PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Hospitalisation rates for children with intellectual disability or autism born in Western Australia 1983 – 1999: a population-based cohort study
AUTHORS	Leonard, Helen; Bebbington, Ami; Glasson, Emma; Bourke, Jenny; de Klerk, Nicholas

VERSION 1 - REVIEW

REVIEWER	Eyal Cohen Toronto, Canada
REVIEW RETURNED	06-Dec-2012

THE STUDY	1) Unclear what the end of the observation period was - ?18 years. Graphs in Figure 2 go beyond age 20 for some groups and only to age 10 in others. Needs to be clarified, and should be identical for all birth cohorts to make sense of the findings. 2) Dichotomization of ID into known biomedical causes is unclear. How was this determined? Did you use an ICD list? What about kids with a suspected but undiagnosed genetic anomaly? This is a very common cause of ID. 3) A key reference is missing http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001158 Berry and colleagues also looked at secular trends in hospitalization of children with neurodisabilities in a very large US database.
RESULTS & CONCLUSIONS	1) Why are most common reasons for admissions not presented? If describing trends in hospitalizations this is very important to help policy makers understand whether any of these admissions are preventable. 2) Some findings that are described in detail are well known. For instance, prematurity is a hospitalization risk particularly early in life, as these children are at high risk of bronchiolitis, a very common reason for hospitalization. Again, common diagnoses for hospitalization would help contextualize the findings. The most important point (that gestational age didn't affect the findings) can be summarized more succinctly. In the discussion, I'm not sure the sentence "an increasing discrepancy in hospitalizations over time between severe ID/no ASD and those with biomedical causes …" is well explained. I read over Figure 2 a few times and am not seeing the amplified differences well – suggest re-wording, and emphasizing the statistical test for which this inference was made. An alternative explanation for this finding is an issue of diagnostic accuracy as I am not convinced (as per my earlier comment) that you have accurately ascertained 'biomedical causes'. Another alternative explanation is perhaps an increase in survival over time of children with severe ID who would have died in a previous era but now survive but are medically fragile.

	3) The fluctuant appearance of the graphs in Figure 3 for ASDs and severe ID may be a sampling issue. Western Australia is not highly populated and the size of these subgroups is very small (<1000 each and I presume much smaller for each birth year although I didn't see those data presented). I would think random variation is a much more plausible explanation than anything else. Suggest: a) show some statistics to back up this result, and b) show confidence intervals in the Figure. 4) In your limitations, you mention accounting preterm birth as a strength (I agree), but were you able to account for other potential important confounders (e.g.birth weight, socioeconomic status, comorbidities)? I think that it is important to consider what else may be driving the trends you observed. 5) The findings of differences between children with ID and those with ASD are interesting. I do wonder whether beyond 'more research is needed to unpack the association between these disorders ...', whether the authors feel that the diagnostic distinction between different causes of neuro-disabilities really helps in resource planning. Beyond knowing that children with neuro-disabilities are at increased risk, does it matter what the underlying diagnosis is?
GENERAL COMMENTS	I think an important strength of this study is the utilization of very comprehensive linked health administrative databases.

REVIEWER	Khanna, Rahul University of Mississippi, Pharmacy Administration
REVIEW RETURNED	03-Jan-2013

THE STUDY	No further documentation required.
GENERAL COMMENTS	**Overall Comments**: The study provides information related to hospitalization rates among children with intellectual disability and autism spectrum disorders. The study is well written and conceptualized. To date, only two studies (Lokhandwala et al.2012; Atladottir et al. 2012) have been published in the literature that provide hospitalization-related information among individuals with ASDs. Given the limited information, the study adds significant value to this area of research. There are some minor grammatical errors. There are several verbose sentences in the manuscript. Several sentences include multiple levels of information and can easily be split (for example – Page 4 Line 20-24; Page 6 Line 33-42). **Introduction** • Page 4 Line 33 – Please report updated estimates of autism prevalence (most recent study reports 1 in 88 prevalence – Baio 2012). • Information concerning previous such studies is lacking. Authors should consider providing key results of previous studies that have looked at hospitalizations among individuals with ASD. This should then be followed by a few sentences describing how their study differs from previous studies in this area. **Methods** • Page 7 Line 4-11 – Is there a reason for excluding these kinds of hospitalizations (multiple same day, transfer based)? If so, the authors should consider including that in the manuscript. Also, it may be important to describe how many such hospitalizations took place.

	• Were there any other factors (besides those listed in the results section) that were controlled for in the Cox regression model?

VERSION 1 – AUTHOR RESPONSE

Reviewer: Eyal Cohen
Hospital for Sick Kids
Toronto, Canada

1) Unclear what the end of the observation period was - ?18 years. Graphs in Figure 2 go beyond age 20 for some groups and only to age 10 in others. Needs to be clarified, and should be identical for all birth cohorts to make sense of the findings.

For all individuals the end of the observation period was 31/12/2004, unless they had died before that date, so that the end of the observation period for deceased cases was date of death. Therefore, depending on when the child was born, the observation period was between 5 years (those born in 1999) and 21 years (those born in 1983). Using time to event analysis rather than a Poisson model negates the need for the observation period to be identical for all birth cohorts. We have now clarified this in Methods and Results.

2) Dichotomization of ID into known biomedical causes is unclear. How was this determined? Did you use an ICD list? What about kids with a suspected but undiagnosed genetic anomaly? This is a very common cause of ID.

This categorisation is based on the information in the Intellectual Disability (IDEA) Database where assignment of diagnosis was made by the attending clinician according to an AAMR classification system. In this study we followed a similar protocol to that used in previous published research.
The diagnostic codes assigned to study subjects were categorised as biomedical or otherwise based loosely on the terminology used by Yeargin-Allsopp, Murphy, Cordero, Decoufle, and Hollowell (1997). Biomedical diagnoses include genetic
conditions (chromosomal and Mendelian), recognized teratogenic effects such as congenital infections and birth defects, neonatal and postneonatal infections,
trauma and other events (e.g. neoplasm). Like Yeargin-Allsopp et al. (1997) we excluded diagnostic categories (e.g. preterm birth) that are associated with
but are not necessarily a sufficient cause of ID.
We acknowledge that those with an undiagnosed genetic anomaly would therefore not be classified in the ‘biomedical cause’ group, and are likely to be in the ‘severe ID of no known cause’ group, influencing the findings for this group. This is a key point in the second paragraph of our discussion where we note that in more recent years the aetiology of severe intellectual disability is being increasingly identified through new genetic techniques and thus there has been a diagnostic transfer from those with severe ID of unknown cause to those with a biomedical cause over time.

3) A key reference is missing

http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001158

Berry and colleagues also looked at secular trends in hospitalization of children with neurodisabilities in a very large US database.

We have now made reference to this important paper and concur with their conclusions .

1) Why are most common reasons for admissions not presented? If describing trends in hospitalizations this is very important to help policy makers understand whether any of these admissions are preventable.

It was not the purpose of this paper to describe the reasons for admissions. We appreciate this is very important and plan to do this in future research. It is a fairly complex process comparing the types of hospitalizations of those in our case group with the unaffected population. Therefore we felt this warranted a manuscript of its own and plan further work looking at the reason for hospitalization with an updated dataset.

2) Some findings that are described in detail are well known. For instance, prematurity is a hospitalization risk particularly early in life, as these children are at high risk of bronchiolitis, a very common reason for hospitalization. Again, common diagnoses for hospitalization would help contextualize the findings. The most important point (that gestational age didn't affect the findings) can be summarized more succinctly.

We have further summarized the paragraph on prematurity. However we think it is important to show the ongoing effect of prematurity on hospitalization risk beyond the first year of life for all case groups (Figure 4).

In the discussion, I'm not sure the sentence "an increasing discrepancy in hospitalizations over time between severe ID/no ASD and those with biomedical causes …" is well explained. I read over Figure 2 a few times and am not seeing the amplified differences well – suggest re-wording, and emphasizing the statistical test for which this inference was made. An alternative explanation for this finding is an issue of diagnostic accuracy as I am not convinced (as per my earlier comment) that you have accurately ascertained 'biomedical causes'. Another alternative explanation is perhaps an increase in survival over time of children with severe ID who would have died in a previous era but now survive but are medically fragile.

We appreciate the difficulty in seeing the trend we have described from the graphs and so have added additional detail in the form of adjusted rate estimates based on models reported in the text. The rate estimates provide a measure of the difference in hazard estimates between the different birth-year bands stratified across case-status groups.

The information provided in supplementary table 2 clearly shows that the hazard estimates rate increases for biomedical and the severe ID groups are higher than those of the other groups, but also, that the severe ID (no ASD) group hazard estimate increase more sharply than those of the biomedical ID group.

This confirms our finding of an increase in hospitalizations for those with a biomedical cause over the time period.. Results also show that those with severe ID (no ASD) show greater increase in hazard estimate relative to all other groups. One explanation for the rate increase in the biomedical relative to the severe ID (no ASD) we have offered is the possibility of improved identification of genetic aetiology in children previously diagnosed with severe ID of unknown cause. You have also suggested improved survival in those with severe ID of unknown cause, which is associated with ongoing high medical needs, might explain the current findings. We have added both possible explanations to the Discussion.

3) The fluctuant appearance of the graphs in Figure 3 for ASDs and severe ID may be a sampling issue. Western Australia is not highly populated and the size of these subgroups is very small (<1000

each and I presume much smaller for each birth year although I didn't see those data presented). I would think random variation is a much more plausible explanation than anything else. Suggest: a) show some statistics to back up this result, and b) show confidence intervals in the Figure.

We feel that adding confidence intervals to the graph will make interpretation more cumbersome and may potentially distract the reader from observing the general trends that we feel exist. We have added a table with the information requested in preference to adding confidence intervals to an already information-dense figure (figure 3). Supplementary table 1 provides an adjusted estimate of case status specific yearly hazard estimates and associated confidence intervals (significance values are assessed relative to a reference category of those born in 1983 who do not have ID or ASD). This table shows, as the reviewer notes, that while there is some birth-year based fluctuation in the hazard ratios, an increased hazard ratio estimate associated with later birth year is observable.

We believe this effect is at least partially attributable to different ages at risk captured in our 1983 – 2004 follow up period. Young children tend to be hospitalized more than older children, so for those born in 1999, we are capturing their time at risk when they are young and more likely to be hospitalized, and not capturing the time at risk when they are older and perhaps less likely to be hospitalized. Conversely, for those born in 1983, we are capturing both their childhood (high risk of hospitalization) and their adolescence (time at risk of hospitalization but with a lower overall hospitalization rate). This is why we adjusted for birth-year in our model for hospitalization hazard, as we suspected that the baseline hazard of hospitalization estimate could vary between different birth-years.

4) In your limitations, you mention accounting preterm birth as a strength (I agree), but were you able to account for other potential important confounders (e.g.birth weight, socioeconomic status, comorbidities)? I think that it is important to consider what else may be driving the trends you observed.

We agree this is a limitation of the paper. Unfortunately we didn't have information about comorbidities in this dataset but will in future research and certainly agree that both socioeconomic status and comorbidities are important variables. For simplicity's sake only the three predictors were used in the paper.

5) The findings of differences between children with ID and those with ASD are interesting. I do wonder whether beyond 'more research is needed to unpack the association between these disorders ...', whether the authors feel that the diagnostic distinction between different causes of neuro-disabilities really helps in resource planning. Beyond knowing that children with neuro-disabilities are at increased risk, does it matter what the underlying diagnosis is?

We do believe that it is of value to separate out the differences between children with ID and those with ASD. At the present time there is a much greater emphasis and much more published work on ASD at the neglect of those with ID who in terms of morbidity are more affected. In further research we will aim to determine whether the types of morbidities (hospitalizations) are different for children with ID compared with ASD.

Moreover whether the child has intellectual disability or ASD is important for service planning. For example, while a child with mild intellectual disability but not autism may have difficulty understanding what nurses and doctors say, they may not face as severe difficulties communicating their needs. On the other hand a child with ASD and no intellectual disability may understand medical staff communication quite well, but they may have severe difficulties expressing their needs. This would be

a clear example where a different assistance requirement would exist (perhaps extra explanation for a person with mild ID, but training in adaptive communication for a person with ASD and no ID).

I think an important strength of this study is the utilization of very comprehensive linked health administrative databases.

Reviewer: Rahul Khanna
University of Mississippi, Pharmacy Administration

There are no competing interests.

Overall Comments: The study provides information related to hospitalization rates among children with intellectual disability and autism spectrum disorders. The study is well written and conceptualized. To date, only two studies (Lokhandwala et al.2012; Atladottir et al. 2012) have been published in the literature that provide hospitalization-related information among individuals with ASDs. Given the limited information, the study adds significant value to this area of research.
There are some minor grammatical errors. There are several verbose sentences in the manuscript. Several sentences include multiple levels of information and can easily be split (for example – Page 4 Line 20-24; Page 6 Line 33-42).

We have attended to the grammatical errors and tried to make the sentence structure less verbose.

Introduction
• Page 4 Line 33 – Please report updated estimates of autism prevalence (most recent study reports 1 in 88 prevalence – Baio 2012).

We have now included this information.
• Information concerning previous such studies is lacking. Authors should consider providing key results of previous studies that have looked at hospitalizations among individuals with ASD. This should then be followed by a few sentences describing how their study differs from previous studies in this area.

We have now included in our Discussion the main findings from the Lokhandwala et al.2012 and Atladottir et al. 2012 papers, highlighted the differences and described the new information our paper provides.

Methods
• Page 7 Line 4-11 – Is there a reason for excluding these kinds of hospitalizations (multiple same day, transfer based)? If so, the authors should consider including that in the manuscript. Also, it may be important to describe how many such hospitalizations took place.

These hospitalizations were not excluded, rather they were collapsed, so that on a day by day basis, if a person was in hospital (as a part of a single admission, as a part of a same day admission, or as a transfer) it was considered as only one event. The only hospitalization records excluded were those in the first year of life, due to reasons discussed in the paper, and those where records had been duplicated (the same admission recorded more than once, due likely to computing difficulties, there were very few of these). We have amended our explanation in Methods.

• Were there any other factors (besides those listed in the results section) that were controlled for in the Cox regression model?

No there were not, but we recognize that this would be an improvement. Future work is planned to further develop the models of hospitalization risk for this cohort.