PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence and incidence rates of autism in the United Kingdom: time trend from 2004-2010 in children aged 8 years
AUTHORS	Jick, Hershel; Taylor, Brent; MacLaughlin, Dean

VERSION 1 - REVIEW

REVIEWER	Alan Emond Professor of Community Child Health University of Bristol I have no competing interests
REVIEW RETURNED	04-Jun-2013

THE STUDY	The debate continues over whether the incidence of autistic spectrum disorders (ASD) is increasing, or whether the perceived rise in prevalent cases reflects increased recognition- so this paper makes a useful contribution. However there are several ways it could be improved. 1 Firstly the issue of semantics should be addressed in the introduction. Autism is a spectrum condition made up of a group of developmental disabilities characterized by impairments in social interaction and communication and by restricted, repetitive, and stereotyped patterns of behaviour. The authors should explain that they are using 'autism' and autistic' to include the spectrum of the condition (ASD or ASC), not as a specific ICD10 or DSMIV diagnostic category. 2. The GP research data base is maintained by practicing GPs, but they do not make the diagnosis of autism (p14). In the UK, national guideance is clear that the diagnosis in children and young people should be made by specialist multidisciplinary teams- so the GPs have assigned diagnoses made by others in the health service. More detail is required over what diagnostic categories were coded as 'autism' by the participating GPs- or was it simply any mention of the diagnosis in a letter from a consultant? Other studies (eg Williams 2008, Pettygrove 2012) have shown that over a third of cases at school age are identified by education services, not health services- this should be recognised. The authors boldy state 'This was a population study, fully representative of the UK' but no critical reflection of this is provided, as far as ASD is concerned
RESULTS & CONCLUSIONS	3. There is no recognition of the impact of the national guidance introduced in the UK for the diagnosis of autistic spectrum disorders- eg national autism plan for children, NICE guidelines, guidelines from National Collaborative Centre for Womens and Children's health, and no discussion over whether changes in service configuration has impacted on diagnosis rates in the 2000s compared to the 1990s

	4. The discussion is very long and has a large section on the MMR story, which is of limited relevence to the diagnosis of ASD in 2004-2008. The discussion should refer to other population-based UK studies of prevalence- eg SNAP study (Baird 2006), ALSPAC (Williams 2008) or Millennium cohort (Russell 2012)- and attempt to explain why the calculated prevalence from GPRD is so different

REVIEWER	Katherine M. Keyes Assistant Professor of Epidemiology Columbia University, USA
REVIEW RETURNED	08-Jun-2013

THE STUDY	I have concerns about the design of the study and the analysis, detailed in my review.
RESULTS & CONCLUSIONS	The authors focus on only one study from the USA, and I have concerns about the methods used for the paper and the conclusions that can be drawn from it.
GENERAL COMMENTS	The present study estimates the incidence and prevalence of autism diagnoses using an electronic medical database of GPs in the UK. They find no evidence of increasing diagnosis. I have several overall concerns regarding the design and approach: 1. To what extent are GPs capturing cases of autism? The authors note that diagnoses were made by specialists and that the quality of the GP records is good, but only to the extent that the GP is aware of the diagnosis. For cases on the high functioning end of the spectrum, the GP may not be involved in diagnosis or treatment. Authors should address this possibility. 2. The authors chose to estimate prevalence at age 8, because a publication from the USA used a similar method. If the authors have information on autism diagnoses across the full range of development, why not maximize the information available and use all available information? 3. Further, many other studies in a diverse array of countries worldwide have shown increasing rates of autism diagnosis, yet the authors focus on a single publication from the CDC. Authors should expand the literature review and note that autism diagnostic rates are increasing in many countries worldwide. 4. The description of the analysis was confusing. Specifically, authors say that they estimated “annual prevalence rates” among 8 year olds – does this mean that any diagnosis in the history of the child was recorded as a prevalent case? Please clarify. 5. A more sophisticated analytic technique may allow for a greater understanding of autism diagnoses in this sample. A number of studies have demonstrated strong birth cohort effects on autism diagnoses. Authors are encouraged to construct birth cohorts from their data and display the annual incidence of diagnosis at each age (age 2, 3, 4, etc.) for each birth cohort 6. The figure is unnecessary. Authors can summarize in the text what this previous study found. 7. Authors note that confidence intervals for incidence and prevalence overlap but no confidence intervals are given in the tables. 8. In the discussion, authors state that prevalence rates ‘require accurate identification of newly diagnosed cases’ – this is not true. Prevalence is the proportion of existing cases (not new cases) at a given point in time or over a certain time period. 9. The authors use the New York Post as an academic reference for

	the “false epidemic of autism” – this is unacceptable. Please remove all references to a “false epidemic of autism”. Authors could describe the potential explanations for the increase in autism diagnoses in a scholarly manner, noting that at this time, it is unclear to what extent the increase is due to potential increased ascertainment and awareness, diagnostic shift and drift towards less severe cases, or a change in the distribution of risk factors (e.g., increasing average paternal age). Authors should also remove the direct quotes from and reference to an article in Scientific American. Please include only scholarly publications that have been peer-reviewed as references.

VERSION 1 – AUTHOR RESPONSE

1. Firstly the issue of semantics should be addressed in the introduction. Autism is a spectrum condition made up of a group of developmental disabilities characterized by impairments in social interaction and communication and by restricted, repetitive, and stereotyped patterns of behaviour. The authors should explain that they are using ‘autism’ and autistic’ to include the spectrum of the condition (ASD or ASC), not as a specific ICD10 or DSMIV diagnostic category.
Authors’ response: Regarding the semantics of autism: The cases referred to in the text reflected the entry by each GP of an Oxmis code in the 1990s and/or a Read code begun in 1998. Oxmis codes were mapped to Read codes after Read codes were introduced. There were more than twenty codes that included the term autism. However more than 90% of the estimated 15,000 children were recorded using 1 or more of 3 codes from 1990-2010. Asperger’s syndrome was recorded in more than 6400 children. Review of case records in diagnosed children, showed more than 90% had multiple visits with continuing follow-up often with consultants across multiple disciplines.
2. The GP research data base is maintained by practicing GPs, but they do not make the diagnosis of autism (p14). In the UK, national guidance is clear that the diagnosis in children and young people should be made by specialist multidisciplinary teams- so the GPs have assigned diagnoses made by others in the health service. More detail is required over what diagnostic categories were coded as ‘autism’ by the participating GPs- or was it simply any mention of the diagnosis in a letter from a consultant? Other studies (e.g. Williams 2008, Pettygrove 2012) have shown that over a third of cases at school age are identified by education services, not health services - this should be recognized.
The authors boldly state ‘This was a population study, fully representative of the UK’ but no critical reflection of this is provided, as far as ASD is concerned.
Authors’ response: The formal criteria for the clinical diagnosis of autism have changed over the years in the UK and US and continue to be widely debated. The cases we have included in this study are restricted to those diagnosed by some 1000 GPs who have regularly continued in the same practice in the same 350 practices initially enrolled in the database prior to 1997. Children diagnosed as autistic who did not come to the attention of their GP would not have been identified. As far as we can tell, all the cases we included were referred to and diagnosed by a specialist(s). The diagnosis was routinely recorded by the GP from the consultants’ letters. However, it is important to note that since 2004 the incidence and prevalence have been remarkably stable in this population indicating that whatever the criteria for diagnosis of autism it has remained little changed over this period of time. We have addressed this issue in the text.
3. There is no recognition of the impact of the national guidance introduced in the U.K. for the diagnosis of autistic spectrum disorders - e.g. national autism plan for children, NICE guidelines, guidelines from National Collaborative Centre for Women’s and Children’s Health, and no discussion over whether changes in service configuration has impacted on diagnosis rates in the 2000s compared to the 1990s
Authors’ response: The clear evidence indicates that the incidence and therefore the prevalence of autism became steady with the birth cohorts of 1996-98 and continued steady in later birth cohorts.

This indicates that the guidelines had little influence on the rate of autism as diagnosed in general practice. The influence of this possibility on the overall rates of diagnosis that were made separately without the knowledge of the GPs, is purely speculative and beyond the scope of this study.
4. The discussion is very long and has a large section on the MMR story, which is of limited relevance to the diagnosis of ASD in 2004-2008. The discussion should refer to other population-based U.K. studies of prevalence - e.g. SNAP study (Baird 2006), ALSPAC (Williams 2008) or Millennium cohort (Russell 2012) - and attempt to explain why the calculated prevalence from GPRD is so different.
Authors' response: The MMR issue is an important background to the current study because it again reinforces the notion that the source of this 20 year longitudinal data base has from the start yielded firmly accurate and complete clinical information entirely consistent with other reported results and documented in dozens of prior publications. (The GPs who initially participated were trained for a year on all aspects data entry matters according to a detailed written protocol). The results of other published studies, excepting the CDC study, are not comparable to the current one. They cover different ages, duration, geographic area and calendar time periods. Estimates of incidence and prevalence over time vary a great deal depending on the stability and characteristics of the study population over time as described in detail in the discussion. In particular, the age reference is crucial for estimating prevalence rates over many calendar years and for valid and proper comparison with other studies. Such rates differ from age to age. Prevalence rates for each age from 2-8 year olds are different because they are highly correlated with incidence rates that change with age. The CDC chose to estimate the prevalence rates in 8 year olds in each year from 2004-8 and concluded they had substantially increased. Logically we chose to use the same age group over these years for direct comparison. The time trend goals of both studies are unprecedented since the scope and specificity of the data sources over time has not been previously available. An informed judgment on the reliability and wide capability of the UK databases used in this study may be evaluated and judged by review of references 4-11 and other references found in these publications. We thought it necessary to go into the considerable detail of the analysis particularly prevalence rates. We, as authors ourselves, had to review the internal elements and evolution of the final results at considerable length to appreciate their extraordinary symmetry and specificity. The definition and application of the term "prevalence rates" in the text is correct.
Reviewer: Katherine M. Keyes
Assistant Professor of Epidemiology
Columbia University, USA

I have concerns about the design of the study and the analysis, detailed in my review. The authors focus on only one study from the USA, and I have concerns about the methods used for the paper and the conclusions that can be drawn from it.
Authors' response: The present study is the latest of a sequence of related studies undertaken over many years. The trigger was the recent CDC report from the US, itself one of a sequence and representative of similar studies in the US and the UK.
The present study estimates the incidence and prevalence of autism diagnoses using an electronic medical database of GPs in the UK. They find no evidence of increasing diagnosis. I have several overall concerns regarding the design and approach:
1. To what extent are GPs capturing cases of autism? The authors note that diagnoses were made by specialists and that the quality of the GP records is good, but only to the extent that the GP is aware of the diagnosis. For cases on the high functioning end of the spectrum, the GP may not be involved in diagnosis or treatment. Authors should address this possibility.
The definition of incidence and prevalence rates are well established in epidemiology. The conclusions are strictly based on these definitions together with the results as clearly presented in the tables. The methodology of GPRD analyses has been reported in depth in many previous papers, as has the validity of the diagnosis of autism in the GPRD (see references).
2. The authors chose to estimate prevalence at age 8, because a publication from the USA used a similar method. If the authors have information on autism diagnoses across the full range of

development, why not maximize the information available and use all available information?

Authors' response: The prevalence rates presented are based on all of the recorded information for 20 years. Prevalence rates differ within each age group. Such rates differ from age to age within each year and the specific children change from year to year as new cases are diagnosed and other prior prevalent cases reach age 9. The study reflects a time trend over 7 years in 8 year olds as does the widely publicized CDC study and in that regard are comparable. We could have estimated rates for 3 or 5 year olds from within these data but there is no other published study for comparison. Any comparisons with other published studies on autism frequencies do not appear to be valid. We have referenced such other studies that are themselves of different ages, durations, and calendar times, and the reader can use their own judgment on their general views of the issue. We concentrated on the question of whether the prevalence rates changed over this 7 year period as it was suggested by the CDC study to be the case in the US.

3. Further, many other studies in a diverse array of countries worldwide have shown increasing rates of autism diagnosis, yet the authors focus on a single publication from the CDC. Authors should expand the literature review and note that autism diagnostic rates are increasing in many countries worldwide.

Authors' response: As noted above, other published studies vary in populations, age, calendar time, geography, diagnosis source etc. They can each be evaluated on their merit.

4. The description of the analysis was confusing. Specifically, authors say that they estimated "annual prevalence rates" among 8 year olds – does this mean that any diagnosis in the history of the child was recorded as a prevalent case? Please clarify.

Authors' response: Yes, any child diagnosed prior to or at age 8 in a given calendar year was considered a prevalent case. This matter is considered in an important paragraph in the discussion. It is important that the relevant data is being routinely recorded automatically and continuously in real time by some 1000 GPs and becomes available directly from the medical record for inclusion as recorded in future studies. It seems extraordinary, but it is repeatedly documented as true (see references 4-11).

5. A more sophisticated analytic technique may allow for a greater understanding of autism diagnoses in this sample. A number of studies have demonstrated strong birth cohort effects on autism diagnoses. Authors are encouraged to construct birth cohorts from their data and display the annual incidence of diagnosis at each age (age 2, 3, 4, etc.) for each birth cohort.

Authors' response: Our initial studies from the 1990s were based on birth cohorts up to age 5 as is shown in the figure. As time moves on, the diagnosis has become more frequent in older children and this approach become more complex and useful. Birth cohorts provide qualitative incidences by birth year. As the age increases the duration of the study becomes longer. Per year, annual rates become a clearer, more informative estimate as opposed to continuing birth cohort analysis as opposed to cumulative incidence which is provided by birth cohort analysis. Furthermore, prior studies and the current one provide compelling evidence that incidence rates have remained steady in children born since the late 1990s in the UK – at least as diagnosed and recorded in general practice. The current study documents that rates remained steady through 2010.

6. The figure is unnecessary. Authors can summarize in the text what this previous study found.

Authors' response: The figure is important as the present results provide a clear contrast to the findings in the figure, obtained during the early 10 years of this real time data resource as compared to the extraordinary findings recorded in the last decade from the identical resource. This moving picture yields, yet again, compelling evidence that this database provides comprehensive, valid clinical information as a basis for research which show the frequency obtained during the early years.

7. Authors note that confidence intervals for incidence and prevalence overlap but no confidence intervals are given in the tables.

Authors' response: The numbers provided in the tables clearly demonstrate that the rates remained quite steady over time; so adding CIs to the tables is unnecessary and would render the important results lost in a mass of numbers. In addition, confidence intervals can be readily and quickly

calculated by anyone who might want them, from the numbers in the tables with a simple, well described formula by anyone who might want the CIs from the numbers on the tables.
8. In the discussion, authors state that prevalence rates 'require accurate identification of newly diagnosed cases' – this is not true. Prevalence is the proportion of existing cases (not new cases) at a given point in time or over a certain time period.
Authors' response: Our point simply reinforces that the recording of accurate prevalent rates depend on complete recording of relevant diagnoses. In fact, in a longitudinal database like this one, a person diagnosed in a given year is technically considered as both an incident and a prevalent case in that year. In future years, they are considered to be prevalent cases until they reach age 9.
9. The authors use the New York Post as an academic reference for the "false epidemic of autism" – this is unacceptable. Please remove all references to a "false epidemic of autism". Authors could describe the potential explanations for the increase in autism diagnoses in a scholarly manner, noting that at this time, it is unclear to what extent the increase is due to potential increased ascertainment and awareness, diagnostic shift and drift towards less severe cases, or a change in the distribution of risk factors (e.g., increasing average paternal age). Authors should also remove the direct quotes from and reference to an article in Scientific American. Please include only scholarly publications that have been peer-reviewed as references.
Authors' response: We have excluded any reference to the "false epidemic of autism" or the Scientific American report. Having done that, we would comment to the reviewer that the newspaper article is a reflection of the large debate that continues to go on in the medical community relative to the diagnostic issues and "frequency" of autism over time. In this regard, we think our article makes a well-documented and thoughtful scientific contribution to that debate.

VERSION 2 – REVIEW

REVIEWER	Prof Alan Emond University of Bristol
REVIEW RETURNED	01-Aug-2013

RESULTS & CONCLUSIONS	I was disappointed to read the revised manuscript, because the authors have not taken on board many of the criticisms I made on my first review, and have only added a few sentences in the revision (p13, p23/4) I still advise: 1. that there is too much detail of the US CDC data (this is a report of UK data)- eg remove the final sentence of the abstract p3, remove discussion of the CDC report p12, remove final sentence of conclusion p14 2. add a sentence to the methods of the abstract stating that the GPRD was the dataset used for this analysis. 3.add a section to discusion comparing the prevalence of autism using the GPRD with other UK studies undertaken at the same time - eg ALSPAC (Williams 2008) SNAP (Baird 2006) 4. Acknowledge that GPRD does not contain GP diagnosed cases, but GP reported cases. We have very clear gulidelines in the UK about specialist multidisciplinary team diagnosis of autism (Eg Autism Plan and NICE guidelines, which are still not referenced)- so GPs should be informed of a diagnosis by specialists. This is stated in the limitations, but 'GP-diagnosed' needs correcting to 'GP recorded' in the discussion on p12 and 13
GENERAL COMMENTS	This paper still reads like it is written from an American perspective about UK data. Comparison should be made with the CDC report, but the UK data should come first in the discussion-eg put second para p12 (in the present paper we review....)as the opener to the discussion. This would be more logical than leading off the discussion with 4 pages of historical background aboout US data

	sets and the MMR story before you come to any discussion about the current findings. As noted above, the prevalence results should be compared with other published UK data using different methodologies, and not just US and Denmark.

REVIEWER	Katherine M. Keyes Assistant Professor of Epidemiology Columbia University, USA
REVIEW RETURNED	01-Aug-2013

THE STUDY	As noted in my initial review, a more comprehensive examination of incidence rates of autism in the UK would be age specific - that is, the annual incidence by age and by year. The incidence across age by year could obscure relevant trends. Further, the authors note in the paper that confidence intervals for incidence and prevalence estimates overlap, but no standard error or confidence intervals are given in the article.
RESULTS & CONCLUSIONS	As noted above, incidence rates by year and by age among those at risk would answer the research question more directly.
GENERAL COMMENTS	The authors have responded to the comments of the reviewers, but two central concerns remain. First, the authors have noted that they estimate incidence and prevalence at age 8 to be consistent with the US report that motivated the study. Given the quality of their data, however, incidence rates by age and by year would be more informative, and more in line with many other international studies that have been conducted. The authors could provide this information to the research community as well as show the annual incidence at age 8 to be comparative with the US study. Without the annual incidence by age and by year, the paper is less informative to the research community. Authors state in the response that confidence intervals can easily be calculated by readers from their tables. Given that in the results they state that confidence intervals widely overlap, I believe that the confidence intervals should be reported by the authors, at least in a supplementary table.

VERSION 2 – AUTHOR RESPONSE

Reviewer: Katherine Keyes Columbia University

As noted in my initial review, a more comprehensive examination of incidence rates of autism in the UK would be age specific - that is, the annual incidence by age and by year. The incidence across age by year could obscure relevant trends.

There are all sorts of additional analyses that could be done, but we have done the analyses most suited to answer the research question we set. We feel the suggested additional analyses would not add to the scientific value of this paper and only cloud the message of the present clear results.

Further, the authors note in the paper that confidence intervals for incidence and prevalence estimates overlap, but no standard error or confidence intervals are given in the article.

We have now provided confidence intervals in the tables as the referee requests.

The authors have responded (at length and in detail) to the comments of the reviewers, but two central concerns remain.

First, the authors have noted that they estimate incidence and prevalence at age 8 to be consistent with the US report that motivated the study. Given the quality of their data, however, incidence rates by age and by year would be more informative, and more in line with many other international studies that have been conducted.
The CDC study is the only other study that appears to have used annual prevalence estimates, rather than birth cohort analyses. Comparisons with other studies would not be valid, as we explained in our previous response to the referee.
The authors could provide this information to the research community as well as show the annual incidence at age 8 to be comparative with the US study. Without the annual incidence by age and by year, the paper is less informative to the research community.
We do not accept this opinion. The present paper provides very important information as it is. We feel additional information would only cloud the message.
Authors state in the response that confidence intervals can easily be calculated by readers from their tables. Given that in the results they state that confidence intervals widely overlap, I believe that the confidence intervals should be reported by the authors, at least in a supplementary table.
We now provide the tables with confidence intervals as the referee suggests.

Reviewer: Prof Alan Emond University of Bristol
I was disappointed to read the revised manuscript, because the authors have not taken on board many of the criticisms I made on my first review, and have only added a few sentences in the revision (p13, p23/4)
I still advise:
1. that there is too much detail of the US CDC data (this is a report of UK data)- eg remove the final sentence of the abstract p3, remove discussion of the CDC report p12, remove final sentence of conclusion p14
We do not accept this opinion. The CDC study has been widely quoted in the UK and other international media as well as in the USA. The results of that study, which did not use the usual birth cohort analyses, but presented (highly appropriate) annual estimates of prevalence, needed confirming or refuting. The GPRD provided a unique opportunity to do so using immediately available data. Other prevalence studies, using different methodologies, are not valid for comparison.
2. add a sentence to the methods of the abstract stating that the GPRD was the dataset used for this analysis.
Now included
3.add a section to discusion comparing the prevalence of autism using the GPRD with other UK studies undertaken at the same time - eg ALSPAC (Williams 2008) SNAP (Baird 2006)
Now included in a new section in the discussion.
4. Acknowledge that GPRD does not contain GP diagnosed cases, but GP reported cases. We have very clear guidelines in the UK about specialist multidisciplinary team diagnosis of autism (e.g., Autism Plan and NICE guidelines, which are still not referenced)- so GPs should be informed of a diagnosis by specialists. This is stated in the limitations, but 'GP-diagnosed' needs correcting to 'GP recorded' in the discussion on pages 12 and 13
Now clarified in the methods section and in the discussion.
This paper still reads like it is written from an American perspective about UK data. Comparison should be made with the CDC report, but the UK data should come first in the discussion-e.g., put second paragraph p12 (in the present paper we review....)as the opener to the discussion. This would be more logical than leading off the discussion with 4 pages of historical background about US data sets and the MMR story before you come to any discussion about the current findings. As noted above, the prevalence results should be compared with other published UK data using different methodologies, and not just US and Denmark.

We have changed the order of the discussion as the reviewer suggests and included other prevalence studies.