exploration of the annual rates of autism in young children as recorded in real time and derived from a unique carefully designed medical database in the UK. In a series of formal analyses of the data recorded continuously in the GPRD by some 1000 GPs, we have documented that the cumulative incidence of autism in children born from 1988-1995 began to increase and continued to rise from a low level by more than five fold during these years.[14-16] The present study demonstrates that the annual incidence then leveled off and reached a steady state in children born from 1996-2001.

In order to compare the UK experience with that reported by the CDC, we restricted

our current prevalence study to annual calendar years 2004-2010 in children 8 years of age. These children would have all been born after 1995. Combined, the results in this 20-year population-based UK resource, provide compelling evidence that a major rise in incidence rates of autism, recorded in general practice, occured in the decade of the 1990s but reached a plateau shortly after 2000 and has remained steady through 2010. This incidence plateau was necessarily accompanied by steady prevalence rates for 8 year old children.

It is possible that at least a part of the early rise was related to changing and broadening diagnostic criteria to include a spectrum of disorders,[17-18] as well as social influences[19], including increased general medical and public awareness.[20] However, it seems unlikely that these factors materially explain the extraordinary increase in the number of children diagnosed in the 1990s; nor the steady state that followed thereafter in 2004 through 2010. While the MMR vaccine was surely not the cause of the dramatic rise in the 1990s, the actual cause remains in large part a mystery. ~~The current study provides compelling evidence that incidence rates, as recorded in general practice, have remained steady in children born since the late 1990's in the UK.~~ (omit as duplication)

For many years the terms incidence and prevalence were applied in medicine primarily to describe acute outbreaks of infectious diseases such as influenza, measles and mumps. Since the mid 1950s, these terms have also been applied to chronic diseases such as diabetes, cancer and more recently autism. Even a superficial consideration of

the use of these general terms will reveal the complexity and subtlety of their application in quantitative observational time trend studies in clinical medicine.

The term "prevalence"alone is used widely to describe a general property possessed by an indefinite quantity of a condition e.g., the prevalence of conservative voters is higher in rural compared to urban areas. It is also used in public health as a general frequency or quantity, e.g., the prevalence of influenza is higher in winter than in the summer .

By contrast, in formal epidemiological research, reliable quantitative estimates of incidence and prevalence "rates" require accurate identification of the number of newly diagnosed cases in a defined population from which the cases were derived, at a given age during a given time period. Valid comparisons of annual rate estimates over many years are dependent on the stability of the base population and the ascertainment of the condition under study.

In 1996, the CDC conducted a study based on screening and abstraction of records in the 5 counties of Atlanta Georgia.[21] The prevalence was estimated to be 3.4 per 1000 among children aged 3 to 10. Surveys in California in 1983-85 and in 1993-95 based on birth cohorts[22-23] found that during years 1980-1994 there was a large annual secular increase in the number of cases of autism; these increases were estimated as a prevalence of 44 per 100,000 live births in the 1980 cohort and 208 in the 1994 cohort[24]. A study from Denmark estimated that the prevalence of autism rose from less than 2

per 10,000 prior to 1990 to more than 10 per 10,000 in 2000.[25] Taken together these reports and others provided clear evidence that there was a substantial increase in the number of young children diagnosed as autistic in the US and Europe during the decade of the 1990s.

We could have estimated culmulative incidence and annual prevalence rates for other age ranges, e.g., for 3 or 5 year olds, from within the GPRD dataset, but there are no other published studies for comparison. Any comparisons of our results with other published studies on autism frequencies do not appear to be valid. There have been many studies investigating the prevalence of autism – in various countries across the world, assessing different ages, durations, and varying calendar times[26]. Few studies have been able to assess culmulative incidence. Prevalence estimates have varied from 2.8 to 94 for autistic disorder and 1 to 189 for "pervasive developmental disorders"[26]. Recent studies have tended to show higher prevalence rates.

Cohort effects have been identified[27] as well as marked spatial clustering[28]. Reported numbers of cases in some studies have been low and have tended to vary (e.g. 86 children with autistic spectrum disorder (ASD) at age 11 in the UK Avon study[29] and 158 from a screened population of 56,946 children age 9-10 years in the UK Special Need and Autism Project[30]), with different studies showing widely varying proportions of sub-groups of autism. Denominators have sometimes been unclear.

Some studies have based their findings on ASD screening questionnaires, which typically misidentify substantial numbers of children who have other difficulties, but not an ASD[31]. Using strict or less demanding diagnostic criteria, even within a single study where design and methodological factors are invariant, can affect prevalence estimates by up to 4.5 times[32]. There were some regional variations in rates of recorded autism in the GPRD, possibly reflecting regional variation in diagnostic practice, but rates within areas remained steady overall during the study period. This was a real-life clinically-based study, with no attempt to screen the child population for autism. Such screening may contribute to over-diagnosis[31].

In February 1998 Wakefield et al reported a case series of 12 autistic children with bowel disorders most of whom had recently received the MMR vaccine[33]. The authors suggested that the MMR vaccine may have been causally related to these gastro-intestinal conditions. This widely publicised paper led to subsequent studies to evaluate the proposition that the MMR vaccine might be causally related to autism.

In the following year, Taylor et al reported results from a study based on birth cohorts from 1979-1992 in the North East Thames (UK) health region[34]. They reviewed special needs records and found that fewer than 10 children per year born from 1979 through 1986 were diagnosed as autistic. Subsequently, the number increased to almost 50 in children born in 1992. They found no correlation between MMR vaccination and the rise in the prevalence of autism.

Shortly thereafter, the BCDSP examined experience accrued in the GPRD since 1990 to estimate annual cumulative incidence rates of autism for birth cohorts from 1988-93 for boys age 2-5 years and found that cumulative incidence rates increased some 5 fold from an estimate of 6 per 10,000 in boys born in 1988 to 30 per 10,000 in those born in 1993. At the same time MMR vaccination was given to over 90% of young children ruling out an association between the vaccine and the dramatic increase in rates. [14]

Subsequent studies also found no association between MMR and autism. [14, 24-25, 35-36,] Lingam et al suggested that the previously observed annual increase in prevalence in North-East London may have been leveling off by the mid-1990s. [36]

The BCDSP continued to assess time trends by updating the findings recorded in the GPRD for additional birth cohorts. Results for birth cohorts from 1994 to 1995 continued to show a rise in the cumulative incidence of diagnosed autism but results for 1996-97 indicated that the rise may have reached a plateau.[15] Subsequent follow up demonstrated that rates had in fact plateaued in the 1996 cohort and remained steady for 1996 through the 2001 birth cohort[16] (See Figure 1). Children born in 2001 would have been diagnosed as autistic at age 2-4 in 2003-2005.

Taken together the published findings conclusively demonstrated that there was a dramatic similtaneous rise in the number of children diagnosed as autistic in the US,

UK and Denmark during the 1990s. In addition, there was highly persuasive evidence that MMR vaccine was not the cause of the rise. Despite firm evidence that a steady state occurred in children born from 1996 through 2001 in the UK, vaccine/autism litigation continued in US courts until 2010.

The initial autism studies[5, 14-16, 34-36] were based primarily on birth cohorts usually aged 2-5 years. In that design the number of newly diagnosed (incident) cases is determined separately for each annual birth cohort. By contrast, the nature and interpretation of annual prevalence "rates" of autism, as reported in the present and the recent CDC studies, are far more complex and superficially counterintuitive, particularly where the design objective is to estimate changes in yearly time trends or to compare results with other similarly designed studies.

The CDC chose to estimate annual prevalence rates for children of the same age - 8 years – in each of successive calendar years. Annual prevalence estimates apply to children who encompass a large age range e.g., 2-8 years and each of the autism cases may be included as prevalent in multiple years. For example, when examining the period 2004 to 2010, a child diagnosed at age 2 years in 2004 would be included in the prevalence estimate for each of the next six years until the child reached age 9 years and no longer is considered a prevalent case. Children diagnosed at age 6 in 2005 would be included in the prevalence estimates for only 3 years thereafter. Year of age at first diagnosis, including prior to 2004, is thus a critical variable in estimating the

annual prevalence rates at age 8 over many years. The full detail that yielded the annual prevalence rates could be reviewed directly for consistency.

The 2012 CDC report[2] was a follow up to studies of 8 year old children initiated in 2000 and repeated every two years thereafter. The results were derived from a network of 6-11 US states depending on the years, and based on school or medical records or both. Early reports estimated annual prevalence rates of 6.7 and 6.6 per 1000 children in 2000 and 2002. Starting in 2004, prevalence rate estimates rose steadily until 2008 when they reached 11.3 per 1000, a rise of 78% from 2004. The latest prevalence rate estimates varied widely from state to state – from 4.1/1000 in Alabama to 21.2/1000 in Utah. A detailed commentary on the limitations of the CDC report was published shortly after it was released.[37] This commentary raised important questions related to the accuracy and specificity of the combined rate estimates over the years.

There are many similarities between the results found in the US and UK in the secular epidemiology of autism. Few children were diagnosed as autistic in either country prior to 1990. A continuous simultaneous extraordinary rise in the number of children diagnosed as autistic began in both countries in the early 1990s and lasted for a decade. The distribution of first time diagnosis according to age and gender was the same. These similarities between countries as well as within different locations in each country point to a common etiology for this extraordinary medical story.

By contrast, there is a large difference in the percentage of children diagnosed as autistic in the two countries. The estimated prevalence rates of autism in the UK population, about 4 per 1000 in 8 year old boys in 2008, is far lower than the more than 11 per 1000 in 8 year old boys reported by the CDC from the US for the same calendar year. This large difference between countries is closely similar to differences in rates reported for children diagnosed and treated for attention deficit hyperactivity disorder (ADHD) in the two countries. [38, 39]

The GPRD is a uniquely constructed resource of clinical medical information that has succeeded in providing a reliable continuous standardized accounting of demographics, medical diagnoses and prescribed medicines over more than 20 years. The substance of its construction and implementation is highly complex. Nowhere is this clearer than in the current findings related to the enormously complex secular epidemiology of autism.

In conclusion, the annual prevalence of clinically confirmed autism recorded by UK general practitioners remained steady for the 7-year period 2004-10. Whether it has increased in the US over these years remains uncertain.

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Contributors The GPRD data source was constructed by HJ and DM. The study was designed by HJ and BT. The database access was created by DM. Data analysis was done by HJ and BT. The manuscript was written by BT and HJ. All the authors vouch for the accuracy and completeness of the data and the analyses as presented. They also vouch for the fidelity of the final report.

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Competing interests None

Ethics The study protocol was approved by the MHRA's Independent Scientific Advisory Committee (ISAC) . All data were anonymised.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data available

Figure 1*

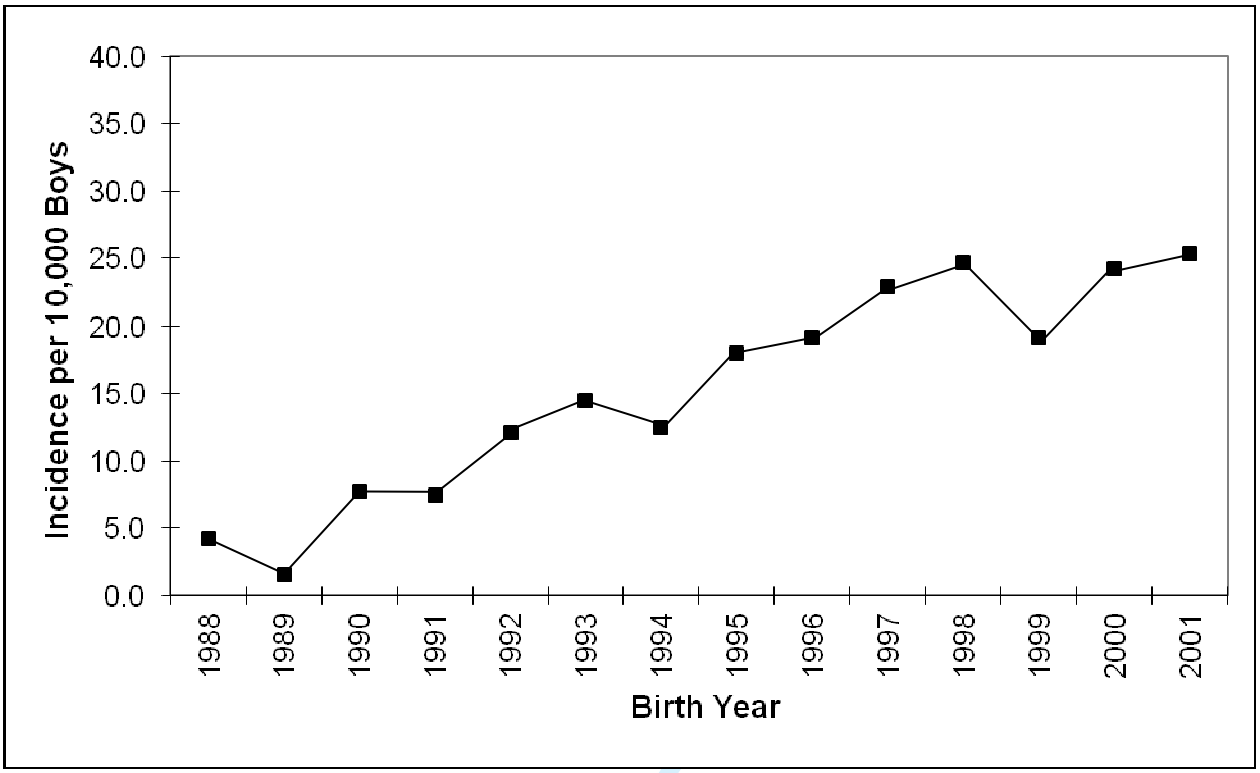

Figure. Three-year cumulative incidence of diagnosed autism among boys age 2-4 years, in birth cohorts.[16]

*Adapted from Hagberg KW, Jick H. "Autism in the UK for birth cohorts 1988-2001". Epidemiology 2010;21:426-427.

Table 1. Prevalence and Incidence Rates of Boys Aged 8 for Years 2004 – 2010

Year	Number of Boys aged 8 in GPRD	Number of Prevalent Cases	Prevalence Rate per 1000	95% Confidence Intervals	Number of Incident Cases	Incidence Rate per 1000	95% Confidence Intervals
2004	145,483	521	3.58	3.28-3.80	172	1.18	1.01-1.37
2005	143,721	535	3.72	3.41-4.05	170	1.17	1.00-1.35
2006	147,049	568	3.86	3.56-4.19	190	1.29	1.12-1.49
2007	142,229	540	3.79	3.49-4.13	173	1.21	1.05-1.41
2008	138,847	543	3.91	3.59-4.25	170	1.22	1.05-1.42
2009	138,317	566	4.09	3.77-4.40	180	1.30	1.02-1.50
2010	132,143	515	3.90	3.57-4.24	135	1.02	0.86-1.20

Table 2. Prevalence and Incidence Rates of Girls Aged 8 for Years 2004 – 2010

Year	Number of Girls aged 8 in GPRD	Number of Prevalent Cases	Prevalence Rate per 1000	95% Confidence Intervals	Number of Incident Cases	Incidence Rate per 1000	95% Confidence Intervals
2004	136,752	109	0.80	0.66-0.96	27	0.20	0.14-0.28
2005	135,511	112	0.83	0.68-0.99	30	0.22	0.15-0.31
2006	138,548	112	0.81	0.69-0.97	34	0.25	0.17-0.39
2007	134,083	125	0.93	0.78-1.11	41	0.31	0.22-0.41
2008	130,876	107	0.82	0.67-0.98	29	0.21	0.14-0.29
2009	130,367	106	0.81	0.67-0.98	30	0.23	0.16-0.32
2010	124,135	101	0.81	0.67-0.99	26	0.21	0.14-0.30

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Page 1 (prevalence, incidence, time trend)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Pages 2-3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses Page 4 ('…to derive annual prevalence rate estimates for children in the UK')
Methods		
Study design	4	Present key elements of study design early in the paper Page 4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 4-5 (details of the GPRD, with references)
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Page 4-6 (details of the GPRD with references, including validity of autism diagnoses)
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page 4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page 4-6
Bias	9	Describe any efforts to address potential sources of bias N/A (population-based clinical database)
Study size	10	Explain how the study size was arrived at N/A (population-based clinical database)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why N/A
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding N/A – tabulations only – no statistical analysis
		(*b*) Describe any methods used to examine subgroups and interactions N/A
		(*c*) Explain how missing data were addressed Not addressed per se; this analysis was based on general-practitioner-recorded diagnoses
		(*d*) If applicable, explain how loss to follow-up was addressed N/A (although cases may have entered or left the individual practices over time, our analysis is based on annual figures.
		(*e*) Describe any sensitivity analyses N/A
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Page 6-7 and Tables 1 and 2
		(b) Give reasons for non-participation at each stage N/A
		(c) Consider use of a flow diagram ?
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and

		information on exposures and potential confounders Representative UK general practice population
		(b) Indicate number of participants Table 1 and 2 with missing data for each variable of interest N/A
		(c) Summarise follow-up time (eg, average and total amount) Annual numbers of children with autism diagnosed 2004-2010, as explained on page
Outcome data	15*	Report numbers of outcome events or summary measures over time Table 1 and 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included N/A
		(*b*) Report category boundaries when continuous variables were categorized N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses N/A
Discussion		
Key results	18	Summarise key results with reference to study objectives Page 14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Not really mentioned in the present discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page 12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results Page 12-14
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based No grant funding for this project.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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