



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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-003219
Article Type:	Research
Date Submitted by the Author:	13-May-2013
Complete List of Authors:	Jick, Hershel; Boston University School of Medicine, Boston Collaborative Drug Surveillance Program Taylor, Brent; UCL Institute of Child Health, General and Adolescent Paediatric Unit; MacLaughlin, Dean; Boston University School of Public Health, Boston Collaborative Drug Surveillance Program
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Evidence based practice
Keywords:	Neurogenetics < NEUROLOGY, Paediatric neurology < NEUROLOGY, Community child health < PAEDIATRICS, Paediatric neurology < PAEDIATRICS, Anxiety disorders < PSYCHIATRY, Child & adolescent psychiatry < PSYCHIATRY

SCHOLARONE™
Manuscripts

Only

1
2
3
4
5 **Prevalence and incidence rates of autism in the United Kingdom:**
6
7
8 **time trend from 2004-2010 in children aged 8 years.**
9
10

11
12 Brent Taylor, PhD, FRCPCH¹
13

14 Hershel Jick, MD²
15

16
17 Dean MacLaughlin, PhD²
18
19
20
21

22 ¹ General and Adolescent Paediatric Unit, UCL Institute of Child Health, Guilford
23
24 Street, London WC1N 1EH, UK. Tel: +44 20 7905 2190. e-mail: brent.taylor@ucl.ac.uk
25
26

27 ²Boston Collaborative Drug Surveillance Program, Boston University School of
28
29 Medicine, 11 Muzzey Street, Lexington, MA 02421. Tel: 781-862-6660,
30
31 Fax: 781-862-1680
32
33
34
35
36

37 Corresponding Author: Hershel Jick, MD, Boston Collaborative Drug Surveillance
38
39 Program, Boston University School of Medicine, 11 Muzzey Street, Lexington, MA
40
41 02421. Tel: 781-862-6660,
42
43 Fax: 781-862-1680, e-mail: hjick@bu.edu
44
45
46
47

48 Running head: Autism in the UK 2004-2010
49

50 Key words: Autism, Prevalence, Incidence.
51

52
53 Word Count: 2,974
54
55
56
57
58
59
60

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.

For peer review only

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

1
2
3 highly sensitive. The GPRD is a uniquely constructed resource of clinical medical
4
5 information that has succeeded in providing a reliable continuous standardized
6
7 accounting of demographics, medical diagnoses and prescribed medicines over more
8
9 than 20 years.
10
11

12
13
14
15
16 There may have been unidentified cases (false negatives) in the study population.
17

18
19 However this was a real-life clinically-based study with no attempt to screen the child
20
21 population for autism. Such screening may have contributed to the diagnosis being
22
23 made too frequently.
24
25

26 27 28 29 **Background**

30
31 In March 2012, the US Centre for Disease Control (CDC) issued a press release¹ that
32
33 described the results of a long term study on the annual prevalence rate of autism in 8
34
35 year old children². They reported that 1 of 88 children aged 8 years had been
36
37 diagnosed as autistic in or prior to 2008. This represented a 78% increase from the
38
39 estimate in 2004. The press release received wide media attention and prompted us to
40
41 review and update the information accrued in the United Kingdom (UK) General
42
43 Practice Research Database (GPRD) over the last 20 years to derive annual prevalence
44
45 rate estimates in children in the UK for the years 2004 -2010. For direct comparison
46
47 with the CDC study, we restricted our results to 8 year old children.
48
49
50
51
52
53
54
55
56
57
58
59
60

Methods

The GPRD is a unique longitudinal electronic medical database constructed and implemented in 1990 through a combined effort of the Boston Collaborative Drug Surveillance 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

1
2
3 derived from review of the extensive specialist referral reports.⁵ The quality and
4
5 specificity of the diagnosis of autism in the GPRD were subsequently confirmed by an
6
7 independent research group based on DSM4 criteria.¹²⁻¹³
8
9

10
11
12 Annual prevalence rates were calculated by dividing the number of children aged 8
13
14 years diagnosed as autistic and recorded in the continuous medical record by the GP at
15
16 any prior time, by the number of 8 year olds active in the database that year. For
17
18 example, prevalence rates for 2004 were based on the number of children who were
19
20 aged 8 in 2004 and had been diagnosed as autistic during the 8 prior years 1996-2004.
21
22 Continuous prevalence rates were similarly estimated for each subsequent calendar
23
24 year.
25
26
27
28
29
30
31
32

33
34 We also calculated annual incidence rates by dividing the annual number of children
35
36 aged 2-8 newly diagnosed with autism in each year (2004 - 2010), by the number of
37
38 children aged 2-8 active in the practices in that year. Practices enrolled in the GPRD
39
40 only after 1996 were excluded from the study.
41
42
43
44
45

46
47 The study protocol was approved by the MHRA's Independent Scientific Advisory
48
49 Committee (ISAC) . All data were anonymised. The GPRD data source was constructed
50
51 by Hershel Jick and Dean MacLaughlin. The study was designed by Hershel Jick and
52
53 Brent Taylor. The database access was created by Dean MacLaughlin. Data analysis
54
55 was done by Hershel Jick and Brent Taylor. The manuscript was written by Brent
56
57
58
59
60

1
2
3 Taylor and Hershel Jick. All the authors vouch for the accuracy and completeness of
4
5 the data and the analyses as presented. They also vouch for the fidelity of the final
6
7 report. This research received no specific grant from any funding agency in the public,
8
9 commercial or not-for-profit sectors
10
11
12

13 14 15 16 **Results**

17
18 Table 1 shows the annual number of boys aged 8 years who had been diagnosed as
19
20 autistic in each or any prior year i.e., prevalent cases. The annual number of prevalent
21
22 cases (a reflection of the cumulative incidence) is remarkably similar over calendar time,
23
24 as is the number of boys active in the population from 2004 -2010. The resulting annual
25
26 prevalence rate estimates of about 3.8/1000 boys are steady over time. The 95%
27
28 confidence limits widely overlapped in each year.
29
30
31
32

33
34
35
36 Table 1 also shows the annual number of boys aged 2-8 diagnosed as autistic for the
37
38 first time (incident) in each year from 2004-2010. The annual number of incident cases
39
40 is again remarkably similar over time as is the number of boys active in the practices
41
42 each year, resulting in annual incidence estimates of about 1.2/1000 boys over the
43
44 years. The total number of boys was 1190.
45
46
47
48

49
50
51 The number of girls initially diagnosed as autistic from 2004-2010 was 217. Table 2
52
53 provides the annual prevalence and incidence rate estimates over time for girls. Girls
54
55 were about one fifth as likely to be diagnosed with autism as boys.
56
57
58

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

1
2
3 among children aged 3 to 10. Surveys in California in 1983-85 and in 1993-95 based on
4
5 birth cohorts¹⁵⁻¹⁶ found that during years 1980-1994 there was a large annual secular
6
7 increase in the number of cases of autism; these increases were estimated as a
8
9 prevalence of 44 per 100,000 live births in the 1980 cohort and 208 in the 1994 cohort¹⁷.
10
11
12 A study from Denmark estimated that the prevalence of autism rose from less than 2
13
14 per 10,000 prior to 1990 to more than 10 per 10,000 in 2000.¹⁸ Taken together these
15
16 reports provided clear evidence that there was a substantial increase in the number of
17
18 young children diagnosed as autistic in the US and Europe during the decade of the
19
20 1990s.
21
22
23
24
25
26
27
28

29 In February 1998 Wakefield et al reported a case series of 12 autistic children with
30
31 bowel disorders most of whom had recently received the MMR vaccine¹⁹. The authors
32
33 suggested that the MMR vaccine may have been causally related to these gastro-
34
35 intestinal conditions. This widely publicised paper led to subsequent studies to
36
37 evaluate the proposition that the MMR vaccine might be causally related to autism.
38
39
40
41
42
43

44 In the following year, Taylor et al reported results from a study based on birth cohorts
45
46 from 1979-1992 in the North East Thames (UK) health region²⁰. They reviewed special
47
48 needs records and found that fewer than 10 children per year born from 1979 through
49
50 1986 were diagnosed as autistic. Subsequently, the number increased to almost 50 in
51
52 children born in 1992. They found no correlation between MMR vaccination and the
53
54 rise in the prevalence of autism.
55
56
57
58
59
60

1
2
3 Shortly thereafter, the BCDSPP examined experience accrued in the GPRD since 1990 to
4
5 estimate annual cumulative incidence rates for birth cohorts from 1988-93 for boys age
6
7 2-5 years and found that the autism cumulative incidence rates increased some 5 fold
8
9 from an estimated of 6 per 10,000 in boys born in 1988 to 30 per 10,000 in those born in
10
11 1993. At the same time MMR vaccination was given to over 90% of young children
12
13 ruling out an association between the vaccine and the dramatic increase in rates.²¹
14
15

16
17
18
19
20
21 Subsequent studies also found no association between MMR and autism.^{17, 18, 22, 23,}
22

23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
Lingam et al suggested that the previously observed annual increase in prevalence may
have been leveling off by the mid-1990s.²³

31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
The BCDSPP 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 cohort²⁵ (See Figure 1). Children born in 2001 would
have been diagnosed as autistic at aged 2-4 in 2003-2005.

52
53
54
55
56
57
58
59
60
Taken together the published findings conclusively demonstrated that there was a
dramatic simultaneous 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

1
2
3 that MMR vaccine was not the cause of the rise. Despite firm evidence that a steady
4
5 state occurred in children born from 1996 through 2001 in the UK, litigation continued
6
7 in US courts until 2010.
8
9

10
11
12 The initial autism studies^{5, 15-18, 20-25} were based primarily on birth cohorts usually aged
13
14 2-5 years. In this design the number of newly diagnosed (incident) cases is determined
15
16 separately for each annual birth cohort. By contrast, the nature and interpretation of
17
18 annual prevalence “rates” of autism are far more complex and superficially
19
20 counterintuitive, particularly where the design objective is to estimate changes in yearly
21
22 time trends or to compare results with other similarly designed studies.
23
24
25
26
27
28

29
30
31 The CDC chose to estimate annual prevalence rates for children of the same age - 8
32
33 years - in each of successive calendar years. Annual prevalence estimates apply to
34
35 children who encompass a large age range e.g., 2-8 years and each of the autism cases
36
37 may be included as prevalent in multiple years. For example, when examining the
38
39 period 2004 to 2010, a child diagnosed at age 2 in 2004 would be included in the
40
41 prevalence estimate for each of the next six years until the child reached age 9 years
42
43 and no longer is a prevalent case. Children diagnosed at age 6 in 2005 would be
44
45 included in the prevalence estimates for only 3 years thereafter. Year of age at first
46
47 diagnosis is thus a critical variable in estimating the annual prevalence rates over many
48
49
50
51
52
53
54
55
56
57
58
59
60 years.

1
2
3 The 2012 CDC report² was a follow up to studies of 8 year old children initiated in 2000
4 and repeated every two years thereafter. The results were derived from a network of 6-
5
6
7
8
9 11 US states depending on the years, and based on school or medical records or both.
10
11 Early reports estimated annual prevalence rates of 6.7 and 6.6 per 1000 children in 2000
12 and 2002. Starting in 2004, prevalence rate estimates rose steadily until 2008 when they
13
14 reached 11.3 per 1000, a rise of 78% from 2004. The latest prevalence rate estimates
15
16
17
18 varied widely from state to state – 4.1/1000 in Alabama to 21.2/1000 in Utah. A
19
20 detailed commentary on the limitations of the CDC report was published shortly after it
21
22 was released.²⁶ This commentary raised important questions related to the accuracy
23
24 and specificity of the combined rate estimates over the years.
25
26
27
28
29
30

31
32 In the present paper we review and update an extraordinary 20-year exploration of the
33
34 annual rates of autism in young children as recorded in real time and derived from a
35
36 unique carefully designed medical database in the UK. In a formal analysis of the data
37
38 recorded continuously by some 1000 GPs, we have documented that the cumulative
39
40 incidence of autism in children born from 1988-1995 began to increase and continued to
41
42 rise from a low level by more than five fold during these years. The annual incidence
43
44 then leveled off and reached a steady state in children born from 1996-2001.
45
46
47
48
49
50

51
52 In order to compare the UK experience with that reported by the CDC, we restricted
53
54 our current prevalence study to annual calendar years 2004-2010 in children 8 years of
55
56 age. These children would have all been born after 1995. Combined, the results in this
57
58
59
60

1
2
3 20-year population-based UK resource, provide highly persuasive evidence that a major
4
5 rise in GP-diagnosed incidence rates of autism occurred in the decade of the 1990s but
6
7 reached a plateau shortly after 2000 and remained steady through 2010. This incidence
8
9 plateau was necessarily accompanied by steady prevalence rates for 8 year old children.
10
11
12
13

14
15
16 It is possible that at least a part of the early rise was related to changing and broadening
17
18 diagnostic criteria to include a spectrum of disorders²⁷⁻²⁸ as well as increased general
19
20 medical and public awareness.²⁹ However, it seems unlikely that these factors
21
22 materially explain the extraordinary increase in the number of children diagnosed in
23
24 the 1990s; nor the steady state that followed thereafter in 2004 through 2010. While the
25
26 MMR vaccine is surely not the cause of the dramatic rise in the 1990s, the actual cause
27
28 remains in large part a mystery.
29
30
31
32
33
34
35
36

37 There are important similarities between the results found in the US and UK in the
38
39 secular epidemiology of autism. Few children were diagnosed as autistic in either
40
41 country prior to 1990. A continuous simultaneous extraordinary rise in the number of
42
43 children diagnosed as autistic began in both countries in the early 1990s and lasted for a
44
45 decade. The distribution of first time diagnosis according to age and gender was the
46
47 same. These similarities between countries as well as within different locations in each
48
49 country point to a common etiology for this extraordinary medical story.
50
51
52
53
54
55
56
57
58
59
60

1
2
3 By contrast, there is a large difference in the percentage of children diagnosed as autistic
4
5 in the two countries. The estimated prevalence rates of autism in the UK population,
6
7 about 4 per 1000 in 8 year old boys in 2008, is far lower than the more than 11 per 1000
8
9 in 8 year old boys reported by the CDC from the US for the same calendar year. This
10
11 large difference between countries is closely similar to differences in rates reported in
12
13 children diagnosed and treated for attention deficit hyperactivity disorder (ADHD) in
14
15 the two countries.^{30, 31}
16
17
18
19
20
21
22
23

24 There is wide-spread concern that the diagnosis of autism using the present criteria has
25
26 become too broad and that the diagnosis is made too frequently. "If the *DSM-IV* criteria
27
28 are taken too literally, anybody in the world could qualify for Asperger's or PDD-NOS,"
29
30 Catherine Lord, one of the members of the APA's *DSM-V* Development
31
32 Neurodevelopmental Disorders Work Group has said. "The specificity is terrible. We
33
34 need to make sure the criteria are not pulling in kids who do not have these
35
36 disorders."³² The forthcoming *DSM-V* criteria will considerably tighten criteria. This
37
38 tightening should affect what has been described as the 'false epidemic of autism'.³³
39
40
41
42
43
44
45
46

47 The GPRD is a uniquely constructed resource of clinical medical information that has
48
49 succeeded in providing a reliable continuous standardized accounting of
50
51 demographics, medical diagnoses and prescribed medicines over more than 20 years.
52
53
54 The substance of its construction and implementation is highly complex. Nowhere is
55
56
57
58
59
60

1
2
3 this clearer than in the current findings related to the enormously complex secular
4
5 epidemiology of autism.
6
7
8
9

10
11 In conclusion, the annual prevalence of clinically confirmed autism recorded by UK
12
13 general practitioners remained steady for the 7-year period 2004-10. Whether it has
14
15 increased in the US over these years remains uncertain.
16
17
18
19

20 21 **Acknowledgements** 22

23
24 The authors gratefully acknowledge the excellent work of the general practitioners who
25
26 have contributed to the GPRD.
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 1*

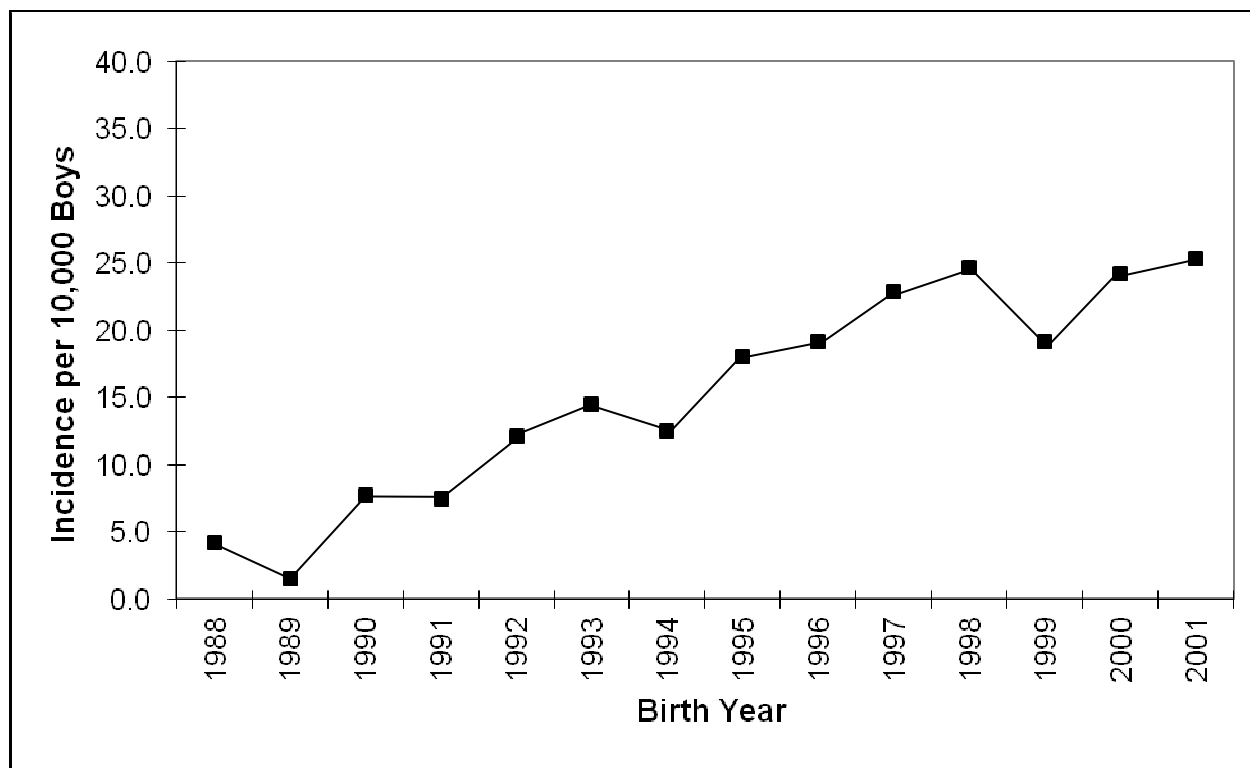


Figure. Three-year cumulative incidence of diagnosed autism among boys age 2-4 years, by year of birth.²⁵

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

Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Lippincott Williams & Wilkins. Please contact journalpermissions@lww.com for further information.

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

References

1. CDC Division of News & Electronic Media □(404) 639-3286
(http://www.cdc.gov/media/releases/2012/p0329_autism_disorder.html)
2. CDC Surveillance Summaries. Prevalence of Autism Spectrum Disorders – Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2008. MMWR 2012; 61:3;1-19.
(http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6103a1.htm?s_cid=ss6103a1)
3. Jick H, Jick S, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. Brit Med J 1991; 302: 766-768.
4. Jick H, Terris BZ, Derby LE, Jick SS. Further validation of information recorded on a general practitioner based computerized data resource in the United Kingdom. Pharmacoepidemiology & Drug Safety 1992;1:347-349.
5. Black C, Kaye JA, Jick H. Relation of childhood gastrointestinal disorders to autism: nested case-control study using data from the UK General Practice Research database. Brit Med J 2002;325:419-21.
6. Derby LE, Jick H, Henry DA, Dean AD. Cholestatic hepatitis associated with flucloxacillin. Med J Australia 1993;158:596-600.
7. Melero Montes MM, Jick H. Hyperemesis gravidarum and the sex of the baby. Epidemiology 2000;12:123-4.

- 1
2
3 8. Kaye JA, Derby LE, Melero-Montes MM, Quinn M, Jick H. Breast cancer
4
5 incidence among women aged 35 to 69 in the U.K. B comparison of estimates
6
7 from the General Practice Research Database with cancer registration data. *Brit J*
8
9 *Cancer* 2000;83:1556-1558.
10
- 11
12 9. Jick SS, Hagberg KW, Kaye JA, Jick H. Postmenopausal estrogen-containing
13
14 hormone therapy and the risk of breast cancer. *Obstet Gynecol* 2009;113(1):74-80.
15
- 16
17 10. Jick H, Chamberlin DP, Hagberg KW. The origin and spread of a mumps
18
19 epidemic - United Kingdom, 2003-2006. *Epidemiology* 2009;20:656-61.
20
21
- 22
23 11. Jick H, MacLaughlin DS, Egger P, Wiggins P. The United Kingdom 2009 swine
24
25 flu outbreak in real time. *Epidemiol Res Intl* doi:10.1155/2011/381597.
26
27
- 28
29 12. Fombonne E, Heavey L, Smeeth L, et al. Validation of the diagnosis of autism in
30
31 general practitioner records. *BMC Public Health* 2004 Mar 3;4:5.
32
33
- 34
35 13. Smeeth L, Cook C, Fombonne E, Heavey L, Rodrigues LC, Smith PG, Hall AJ.
36
37 MMR vaccination and pervasive developmental disorders: A case-control study.
38
39 *Lancet* 2004; 364: 963-969.
40
- 41
42 14. Yergin-Allsop M, Rice C, Karapurkar T, Doernberg N, Boyle C, Murphy C.
43
44 Prevalence of autism in a US metropolitan area. *JAMA* 2003;289:49-55.
45
46
- 47
48 15. Department of Developmental Services. Changes in population of persons with
49
50 autism and pervasive developmental disorders in California's Developmental
51
52 Services System: 1987 through 1998: a report to the Legislature March 1, 1999.
53
54
55 Sacramento: California Health and Human Services Agency; 1999.
56
57
58
59
60

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
16. Department of Developmental Services. Autism spectrum disorders: changes in the California caseload an update: 1999 through 2002. Sacramento, CA: Department of Developmental Services, California Health and Human Services Agency; 2003.
17. Dales L, Hammer SJ, Smith NJ. Time trends in autism and MMR immunisation in California. *JAMA* 2001;285:1183-1185.
18. Madsen KM, Hviid A, Vestergaard M, Schendel D, Wohlfahrt J, Thorsen P, Olsen J, Melbye M. A population-based study of measles, mumps, and rubella vaccination and autism. *New Eng J Med* 2002;347:1477-82.
19. Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, Berelowitz M, Dhillon AP, Thomson MA, Harvey P, Valentine A, Davies SE, Walker-Smith JA. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998;351:637-41.
20. Taylor B, Miller E, Farrington CP, Petropoulos M-C, Favot-Mayaud I, Li J, Waight PA. Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. *Lancet* 1999;353:2026-9.
21. Taylor B, Miller E, Lingam R, Andrews N, Simmons A, Stowe J. Measles, mumps, and rubella vaccination and bowel problems or developmental regression in children with autism: population study. *British Medical Journal* 2002;324:393-396.
22. Kaye JA, Melero-Montes M, Jick H. Mumps, measles, and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend analysis.

- 1
2
3 Br Med J 2001;322:460-3.
4
5
6 23. Lingam R, Simmons A, Andrews N, Miller E, Stowe J, Taylor B. Prevalence of
7
8 autism and parentally reported triggers in a North East London population. Arch
9
10 Dis Child 2003;88:666-70.
11
12
13 24. Jick H, Kaye JA, Black C. Changes in the risk of autism in the UK for birth
14
15 cohorts 1990-1998. Epidemiology 2003;14:630-632.
16
17
18 25. Hagberg KW, Jick H. Autism in the UK for birth cohorts 1988-2001.
19
20
21 Epidemiology 2010;21:426-427.
22
23
24 26. Carey M. A summary of the CDC autism prevalence report. 2012; 1-8.
25
26 <http://autismsciencefoundation.wordpress.com/2012/03/29/a-summary-of->
27
28 [the-cdc-autism-prevalence-report/](http://autismsciencefoundation.wordpress.com/2012/03/29/a-summary-of-the-cdc-autism-prevalence-report/)
29
30
31 27. King M, Bearman P. Diagnostic change and the increased prevalence of autism.
32
33 International Journal of Epidemiology 2009;38:1224-1234.
34
35
36 28. Fisch GS. Nosology and Epidemiology in Autism: Classification Counts
37
38 American Journal of Medical Genetics Part C (Seminars in Medical Genetics)
39
40 2012; 160C: 91-103(2012).
41
42
43 29. Taylor B. Vaccines and the changing epidemiology of autism. Child: care, health
44
45 and development 2006;32:511-519.
46
47
48 30. Jick H, Kaye JA, Black C. Incidence and prevalence of drug-treated attention
49
50 deficit disorder in the UK. Br J Gen Prac 2004;54:345-347.
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
31. Jick H, Wilson A, Wiggins P, Chamberlin DP. Comparison of prescription drug costs in the United States and the United Kingdom, Part 3: methylphenidate. *Pharmacotherapy*. 2012 Nov;32(11):970-3. doi: 10.1002/phar.1141. Epub 2012 Oct 26.
32. Jabr F. Redefining Autism: Will new *DSM-5* criteria for ASD exclude some people? *Scientific American*. 2012 Jan 30.
<http://scientificamerican.com/article.cfm?id=autism-new-criteria&print=true>
33. Frances A. America's false autism epidemic. *New York Post*, 23 April 2012.
http://www.nypost.com/f/print/news/op0inion/opedcolumnists/america_false_autism_epidemic_jfl7XORH94lcUB795b6f7L#axzz2056kKS4R

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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>.

Please wait...

If this message is not eventually replaced by the proper contents of the document, your PDF viewer may not be able to display this type of document.

You can upgrade to the latest version of Adobe Reader for Windows®, Mac, or Linux® by visiting <http://www.adobe.com/products/acrobat/readstep2.html>.

For more assistance with Adobe Reader visit <http://www.adobe.com/support/products/acrreader.html>.

Windows is either a registered trademark or a trademark of Microsoft Corporation in the United States and/or other countries. Mac is a trademark of Apple Inc., registered in the United States and other countries. Linux is the registered trademark of Linus Torvalds in the U.S. and other countries.

To view the full contents of this document, you need a later version of the PDF viewer. You can upgrade to the latest version of Adobe Reader from www.adobe.com/products/acrobat/readstep2.html

For further support, go to www.adobe.com/support/products/acrreader.html

Please wait...

If this message is not eventually replaced by the proper contents of the document, your PDF viewer may not be able to display this type of document.

You can upgrade to the latest version of Adobe Reader for Windows®, Mac, or Linux® by visiting http://www.adobe.com/go/reader_download.

For more assistance with Adobe Reader visit <http://www.adobe.com/go/acrreader>.

Windows is either a registered trademark or a trademark of Microsoft Corporation in the United States and/or other countries. Mac is a trademark of Apple Inc., registered in the United States and other countries. Linux is the registered trademark of Linus Torvalds in the U.S. and other countries.



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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-003219.R1
Article Type:	Research
Date Submitted by the Author:	11-Jul-2013
Complete List of Authors:	Jick, Hershel; Boston University School of Medicine, Boston Collaborative Drug Surveillance Program Taylor, Brent; UCL Institute of Child Health, General and Adolescent Paediatric Unit; MacLaughlin, Dean; Boston University School of Public Health, Boston Collaborative Drug Surveillance Program
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Evidence based practice
Keywords:	Neurogenetics < NEUROLOGY, Paediatric neurology < NEUROLOGY, Community child health < PAEDIATRICS, Paediatric neurology < PAEDIATRICS, Anxiety disorders < PSYCHIATRY, Child & adolescent psychiatry < PSYCHIATRY

SCHOLARONE™
Manuscripts

Only

1
2
3
4
5 **Prevalence and incidence rates of autism in the United Kingdom:**
6
7
8 **time trend from 2004-2010 in children aged 8 years.**
9

10
11
12 Brent Taylor, PhD, FRCPCH¹

13
14 Hershel Jick, MD²

15
16
17 Dean MacLaughlin, PhD²
18
19
20
21

22 ¹ General and Adolescent Paediatric Unit, UCL Institute of Child Health, Guilford
23 Street, London WC1N 1EH, UK. Tel: +44 20 7905 2190. e-mail: brent.taylor@ucl.ac.uk
24
25

26
27 ²Boston Collaborative Drug Surveillance Program, Boston University School of
28 Medicine, 11 Muzzey Street, Lexington, MA 02421. Tel: 781-862-6660,
29
30
31 Fax: 781-862-1680
32
33
34

35
36
37 Corresponding Author: Hershel Jick, MD, Boston Collaborative Drug Surveillance
38 Program, Boston University School of Medicine, 11 Muzzey Street, Lexington, MA
39
40
41 02421. Tel: 781-862-6660,
42
43
44 Fax: 781-862-1680, e-mail: hjick@bu.edu
45
46
47

48 Running head: Autism in the UK 2004-2010
49

50 Key words: Autism, Incidence, Prevalence, UK, 2004-2010.
51

52
53 Word Count: 2,915
54
55
56
57
58
59
60

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.

For peer review only

Background

In March 2012, the US Centre for Disease Control (CDC) issued a press release¹ that described the results of a long term study on the annual prevalence rate of autism in 8 year old children². 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 Surveillance 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

1
2
3 constructed a unique comprehensive computer file structure that integrated all the
4
5 information into a unified resource that allowed for rapid access to the full dataset,
6
7 updated annually. Early validation studies found an 87% correlation between the
8
9 diagnoses in consultant's letters and those in the GPRD record.³ The high quality,
10
11 stability and consistency of the recorded information over time has been repeatedly
12
13 demonstrated in more than 150 publications.⁴⁻¹¹
14
15
16
17
18
19
20

21 Autism is a developmental disorder manifested early in childhood and characterized by
22
23 a spectrum of abnormal social and communication skills and unusual behaviour. The
24
25 condition was infrequently diagnosed prior to 1990. However, an awareness of a
26
27 gradual increase in the frequency of diagnosed autism was anecdotally noted during
28
29 the early 1990s. The validity of the autism diagnosis recorded by GPs in this study was
30
31 derived from review of the extensive specialist referral reports.⁵ The quality and
32
33 specificity of the diagnosis of autism in the GPRD were subsequently confirmed by an
34
35 independent research group based on DSM4 criteria.¹²⁻¹³
36
37
38
39
40
41
42
43

44 Annual prevalence rates were calculated by dividing the number of children aged 8
45
46 years diagnosed as autistic and recorded in the continuous medical record by the GP at
47
48 any prior time, by the number of 8 year olds active in the database that year. For
49
50 example, prevalence rates for 2004 were based on the number of children who were
51
52 aged 8 in 2004 and had been diagnosed as autistic during the 8 prior years 1996-2004.
53
54
55
56
57
58
59
60

1
2
3 Continuous prevalence rates were similarly estimated for each subsequent calendar
4
5
6 year.
7
8

9
10
11 We also calculated annual incidence rates by dividing the annual number of children
12
13 aged 2-8 newly diagnosed with autism in each year (2004 – 2010), by the number of
14
15 children aged 2-8 active in the practices in that year. Practices enrolled in the GPRD
16
17 only after 1996 were excluded from the study.
18
19
20

21
22
23 The study protocol was approved by the MHRA's Independent Scientific Advisory
24
25 Committee (ISAC) . All data were anonymised. The GPRD data source was constructed
26
27
28 by Hershel Jick and Dean MacLaughlin. The study was designed by Hershel Jick and
29
30 Brent Taylor. The database access was created by Dean MacLaughlin. Data analysis
31
32 was done by Hershel Jick and Brent Taylor. The manuscript was written by Brent
33
34 Taylor and Hershel Jick. All the authors vouch for the accuracy and completeness of
35
36 the data and the analyses as presented. They also vouch for the fidelity of the final
37
38 report. This research received no specific grant from any funding agency in the public,
39
40 commercial or not-for-profit sectors.
41
42
43
44
45
46
47
48

49 **Results**

50
51
52 Table 1 shows the annual number of boys aged 8 years who had been diagnosed as
53
54 autistic in each or any prior year i.e., prevalent cases. The annual number of prevalent
55
56 cases (a reflection of the cumulative incidence) is remarkably similar over calendar time,
57
58
59
60

1
2
3 as is the number of boys active in the population from 2004 -2010. The resulting annual
4
5 prevalence rate estimates of about 3.8/1000 boys are steady over time. The 95%
6
7 confidence limits widely overlapped in each year.
8
9

10
11
12
13
14 Table 1 also shows the annual number of boys aged 2-8 diagnosed as autistic for the
15
16 first time (incident) in each year from 2004-2010. The annual number of incident cases
17
18 is again remarkably similar over time as is the number of boys active in the practices
19
20 each year, resulting in annual incidence estimates of about 1.2/1000 boys over the
21
22 years. The total number of boys was 1190.
23
24
25
26
27
28

29 The number of girls initially diagnosed as autistic from 2004-2010 was 217. Table 2
30
31 provides the annual prevalence and incidence rate estimates over time for girls. Girls
32
33 were about one fifth as likely to be diagnosed with autism as boys.
34
35
36

37 **Discussion**

38
39 For many years the terms incidence and prevalence were applied in medicine primarily
40
41 to describe acute outbreaks of infectious diseases such as influenza, measles and
42
43 mumps. Since the mid 1950s, these terms have also been applied to chronic diseases
44
45 such as diabetes, cancer and more recently autism. Even a superficial consideration of
46
47 the use of these general terms will reveal the complexity and subtlety of their
48
49 application in quantitative observational time trend studies in clinical medicine.
50
51
52
53
54
55
56
57
58
59
60

1
2
3 The term “prevalence” alone is used widely to describe a general property possessed by
4 an indefinite quantity of a condition e.g., the prevalence of conservative voters is higher
5 in rural compared to urban areas. It is also used in public health as a general frequency
6 or quantity, e.g., the prevalence of flu is higher in the winter than in the summer .
7
8
9
10
11
12

13
14
15
16 By contrast, in formal epidemiological research, reliable quantitative estimates of
17 incidence and prevalence “rates” require accurate identification of the number of newly
18 diagnosed cases in a defined population from which the cases were derived, at a given
19 age during a given time period. Valid comparisons of annual rate estimates over many
20 years are dependent on the stability of the base population and the ascertainment of the
21 condition under study.
22
23
24
25
26
27
28
29
30
31
32

33 In 1996, the CDC conducted a study based on screening and abstraction of records in
34 the 5 counties of Atlanta Georgia.¹⁴ The prevalence was estimated to be 3.4 per 1000
35 among children aged 3 to 10. Surveys in California in 1983-85 and in 1993-95 based on
36 birth cohorts¹⁵⁻¹⁶ found that during years 1980-1994 there was a large annual secular
37 increase in the number of cases of autism; these increases were estimated as a
38 prevalence of 44 per 100,000 live births in the 1980 cohort and 208 in the 1994 cohort¹⁷.
39
40
41
42
43
44
45
46
47

48 A study from Denmark estimated that the prevalence of autism rose from less than 2
49 per 10,000 prior to 1990 to more than 10 per 10,000 in 2000.¹⁸ Taken together these
50 reports provided clear evidence that there was a substantial increase in the number of
51
52
53
54
55
56
57
58
59
60

1
2
3 young children diagnosed as autistic in the US and Europe during the decade of the
4
5
6 1990s.
7
8
9

10
11 In February 1998 Wakefield et al reported a case series of 12 autistic children with
12
13 bowel disorders most of whom had recently received the MMR vaccine¹⁹. The authors
14
15 suggested that the MMR vaccine may have been causally related to these gastro-
16
17 intestinal conditions. This widely publicised paper led to subsequent studies to
18
19 evaluate the proposition that the MMR vaccine might be causally related to autism.
20
21
22
23

24
25
26 In the following year, Taylor et al reported results from a study based on birth cohorts
27
28 from 1979-1992 in the North East Thames (UK) health region²⁰. They reviewed special
29
30 needs records and found that fewer than 10 children per year born from 1979 through
31
32 1986 were diagnosed as autistic. Subsequently, the number increased to almost 50 in
33
34 children born in 1992. They found no correlation between MMR vaccination and the
35
36 rise in the prevalence of autism.
37
38
39

40
41 Shortly thereafter, the BCDSPP examined experience accrued in the GPRD since 1990 to
42
43 estimate annual cumulative incidence rates for birth cohorts from 1988-93 for boys age
44
45 2-5 years and found that the autism cumulative incidence rates increased some 5 fold
46
47 from an estimated of 6 per 10,000 in boys born in 1988 to 30 per 10,000 in those born in
48
49 1993. At the same time MMR vaccination was given to over 90% of young children
50
51 ruling out an association between the vaccine and the dramatic increase in rates.²¹
52
53
54
55
56
57
58
59
60

1
2
3 Subsequent studies also found no association between MMR and autism.^{17, 18, 22, 23,}
4

5
6 Lingam et al suggested that the previously observed annual increase in prevalence may
7
8 have been leveling off by the mid-1990s.²³
9

10
11
12
13 The BCDSPP continued to assess time trends by updating the findings recorded in the
14
15 GPRD for additional birth cohorts. Results for birth cohorts from 1994 to 1995
16
17 continued to show a rise in the cumulative incidence of diagnosed autism but results for
18
19 1996-97 indicated that the rise may have reached a plateau.²⁴ Subsequent follow up
20
21 demonstrated that rates had in fact plateaued in the 1996 cohort and remained steady
22
23 for 1996 through the 2001 birth cohort²⁵ (See Figure 1). Children born in 2001 would
24
25 have been diagnosed as autistic at aged 2-4 in 2003-2005.
26
27
28
29
30
31
32
33

34 Taken together the published findings conclusively demonstrated that there was a
35
36 dramatic simultaneous rise in the number of children diagnosed as autistic in the US,
37
38 UK, and Denmark during the 1990s. In addition, there was highly persuasive evidence
39
40 that MMR vaccine was not the cause of the rise. Despite firm evidence that a steady
41
42 state occurred in children born from 1996 through 2001 in the UK, litigation continued
43
44 in US courts until 2010.
45
46
47
48
49
50
51

52 The initial autism studies^{5, 15-18, 20-25} were based primarily on birth cohorts usually aged
53
54 2-5 years. In this design the number of newly diagnosed (incident) cases is determined
55
56 separately for each annual birth cohort. By contrast, the nature and interpretation of
57
58
59
60

1
2
3 annual prevalence “rates” of autism are far more complex and superficially
4
5 counterintuitive, particularly where the design objective is to estimate changes in yearly
6
7 time trends or to compare results with other similarly designed studies.
8
9

10
11
12 The CDC chose to estimate annual prevalence rates for children of the same age - 8
13
14 years – in each of successive calendar years. Annual prevalence estimates apply to
15
16 children who encompass a large age range e.g., 2-8 years and each of the autism cases
17
18 may be included as prevalent in multiple years. For example, when examining the
19
20 period 2004 to 2010, a child diagnosed at age 2 in 2004 would be included in the
21
22 prevalence estimate for each of the next six years until the child reached age 9 years
23
24 and no longer is a prevalent case. Children diagnosed at age 6 in 2005 would be
25
26 included in the prevalence estimates for only 3 years thereafter. Year of age at first
27
28 diagnosis, including prior to 2004, is thus a critical variable in estimating the annual
29
30 prevalence rates at age 8 over many years. The full detail that yielded the annual
31
32 prevalence rates could be reviewed directly for consistency.
33
34
35
36
37
38
39
40
41
42
43

44 The 2012 CDC report² was a follow up to studies of 8 year old children initiated in 2000
45
46 and repeated every two years thereafter. The results were derived from a network of 6-
47
48 11 US states depending on the years, and based on school or medical records or both.

49
50 Early reports estimated annual prevalence rates of 6.7 and 6.6 per 1000 children in 2000
51
52 and 2002. Starting in 2004, prevalence rate estimates rose steadily until 2008 when they
53
54 reached 11.3 per 1000, a rise of 78% from 2004. The latest prevalence rate estimates
55
56
57
58
59
60

1
2
3 varied widely from state to state – 4.1/1000 in Alabama to 21.2/1000 in Utah. A
4
5 detailed commentary on the limitations of the CDC report was published shortly after it
6
7 was released.²⁶ This commentary raised important questions related to the accuracy
8
9 and specificity of the combined rate estimates over the years.
10
11
12

13
14
15
16 In the present paper we review and update an extraordinary 20-year exploration of the
17
18 annual rates of autism in young children as recorded in real time and derived from a
19
20 unique carefully designed medical database in the UK. In a formal analysis of the data
21
22 recorded continuously by some 1000 GPs, we have documented that the cumulative
23
24 incidence of autism in children born from 1988-1995 began to increase and continued to
25
26 rise from a low level by more than five fold during these years. The annual incidence
27
28 then leveled off and reached a steady state in children born from 1996-2001.
29
30
31
32

33
34
35
36 In order to compare the UK experience with that reported by the CDC, we restricted
37
38 our current prevalence study to annual calendar years 2004-2010 in children 8 years of
39
40 age. These children would have all been born after 1995. Combined, the results in this
41
42 20-year population-based UK resource, provide highly persuasive evidence that a major
43
44 rise in GP-diagnosed incidence rates of autism occurred in the decade of the 1990s but
45
46 reached a plateau shortly after 2000 and remained steady through 2010. This incidence
47
48 plateau was necessarily accompanied by steady prevalence rates for 8 year old children.
49
50
51
52

53
54
55
56 It is possible that at least a part of the early rise was related to changing and broadening
57
58
59
60

1
2
3 diagnostic criteria to include a spectrum of disorders²⁷⁻²⁸ as well as increased general
4
5 medical and public awareness.²⁹ However, it seems unlikely that these factors
6
7
8 materially explain the extraordinary increase in the number of children diagnosed in
9
10 the 1990s; nor the steady state that followed thereafter in 2004 through 2010. While the
11
12 MMR vaccine is surely not the cause of the dramatic rise in the 1990s, the actual cause
13
14 remains in large part a mystery. The current study provides compelling evidence that
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
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

1
2
3 children diagnosed and treated for attention deficit hyperactivity disorder (ADHD) in
4
5 the two countries.^{30, 31}
6
7
8
9

10
11 The GPRD is a uniquely constructed resource of clinical medical information that has
12
13 succeeded in providing a reliable continuous standardized accounting of
14
15 demographics, medical diagnoses and prescribed medicines over more than 20 years.
16
17
18 The substance of its construction and implementation is highly complex. Nowhere is
19
20 this clearer than in the current findings related to the enormously complex secular
21
22 epidemiology of autism.
23
24
25
26
27
28

29 In conclusion, the annual prevalence of clinically confirmed autism recorded by UK
30
31 general practitioners remained steady for the 7-year period 2004-10. Whether it has
32
33 increased in the US over these years remains uncertain.
34
35
36
37
38

39 **Acknowledgements**

40
41 The authors gratefully acknowledge the excellent work of the general practitioners who
42
43 have contributed to the GPRD.
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 1*

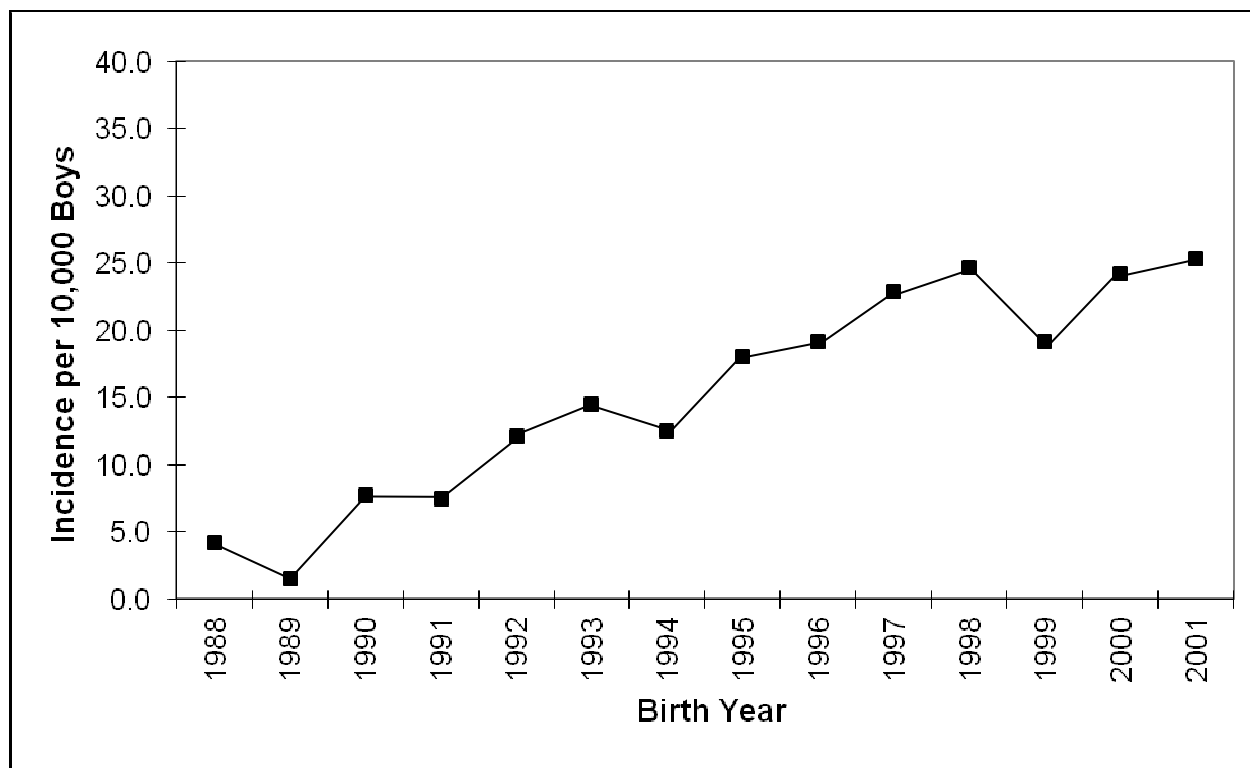


Figure. Three-year cumulative incidence of diagnosed autism among boys age 2-4 years, by year of birth.²⁵

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

Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Lippincott Williams & Wilkins. Please contact journalpermissions@lww.com for further information.

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

References

1. CDC Division of News & Electronic Media □(404) 639-3286
(http://www.cdc.gov/media/releases/2012/p0329_autism_disorder.html)
2. CDC Surveillance Summaries. Prevalence of Autism Spectrum Disorders — Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2008. MMWR 2012; 61:3;1-19.
(http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6103a1.htm?s_cid=ss6103a1)
3. Jick H, Jick S, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. Brit Med J 1991; 302: 766-768.
4. Jick H, Terris BZ, Derby LE, Jick SS. Further validation of information recorded on a general practitioner based computerized data resource in the United Kingdom. Pharmacoepidemiology & Drug Safety 1992;1:347-349.
5. Black C, Kaye JA, Jick H. Relation of childhood gastrointestinal disorders to autism: nested case-control study using data from the UK General Practice Research database. Brit Med J 2002;325:419-21.
6. Derby LE, Jick H, Henry DA, Dean AD. Cholestatic hepatitis associated with flucloxacillin. Med J Australia 1993;158:596-600.
7. Melero Montes MM, Jick H. Hyperemesis gravidarum and the sex of the baby. Epidemiology 2000;12:123-4.

- 1
2
3 8. Kaye JA, Derby LE, Melero-Montes MM, Quinn M, Jick H. Breast cancer
4
5 incidence among women aged 35 to 69 in the U.K. B comparison of estimates
6
7 from the General Practice Research Database with cancer registration data. *Brit J*
8
9 *Cancer* 2000;83:1556-1558.
10
- 11 9. Jick SS, Hagberg KW, Kaye JA, Jick H. Postmenopausal estrogen-containing
12
13 hormone therapy and the risk of breast cancer. *Obstet Gynecol* 2009;113(1):74-80.
14
15
- 16 10. Jick H, Chamberlin DP, Hagberg KW. The origin and spread of a mumps
17
18 epidemic - United Kingdom, 2003-2006. *Epidemiology* 2009;20:656-61.
19
20
- 21 11. Jick H, MacLaughlin DS, Egger P, Wiggins P. The United Kingdom 2009 swine
22
23 flu outbreak in real time. *Epidemiol Res Intl* doi:10.1155/2011/381597.
24
25
- 26 12. Fombonne E, Heavey L, Smeeth L, et al. Validation of the diagnosis of autism in
27
28 general practitioner records. *BMC Public Health* 2004 Mar 3;4:5.
29
30
- 31 13. Smeeth L, Cook C, Fombonne E, Heavey L, Rodrigues LC, Smith PG, Hall AJ.
32
33 MMR vaccination and pervasive developmental disorders: A case-control study.
34
35 *Lancet* 2004; 364: 963-969.
36
37
- 38 14. Yergin-Allsop M, Rice C, Karapurkar T, Doernberg N, Boyle C, Murphy C.
39
40 Prevalence of autism in a US metropolitan area. *JAMA* 2003;289:49-55.
41
42
- 43 15. Department of Developmental Services. Changes in population of persons with
44
45 autism and pervasive developmental disorders in California's Developmental
46
47 Services System: 1987 through 1998: a report to the Legislature March 1, 1999.
48
49
50
51
52
53
54
55
56
57
58
59
60 Sacramento: California Health and Human Services Agency; 1999.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
16. Department of Developmental Services. Autism spectrum disorders: changes in the California caseload an update: 1999 through 2002. Sacramento, CA: Department of Developmental Services, California Health and Human Services Agency; 2003.
 17. Dales L, Hammer SJ, Smith NJ. Time trends in autism and MMR immunisation in California. *JAMA* 2001;285:1183-1185.
 18. Madsen KM, Hviid A, Vestergaard M, Schendel D, Wohlfahrt J, Thorsen P, Olsen J, Melbye M. A population-based study of measles, mumps, and rubella vaccination and autism. *New Eng J Med* 2002;347:1477-82.
 19. Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, Berelowitz M, Dhillon AP, Thomson MA, Harvey P, Valentine A, Davies SE, Walker-Smith JA. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998;351:637-41.
 20. Taylor B, Miller E, Farrington CP, Petropoulos M-C, Favot-Mayaud I, Li J, Waight PA. Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. *Lancet* 1999;353:2026-9.
 21. Taylor B, Miller E, Lingam R, Andrews N, Simmons A, Stowe J. Measles, mumps, and rubella vaccination and bowel problems or developmental regression in children with autism: population study. *British Medical Journal* 2002;324:393-396.
 22. Kaye JA, Melero-Montes M, Jick H. Mumps, measles, and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend analysis.

- 1
2
3 Br Med J 2001;322:460-3.
4
5
6 23. Lingam R, Simmons A, Andrews N, Miller E, Stowe J, Taylor B. Prevalence of
7
8 autism and parentally reported triggers in a North East London population. Arch
9
10 Dis Child 2003;88:666-70.
11
12
13 24. Jick H, Kaye JA, Black C. Changes in the risk of autism in the UK for birth
14
15 cohorts 1990-1998. Epidemiology 2003;14:630-632.
16
17
18 25. Hagberg KW, Jick H. Autism in the UK for birth cohorts 1988-2001.
19
20 Epidemiology 2010;21:426-427.
21
22
23 26. Carey M. A summary of the CDC autism prevalence report. 2012; 1-8.
24
25 [http://autismsciencefoundation.wordpress.com/2012/03/29/a-summary-of-](http://autismsciencefoundation.wordpress.com/2012/03/29/a-summary-of-the-cdc-autism-prevalence-report/)
26
27 [the-cdc-autism-prevalence-report/](http://autismsciencefoundation.wordpress.com/2012/03/29/a-summary-of-the-cdc-autism-prevalence-report/)
28
29
30
31 27. King M, Bearman P. Diagnostic change and the increased prevalence of autism.
32
33 International Journal of Epidemiology 2009;38:1224-1234.
34
35
36 28. Fisch GS. Nosology and Epidemiology in Autism: Classification Counts
37
38 American Journal of Medical Genetics Part C (Seminars in Medical Genetics)
39
40 2012; 160C: 91-103(2012).
41
42
43 29. Taylor B. Vaccines and the changing epidemiology of autism. Child: care, health
44
45 and development 2006;32:511-519.
46
47
48
49 30. Jick H, Kaye JA, Black C. Incidence and prevalence of drug-treated attention
50
51 deficit disorder in the UK. Br J Gen Prac 2004;54:345-347.
52
53
54
55
56
57
58
59
60

- 1
2
3
4 31. Jick H, Wilson A, Wiggins P, Chamberlin DP. Comparison of prescription drug
5
6 costs in the United States and the United Kingdom, Part 3: methylphenidate.
7
8
9 Pharmacotherapy. 2012 Nov;32(11):970-3. doi: 10.1002/phar.1141. Epub 2012
10
11 Oct 26.
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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>.

Please wait...

If this message is not eventually replaced by the proper contents of the document, your PDF viewer may not be able to display this type of document.

You can upgrade to the latest version of Adobe Reader for Windows®, Mac, or Linux® by visiting <http://www.adobe.com/products/acrobat/readstep2.html>.

For more assistance with Adobe Reader visit <http://www.adobe.com/support/products/acrreader.html>.

Windows is either a registered trademark or a trademark of Microsoft Corporation in the United States and/or other countries. Mac is a trademark of Apple Inc., registered in the United States and other countries. Linux is the registered trademark of Linus Torvalds in the U.S. and other countries.

Please wait...

If this message is not eventually replaced by the proper contents of the document, your PDF viewer may not be able to display this type of document.

You can upgrade to the latest version of Adobe Reader for Windows®, Mac, or Linux® by visiting http://www.adobe.com/go/reader_download.

For more assistance with Adobe Reader visit <http://www.adobe.com/go/acrreader>.

Windows is either a registered trademark or a trademark of Microsoft Corporation in the United States and/or other countries. Mac is a trademark of Apple Inc., registered in the United States and other countries. Linux is the registered trademark of Linus Torvalds in the U.S. and other countries.

To view the full contents of this document, you need a later version of the PDF viewer. You can upgrade to the latest version of Adobe Reader from www.adobe.com/products/acrobat/readstep2.html

For further support, go to www.adobe.com/support/products/acrreader.html

1
2
3
4
5 **Prevalence and incidence rates of autism in the United Kingdom:**
6
7 **time trend from 2004-2010 in children aged 8 years.**
8
9

10
11
12 Brent Taylor, PhD, FRCPCH¹

13
14 Hershel Jick, MD²

15
16
17 Dean MacLaughlin, PhD²
18
19

20
21
22 ¹ General and Adolescent Paediatric Unit, UCL Institute of Child Health, Guilford
23
24 Street, London WC1N 1EH, UK. Tel: +44 20 7905 2190. e-mail: brent.taylor@ucl.ac.uk
25
26

27
28 ²Boston Collaborative Drug Surveillance Program, Boston University School of
29
30 Medicine, 11 Muzzey Street, Lexington, MA 02421. Tel: 781-862-6660,
31
32 Fax: 781-862-1680
33
34

35
36
37 Corresponding Author: Hershel Jick, MD, Boston Collaborative Drug Surveillance
38
39 Program, Boston University School of Medicine, 11 Muzzey Street, Lexington, MA
40
41 02421. Tel: 781-862-6660,
42
43 Fax: 781-862-1680, e-mail: hjick@bu.edu
44
45
46

47
48 Running head: Autism in the UK 2004-2010
49

50
51 Key words: Autism, Incidence, Prevalence, UK, 2004-2010.
52

53
54 Word Count: 2,915
55
56
57
58
59
60

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.

For peer review only

Background

In March 2012, the US Centre for Disease Control (CDC) issued a press release¹ that described the results of a long term study on the annual prevalence rate of autism in 8 year old children². 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 Surveillance 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

1
2
3 constructed a unique comprehensive computer file structure that integrated all the
4 information into a unified resource that allowed for rapid access to the full dataset,
5 updated annually. Early validation studies found an 87% correlation between the
6 diagnoses in consultant's letters and those in the GPRD record.³ The high quality,
7 stability and consistency of the recorded information over time has been repeatedly
8 demonstrated in more than 150 publications.⁴⁻¹¹
9
10
11
12
13
14
15
16
17
18
19
20

21 Autism is a developmental disorder manifested early in childhood and characterized by
22 a spectrum of abnormal social and communication skills and unusual behaviour. The
23 condition was infrequently diagnosed prior to 1990. However, an awareness of a
24 gradual increase in the frequency of diagnosed autism was anecdotally noted during
25 the early 1990s. The validity of the autism diagnosis recorded by GPs in this study was
26 derived from review of the extensive specialist referral reports.⁵ The quality and
27 specificity of the diagnosis of autism in the GPRD were subsequently confirmed by an
28 independent research group based on DSM4 criteria.¹²⁻¹³
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43

44 Annual prevalence rates were calculated by dividing the number of children aged 8
45 years diagnosed as autistic and recorded in the continuous medical record by the GP at
46 any prior time, by the number of 8 year olds active in the database that year. For
47 example, prevalence rates for 2004 were based on the number of children who were
48 aged 8 in 2004 and had been diagnosed as autistic during the 8 prior years 1996-2004.
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Continuous prevalence rates were similarly estimated for each subsequent calendar
4
5
6 year.
7
8
9

10
11 We also calculated annual incidence rates by dividing the annual number of children
12
13 aged 2-8 newly diagnosed with autism in each year (2004 - 2010), by the number of
14
15 children aged 2-8 active in the practices in that year. Practices enrolled in the GPRD
16
17 only after 1996 were excluded from the study.
18
19
20

21
22
23 The study protocol was approved by the MHRA's Independent Scientific Advisory
24
25 Committee (ISAC) . All data were anonymised. The GPRD data source was constructed
26
27
28 by Hershel Jick and Dean MacLaughlin. The study was designed by Hershel Jick and
29
30 Brent Taylor. The database access was created by Dean MacLaughlin. Data analysis
31
32 was done by Hershel Jick and Brent Taylor. The manuscript was written by Brent
33
34 Taylor and Hershel Jick. All the authors vouch for the accuracy and completeness of
35
36 the data and the analyses as presented. They also vouch for the fidelity of the final
37
38 report. This research received no specific grant from any funding agency in the public,
39
40 commercial or not-for-profit sectors.
41
42
43
44
45
46
47
48

49 **Results**

50
51 Table 1 shows the annual number of boys aged 8 years who had been diagnosed as
52
53 autistic in each or any prior year i.e., prevalent cases. The annual number of prevalent
54
55 cases (a reflection of the cumulative incidence) is remarkably similar over calendar time,
56
57
58
59
60

1
2
3 as is the number of boys active in the population from 2004 -2010. The resulting annual
4
5 prevalence rate estimates of about 3.8/1000 boys are steady over time. The 95%
6
7 confidence limits widely overlapped in each year.
8
9

10
11
12
13
14 Table 1 also shows the annual number of boys aged 2-8 diagnosed as autistic for the
15
16 first time (incident) in each year from 2004-2010. The annual number of incident cases
17
18 is again remarkably similar over time as is the number of boys active in the practices
19
20 each year, resulting in annual incidence estimates of about 1.2/1000 boys over the
21
22 years. The total number of boys was 1190.
23
24
25
26
27
28

29 The number of girls initially diagnosed as autistic from 2004-2010 was 217. Table 2
30
31 provides the annual prevalence and incidence rate estimates over time for girls. Girls
32
33 were about one fifth as likely to be diagnosed with autism as boys.
34
35
36

37 **Discussion**

38
39 For many years the terms incidence and prevalence were applied in medicine primarily
40
41 to describe acute outbreaks of infectious diseases such as influenza, measles and
42
43 mumps. Since the mid 1950s, these terms have also been applied to chronic diseases
44
45 such as diabetes, cancer and more recently autism. Even a superficial consideration of
46
47 the use of these general terms will reveal the complexity and subtlety of their
48
49 application in quantitative observational time trend studies in clinical medicine.
50
51
52
53
54
55
56
57
58
59
60

1
2
3 The term “prevalence” alone is used widely to describe a general property possessed by
4 an indefinite quantity of a condition e.g., the prevalence of conservative voters is higher
5 in rural compared to urban areas. It is also used in public health as a general frequency
6 or quantity, e.g., the prevalence of flu is higher in the winter than in the summer .
7
8
9
10
11
12

13
14
15
16 By contrast, in formal epidemiological research, reliable quantitative estimates of
17 incidence and prevalence “rates” require accurate identification of the number of newly
18 diagnosed cases in a defined population from which the cases were derived, at a given
19 age during a given time period. Valid comparisons of annual rate estimates over many
20 years are dependent on the stability of the base population and the ascertainment of the
21 condition under study.
22
23
24
25
26
27
28
29
30
31
32

33 In 1996, the CDC conducted a study based on screening and abstraction of records in
34 the 5 counties of Atlanta Georgia.¹⁴ The prevalence was estimated to be 3.4 per 1000
35 among children aged 3 to 10. Surveys in California in 1983-85 and in 1993-95 based on
36 birth cohorts¹⁵⁻¹⁶ found that during years 1980-1994 there was a large annual secular
37 increase in the number of cases of autism; these increases were estimated as a
38 prevalence of 44 per 100,000 live births in the 1980 cohort and 208 in the 1994 cohort¹⁷.
39
40
41
42
43
44
45
46
47

48 A study from Denmark estimated that the prevalence of autism rose from less than 2
49 per 10,000 prior to 1990 to more than 10 per 10,000 in 2000.¹⁸ Taken together these
50 reports provided clear evidence that there was a substantial increase in the number of
51
52
53
54
55
56
57
58
59
60

1
2
3 young children diagnosed as autistic in the US and Europe during the decade of the
4
5
6 1990s.
7
8
9

10
11 In February 1998 Wakefield et al reported a case series of 12 autistic children with
12
13 bowel disorders most of whom had recently received the MMR vaccine¹⁹. The authors
14
15 suggested that the MMR vaccine may have been causally related to these gastro-
16
17 intestinal conditions. This widely publicised paper led to subsequent studies to
18
19 evaluate the proposition that the MMR vaccine might be causally related to autism.
20
21
22
23

24
25
26 In the following year, Taylor et al reported results from a study based on birth cohorts
27
28 from 1979-1992 in the North East Thames (UK) health region²⁰. They reviewed special
29
30 needs records and found that fewer than 10 children per year born from 1979 through
31
32 1986 were diagnosed as autistic. Subsequently, the number increased to almost 50 in
33
34 children born in 1992. They found no correlation between MMR vaccination and the
35
36 rise in the prevalence of autism.
37
38
39

40
41 Shortly thereafter, the BCDSPP examined experience accrued in the GPRD since 1990 to
42
43 estimate annual cumulative incidence rates for birth cohorts from 1988-93 for boys age
44
45 2-5 years and found that the autism cumulative incidence rates increased some 5 fold
46
47 from an estimated of 6 per 10,000 in boys born in 1988 to 30 per 10,000 in those born in
48
49 1993. At the same time MMR vaccination was given to over 90% of young children
50
51 ruling out an association between the vaccine and the dramatic increase in rates.²¹
52
53
54
55
56
57
58
59
60

1
2
3 Subsequent studies also found no association between MMR and autism.^{17, 18, 22, 23,}

4
5
6 Lingam et al suggested that the previously observed annual increase in prevalence may
7
8 have been leveling off by the mid-1990s.²³

9
10
11
12
13 The BCDSRP continued to assess time trends by updating the findings recorded in the
14
15 GPRD for additional birth cohorts. Results for birth cohorts from 1994 to 1995
16
17 continued to show a rise in the cumulative incidence of diagnosed autism but results for
18
19 1996-97 indicated that the rise may have reached a plateau.²⁴ Subsequent follow up
20
21 demonstrated that rates had in fact plateaued in the 1996 cohort and remained steady
22
23 for 1996 through the 2001 birth cohort²⁵ (See Figure 1). Children born in 2001 would
24
25 have been diagnosed as autistic at aged 2-4 in 2003-2005.
26
27
28
29
30
31
32
33

34 Taken together the published findings conclusively demonstrated that there was a
35
36 dramatic simultaneous rise in the number of children diagnosed as autistic in the US,
37
38 UK, and Denmark during the 1990s. In addition, there was highly persuasive evidence
39
40 that MMR vaccine was not the cause of the rise. Despite firm evidence that a steady
41
42 state occurred in children born from 1996 through 2001 in the UK, litigation continued
43
44 in US courts until 2010.
45
46
47
48
49
50
51

52 The initial autism studies^{5, 15-18, 20-25} were based primarily on birth cohorts usually aged
53
54 2-5 years. In this design the number of newly diagnosed (incident) cases is determined
55
56 separately for each annual birth cohort. By contrast, the nature and interpretation of
57
58
59
60

1
2
3 annual prevalence “rates” of autism are far more complex and superficially
4
5 counterintuitive, particularly where the design objective is to estimate changes in yearly
6
7 time trends or to compare results with other similarly designed studies.
8
9

10
11
12
13 The CDC chose to estimate annual prevalence rates for children of the same age - 8
14
15 years - in each of successive calendar years. Annual prevalence estimates apply to
16
17 children who encompass a large age range e.g., 2-8 years and each of the autism cases
18
19 may be included as prevalent in multiple years. For example, when examining the
20
21 period 2004 to 2010, a child diagnosed at age 2 in 2004 would be included in the
22
23 prevalence estimate for each of the next six years until the child reached age 9 years
24
25 and no longer is a prevalent case. Children diagnosed at age 6 in 2005 would be
26
27 included in the prevalence estimates for only 3 years thereafter. Year of age at first
28
29 diagnosis, including prior to 2004, is thus a critical variable in estimating the annual
30
31 prevalence rates at age 8 over many years. The full detail that yielded the annual
32
33 prevalence rates could be reviewed directly for consistency.
34
35
36
37
38
39
40
41
42
43

44 The 2012 CDC report² was a follow up to studies of 8 year old children initiated in 2000
45
46 and repeated every two years thereafter. The results were derived from a network of 6-
47
48 11 US states depending on the years, and based on school or medical records or both.
49

50 Early reports estimated annual prevalence rates of 6.7 and 6.6 per 1000 children in 2000
51
52 and 2002. Starting in 2004, prevalence rate estimates rose steadily until 2008 when they
53
54 reached 11.3 per 1000, a rise of 78% from 2004. The latest prevalence rate estimates
55
56
57
58
59
60

1
2
3 varied widely from state to state – 4.1/1000 in Alabama to 21.2/1000 in Utah. A
4
5 detailed commentary on the limitations of the CDC report was published shortly after it
6
7 was released.²⁶ This commentary raised important questions related to the accuracy
8
9 and specificity of the combined rate estimates over the years.
10
11
12

13
14
15
16 In the present paper we review and update an extraordinary 20-year exploration of the
17
18 annual rates of autism in young children as recorded in real time and derived from a
19
20 unique carefully designed medical database in the UK. In a formal analysis of the data
21
22 recorded continuously by some 1000 GPs, we have documented that the cumulative
23
24 incidence of autism in children born from 1988-1995 began to increase and continued to
25
26 rise from a low level by more than five fold during these years. The annual incidence
27
28 then leveled off and reached a steady state in children born from 1996-2001.
29
30
31
32
33
34
35
36

37 In order to compare the UK experience with that reported by the CDC, we restricted
38
39 our current prevalence study to annual calendar years 2004-2010 in children 8 years of
40
41 age. These children would have all been born after 1995. Combined, the results in this
42
43 20-year population-based UK resource, provide highly persuasive evidence that a major
44
45 rise in GP-diagnosed incidence rates of autism occurred in the decade of the 1990s but
46
47 reached a plateau shortly after 2000 and remained steady through 2010. This incidence
48
49 plateau was necessarily accompanied by steady prevalence rates for 8 year old children.
50
51
52
53
54
55
56

57 It is possible that at least a part of the early rise was related to changing and broadening
58
59
60

1
2
3 diagnostic criteria to include a spectrum of disorders²⁷⁻²⁸ as well as increased general
4
5 medical and public awareness.²⁹ However, it seems unlikely that these factors
6
7
8 materially explain the extraordinary increase in the number of children diagnosed in
9
10 the 1990s; nor the steady state that followed thereafter in 2004 through 2010. While the
11
12 MMR vaccine is surely not the cause of the dramatic rise in the 1990s, the actual cause
13
14 remains in large part a mystery. The current study provides compelling evidence that
15
16 incidence rates have remained steady in children born since the late 1990's in the UK –
17
18
19 at least as diagnosed and recorded in general practice.
20
21
22
23
24
25

26 There are important similarities between the results found in the US and UK in the
27
28 secular epidemiology of autism. Few children were diagnosed as autistic in either
29
30 country prior to 1990. A continuous simultaneous extraordinary rise in the number of
31
32 children diagnosed as autistic began in both countries in the early 1990s and lasted for a
33
34 decade. The distribution of first time diagnosis according to age and gender was the
35
36 same. These similarities between countries as well as within different locations in each
37
38 country point to a common etiology for this extraordinary medical story.
39
40
41
42
43
44
45

46 By contrast, there is a large difference in the percentage of children diagnosed as autistic
47
48 in the two countries. The estimated prevalence rates of autism in the UK population,
49
50 about 4 per 1000 in 8 year old boys in 2008, is far lower than the more than 11 per 1000
51
52 in 8 year old boys reported by the CDC from the US for the same calendar year. This
53
54 large difference between countries is closely similar to differences in rates reported in
55
56
57
58
59
60

1
2
3 children diagnosed and treated for attention deficit hyperactivity disorder (ADHD) in
4
5 the two countries.^{30, 31}
6
7
8
9

10
11 The GPRD is a uniquely constructed resource of clinical medical information that has
12
13 succeeded in providing a reliable continuous standardized accounting of
14
15 demographics, medical diagnoses and prescribed medicines over more than 20 years.
16
17 The substance of its construction and implementation is highly complex. Nowhere is
18
19 this clearer than in the current findings related to the enormously complex secular
20
21 epidemiology of autism.
22
23
24
25
26
27
28

29 In conclusion, the annual prevalence of clinically confirmed autism recorded by UK
30
31 general practitioners remained steady for the 7-year period 2004-10. Whether it has
32
33 increased in the US over these years remains uncertain.
34
35
36
37
38

39 **Acknowledgements**

40
41 The authors gratefully acknowledge the excellent work of the general practitioners who
42
43 have contributed to the GPRD.
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 1*

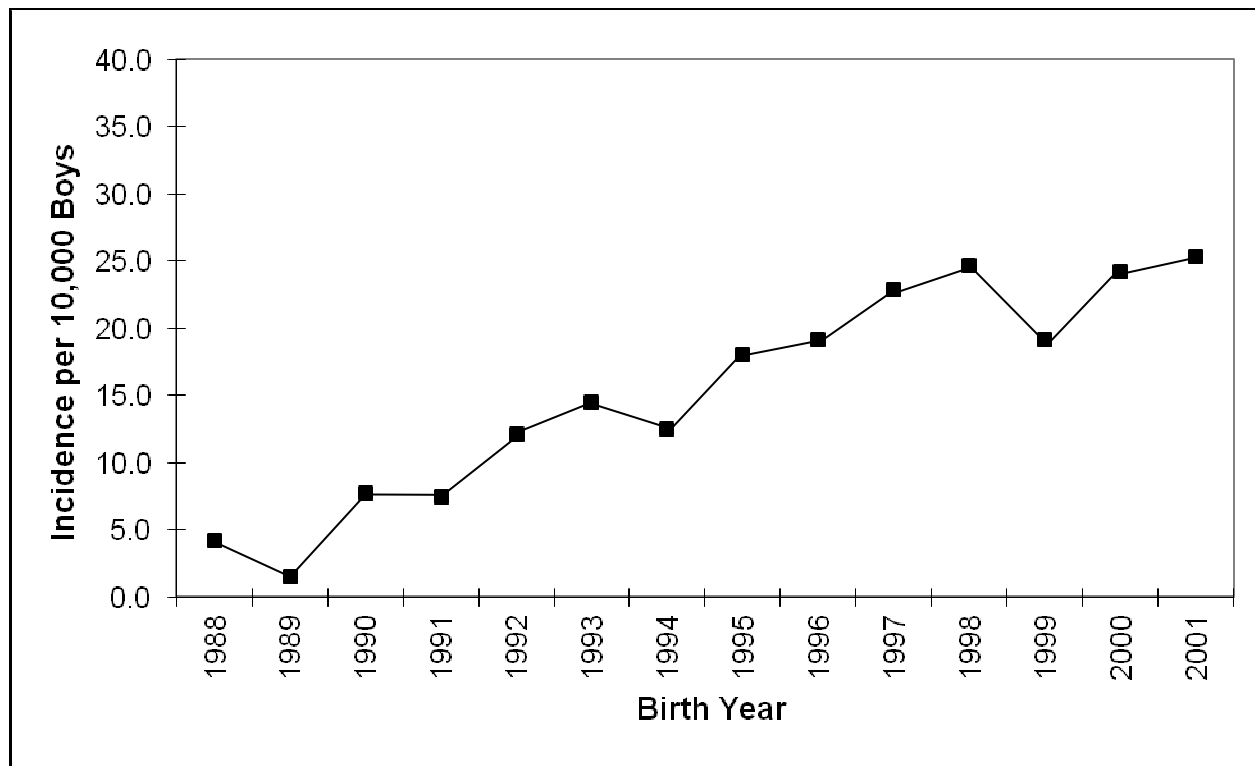


Figure. Three-year cumulative incidence of diagnosed autism among boys age 2-4 years, by year of birth.²⁵

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

Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Lippincott Williams & Wilkins. Please contact journalpermissions@lww.com for further information.

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

References

1. CDC Division of News & Electronic Media □(404) 639-3286
(http://www.cdc.gov/media/releases/2012/p0329_autism_disorder.html)
2. CDC Surveillance Summaries. Prevalence of Autism Spectrum Disorders – Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2008. MMWR 2012; 61:3;1-19.
(http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6103a1.htm?s_cid=ss6103a1)
3. Jick H, Jick S, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. Brit Med J 1991; 302: 766-768.
4. Jick H, Terris BZ, Derby LE, Jick SS. Further validation of information recorded on a general practitioner based computerized data resource in the United Kingdom. Pharmacoepidemiology & Drug Safety 1992;1:347-349.
5. Black C, Kaye JA, Jick H. Relation of childhood gastrointestinal disorders to autism: nested case-control study using data from the UK General Practice Research database. Brit Med J 2002;325:419-21.
6. Derby LE, Jick H, Henry DA, Dean AD. Cholestatic hepatitis associated with flucloxacillin. Med J Australia 1993;158:596-600.
7. Melero Montes MM, Jick H. Hyperemesis gravidarum and the sex of the baby. Epidemiology 2000;12:123-4.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
8. Kaye JA, Derby LE, Melero-Montes MM, Quinn M, Jick H. Breast cancer incidence among women aged 35 to 69 in the U.K. B comparison of estimates from the General Practice Research Database with cancer registration data. *Brit J Cancer* 2000;83:1556-1558.
9. Jick SS, Hagberg KW, Kaye JA, Jick H. Postmenopausal estrogen-containing hormone therapy and the risk of breast cancer. *Obstet Gynecol* 2009;113(1):74-80.
10. Jick H, Chamberlin DP, Hagberg KW. The origin and spread of a mumps epidemic - United Kingdom, 2003-2006. *Epidemiology* 2009;20:656-61.
11. Jick H, MacLaughlin DS, Egger P, Wiggins P. The United Kingdom 2009 swine flu outbreak in real time. *Epidemiol Res Intl* doi:10.1155/2011/381597.
12. Fombonne E, Heavey L, Smeeth L, et al. Validation of the diagnosis of autism in general practitioner records. *BMC Public Health* 2004 Mar 3;4:5.
13. Smeeth L, Cook C, Fombonne E, Heavey L, Rodrigues LC, Smith PG, Hall AJ. MMR vaccination and pervasive developmental disorders: A case-control study. *Lancet* 2004; 364: 963-969.
14. Yergin-Allsop M, Rice C, Karapurkar T, Doernberg N, Boyle C, Murphy C. Prevalence of autism in a US metropolitan area. *JAMA* 2003;289:49-55.
15. Department of Developmental Services. Changes in population of persons with autism and pervasive developmental disorders in California's Developmental Services System: 1987 through 1998: a report to the Legislature March 1, 1999. Sacramento: California Health and Human Services Agency; 1999.

- 1
2
3 16. Department of Developmental Services. Autism spectrum disorders: changes in
4 the California caseload an update: 1999 through 2002. Sacramento, CA:
5
6 Department of Developmental Services, California Health and Human Services
7
8 Agency; 2003.
9
10
- 11
12 17. Dales L, Hammer SJ, Smith NJ. Time trends in autism and MMR immunisation
13 in California. *JAMA* 2001;285:1183-1185.
14
15
- 16
17 18. Madsen KM, Hviid A, Vestergaard M, Schendel D, Wohlfahrt J, Thorsen P, Olsen
18 J, Melbye M. A population-based study of measles, mumps, and rubella
19 vaccination and autism. *New Eng J Med* 2002;347:1477-82.
20
21
- 22
23 19. Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, Berelowitz
24 M, Dhillon AP, Thomson MA, Harvey P, Valentine A, Davies SE, Walker-Smith
25 JA. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive
26 developmental disorder in children. *Lancet* 1998;351:637-41.
27
28
- 29
30 20. Taylor B, Miller E, Farrington CP, Petropoulos M-C, Favot-Mayaud I, Li J,
31 Waight PA. Autism and measles, mumps, and rubella vaccine: no
32 epidemiological evidence for a causal association. *Lancet* 1999;353:2026-9.
33
34
- 35
36 21. Taylor B, Miller E, Lingam R, Andrews N, Simmons A, Stowe J. Measles,
37 mumps, and rubella vaccination and bowel problems or developmental
38 regression in children with autism: population study. *British Medical Journal*
39 2002;324:393-396.
40
41
- 42
43 22. Kaye JA, Melero-Montes M, Jick H. Mumps, measles, and rubella vaccine and
44 the incidence of autism recorded by general practitioners: a time trend analysis.
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 Br Med J 2001;322:460-3.
4
5
6 23. Lingam R, Simmons A, Andrews N, Miller E, Stowe J, Taylor B. Prevalence of
7
8 autism and parentally reported triggers in a North East London population. Arch
9
10 Dis Child 2003;88:666-70.
11
12
13 24. Jick H, Kaye JA, Black C. Changes in the risk of autism in the UK for birth
14
15 cohorts 1990-1998. Epidemiology 2003;14:630-632.
16
17
18 25. Hagberg KW, Jick H. Autism in the UK for birth cohorts 1988-2001.
19
20 Epidemiology 2010;21:426-427.
21
22
23 26. Carey M. A summary of the CDC autism prevalence report. 2012; 1-8.
24
25 [http://autismsciencefoundation.wordpress.com/2012/03/29/a-summary-of-](http://autismsciencefoundation.wordpress.com/2012/03/29/a-summary-of-the-cdc-autism-prevalence-report/)
26
27 [the-cdc-autism-prevalence-report/](http://autismsciencefoundation.wordpress.com/2012/03/29/a-summary-of-the-cdc-autism-prevalence-report/)
28
29
30
31 27. King M, Bearman P. Diagnostic change and the increased prevalence of autism.
32
33 International Journal of Epidemiology 2009;38:1224-1234.
34
35
36 28. Fisch GS. Nosology and Epidemiology in Autism: Classification Counts
37
38 American Journal of Medical Genetics Part C (Seminars in Medical Genetics)
39
40 2012; 160C: 91-103(2012).
41
42
43 29. Taylor B. Vaccines and the changing epidemiology of autism. Child: care, health
44
45 and development 2006;32:511-519.
46
47
48
49 30. Jick H, Kaye JA, Black C. Incidence and prevalence of drug-treated attention
50
51 deficit disorder in the UK. Br J Gen Pract 2004;54:345-347.
52
53
54
55
56
57
58
59
60

- 1
2
3 31. Jick H, Wilson A, Wiggins P, Chamberlin DP. Comparison of prescription drug
4 costs in the United States and the United Kingdom, Part 3: methylphenidate.
5
6 Pharmacotherapy. 2012 Nov;32(11):970-3. doi: 10.1002/phar.1141. Epub 2012
7
8
9 Oct 26.
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-003219.R2
Article Type:	Research
Date Submitted by the Author:	27-Aug-2013
Complete List of Authors:	Taylor, Brent; UCL Institute of Child Health, General and Adolescent Paediatric Unit; Jick, Hershel; Boston University School of Medicine, Boston Collaborative Drug Surveillance Program MacLaughlin, Dean; Boston University School of Public Health, Boston Collaborative Drug Surveillance Program
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

SCHOLARONE™
Manuscripts

Only

1
2
3
4
5 **Prevalence and incidence rates of autism in the United Kingdom:**
6
7
8 **time trend from 2004-2010 in children aged 8 years.**
9
10

11
12 Brent Taylor, PhD, FRCPCH¹

13
14 Hershel Jick, MD²

15
16
17 Dean MacLaughlin, PhD²
18
19
20
21

22 ¹ General and Adolescent Paediatric Unit, UCL Institute of Child Health, Guilford
23
24 Street, London WC1N 1EH, UK. Tel: +44 20 7905 2190. e-mail: brent.taylor@ucl.ac.uk
25
26

27 ²Boston Collaborative Drug Surveillance Program, Boston University School of
28
29 Medicine, 11 Muzzey Street, Lexington, MA 02421. Tel: 781-862-6660,
30
31 Fax: 781-862-1680
32
33
34
35
36

37 Corresponding Author: Hershel Jick, MD, Boston Collaborative Drug Surveillance
38
39 Program, Boston University School of Medicine, 11 Muzzey Street, Lexington, MA
40
41 02421. Tel: 781-862-6660,
42
43 Fax: 781-862-1680, e-mail: hjick@bu.edu
44
45
46
47

48 Running head: Autism in the UK 2004-2010
49

50 Key words: Autism, Incidence, Prevalence, UK, 2004-2010.
51

52 Word Count: 2,922 (excluding abstract, summary, references and acknowledgements)
53
54
55
56
57
58
59
60

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

1
2
3 Annual prevalence rates for each year were steady at approximately 3.8/1000 boys and
4
5 0.8/1000 girls. Annual incidence rates each year were also steady at about 1.2/1000
6
7 boys and 0.2/1000 girls.
8
9

10 11 12 13 **Conclusions**

14
15
16 Following a five fold increase in the annual incidence rates of autism during the 1990s
17
18 in the UK, the incidence and prevalence rates in 8 year-old children reached a plateau in
19
20 the early 2000s and remained steady through 2008. Whether prevalence rates have
21
22 increased from the early 2000s in the US remains uncertain.
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 demographics, medical diagnoses and prescribed medicines over more than 20
4
5
6 years. It is one of the largest sources of primary care data in the world.
7

- 8 • There may have been unidentified cases (false negatives) in the study population
9
10 - individual children with autism who were diagnosed elsewhere and not
11
12 notified to their GP's or others who remained undiagnosed.
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Background

In March 2012, the US Centre for Disease Control (CDC) issued a press release¹ that described the results of a long term study on the annual prevalence rate of autism in 8 year old children². 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 Surveillance 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

1
2
3 information into a unified resource that allowed for rapid access to the full dataset,
4
5 updated annually. Early validation studies found an 87% correlation between the
6
7 diagnoses in consultant's letters and those in the GPRD record.³ The high quality,
8
9 stability and consistency of the recorded information over time has been repeatedly
10
11 demonstrated in more than 150 publications.⁴⁻¹¹
12
13

14
15 Autism is a developmental disorder manifested early in childhood and characterized by
16
17 a spectrum of abnormal social and communication skills and unusual behaviour. The
18
19 condition was infrequently diagnosed prior to 1990. However, an awareness of a
20
21 gradual increase in the frequency of diagnosed autism was anecdotally noted during
22
23 the early 1990s. GPs do not themselves make the diagnosis of autism, referring
24
25 children suspected of having the condition for specialist multidisciplinary assessment,
26
27 which usually takes place over a period of months. Referral letters to GPRD-
28
29 participating GPs from consultants and others are scanned and diagnostic information
30
31 therein coded and recorded in the child's clinical record. The validity of the autism
32
33 diagnosis recorded by GPs was confirmed in the earlier phases of this study by review
34
35 of the extensive specialist referral reports.⁵ The quality and specificity of the diagnosis
36
37 of autism in the GPRD have also been validated by an independent research group
38
39 based on DSM4 criteria;¹²⁻¹³ in 318 cases diagnosed with autism or a related condition
40
41 such as Asperger's syndrome, the researchers, using specialist reports from consultants
42
43 or multidisciplinary teams in the GP record, were able to confirm the diagnosis for 294
44
45 (92.5%).
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Annual prevalence rates were calculated by dividing the number of children aged 8
4 years diagnosed as autistic and recorded in the continuous medical record by the GP at
5 any prior time, by the number of 8 year olds active in the database that year. For
6 example, prevalence rates for 2004 were based on the number of children who were
7 aged 8 in 2004 and had been diagnosed as autistic during the 8 prior years 1996-2004.
8 Continuous prevalence rates were similarly estimated for each subsequent calendar
9 year.
10
11
12
13
14
15
16
17
18
19
20
21
22
23

24 We also calculated annual incidence rates by dividing the annual number of children
25 aged 2-8 newly diagnosed with autism in each year (2004 - 2010), by the number of
26 children aged 2-8 active in the practices in that year. Practices enrolled in the GPRD
27 only after 1996 were excluded from the study.
28
29
30
31
32
33
34
35
36

37 Results

38
39 Table 1 shows the annual number of boys aged 8 years who had been diagnosed as
40 autistic in each or any prior year i.e., prevalent cases. The annual number of prevalent
41 cases (a reflection of the cumulative incidence) is remarkably similar over calendar time,
42 as is the number of boys active in the population from 2004 -2010. The resulting annual
43 prevalence rate estimates of about 3.8/1000 boys are steady over time. The 95%
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Table 1 also shows the annual number of boys aged 2-8 diagnosed as autistic for the
4 first time (incident) in each year from 2004-2010. The annual number of incident cases
5 is again remarkably similar over time as is the number of boys active in the practices
6 each year, resulting in annual incidence estimates of about 1.2/1000 boys over the
7 years. The total number of boys was 1190.
8
9
10
11
12
13
14
15
16
17
18

19 The number of girls initially diagnosed as autistic from 2004-2010 was 217. Table 2
20 provides the annual prevalence and incidence rate estimates over time for girls. Girls
21 were about one fifth as likely to be diagnosed with autism as boys.
22
23
24
25
26
27
28

29 Discussion

30
31
32 In the present paper we review and update an extraordinary 20-year exploration of the
33 annual rates of autism in young children as recorded in real time and derived from a
34 unique carefully designed medical database in the UK. In a series of formal analyses of
35 the data recorded continuously in the GPRD by some 1000 GPs, we have documented
36 that the cumulative incidence of autism in children born from 1988-1995 began to
37 increase and continued to rise from a low level by more than five fold during these
38 years.¹⁴⁻¹⁶ The present study demonstrates that the annual incidence then leveled off
39 and reached a steady state in children born from 1996-2001.
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54

55 In order to compare the UK experience with that reported by the CDC, we restricted
56
57
58
59
60

1
2
3 our current prevalence study to annual calendar years 2004-2010 in children 8 years of
4 age. These children would have all been born after 1995. Combined, the results in this
5
6
7
8
9 20-year population-based UK resource, provide compelling evidence that a major rise in
10
11 incidence rates of autism, recorded in general practice, occurred in the decade of the
12
13 1990s but reached a plateau shortly after 2000 and has remained steady through 2010.
14
15 This incidence plateau was necessarily accompanied by steady prevalence rates for 8
16
17
18
19 year old children.
20

21
22
23
24 It is possible that at least a part of the early rise was related to changing and broadening
25
26 diagnostic criteria to include a spectrum of disorders,¹⁷⁻¹⁸ as well as social influences¹⁹,
27
28 including increased general medical and public awareness.²⁰ However, it seems
29
30 unlikely that these factors materially explain the extraordinary increase in the number
31
32 of children diagnosed in the 1990s; nor the steady state that followed thereafter in 2004
33
34 through 2010. While the MMR vaccine was surely not the cause of the dramatic rise in
35
36 the 1990s, the actual cause remains in large part a mystery. ~~The current study provides
37
38 compelling evidence that incidence rates, as recorded in general practice, have
39
40 remained steady in children born since the late 1990's in the UK. (omit as duplication)~~
41
42
43
44
45
46
47
48

49 For many years the terms incidence and prevalence were applied in medicine primarily
50
51 to describe acute outbreaks of infectious diseases such as influenza, measles and
52
53 mumps. Since the mid 1950s, these terms have also been applied to chronic diseases
54
55 such as diabetes, cancer and more recently autism. Even a superficial consideration of
56
57
58
59
60

1
2
3 the use of these general terms will reveal the complexity and subtlety of their
4
5 application in quantitative observational time trend studies in clinical medicine.
6
7
8
9

10
11 The term “prevalence” alone is used widely to describe a general property possessed by
12
13 an indefinite quantity of a condition e.g., the prevalence of conservative voters is higher
14
15 in rural compared to urban areas. It is also used in public health as a general frequency
16
17 or quantity, e.g., the prevalence of influenza is higher in winter than in the summer .
18
19
20

21
22
23 By contrast, in formal epidemiological research, reliable quantitative estimates of
24
25 incidence and prevalence “rates” require accurate identification of the number of newly
26
27 diagnosed cases in a defined population from which the cases were derived, at a given
28
29 age during a given time period. Valid comparisons of annual rate estimates over many
30
31 years are dependent on the stability of the base population and the ascertainment of the
32
33 condition under study.
34
35
36
37
38
39

40
41 In 1996, the CDC conducted a study based on screening and abstraction of records in
42
43 the 5 counties of Atlanta Georgia.²¹ The prevalence was estimated to be 3.4 per 1000
44
45 among children aged 3 to 10. Surveys in California in 1983-85 and in 1993-95 based on
46
47 birth cohorts²²⁻²³ found that during years 1980-1994 there was a large annual secular
48
49 increase in the number of cases of autism; these increases were estimated as a
50
51 prevalence of 44 per 100,000 live births in the 1980 cohort and 208 in the 1994 cohort²⁴.
52
53
54

55
56 A study from Denmark estimated that the prevalence of autism rose from less than 2
57
58
59
60

1
2
3 per 10,000 prior to 1990 to more than 10 per 10,000 in 2000.²⁵ Taken together these
4
5 reports and others provided clear evidence that there was a substantial increase in the
6
7 number of young children diagnosed as autistic in the US and Europe during the
8
9 decade of the 1990s.
10
11
12

13
14
15
16 We could have estimated cumulative incidence and annual prevalence rates for other
17
18 age ranges, e.g., for 3 or 5 year olds, from within the GPRD dataset, but there are no
19
20 other published studies for comparison. Any comparisons of our results with other
21
22 published studies on autism frequencies do not appear to be valid. There have been
23
24 many studies investigating the prevalence of autism – in various countries across the
25
26 world, assessing different ages, durations, and varying calendar times²⁶. Few studies
27
28 have been able to assess cumulative incidence. Prevalence estimates have varied from
29
30 2.8 to 94 for autistic disorder and 1 to 189 for “pervasive developmental disorders”²⁶.
31
32 Recent studies have tended to show higher prevalence rates.
33
34
35
36
37
38
39
40

41 Cohort effects have been identified²⁷ as well as marked spatial clustering²⁸. Reported
42
43 numbers of cases in some studies have been low and have tended to vary (e.g. 86
44
45 children with autistic spectrum disorder (ASD) at age 11 in the UK Avon study²⁹ and
46
47 158 from a screened population of 56,946 children age 9-10 years in the UK Special
48
49 Need and Autism Project³⁰), with different studies showing widely varying proportions
50
51 of sub-groups of autism. Denominators have sometimes been unclear.
52
53
54
55
56
57
58
59
60

1
2
3 Some studies have based their findings on ASD screening questionnaires, which
4 typically misidentify substantial numbers of children who have other difficulties, but
5 not an ASD³¹. Using strict or less demanding diagnostic criteria, even within a single
6 study where design and methodological factors are invariant, can affect prevalence
7 estimates by up to 4.5 times³². There were some regional variations in rates of recorded
8 autism in the GPRD, possibly reflecting regional variation in diagnostic practice, but
9 rates within areas remained steady overall during the study period. This was a real-life
10 clinically-based study, with no attempt to screen the child population for autism. Such
11 screening may contribute to over-diagnosis³¹.
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28

29 In February 1998 Wakefield et al reported a case series of 12 autistic children with
30 bowel disorders most of whom had recently received the MMR vaccine³³. The authors
31 suggested that the MMR vaccine may have been causally related to these gastro-
32 intestinal conditions. This widely publicised paper led to subsequent studies to
33 evaluate the proposition that the MMR vaccine might be causally related to autism.
34
35
36
37
38
39
40
41
42
43
44

45 In the following year, Taylor et al reported results from a study based on birth cohorts
46 from 1979-1992 in the North East Thames (UK) health region³⁴. They reviewed special
47 needs records and found that fewer than 10 children per year born from 1979 through
48 1986 were diagnosed as autistic. Subsequently, the number increased to almost 50 in
49 children born in 1992. They found no correlation between MMR vaccination and the
50 rise in the prevalence of autism.
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6 Shortly thereafter, the BCDSP examined experience accrued in the GPRD since 1990 to
7
8 estimate annual cumulative incidence rates of autism for birth cohorts from 1988-93 for
9
10 boys age 2-5 years and found that cumulative incidence rates increased some 5 fold
11
12 from an estimate of 6 per 10,000 in boys born in 1988 to 30 per 10,000 in those born in
13
14 1993. At the same time MMR vaccination was given to over 90% of young children
15
16 ruling out an association between the vaccine and the dramatic increase in rates.¹⁴
17
18
19

20
21
22
23
24 Subsequent studies also found no association between MMR and autism.^{14, 24-25, 35-36,}

25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
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

34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
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 cohort¹⁶ (See Figure 1). Children born in 2001 would
have been diagnosed as autistic at age 2-4 in 2003-2005.

54
55
56
57
58
59
60
Taken together the published findings conclusively demonstrated that there was a
dramatic simultaneous rise in the number of children diagnosed as autistic in the US,

1
2
3 UK and Denmark during the 1990s. In addition, there was highly persuasive evidence
4 that MMR vaccine was not the cause of the rise. Despite firm evidence that a steady
5 state occurred in children born from 1996 through 2001 in the UK, vaccine/autism
6 litigation continued in US courts until 2010.
7
8
9
10
11
12

13
14
15
16 The initial autism studies^{5, 14-16, 34-36} were based primarily on birth cohorts usually aged
17 2-5 years. In that design the number of newly diagnosed (incident) cases is determined
18 separately for each annual birth cohort. By contrast, the nature and interpretation of
19 annual prevalence “rates” of autism, as reported in the present and the recent CDC
20 studies, are far more complex and superficially counterintuitive, particularly where the
21 design objective is to estimate changes in yearly time trends or to compare results with
22 other similarly designed studies.
23
24
25
26
27
28
29
30
31
32
33
34
35
36

37 The CDC chose to estimate annual prevalence rates for children of the same age - 8
38 years - in each of successive calendar years. Annual prevalence estimates apply to
39 children who encompass a large age range e.g., 2-8 years and each of the autism cases
40 may be included as prevalent in multiple years. For example, when examining the
41 period 2004 to 2010, a child diagnosed at age 2 years in 2004 would be included in the
42 prevalence estimate for each of the next six years until the child reached age 9 years
43 and no longer is considered a prevalent case. Children diagnosed at age 6 in 2005
44 would be included in the prevalence estimates for only 3 years thereafter. Year of age at
45 first diagnosis, including prior to 2004, is thus a critical variable in estimating the
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 annual prevalence rates at age 8 over many years. The full detail that yielded the
4
5 annual prevalence rates could be reviewed directly for consistency.
6
7
8
9

10
11 The 2012 CDC report² was a follow up to studies of 8 year old children initiated in 2000
12
13 and repeated every two years thereafter. The results were derived from a network of 6-
14
15 11 US states depending on the years, and based on school or medical records or both.
16
17 Early reports estimated annual prevalence rates of 6.7 and 6.6 per 1000 children in 2000
18
19 and 2002. Starting in 2004, prevalence rate estimates rose steadily until 2008 when they
20
21 reached 11.3 per 1000, a rise of 78% from 2004. The latest prevalence rate estimates
22
23 varied widely from state to state - from 4.1/1000 in Alabama to 21.2/1000 in Utah.
24
25 A detailed commentary on the limitations of the CDC report was published shortly
26
27 after it was released.³⁷ This commentary raised important questions related to the
28
29 accuracy and specificity of the combined rate estimates over the years.
30
31
32
33
34
35
36
37
38

39 There are many similarities between the results found in the US and UK in the secular
40
41 epidemiology of autism. Few children were diagnosed as autistic in either country
42
43 prior to 1990. A continuous simultaneous extraordinary rise in the number of children
44
45 diagnosed as autistic began in both countries in the early 1990s and lasted for a decade.
46
47 The distribution of first time diagnosis according to age and gender was the same.
48
49 These similarities between countries as well as within different locations in each
50
51 country point to a common etiology for this extraordinary medical story.
52
53
54
55
56
57
58
59
60

1
2
3 By contrast, there is a large difference in the percentage of children diagnosed as autistic
4
5
6 in the two countries. The estimated prevalence rates of autism in the UK population,
7
8
9 about 4 per 1000 in 8 year old boys in 2008, is far lower than the more than 11 per 1000
10
11 in 8 year old boys reported by the CDC from the US for the same calendar year. This
12
13 large difference between countries is closely similar to differences in rates reported for
14
15 children diagnosed and treated for attention deficit hyperactivity disorder (ADHD) in
16
17 the two countries.^{38, 39}
18
19
20
21
22
23

24 The GPRD is a uniquely constructed resource of clinical medical information that has
25
26 succeeded in providing a reliable continuous standardized accounting of
27
28 demographics, medical diagnoses and prescribed medicines over more than 20 years.
29
30 The substance of its construction and implementation is highly complex. Nowhere is
31
32 this clearer than in the current findings related to the enormously complex secular
33
34 epidemiology of autism.
35
36
37
38
39
40
41

42 In conclusion, the annual prevalence of clinically confirmed autism recorded by UK
43
44 general practitioners remained steady for the 7-year period 2004-10. Whether it has
45
46 increased in the US over these years remains uncertain.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **Acknowledgements** The authors gratefully acknowledge the excellent work of the
4
5
6 general practitioners who have contributed to the GPRD.
7
8
9

10 **Contributors** The GPRD data source was constructed by HJ and DM. The study
11
12 was designed by HJ and BT. The database access was created by DM. Data analysis
13
14 was done by HJ and BT. The manuscript was written by BT and HJ. All the authors
15
16 vouch for the accuracy and completeness of the data and the analyses as presented.
17
18
19 They also vouch for the fidelity of the final report.
20
21
22

23
24
25 **Funding** This research received no specific grant from any funding agency in
26
27 the public, commercial or not-for-profit sectors.
28
29
30

31
32
33 **Competing interests** None
34
35
36

37
38
39 **Ethics** The study protocol was approved by the MHRA's Independent
40
41 Scientific Advisory Committee (ISAC) . All data were anonymised.
42
43
44

45
46 **Provenance and peer review** Not commissioned; externally peer reviewed.
47
48
49

50
51 **Data sharing statement** No additional data available
52
53
54

Figure 1*

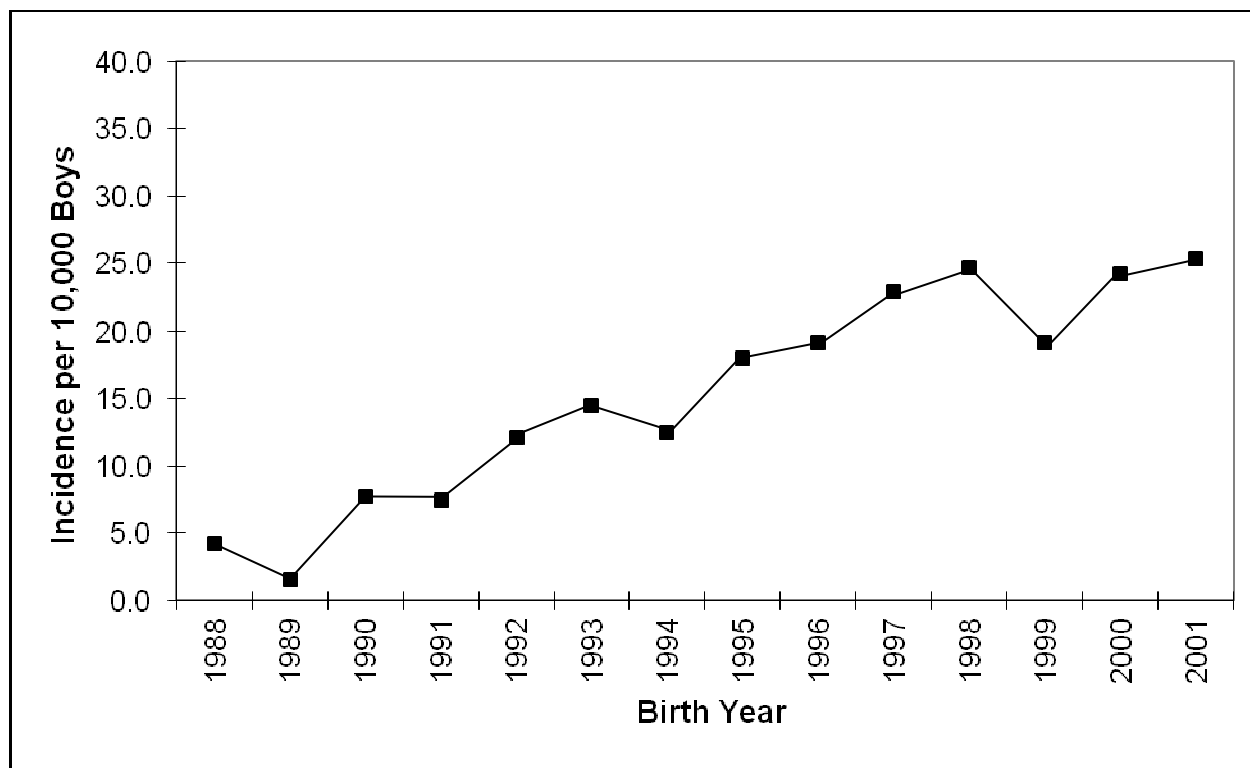


Figure. Three-year cumulative incidence of diagnosed autism among boys age 2-4 years, in birth cohorts.¹⁶

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

Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Lippincott Williams & Wilkins. Please contact journalpermissions@lww.com for further information.

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

References

1. CDC Division of News & Electronic Media □(404) 639-3286
(http://www.cdc.gov/media/releases/2012/p0329_autism_disorder.html)
2. CDC Surveillance Summaries. Prevalence of Autism Spectrum Disorders – Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2008. MMWR 2012; 61:3;1-19.
(http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6103a1.htm?s_cid=ss6103a1)
3. Jick H, Jick S, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. Brit Med J 1991; 302: 766-768.
4. Jick H, Terris BZ, Derby LE, Jick SS. Further validation of information recorded on a general practitioner based computerized data resource in the United Kingdom. Pharmacoepidemiology & Drug Safety 1992;1:347-349.
5. Black C, Kaye JA, Jick H. Relation of childhood gastrointestinal disorders to autism: nested case-control study using data from the UK General Practice Research database. Brit Med J 2002;325:419-21.
6. Derby LE, Jick H, Henry DA, Dean AD. Cholestatic hepatitis associated with flucloxacillin. Med J Australia 1993;158:596-600.
7. Melero Montes MM, Jick H. Hyperemesis gravidarum and the sex of the baby. Epidemiology 2000;12:123-4.
8. Kaye JA, Derby LE, Melero-Montes MM, Quinn M, Jick H. Breast cancer incidence among women aged 35 to 69 in the U.K. B comparison of estimates from the General

- 1
2
3 Practice Research Database with cancer registration data. *Brit J Cancer* 2000;83:1556-
4
5 1558.
6
7
8
9 9. Jick SS, Hagberg KW, Kaye JA, Jick H. Postmenopausal estrogen-containing
10 hormone therapy and the risk of breast cancer. *Obstet Gynecol* 2009;113:74-80.
11
12
13 10. Jick H, Chamberlin DP, Hagberg KW. The origin and spread of a mumps epidemic -
14 United Kingdom, 2003-2006. *Epidemiology* 2009;20:656-61.
15
16
17 11. Jick H, MacLaughlin DS, Egger P, Wiggins P. The United Kingdom 2009 swine flu
18 outbreak in real time. *Epidemiol Res Intl* doi:10.1155/2011/381597.
19
20
21 12. Fombonne E, Heavey L, Smeeth L, et al. Validation of the diagnosis of autism in
22 general practitioner records. *BMC Public Health* 2004;3:4:5.
23
24
25 13. Smeeth L, Cook C, Fombonne E, Heavey L, Rodrigues LC, Smith PG, Hall AJ. MMR
26 vaccination and pervasive developmental disorders: A case-control study. *Lancet*
27 2004; 364: 963-969.
28
29
30 14. Kaye JA, Melero-Montes M, Jick H. Mumps, measles, and rubella vaccine and the
31 incidence of autism recorded by general practitioners: a time trend analysis.
32
33 *Br Med J* 2001;322:460-3.
34
35
36 15. Jick H, Kaye JA, Black C. Changes in the risk of autism in the UK for birth cohorts
37 1990-1998. *Epidemiology* 2003;14:630-632.
38
39
40 16. Hagberg KW, Jick H. Autism in the UK for birth cohorts 1988-2001. *Epidemiology*
41 2010;21:426-427.
42
43
44 17. King M, Bearman P. Diagnostic change and the increased prevalence of autism.
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 18. Fisch GS. Nosology and Epidemiology in Autism: Classification Counts. American
4
5 Journal of Medical Genetics Part C (Seminars in Medical Genetics) 2012; 160C: 91-
6
7 103.
8
9
- 10
11 19. Liu KY, King M, Bearman PS. Social Influence and the Autism Epidemic. American
12
13 Journal of Sociology 2010;115:1387-1434
14
- 15
16 20. Taylor B. Vaccines and the changing epidemiology of autism. Child: care, health
17
18 and development 2006;32:511-519.
19
- 20
21 21. Yergin-Allsop M, Rice C, Karapurkar T, Doernberg N, Boyle C, Murphy C.
22
23 Prevalence of autism in a US metropolitan area. JAMA 2003;289:49-55.
24
- 25
26 22. Department of Developmental Services. Changes in population of persons with
27
28 autism and pervasive developmental disorders in California's Developmental
29
30 Services System: 1987 through 1998: a report to the Legislature March 1, 1999.
31
32 Sacramento: California Health and Human Services Agency; 1999.
33
34
- 35
36 23. Department of Developmental Services. Autism spectrum disorders: changes in the
37
38 California caseload an update: 1999 through 2002. Sacramento, CA: Department of
39
40 Developmental Services, California Health and Human Services Agency; 2003.
41
42
- 43
44 24. Dales L, Hammer SJ, Smith NJ. Time trends in autism and MMR immunisation in
45
46 California. JAMA 2001;285:1183-1185.
47
48
- 49
50 25. Madsen KM, Hviid A, Vestergaard M, Schendel D, Wohlfahrt J, Thorsen P, Olsen J,
51
52 Melbye M. A population-based study of measles, mumps, and rubella vaccination
53
54 and autism. New Eng J Med 2002;347:1477-82.
55
56
- 57
58 26. Elsabbagh M, Divan G, Koh Y-J, Kim YS, Kauchali S, Marcín C, Montiel-Nava C,
59
60

- 1
2
3 Patel V, Paula CS, Wang C, Yasamy MT, Fombonne E. Global prevalence of autism
4 and other pervasive developmental disorders. *Autism Research* 2012; 5: 160-179
5
6
7
8
9 27. Keyes KM, Susser E, Cheslack-Postava K, Fountain C, Liu K, Bearman PS. Cohort
10 effects explain the increase in autism diagnosis among children born from 1992 to
11 2003 in California. *International Journal of Epidemiology* 2012; 41: 495-503
12
13
14
15
16 28. Mazumdar S, King M, Liu K-Y, Zerubavel N, Bearman P. The spatial structure of
17 autism in California, 1993-2001. *Health and Place* 2010; 16: 539-546
18
19
20
21 29. Williams E, Thomas K, Sidebotham H, Emond A. Prevalence and characteristics of
22 autistic spectrum disorders in the ALSPAC cohort. *Developmental Medicine &*
23 *Child Neurology* 2008, 50: 672-677
24
25
26
27
28
29 30. Baird G, Simonoff E, Pickles A, Chandler S, Loucas T, Meldrum D, Charman T.
30 Prevalence of disorders of the autism spectrum in a population cohort of children in
31 South Thames: the Special Needs and Autism Project (SNAP). *Lancet* 2006;368: 210-
32 215
33
34
35
36
37
38
39 31. Lord C. Epidemiology: How common is autism? *Nature* 2011; 474: 166
40
41
42 32. Charman T, Pickles A, Chandler S, Wing L, Bryson S, Simonoff E, Loucas T, Baird G.
43
44 Commentary: Effects of diagnostic thresholds and research vs service and
45 administrative diagnosis on autism prevalence. *International Journal of*
46 *Epidemiology* 2009;38:1234-38
47
48
49
50
51
52 33. Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, Berelowitz M,
53
54 Dhillon AP, Thomson MA, Harvey P, Valentine A, Davies SE, Walker-Smith JA.
55
56 Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive
57
58
59
60

- 1
2
3 developmental disorder in children. *Lancet* 1998;351:637-41.
4
5
6 34. Taylor B, Miller E, Farrington CP, Petropoulos M-C, Favot-Mayaud I, Li J, Waight
7
8 PA. Autism and measles, mumps, and rubella vaccine: no epidemiological evidence
9
10 for a causal association. *Lancet* 1999;353:2026-9.
11
12
13 35. Taylor B, Miller E, Lingam R, Andrews N, Simmons A, Stowe J. Measles, mumps,
14
15 and rubella vaccination and bowel problems or developmental regression in
16
17 children with autism: population study. *British Medical Journal* 2002;324:393-396.
18
19
20
21 36. Lingam R, Simmons A, Andrews N, Miller E, Stowe J, Taylor B. Prevalence of
22
23 autism and parentally reported triggers in a North East London population. *Arch*
24
25 *Dis Child* 2003;88:666-70.
26
27
28
29 37. Carey M. A summary of the CDC autism prevalence report. 2012; 1-8.
30
31 [http://autismsciencefoundation.wordpress.com/2012/03/29/a-summary-of-the-](http://autismsciencefoundation.wordpress.com/2012/03/29/a-summary-of-the-cdc-autism-prevalence-report/)
32
33 [cdc-autism-prevalence-report/](http://autismsciencefoundation.wordpress.com/2012/03/29/a-summary-of-the-cdc-autism-prevalence-report/)
34
35
36
37 38. Jick H, Kaye JA, Black C. Incidence and prevalence of drug-treated attention deficit
38
39 disorder in the UK. *Br J Gen Pract* 2004;54:345-347.
40
41
42 39. Jick H, Wilson A, Wiggins P, Chamberlin DP. Comparison of prescription drug
43
44 costs in the United States and the United Kingdom, Part 3: methylphenidate.
45
46 *Pharmacotherapy*. 2012;32:970-3.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5 **Prevalence and incidence rates of autism in the United Kingdom:**
6
7
8 **time trend from 2004-2010 in children aged 8 years.**
9
10

11
12 Brent Taylor, PhD, FRCPCH¹
13

14 Hershel Jick, MD²
15

16
17 Dean MacLaughlin, PhD²
18
19
20
21

22 ¹ General and Adolescent Paediatric Unit, UCL Institute of Child Health, Guilford
23 Street, London WC1N 1EH, UK. Tel: +44 20 7905 2190. e-mail: brent.taylor@ucl.ac.uk
24
25
26

27 ²Boston Collaborative Drug Surveillance Program, Boston University School of
28 Medicine, 11 Muzzey Street, Lexington, MA 02421. Tel: 781-862-6660,
29
30
31 Fax: 781-862-1680
32
33
34
35
36

37 Corresponding Author: Hershel Jick, MD, Boston Collaborative Drug Surveillance
38 Program, Boston University School of Medicine, 11 Muzzey Street, Lexington, MA
39
40
41 02421. Tel: 781-862-6660,
42
43
44 Fax: 781-862-1680, e-mail: hjick@bu.edu
45
46
47

48 Running head: Autism in the UK 2004-2010
49

50 Key words: Autism, Incidence, Prevalence, UK, 2004-2010.
51

52 Word Count: 2,922 (excluding abstract, summary, references and acknowledgements)
53
54
55
56
57
58
59
60

1
2
3 **Abstract** (257 words)
4
5
6

7 **Background**
8
9

10 Autism was infrequently diagnosed prior to 1990. A dramatic increase in children
11 diagnosed as autistic occurred in the 1990s in the United States (US) and United
12 Kingdom (UK). In March 2012, in a press release widely covered by the media, the
13 Centre for Disease Control (CDC) reported that the autism prevalence rate in 2008 in 8
14 year-old US children was 1 in 88, a 78% increase from a CDC estimate in 2004. The
15 report prompted us to update UK studies begun in the early 1990s on the annual
16 prevalence and incidence rates of autism in children aged 8 from 2004 - 2010, using the
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

General Practice Research Database

32 **Methods**
33
34

35 Annual autism prevalence rates were estimated for children aged 8 in 2004-2010 by
36 dividing the number diagnosed as autistic in each or any prior year by the number of
37 children active in the study population that year. We also calculated annual incidence
38 rates for children aged 2-8, by dividing the number newly diagnosed in 2004 -2010 by
39 the same denominators.
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 demographics, medical diagnoses and prescribed medicines over more than 20
4 years. It is one of the largest sources of primary care data in the world.
5
6

- 7
8
9 • There may have been unidentified cases (false negatives) in the study population
10
11 - individual children with autism who were diagnosed elsewhere and not
12
13 notified to their GP's or others who remained undiagnosed.
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Background

In March 2012, the US Centre for Disease Control (CDC) issued a press release¹ that described the results of a long term study on the annual prevalence rate of autism in 8 year old children². 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 Surveillance 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

1
2
3 information into a unified resource that allowed for rapid access to the full dataset,
4
5 updated annually. Early validation studies found an 87% correlation between the
6
7 diagnoses in consultant's letters and those in the GPRD record.³ The high quality,
8
9 stability and consistency of the recorded information over time has been repeatedly
10
11 demonstrated in more than 150 publications.⁴⁻¹¹
12
13

14
15 Autism is a developmental disorder manifested early in childhood and characterized by
16
17 a spectrum of abnormal social and communication skills and unusual behaviour. The
18
19 condition was infrequently diagnosed prior to 1990. However, an awareness of a
20
21 gradual increase in the frequency of diagnosed autism was anecdotally noted during
22
23 the early 1990s. GPs do not themselves make the diagnosis of autism, referring
24
25 children suspected of having the condition for specialist multidisciplinary assessment,
26
27 which usually takes place over a period of months. Referral letters to GPRD-
28
29 participating GPs from consultants and others are scanned and diagnostic information
30
31 therein coded and recorded in the child's clinical record. The validity of the autism
32
33 diagnosis recorded by GPs was confirmed in the earlier phases of this study by review
34
35 of the extensive specialist referral reports.⁵ The quality and specificity of the diagnosis
36
37 of autism in the GPRD have also been validated by an independent research group
38
39 based on DSM4 criteria;¹²⁻¹³ in 318 cases diagnosed with autism or a related condition
40
41 such as Asperger's syndrome, the researchers, using specialist reports from consultants
42
43 or multidisciplinary teams in the GP record, were able to confirm the diagnosis for 294
44
45 (92.5%).
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Annual prevalence rates were calculated by dividing the number of children aged 8
4 years diagnosed as autistic and recorded in the continuous medical record by the GP at
5
6 any prior time, by the number of 8 year olds active in the database that year. For
7
8
9 example, prevalence rates for 2004 were based on the number of children who were
10
11
12 aged 8 in 2004 and had been diagnosed as autistic during the 8 prior years 1996-2004.
13
14
15 Continuous prevalence rates were similarly estimated for each subsequent calendar
16
17
18 year.
19
20
21
22
23

24 We also calculated annual incidence rates by dividing the annual number of children
25
26 aged 2-8 newly diagnosed with autism in each year (2004 - 2010), by the number of
27
28 children aged 2-8 active in the practices in that year. Practices enrolled in the GPRD
29
30 only after 1996 were excluded from the study.
31
32
33
34
35

36 Results

37
38
39 Table 1 shows the annual number of boys aged 8 years who had been diagnosed as
40
41
42 autistic in each or any prior year i.e., prevalent cases. The annual number of prevalent
43
44 cases (a reflection of the cumulative incidence) is remarkably similar over calendar time,
45
46 as is the number of boys active in the population from 2004 -2010. The resulting annual
47
48 prevalence rate estimates of about 3.8/1000 boys are steady over time. The 95%
49
50 confidence limits widely overlapped in each year.
51
52
53
54
55
56
57
58
59
60

1
2
3 Table 1 also shows the annual number of boys aged 2-8 diagnosed as autistic for the
4 first time (incident) in each year from 2004-2010. The annual number of incident cases
5 is again remarkably similar over time as is the number of boys active in the practices
6 each year, resulting in annual incidence estimates of about 1.2/1000 boys over the
7 years. The total number of boys was 1190.
8
9
10
11
12
13
14
15
16
17
18

19 The number of girls initially diagnosed as autistic from 2004-2010 was 217. Table 2
20 provides the annual prevalence and incidence rate estimates over time for girls. Girls
21 were about one fifth as likely to be diagnosed with autism as boys.
22
23
24
25
26
27
28

29 Discussion

30
31
32 In the present paper we review and update an extraordinary 20-year exploration of the
33 annual rates of autism in young children as recorded in real time and derived from a
34 unique carefully designed medical database in the UK. In a series of formal analyses of
35 the data recorded continuously in the GPRD by some 1000 GPs, we have documented
36 that the cumulative incidence of autism in children born from 1988-1995 began to
37 increase and continued to rise from a low level by more than five fold during these
38 years.¹⁴⁻¹⁶ The present study demonstrates that the annual incidence then leveled off
39 and reached a steady state in children born from 1996-2001.
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54

55 In order to compare the UK experience with that reported by the CDC, we restricted
56
57
58
59
60

1
2
3 our current prevalence study to annual calendar years 2004-2010 in children 8 years of
4
5 age. These children would have all been born after 1995. Combined, the results in this
6
7 20-year population-based UK resource, provide compelling evidence that a major rise in
8
9 incidence rates of autism, recorded in general practice, occurred in the decade of the
10
11 1990s but reached a plateau shortly after 2000 and has remained steady through 2010.
12
13 This incidence plateau was necessarily accompanied by steady prevalence rates for 8
14
15 year old children.
16
17
18
19
20
21
22
23

24 It is possible that at least a part of the early rise was related to changing and broadening
25
26 diagnostic criteria to include a spectrum of disorders,¹⁷⁻¹⁸ as well as social influences¹⁹,
27
28 including increased general medical and public awareness.²⁰ However, it seems
29
30 unlikely that these factors materially explain the extraordinary increase in the number
31
32 of children diagnosed in the 1990s; nor the steady state that followed thereafter in 2004
33
34 through 2010. While the MMR vaccine was surely not the cause of the dramatic rise in
35
36 the 1990s, the actual cause remains in large part a mystery. The current study provides
37
38 compelling evidence that incidence rates, as recorded in general practice, have
39
40 remained steady in children born since the late 1990's in the UK. (omit as duplication)
41
42
43
44
45
46
47
48

49 For many years the terms incidence and prevalence were applied in medicine primarily
50
51 to describe acute outbreaks of infectious diseases such as influenza, measles and
52
53 mumps. Since the mid 1950s, these terms have also been applied to chronic diseases
54
55 such as diabetes, cancer and more recently autism. Even a superficial consideration of
56
57
58
59
60

1
2
3 the use of these general terms will reveal the complexity and subtlety of their
4
5 application in quantitative observational time trend studies in clinical medicine.
6
7
8
9

10
11 The term “prevalence” alone is used widely to describe a general property possessed by
12
13 an indefinite quantity of a condition e.g., the prevalence of conservative voters is higher
14
15 in rural compared to urban areas. It is also used in public health as a general frequency
16
17 or quantity, e.g., the prevalence of influenza is higher in winter than in the summer .
18
19
20

21
22
23 By contrast, in formal epidemiological research, reliable quantitative estimates of
24
25 incidence and prevalence “rates” require accurate identification of the number of newly
26
27 diagnosed cases in a defined population from which the cases were derived, at a given
28
29 age during a given time period. Valid comparisons of annual rate estimates over many
30
31 years are dependent on the stability of the base population and the ascertainment of the
32
33 condition under study.
34
35
36
37
38
39

40
41 In 1996, the CDC conducted a study based on screening and abstraction of records in
42
43 the 5 counties of Atlanta Georgia.²¹ The prevalence was estimated to be 3.4 per 1000
44
45 among children aged 3 to 10. Surveys in California in 1983-85 and in 1993-95 based on
46
47 birth cohorts²²⁻²³ found that during years 1980-1994 there was a large annual secular
48
49 increase in the number of cases of autism; these increases were estimated as a
50
51 prevalence of 44 per 100,000 live births in the 1980 cohort and 208 in the 1994 cohort²⁴.
52
53
54

55
56 A study from Denmark estimated that the prevalence of autism rose from less than 2
57
58
59
60

1
2
3 per 10,000 prior to 1990 to more than 10 per 10,000 in 2000.²⁵ Taken together these
4
5 reports and others provided clear evidence that there was a substantial increase in the
6
7 number of young children diagnosed as autistic in the US and Europe during the
8
9 decade of the 1990s.
10
11
12

13
14
15 We could have estimated cumulative incidence and annual prevalence rates for other
16
17 age ranges, e.g., for 3 or 5 year olds, from within the GPRD dataset, but there are no
18
19 other published studies for comparison. Any comparisons of our results with other
20
21 published studies on autism frequencies do not appear to be valid. There have been
22
23 many studies investigating the prevalence of autism – in various countries across the
24
25 world, assessing different ages, durations, and varying calendar times²⁶. Few studies
26
27 have been able to assess cumulative incidence. Prevalence estimates have varied from
28
29 2.8 to 94 for autistic disorder and 1 to 189 for “pervasive developmental disorders”²⁶.
30
31 Recent studies have tended to show higher prevalence rates.
32
33
34
35
36
37
38
39

40
41 Cohort effects have been identified²⁷ as well as marked spatial clustering²⁸. Reported
42
43 numbers of cases in some studies have been low and have tended to vary (e.g. 86
44
45 children with autistic spectrum disorder (ASD) at age 11 in the UK Avon study²⁹ and
46
47 158 from a screened population of 56,946 children age 9-10 years in the UK Special
48
49 Need and Autism Project³⁰), with different studies showing widely varying proportions
50
51 of sub-groups of autism. Denominators have sometimes been unclear.
52
53
54
55
56
57
58
59
60

1
2
3 Some studies have based their findings on ASD screening questionnaires, which
4
5 typically misidentify substantial numbers of children who have other difficulties, but
6
7 not an ASD³¹. Using strict or less demanding diagnostic criteria, even within a single
8
9 study where design and methodological factors are invariant, can affect prevalence
10
11 estimates by up to 4.5 times³². There were some regional variations in rates of recorded
12
13 autism in the GPRD, possibly reflecting regional variation in diagnostic practice, but
14
15 rates within areas remained steady overall during the study period. This was a real-life
16
17 clinically-based study, with no attempt to screen the child population for autism. Such
18
19 screening may contribute to over-diagnosis³¹.
20
21
22
23
24
25
26
27
28

29 In February 1998 Wakefield et al reported a case series of 12 autistic children with
30
31 bowel disorders most of whom had recently received the MMR vaccine³³. The authors
32
33 suggested that the MMR vaccine may have been causally related to these gastro-
34
35 intestinal conditions. This widely publicised paper led to subsequent studies to
36
37 evaluate the proposition that the MMR vaccine might be causally related to autism.
38
39
40
41
42
43
44

45 In the following year, Taylor et al reported results from a study based on birth cohorts
46
47 from 1979-1992 in the North East Thames (UK) health region³⁴. They reviewed special
48
49 needs records and found that fewer than 10 children per year born from 1979 through
50
51 1986 were diagnosed as autistic. Subsequently, the number increased to almost 50 in
52
53 children born in 1992. They found no correlation between MMR vaccination and the
54
55 rise in the prevalence of autism.
56
57
58
59
60

1
2
3
4
5
6 Shortly thereafter, the BCDSPP examined experience accrued in the GPRD since 1990 to
7
8 estimate annual cumulative incidence rates of autism for birth cohorts from 1988-93 for
9
10 boys age 2-5 years and found that cumulative incidence rates increased some 5 fold
11
12 from an estimate of 6 per 10,000 in boys born in 1988 to 30 per 10,000 in those born in
13
14 1993. At the same time MMR vaccination was given to over 90% of young children
15
16 ruling out an association between the vaccine and the dramatic increase in rates.¹⁴
17
18
19

20
21
22
23
24 Subsequent studies also found no association between MMR and autism.^{14, 24-25, 35-36,}

25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
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

34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
The BCDSPP 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 cohort¹⁶ (See Figure 1). Children born in 2001 would
have been diagnosed as autistic at age 2-4 in 2003-2005.

54
55
56
57
58
59
60
Taken together the published findings conclusively demonstrated that there was a
dramatic simultaneous rise in the number of children diagnosed as autistic in the US,

1
2
3 UK and Denmark during the 1990s. In addition, there was highly persuasive evidence
4 that MMR vaccine was not the cause of the rise. Despite firm evidence that a steady
5 state occurred in children born from 1996 through 2001 in the UK, vaccine/autism
6 litigation continued in US courts until 2010.
7
8
9
10
11

12
13
14
15
16 The initial autism studies^{5, 14-16, 34-36} were based primarily on birth cohorts usually aged
17 2-5 years. In that design the number of newly diagnosed (incident) cases is determined
18 separately for each annual birth cohort. By contrast, the nature and interpretation of
19 annual prevalence “rates” of autism, as reported in the present and the recent CDC
20 studies, are far more complex and superficially counterintuitive, particularly where the
21 design objective is to estimate changes in yearly time trends or to compare results with
22 other similarly designed studies.
23
24
25
26
27
28
29
30
31
32
33
34
35
36

37 The CDC chose to estimate annual prevalence rates for children of the same age - 8
38 years - in each of successive calendar years. Annual prevalence estimates apply to
39 children who encompass a large age range e.g., 2-8 years and each of the autism cases
40 may be included as prevalent in multiple years. For example, when examining the
41 period 2004 to 2010, a child diagnosed at age 2 years in 2004 would be included in the
42 prevalence estimate for each of the next six years until the child reached age 9 years
43 and no longer is considered a prevalent case. Children diagnosed at age 6 in 2005
44 would be included in the prevalence estimates for only 3 years thereafter. Year of age at
45 first diagnosis, including prior to 2004, is thus a critical variable in estimating the
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 annual prevalence rates at age 8 over many years. The full detail that yielded the
4
5 annual prevalence rates could be reviewed directly for consistency.
6
7
8
9

10
11 The 2012 CDC report² was a follow up to studies of 8 year old children initiated in 2000
12
13 and repeated every two years thereafter. The results were derived from a network of 6-
14
15 11 US states depending on the years, and based on school or medical records or both.
16
17 Early reports estimated annual prevalence rates of 6.7 and 6.6 per 1000 children in 2000
18
19 and 2002. Starting in 2004, prevalence rate estimates rose steadily until 2008 when they
20
21 reached 11.3 per 1000, a rise of 78% from 2004. The latest prevalence rate estimates
22
23 varied widely from state to state - from 4.1/1000 in Alabama to 21.2/1000 in Utah.
24
25 A detailed commentary on the limitations of the CDC report was published shortly
26
27 after it was released.³⁷ This commentary raised important questions related to the
28
29 accuracy and specificity of the combined rate estimates over the years.
30
31
32
33
34
35
36
37
38

39 There are many similarities between the results found in the US and UK in the secular
40
41 epidemiology of autism. Few children were diagnosed as autistic in either country
42
43 prior to 1990. A continuous simultaneous extraordinary rise in the number of children
44
45 diagnosed as autistic began in both countries in the early 1990s and lasted for a decade.
46
47 The distribution of first time diagnosis according to age and gender was the same.
48
49 These similarities between countries as well as within different locations in each
50
51 country point to a common etiology for this extraordinary medical story.
52
53
54
55
56
57
58
59
60

1
2
3 By contrast, there is a large difference in the percentage of children diagnosed as autistic
4
5
6 in the two countries. The estimated prevalence rates of autism in the UK population,
7
8
9 about 4 per 1000 in 8 year old boys in 2008, is far lower than the more than 11 per 1000
10
11 in 8 year old boys reported by the CDC from the US for the same calendar year. This
12
13 large difference between countries is closely similar to differences in rates reported for
14
15 children diagnosed and treated for attention deficit hyperactivity disorder (ADHD) in
16
17 the two countries.^{38, 39}
18
19
20
21
22
23

24 The GPRD is a uniquely constructed resource of clinical medical information that has
25
26 succeeded in providing a reliable continuous standardized accounting of
27
28 demographics, medical diagnoses and prescribed medicines over more than 20 years.
29
30 The substance of its construction and implementation is highly complex. Nowhere is
31
32 this clearer than in the current findings related to the enormously complex secular
33
34 epidemiology of autism.
35
36
37
38
39
40
41

42 In conclusion, the annual prevalence of clinically confirmed autism recorded by UK
43
44 general practitioners remained steady for the 7-year period 2004-10. Whether it has
45
46 increased in the US over these years remains uncertain.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **Acknowledgements** The authors gratefully acknowledge the excellent work of the
4
5
6 general practitioners who have contributed to the GPRD.
7
8
9

10 **Contributors** The GPRD data source was constructed by HJ and DM. The study
11
12 was designed by HJ and BT. The database access was created by DM. Data analysis
13
14 was done by HJ and BT. The manuscript was written by BT and HJ. All the authors
15
16 vouch for the accuracy and completeness of the data and the analyses as presented.
17
18
19 They also vouch for the fidelity of the final report.
20
21
22
23
24
25

26 **Funding** This research received no specific grant from any funding agency in
27
28 the public, commercial or not-for-profit sectors.
29
30
31
32
33

34 **Competing interests** None
35
36
37
38

39 **Ethics** The study protocol was approved by the MHRA's Independent
40
41 Scientific Advisory Committee (ISAC) . All data were anonymised.
42
43
44
45

46 **Provenance and peer review** Not commissioned; externally peer reviewed.
47
48
49
50

51 **Data sharing statement** No additional data available
52
53
54
55
56
57
58
59
60

Figure 1*

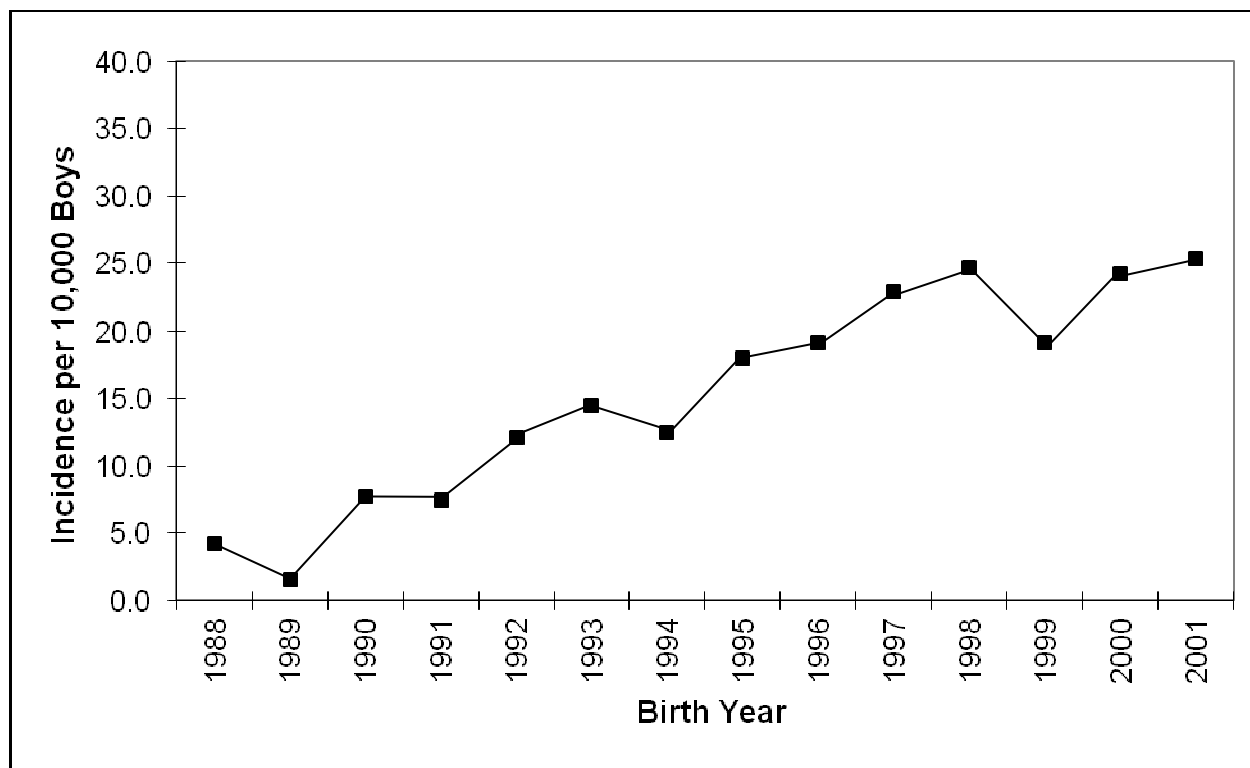


Figure. Three-year cumulative incidence of diagnosed autism among boys age 2-4 years, in birth cohorts.¹⁶

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

Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Lippincott Williams & Wilkins. Please contact journalpermissions@lww.com for further information.

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

References

1. CDC Division of News & Electronic Media □(404) 639-3286
(http://www.cdc.gov/media/releases/2012/p0329_autism_disorder.html)
2. CDC Surveillance Summaries. Prevalence of Autism Spectrum Disorders – Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2008. MMWR 2012; 61:3;1-19.
(http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6103a1.htm?s_cid=ss6103a1)
3. Jick H, Jick S, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. Brit Med J 1991; 302: 766-768.
4. Jick H, Terris BZ, Derby LE, Jick SS. Further validation of information recorded on a general practitioner based computerized data resource in the United Kingdom. Pharmacoepidemiology & Drug Safety 1992;1:347-349.
5. Black C, Kaye JA, Jick H. Relation of childhood gastrointestinal disorders to autism: nested case-control study using data from the UK General Practice Research database. Brit Med J 2002;325:419-21.
6. Derby LE, Jick H, Henry DA, Dean AD. Cholestatic hepatitis associated with flucloxacillin. Med J Australia 1993;158:596-600.
7. Melero Montes MM, Jick H. Hyperemesis gravidarum and the sex of the baby. Epidemiology 2000;12:123-4.
8. Kaye JA, Derby LE, Melero-Montes MM, Quinn M, Jick H. Breast cancer incidence among women aged 35 to 69 in the U.K. B comparison of estimates from the General

- 1
2
3 Practice Research Database with cancer registration data. *Brit J Cancer* 2000;83:1556-
4
5
6 1558.
7
8
9 9. Jick SS, Hagberg KW, Kaye JA, Jick H. Postmenopausal estrogen-containing
10
11 hormone therapy and the risk of breast cancer. *Obstet Gynecol* 2009;113:74-80.
12
13
14 10. Jick H, Chamberlin DP, Hagberg KW. The origin and spread of a mumps epidemic -
15
16 United Kingdom, 2003-2006. *Epidemiology* 2009;20:656-61.
17
18
19 11. Jick H, MacLaughlin DS, Egger P, Wiggins P. The United Kingdom 2009 swine flu
20
21 outbreak in real time. *Epidemiol Res Intl* doi:10.1155/2011/381597.
22
23
24 12. Fombonne E, Heavey L, Smeeth L, et al. Validation of the diagnosis of autism in
25
26 general practitioner records. *BMC Public Health* 2004;3:4:5.
27
28
29 13. Smeeth L, Cook C, Fombonne E, Heavey L, Rodrigues LC, Smith PG, Hall AJ. MMR
30
31 vaccination and pervasive developmental disorders: A case-control study. *Lancet*
32
33 2004; 364: 963-969.
34
35
36 14. Kaye JA, Melero-Montes M, Jick H. Mumps, measles, and rubella vaccine and the
37
38 incidence of autism recorded by general practitioners: a time trend analysis.
39
40 *Br Med J* 2001;322:460-3.
41
42
43 15. Jick H, Kaye JA, Black C. Changes in the risk of autism in the UK for birth cohorts
44
45 1990-1998. *Epidemiology* 2003;14:630-632.
46
47
48 16. Hagberg KW, Jick H. Autism in the UK for birth cohorts 1988-2001. *Epidemiology*
49
50 2010;21:426-427.
51
52
53 17. King M, Bearman P. Diagnostic change and the increased prevalence of autism.
54
55 *International Journal of Epidemiology* 2009;38:1224-1234.
56
57
58
59
60

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
18. Fisch GS. Nosology and Epidemiology in Autism: Classification Counts. *American Journal of Medical Genetics Part C (Seminars in Medical Genetics)* 2012; 160C: 91-103.
 19. Liu KY, King M, Bearman PS. *Social Influence and the Autism Epidemic. American Journal of Sociology* 2010;115:1387-1434
 20. Taylor B. Vaccines and the changing epidemiology of autism. *Child: care, health and development* 2006;32:511-519.
 21. Yergin-Allsop M, Rice C, Karapurkar T, Doernberg N, Boyle C, Murphy C. Prevalence of autism in a US metropolitan area. *JAMA* 2003;289:49-55.
 22. Department of Developmental Services. Changes in population of persons with autism and pervasive developmental disorders in California's Developmental Services System: 1987 through 1998: a report to the Legislature March 1, 1999. Sacramento: California Health and Human Services Agency; 1999.
 23. Department of Developmental Services. Autism spectrum disorders: changes in the California caseload an update: 1999 through 2002. Sacramento, CA: Department of Developmental Services, California Health and Human Services Agency; 2003.
 24. Dales L, Hammer SJ, Smith NJ. Time trends in autism and MMR immunisation in California. *JAMA* 2001;285:1183-1185.
 25. Madsen KM, Hviid A, Vestergaard M, Schendel D, Wohlfahrt J, Thorsen P, Olsen J, Melbye M. A population-based study of measles, mumps, and rubella vaccination and autism. *New Eng J Med* 2002;347:1477-82.
 26. Elsabbagh M, Divan G, Koh Y-J, Kim YS, Kauchali S, Marcín C, Montiel-Nava C,

- 1
2
3 Patel V, Paula CS, Wang C, Yasamy MT, Fombonne E. Global prevalence of autism
4 and other pervasive developmental disorders. *Autism Research* 2012; 5: 160-179
5
6
7
8
9 27. Keyes KM, Susser E, Cheslack-Postava K, Fountain C, Liu K, Bearman PS. Cohort
10 effects explain the increase in autism diagnosis among children born from 1992 to
11 2003 in California. *International Journal of Epidemiology* 2012; 41: 495-503
12
13
14
15
16 28. Mazumdar S, King M, Liu K-Y, Zerubavel N, Bearman P. The spatial structure of
17 autism in California, 1993-2001. *Health and Place* 2010; 16: 539-546
18
19
20
21
22 29. Williams E, Thomas K, Sidebotham H, Emond A. Prevalence and characteristics of
23 autistic spectrum disorders in the ALSPAC cohort. *Developmental Medicine &*
24 *Child Neurology* 2008, 50: 672-677
25
26
27
28
29 30. Baird G, Simonoff E, Pickles A, Chandler S, Loucas T, Meldrum D, Charman T.
30 Prevalence of disorders of the autism spectrum in a population cohort of children in
31 South Thames: the Special Needs and Autism Project (SNAP). *Lancet* 2006;368: 210-
32 215
33
34
35
36
37
38
39 31. Lord C. Epidemiology: How common is autism? *Nature* 2011; 474: 166
40
41
42 32. Charman T, Pickles A, Chandler S, Wing L, Bryson S, Simonoff E, Loucas T, Baird G.
43
44 Commentary: Effects of diagnostic thresholds and research vs service and
45 administrative diagnosis on autism prevalence. *International Journal of*
46 *Epidemiology* 2009;38:1234-38
47
48
49
50
51
52 33. Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, Berelowitz M,
53
54 Dhillon AP, Thomson MA, Harvey P, Valentine A, Davies SE, Walker-Smith JA.
55
56 Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive
57
58
59
60

- 1
2
3 developmental disorder in children. *Lancet* 1998;351:637-41.
4
5
6 34. Taylor B, Miller E, Farrington CP, Petropoulos M-C, Favot-Mayaud I, Li J, Waight
7
8 PA. Autism and measles, mumps, and rubella vaccine: no epidemiological evidence
9
10 for a causal association. *Lancet* 1999;353:2026-9.
11
12
13 35. Taylor B, Miller E, Lingam R, Andrews N, Simmons A, Stowe J. Measles, mumps,
14
15 and rubella vaccination and bowel problems or developmental regression in
16
17 children with autism: population study. *British Medical Journal* 2002;324:393-396.
18
19
20
21 36. Lingam R, Simmons A, Andrews N, Miller E, Stowe J, Taylor B. Prevalence of
22
23 autism and parentally reported triggers in a North East London population. *Arch*
24
25 *Dis Child* 2003;88:666-70.
26
27
28
29 37. Carey M. A summary of the CDC autism prevalence report. 2012; 1-8.
30
31 [http://autismsciencefoundation.wordpress.com/2012/03/29/a-summary-of-the-](http://autismsciencefoundation.wordpress.com/2012/03/29/a-summary-of-the-cdc-autism-prevalence-report/)
32
33 [cdc-autism-prevalence-report/](http://autismsciencefoundation.wordpress.com/2012/03/29/a-summary-of-the-cdc-autism-prevalence-report/)
34
35
36
37 38. Jick H, Kaye JA, Black C. Incidence and prevalence of drug-treated attention deficit
38
39 disorder in the UK. *Br J Gen Pract* 2004;54:345-347.
40
41
42 39. Jick H, Wilson A, Wiggins P, Chamberlin DP. Comparison of prescription drug
43
44 costs in the United States and the United Kingdom, Part 3: methylphenidate.
45
46 *Pharmacotherapy*. 2012;32:970-3.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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>.

Please wait...

If this message is not eventually replaced by the proper contents of the document, your PDF viewer may not be able to display this type of document.

You can upgrade to the latest version of Adobe Reader for Windows®, Mac, or Linux® by visiting <http://www.adobe.com/products/acrobat/readstep2.html>.

For more assistance with Adobe Reader visit <http://www.adobe.com/support/products/acrreader.html>.

Windows is either a registered trademark or a trademark of Microsoft Corporation in the United States and/or other countries. Mac is a trademark of Apple Inc., registered in the United States and other countries. Linux is the registered trademark of Linus Torvalds in the U.S. and other countries.

Please wait...

If this message is not eventually replaced by the proper contents of the document, your PDF viewer may not be able to display this type of document.

You can upgrade to the latest version of Adobe Reader for Windows®, Mac, or Linux® by visiting http://www.adobe.com/go/reader_download.

For more assistance with Adobe Reader visit <http://www.adobe.com/go/acrreader>.

Windows is either a registered trademark or a trademark of Microsoft Corporation in the United States and/or other countries. Mac is a trademark of Apple Inc., registered in the United States and other countries. Linux is the registered trademark of Linus Torvalds in the U.S. and other countries.

To view the full contents of this document, you need a later version of the PDF viewer. You can upgrade to the latest version of Adobe Reader from www.adobe.com/products/acrobat/readstep2.html

For further support, go to www.adobe.com/support/products/acrreader.html