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Title: Hospitalisation rates for children with intellectual disability or autism born in Western Australia 1983 – 1999: a population-based cohort study

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Article Summary

Focus:

- Children with an intellectual disability and/or autism often experience co-occurring morbidities.
- The rate of hospital admissions experienced by these children compared with the rest of the population has not been previously described.

Key Messages:

- The risk of hospitalisation for children with intellectual disability and/or autism is between 2 and 10 times that of those unaffected.
- The increased risk is greatest for those with severe intellectual disability without the presence of autism and least for those with autism and no intellectual disability.
- Pre-term birth was a risk factor for later hospitalisation independently of year of birth or presence of intellectual disability or autism.

Strengths and Limitations:

- A strength of our study has been the ability to link population-based data on childhood disability to hospital admissions.
- The reasons for hospitalisation was not specifically investigated.

There are no additional data available.

Contributor's Statements

Ami Bebbington has contributed to the paper through involvement in study design, statistical analysis and interpretation and manuscript preparation.
Emma Glasson has contributed to the paper through involvement in study design, manuscript editing and revision and final review.
Jenny Bourke has contributed to the paper through involvement in study design, manuscript editing and revision and final approval.
Nicholas de Klerk has contributed to the paper through statistical design and interpretation and final manuscript review.
Helen Leonard has contributed to the paper through involvement in study design, statistical interpretation, manuscript editing, revision and final approval.

ABSTRACT

Objectives: To describe the hospitalisation patterns in children with intellectual disability (ID) and/or autism spectrum disorder (ASD) after the first year of life and compare with those unaffected.

Design : Prospective cohort study using data linkage between births, intellectual disability and hospitalisation population-based data sets.

Setting : Western Australia

Participants : 416,611 individuals born between 1983 -1999 involving 1,027,962 hospital admission records. Five case categories were defined (mild/moderate ID, severe ID, biomedically caused ID, ASD with ID and ASD without ID) and compared with the remainder of children and young people in the birth cohort.

Primary Outcome Measures: Time to event analysis was used to compare time to hospitalisation and rate of hospitalisation between the different case-groups by estimating hazard ratios, accounting for birth year and pre-term birth status.

Results: The presence of ID and/or ASD was found to be associated with an increased risk of hospitalisation compared with the remainder of the population. The increase in risk was highest in those with severe ID and no ASD (HR=10.33, 95% CI 8.66 – 12.31). For those with ID of known biomedical cause or mild ID of unknown cause, the risk of hospitalisation was lower (HR=7.36, 95% CI 6.73 – 8.07 and HR=3.08, 95% CI 2.78 – 3.40, respectively). Those with ASDs had slightly increased risk (HR=2.82, 95% CI 2.26- 3.50 for those with ID and HR=2.09, 95% CI 1.85 – 2.36 for those without ID).

Conclusions: Children with an ID or ASD experience an increased risk of hospitalisation after the first year of life which varied from two to ten times that of the rest of the population. Findings can inform service planning or resource allocation for these children with special needs.

Introduction

Intellectual disability (ID) affects 143 per 10,000 children(1) and is associated with a range of co-morbid health conditions.(2-4) It is heterogeneous,(5) and clustering of some medical conditions may be associated with particular disorders such as Down syndrome (6) or Prader-Willi syndrome.(7) Whilst epilepsy and sensory impairments often occur in association with specific syndromes or more severe cognitive impairment, conditions such as fractures or obesity, may develop as secondary to medication use, nutritional deficiency or lack of mobility.(2) Consequently, children with ID may face greater health challenges than typically developing children and use health care systems more frequently.(8) (9) Mental health problems are also common in people with ID (10) and in a Canadian adolescent and adult population with ID a high proportion of hospitalisations were attributed to the presence of psychiatric conditions.(11)

Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by difficulties in communication and social interaction and associated with repetitive or unusual behaviours.(12) ASD affects between 30 and 60 per 10,000 children(13) but nearly two thirds of children with ASDs also have ID.(14) Therefore, it is not surprising that children with ASD also often experience medical conditions such as epilepsy, bowel dysfunction and autoimmune disorders(15) and that their burden of hospitalisation is considered to be high.(16)

Differences in health care policies and pathways of care may impact on hospitalisation rates and service use for children with developmental disorders over time.(8, 17) For example, a recent Canadian study using administrative data (18) found that those with intellectual or developmental disabilities were more likely than those without to use emergency department services. Families with children affected by ID and/or ASDs may have particular difficulty in accessing primary and specialist health care services, leading to emergency department presentations and hospitalisation rates greater than those not affected by these disorders. A further Canadian study(19) found that

admissions to an emergency department for people with ID were more likely to be for a psychobehavioural rather than a medical reason. However there is little population-based data describing the pattern of hospitalisation among children with ID or ASD. This study uses data linkage between health and disability data sets to investigate temporal trends in hospitalisation risk for children with ID and children with ASD in Western Australia (WA) born 1983-1999. The aim was to compare hospitalisation rates between children with ID and/or ASD to children without these diagnoses, taking into account type of ID, birth cohort and preterm birth.

Methods

Cases of ID were ascertained from the Intellectual Disability Exploring Answers (IDEA) database, (20) a population-based register of individuals in WA with intellectual disability with or without an autism spectrum disorder (ASD). The IDEA database receives information from the Disability Services Commission (DSC) and from the Department of Education on individuals accessing services or educational support for an intellectual disability in WA. The inclusion criteria for the IDEA database are an indication of developmental delay before 18 years of age, a full IQ score below 70, and significant deficits in adaptive behaviour. Cases are categorised into mild ID (IQ between 55 and 69), moderate ID (IQ 40-54) and severe ID (IQ <40) but for the purposes of this study, the mild and moderate ID groups were combined.

As detailed previously (14) individuals with a diagnosis of an ASD (which includes autism, Asperger syndrome or Pervasive Developmental Disorder not otherwise specified) were again identified for this study from three sources; DSC, the Western Australian Register for Autism Spectrum Disorders (a prospective data collection system for diagnostic information for cases diagnosed since 1999), and/or from a case group born 1983-1995 and diagnosed by 1999 as identified by a developmental paediatrician through case-note review. Using record linkage to the

IDEA database, individuals identified with an ASD were sub-divided into those with or without an additional ID. Those for whom an ID status could not be determined were grouped with those with ID, so that the ASD without ID group contained only those definitively known not to have an ID. Individuals were further classified according to whether there was a known biomedical cause for the ID (such as a congenital or genetic conditions e.g. Down syndrome) or otherwise, since, if so there is most probably a greater likelihood of additional comorbidities and need for hospitalisation. Therefore five case categories were defined (mild/moderate ID, severe ID, biomedically caused ID, ASD with ID and ASD without ID) and compared with the remainder of children and young people born in WA between 1983 and 1999 who, at the time of case extraction, were unaffected by ID or ASD.

Information on hospitalisations from 1983-2005 was obtained from the WA Hospital Morbidity Data System, which is a statutory collection of data relating to all inpatient episodes to public, private and freestanding day hospitals in WA since 1970.(21) It contains ICD-coded diagnosis and procedure information. Linkage of all birth records 1983 to 1999 (collected via the Midwives Notification System, a statutory collection of pregnancy, birth and maternal data, recorded at the time of birth,(21)) to hospital and death data was undertaken independently at the WA Data Linkage Branch, where these data sets and others are linked regularly for the purposes of approved research projects (21) and a de-identified dataset was provided for analysis. Pre-term birth was defined as being born at less than 37 weeks gestation with gestational age obtained from the Midwives Notification System.

The analysis was restricted to hospitalisations occurring after the first year of life, thereby excluding individuals who did not survive to this age. The focus of this paper was on hospitalisations occurring in childhood and adolescence, an area lacking in quantitative, population-based research, rather than on the hospitalisations occurring peri-natally or in infancy, where our group has already

quantified the increased burden of hospital care in children with ID (particularly biomedically-caused ID).(8) Hospitalisations occurring on the same day as another recorded hospitalisation, as well as those occurring as part of a nested transfer (the patient moves to another hospital during a stay in hospital) or a transfer sequence (the patient moves between hospitals successively without return home) were excluded.

While we refer to case and comparison groups throughout, this is a cohort study where the different case groups can be thought of as different 'exposures'. Thus time to event analysis was used to compare time to hospitalisation and rate of hospitalisation between the groups, accounting for birth year and pre-term birth status. Hospitalisation rates were represented by incidence rates (IR) in terms of number of admissions per person per year. Group status was used as a categorical predictor of time to hospitalisation, producing Nelson-Aalen cumulative hazard estimates (which in this case represent expected number of hospitalisations experienced by a particular age). Hazard ratios from the Cox proportional hazards model were also used to investigate differences in risk of hospitalisation for the different case groups, with robust standard errors estimated to account for the multiple hospitalisations per individual. The effect of birth year was considered by stratifying year of birth into four eras being 1983- 1985, 1986-1989, 1990-1993 and 1994-1999, such that each group has equal number of records, using STATA's **egen cut** command. In more specific modelling, birth year was included as an indicator variable for each individual year from 1983 to 1999 rather than banded. Ethical approval for this study was granted by the UWA Human Research Ethics Committee.

Results

A dataset of 1,027,962 records representing the time at risk of hospitalisation for 416,611 children (Table 1) and young people born in WA from 1983 to 1999 was created. The total time at risk of hospitalisation in the cohort was 5,146,927.5 person years, while 3,818.6 person years were spent in

hospital (when not on the risk set for hospitalisation). The dataset contained 611,816 admissions to hospital with a median of one hospitalisation per subject, giving an incidence rate (IR) of 0.12 admissions per person per year and median time to hospitalisation of 5.09 years (inter-quartile-range (IQR) 2.26 years – 13.65 years). By the age of ten years, 67.7% (95% CI 67.6% - 67.8%) of individuals had been hospitalised at least once, increasing to 85.0% (95% CI 84.9% - 85.1%) by the age of 18 years. On average, a child of 10 years in this cohort had been hospitalised 1.13 times (cumulative hazard) and a young person of 18 years, 1.90 times.

The highest rate of hospitalisation was observed for cases with severe ID but without an ASD (1.16 hospitalisations/person-year, median time to hospitalisation 1.27 years) followed by cases with a biomedical cause of ID (0.84 hospitalisations/person year, median age of 1.37 years at first hospitalisation), mild or moderate ID without ASD (IR 0.34, median age 1.95 years), and ASDs with ID (IR 0.33, median age of 2.43 years at first hospitalisation). Those children with ASD and no ID had the lowest rate of hospitalisation of the case groups (IR 0.24, median age of 2.89 years at first hospitalisation) however their rate was still higher than that of the general population (IR 0.11, median age of 5.37 years at first hospitalisation). The highest rates of hospitalisation over time were experienced by those with severe ID and those with ID with a known biomedical cause with both groups experiencing five or more hospitalisations by five years of age (Figure 1). The similarity of curves between those with mild/moderate ID and ASD with ID can also be seen. All case groups experienced a higher estimated risk of hospitalisations than the unaffected individuals (Table 2).

Figure 2 shows the time to hospitalisation curves by case status for the four birth cohorts. The curves for the severe ID and the biomedically caused ID groups separate increasingly with advancing age and shows that the difference between these two groups has amplified over time. To measure this more precisely, interaction effects between case status and birth year were included in the Cox proportional hazards modelling and demonstrated that a significantly greater proportion of

the variability in time to hospitalisation was explained by the interaction model than by the main effects model ($p < 0.001$).

Figure 3 shows the hazard ratios over birth year from this interaction model in all six groups. The great increase in risk for all groups compared with the general population is clear, as is the change in hospitalisation relative risk over time both within each group and differing patterns between the groups. In all groups, an increase in risk of hospitalisation was associated with a more recent birth year, however, a small but steadily upwards trend was only observed in the general population and the mild/moderate ID groups. Risk of hospitalisation per birth year fluctuated for those with ASDs (with or without an ID) and for those with severe ID (though from a higher rate).

There were 30,850 births before 37 weeks gestation (7.42% of all births in the cohort) who survived the first year of life. Univariate comparison of time to hospitalisation for those born pre-term vs. full term suggests that those born pre-term are admitted to hospital more frequently (IR 0.17 per person-year for pre-term, 0.11 for full term), and earlier (median time to hospitalisation 3.01 years for pre-term, 5.37 years for full-term) than those born full term. Including birth year and case status factors in the Cox proportional hazards model showed that the hazard ratio for pre-term birth was 1.45 (95% CI 1.39 – 1.51, $p<0.001$), indicating that indeed, pre-term birth was a risk factor for later hospitalisation independently of ID/ASD group or birth year. Including pre-term birth in the model with case group and birth year interaction resulted in the hazard ratio curves shown in Figure 4 where the pre-term and at term lines are separated by a fixed distance which is the independent effect of pre-term birth. The birth year and case-status differences persist after including this pre-term birth effect.

Discussion

This study quantified the rate of hospitalisations for children with an ID and/or ASD compared with the general population. Children diagnosed with ID and/or ASD experienced more hospitalisations than children with neither condition, and this effect persisted after taking into account birth year and pre-term birth status. Whilst overall hospitalisation rates differ by age, the rate of hospitalisation appears to decline with increasing age, particularly for the groups with a known biomedical cause and with severe ID of unknown cause, in contrast to the general population where the rate appears more constant. We also showed that the independent effect of pre-term birth on hospitalisation rates after one year of age is both an increase in frequency and earlier median age at hospitalisation, and this is consistent across all case groups.

The highest rate of hospitalisations occurred among the severe ID group, followed by those with a known biomedical cause for their ID, mild/moderate ID, ASD with ID, ASD without ID and then the comparison population. Thus the rate of hospitalisation was positively correlated with the severity of ID. Although recent studies have investigated the hospitalisation burden for children with autism,(16, 22) this is the first study to compare the hospitalisation patterns of children with ASD and ID with the rest of a total population over an extended time period. The current study was able to show the gradient of risk between the groups over the study period using the same data methods, whole-of-population sampling and controlling for interaction variables. We have shown an increasing discrepancy in hospitalisations over time between those with severe ID and no ASD and those with a biomedical cause, particularly at younger ages. One possible explanation is that in more recent years the aetiology of severe intellectual disability is being increasingly identified through new genetic techniques(23, 24) and thus there has been a diagnostic transfer from those with severe ID of unknown cause to those with a biomedical cause over time.

Various comorbid health conditions affect children with ID, including epilepsy, skin conditions, sensory loss, fractures and psychiatric disorders.(2-4) However apart from individual conditions

such as Down syndrome,(6) Rett syndrome,(25) Tuberous Sclerosis (26) and Angelman syndrome (27) there is a dearth of population-based data on medical co-morbidities associated with ID. Our results would suggest that, although ID may be under-recognised and under-researched in comparison to autism, its associated health burden should not be underestimated. In Canada it has been shown that for ambulatory care sensitive (ACS) conditions, people with an ID are hospitalised at six times the rate of those without an ID, with the rate ratio peaking at double this for those aged 30-39 years.(28) This may reflect a lack of appropriate and accessible primary care for people with ID, particularly for those transitioning from the paediatric health care system. The highest hospitalisation rate ratio was for epilepsy, known to be a common co-morbid condition for people with ID (3), and a condition with a high level of impact on the life of the individual and their family.(29)

As with ID, various comorbid health conditions including gastrointestinal disorders, sleep disturbances, sensory impairments and epilepsy also occur in ASD.(9, 30, 31) Although the hospitalisation burden for children with ASD(16, 22) has previously been reported to be high we have clearly shown in our present study that for children with ID the burden is considerably greater. Behaviour and communication difficulties are reported to be significant barriers to utilising hospital care for children with developmental disabilities (18, 32) and may increase the overall burden and amount of family support necessary.(33, 34) Such challenging behaviours are known to be more frequent in children with ASD than in those with ID and thus may increase the difficulty in their accessing hospital care. Comorbid psychopathology is particularly common in children with ASD (35) and the specific types of behaviours associated with ASD may discourage hospitalisation and also shorten the length of stay.(36) More detailed research on the patterns of primary and secondary health care use for people with an ID and/or ASD, according to health burden and sociodemographic status is needed to unpack the associations between these disorders and increased hospitalisation. Because of the increased risk of hospitalisations of children with ID and ASD

resource planners need to prioritise specialised care allocation for these populations. Lack of medical and nursing staff trained in developmental disability management skills may have in the past led to negative experiences, inadequate care and compounded problems.(37, 38) Qualitative information from parents would help to understand these relationships and identify specific factors that may affect or modify the risk of hospitalisation in these children. Such research would be important in helping to inform resource planning.

A strength of our study has been the ability to use population-based data on children's hospitalisations and link these to sources of disability diagnosis (i.e. presence of ID or ASD). By including birth year in the model we were able to account for these changes over time and show how the patterns of risk of hospitalisation changed for individuals in the different categories. We also accounted for possible confounding by pre-term birth status, known to be associated with increased childhood hospitalisations(39) and demonstrated the consistent effect of pre-term birth on hospitalisation rates across all case groups and the rest of the population. Weaknesses in our study included exclusion from our modelling of hospitalisation history in the first year of life, which may indeed change later risk of hospitalisation. This was lack of access to birth date data (for privacy reasons) and to a change in coding practises in the WA healthcare system that occurred in the mid-1990s.

Children with developmental disabilities have an increased risk of hospitalisation, the extent of which varies according to the type of disability and level of intellectual functioning. Future research should investigate how hospitalisations relate to underlying morbidities, common in intellectual disability and less so in autism, and also consider the role of access to primary care in preventing unnecessary hospitalisation. A better understanding of the patterns of hospitalisation for these children will help establish resource planning opportunities for the specific services required to meet their increasing needs.(40)

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Emma Glasson has contributed to the paper through involvement in study design, manuscript editing and revision and final review.
Jenny Bourke has contributed to the paper through involvement in study design, manuscript editing and revision and final approval.
Nicholas de Klerk has contributed to the paper through statistical design and interpretation and final manuscript review.
Helen Leonard has contributed to the paper through involvement in study design, statistical interpretation, manuscript editing, revision and final approval.

Data sharing statement: There are no additional data available.

References

1. Leonard H, Petterson B, Bower C, et al. Prevalence of intellectual disability in Western Australia. Paediatr Perinat Epidemiol. 2003;**17**:58-67.
2. Jansen DE, Krol B, Groothoff JW, et al. People with intellectual disability and their health problems: a review of comparative studies. J Intell Disabil Res. 2004 Feb;**48**:93-102.
3. Oeseburg B, Dijkstra GJ, Groothoff JW, et al. Prevalence of chronic health conditions in children with intellectual disability: a systematic literature review. Intellect Dev Disabil. 2011 Apr;**49**:59-85.
4. van Schrojenstein Lantman-de Valk HMJ. Health in People with Intellectual Disabilities: Current Knowledge and Gaps in Knowledge. J Appl Res Intellect Disabil. 2005;**18**:325-333.
5. Leonard H, Wen X. The epidemiology of mental retardation: challenges and opportunities in the new millennium. Ment Retard Dev D R. 2002;**8**:117-134.
6. Thomas K, Girdler S, Bourke J, et al. Overview of Health Issues in School-aged Children with Down Syndrome. In: Urbano R, C., editor. Int Rev Res Ment Ret: Academic Press; 2010. p. p. 67-106.
7. Cassidy SB, Schwartz S, Miller JL, et al. Prader-Willi syndrome. Genet Med. 2012 Jan;**14**:10-26.
8. Williams K, Leonard H, Tursan d'Espaignet E, et al. Hospitalisations from birth to 5 years in a population cohort of Western Australian children with intellectual disability. Arch Dis Child. 2005 Dec;**90**:1243-1248.
9. Schieve LA, Gonzalez V, Boulet SL, et al. Concurrent medical conditions and health care use and needs among children with learning and behavioral developmental disabilities, National Health Interview Survey, 2006-2010. Res Dev Disabil. 2012 Mar-Apr;**33**:467-476.
10. Einfeld SL, Tonge BJ. Population prevalence of psychopathology in children and adolescents with intellectual disability: II. Epidemiological findings. J Intell Disabil Res. 1996 Apr;**40**:99-109.
11. Balogh RS, Hunter D, Ouellette-Kuntz H. Hospital Utilization among Persons with an Intellectual Disability, Ontario, Canada, 1995–2001. J Appl Res Intellect Disabil. 2005;**18**:181-190.
12. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Health Disorders 4th Edition. Washington DC: American Psychiatric Association; 1994.
13. Leonard H, Dixon G, Whitehouse A, et al. Unpacking the complex nature of the autism epidemic. Res Autism Spect Dis. 2010 2010/12//;**4**:548-554.
14. Leonard H, Glasson E, Nassar N, et al. Autism and intellectual disability are differentially related to sociodemographic background at birth. PLoS One. 2011;**6**:e17875.
15. Kohane IS, McMurry A, Weber G, et al. The co-morbidity burden of children and young adults with autism spectrum disorders. PLoS One. 2012;**7**:e33224.
16. Lokhandwala T, Khanna R, West-Strum D. Hospitalization burden among individuals with autism. J Autism Dev Disord. 2012 Jan;**42**:95-104.
17. Thomas K, Bourke J, Girdler S, et al. Variation over time in medical conditions and health service utilization of children with Down syndrome. J Pediatr. 2011 Feb;**158**:194-200 e191.
18. Lunsky Y, Lin E, Balogh R, et al. Are adults with developmental disabilities more likely to visit EDs? Am J Emerg Med. 2011 May;**29**:463-465.
19. Lunsky Y, Balogh R, Khodaverdian A, et al. A Comparison of Medical and Psychobehavioral Emergency Department Visits Made by Adults with Intellectual Disabilities. Emergency Medicine International. 2012;**2012**:6.

20. Petterson B, Leonard H, Bourke J, et al. IDEA (Intellectual Disability Exploring Answers): a population-based database for intellectual disability in Western Australia. Ann Hum Biol. 2005 Mar-Apr;**32**:237-243.
21. Holman CD, Bass AJ, Rosman DL, et al. A decade of data linkage in Western Australia: strategic design, applications and benefits of the WA data linkage system. Aust Health Rev. 2008 Nov;**32**:766-777.
22. Atladottir HO, Schendel D, Lauritsen M, et al. Patterns of Contact with Hospital for Children with an Autism Spectrum Disorder: A Danish Register-Based Study. J Autism Dev Disord. 2012;**42**:1717-1728.
23. Jaillard S, Drunat Sv, Bendavid C, et al. Identification of gene copy number variations in patients with mental retardation using array-CGH: Novel syndromes in a large French series. Eur J Med Genet. 2010 2010/4//;**53**:66-75.
24. Koolen DA, Pfundt R, de Leeuw N, et al. Genomic microarrays in mental retardation: A practical workflow for diagnostic applications. Hum Mutat. 2009;**30**:283-292.
25. Young D, Bebbington A, de Klerk N, et al. The relationship between MECP2 mutation type and health status and service use trajectories over time in a Rett syndrome population. Res Autism Spect Dis. 2011;**5**:442-449.
26. Osborne JP, Merrifield J, O'Callaghan FJ. Tuberous sclerosis--what's new? Arch Dis Child. 2008 Sep;**93**:728-731.
27. Williams CA, Driscoll DJ, Dagli AI. Clinical and genetic aspects of Angelman syndrome. Genet Med. 2010 Jul;**12**:385-395.
28. Balogh R, Brownell M, Ouellette-Kuntz H, et al. Hospitalisation rates for ambulatory care sensitive conditions for persons with and without an intellectual disability--a population perspective. J Intell Disabil Res. 2010 Sep;**54**:820-832.
29. Bowley C, Kerr M. Epilepsy and intellectual disability. J Intell Disabil Res. 2000 Oct;**44 (Pt 5)**:529-543.
30. Lauritsen MB, Mors O, Mortensen PB, et al. Medical disorders among inpatients with autism in Denmark according to ICD-8: a nationwide register-based study. J Autism Dev Disord. 2002 Apr;**32**:115-119.
31. Bolton PF. Medical conditions in autism spectrum disorders. J Neurodev Disord. 2009 Jun;**1**:102-113.
32. van Schrojenstein Lantman-de Valk HMJ, van den Akker M, Maaskant MA, et al. Prevalence and incidence of health problems in people with intellectual disability. J Intell Disabil Res. 1997;**41**:42-51.
33. Hemsley B, Balandin S, Togher L. Narrative analysis of the hospital experience for older parents of people who cannot speak. J Aging Stud. 2007;**21**:239-254.
34. Iacono T, Davis R. The experiences of people with developmental disability in Emergency Departments and hospital wards. Res Dev Disabil. 2003 Jul-Aug;**24**:247-264.
35. Brereton AV, Tonge BJ, Einfeld SL. Psychopathology in children and adolescents with autism compared to young people with intellectual disability. J Autism Dev Disord. 2006 Oct;**36**:863-870.
36. Scarpinato N, Bradley J, Kurbjun K, et al. Caring for the child with an autism spectrum disorder in the acute care setting. J Spec Pediatr Nurs. 2010 Jul;**15**:244-254.
37. Lennox N, Diggens J. Knowledge, skills and attitudes: Medical schools' coverage of an ideal curriculum on intellectual disability. J Intellect Dev Dis. 1999;**24**:341.
38. Ouellette-Kuntz H. Understanding Health Disparities and Inequities Faced by Individuals with Intellectual Disabilities. J Appl Res Intellect Disabil. 2005;**18**:113-121.
39. Petrou S, Mehta Z, Hockley C, et al. The impact of preterm birth on hospital inpatient admissions and costs during the first 5 years of life. Pediatrics. 2003 Dec;**112**:1290-1297.

40. Brownell MD, Derksen SA, Jutte DP, et al. Socio-economic inequities in children's injury rates: has the gradient changed over time? Can J Public Health. 2010 Nov-Dec;**101 Suppl 3**:S28-31.

Table 1 – Distribution of individuals in different case groups

Case-comparison group status	Frequency	Percent	Cumulative
No ASD No ID	409,454	98.28	98.28

Mild/mod ID No ASD	4,667	1.12	99.4
Severe ID No ASD	293	0.07	99.47
ASD & ID	767	0.18	99.66
ASD No ID	475	0.11	99.77
Biomedical ID	955	0.23	100
Total	416,611	100	

Figure 1 – Nelson-Aalen Cumulative Hazard for Hospitalisation (number of hospitalisations expected by Age shown on x-axis)

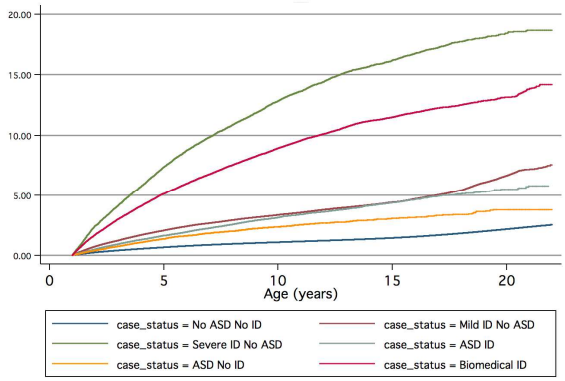


Table 2 - Cox Proportional Hazard Ratios for Hospitalisation by Case Group

Case group	Hazard Ratio	Robust Standard Error	p-value*	95% Confidence Interval	
No ASD No ID	1.0	-			
Mild/mod ID No ASD	3.1	0.16	<0.001	2.8	3.4
Severe ID No ASD	10.3	0.93	<0.001	8.7	12.3
ASD & ID	2.8	0.31	<0.001	2.3	3.5
ASD No ID	2.1	0.13	<0.001	1.8	2.4
Biomedical ID	7.4	0.34	<0.001	6.7	8.1

*Wald test

Figure 2 – Kaplan-Meier Curves showing proportion of individuals in each case group who have not been hospitalised by age, for each birth cohort

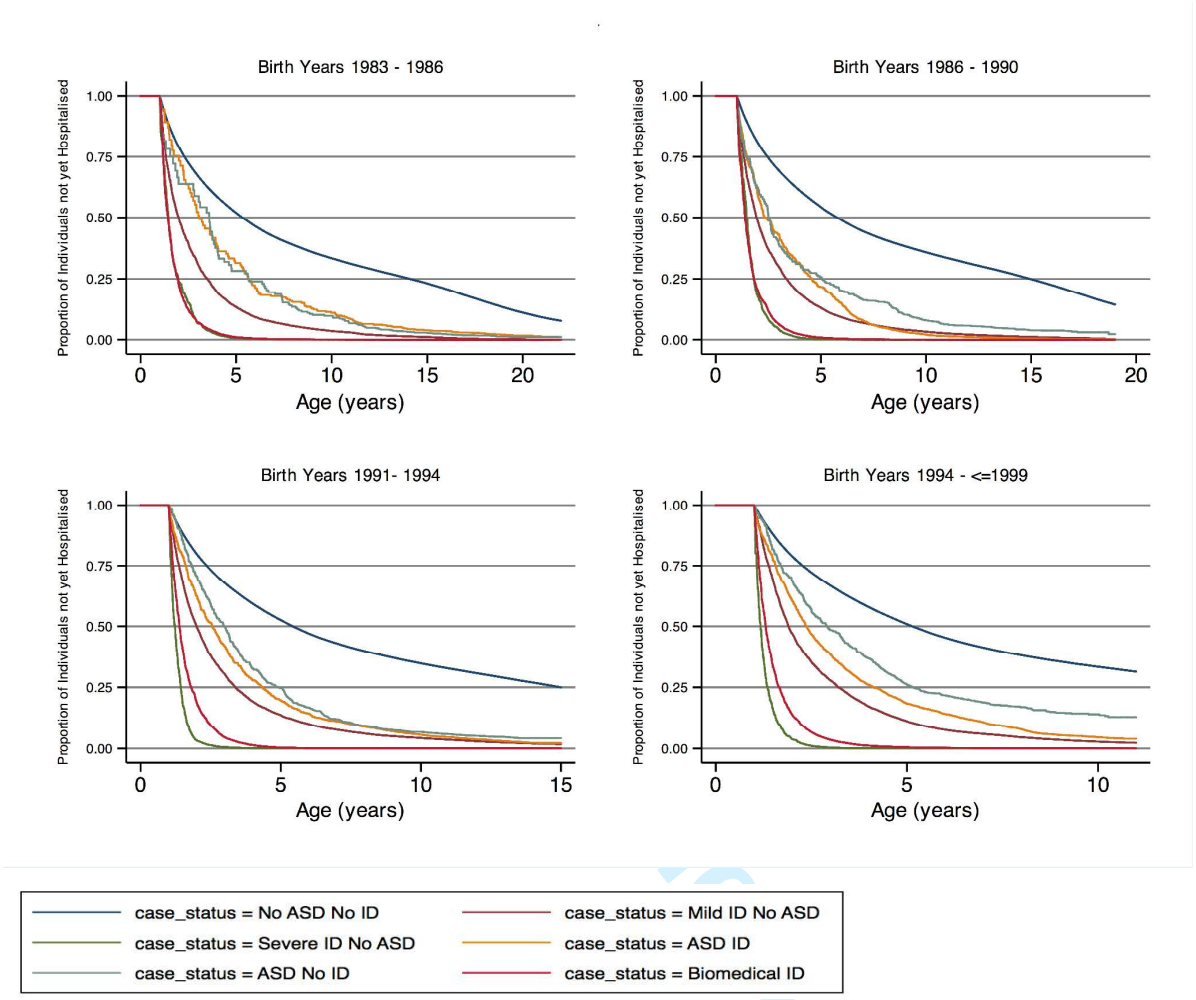


Figure 3 – Hazard Ratios from multivariate interaction model by birth year and case group status

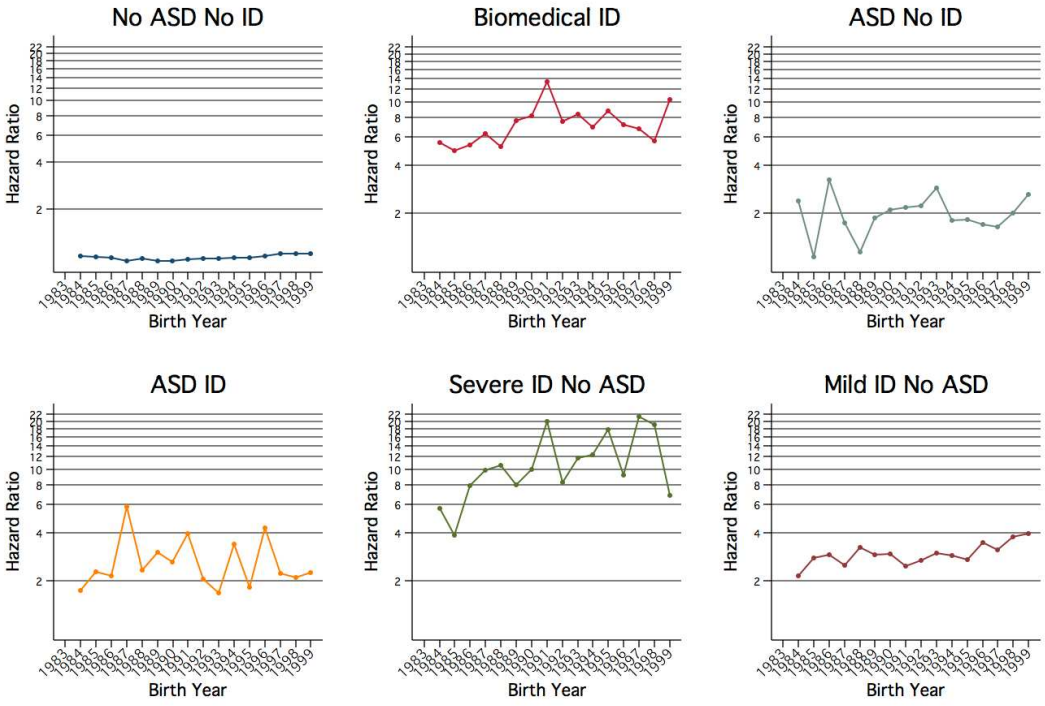
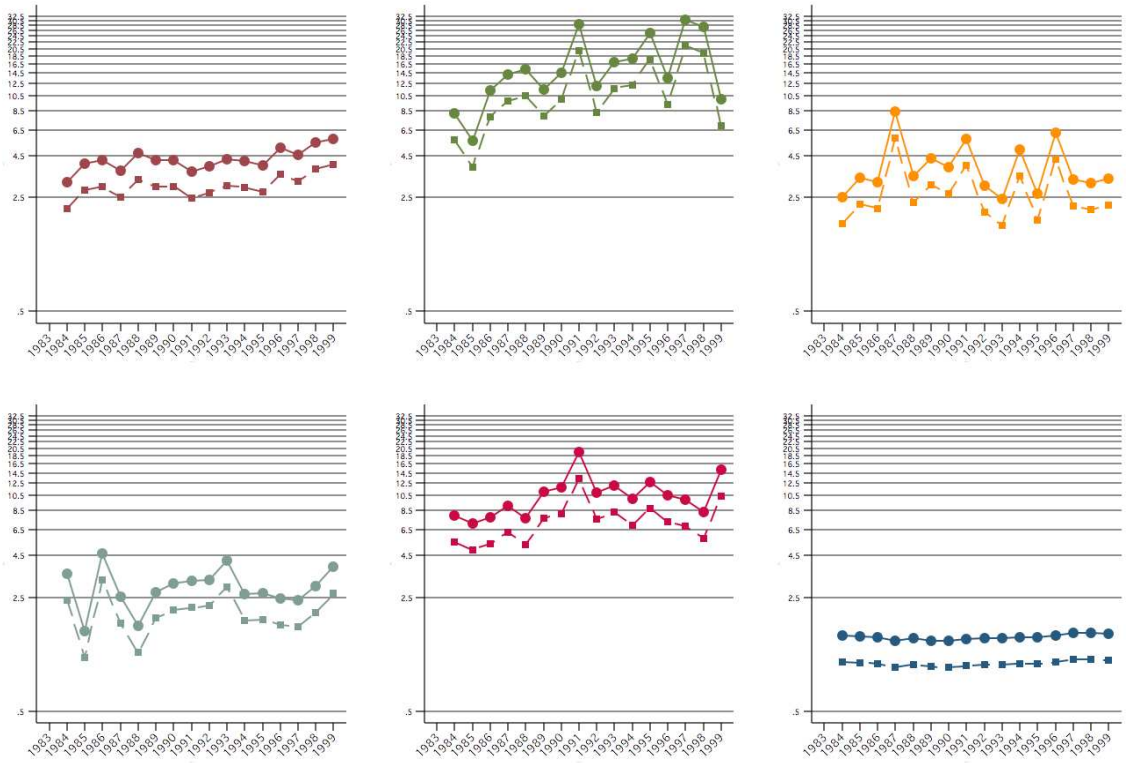
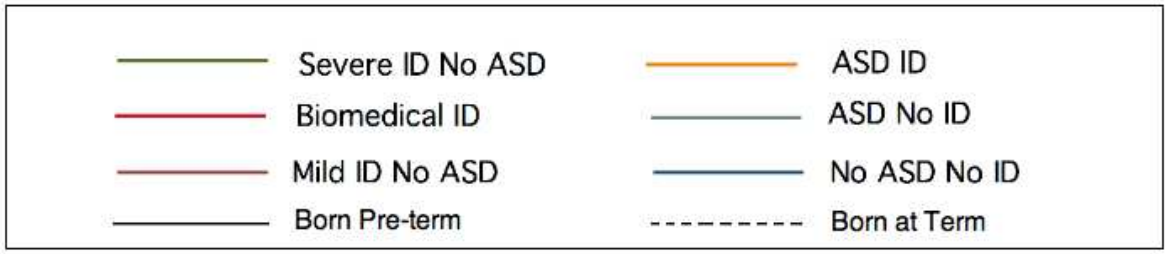
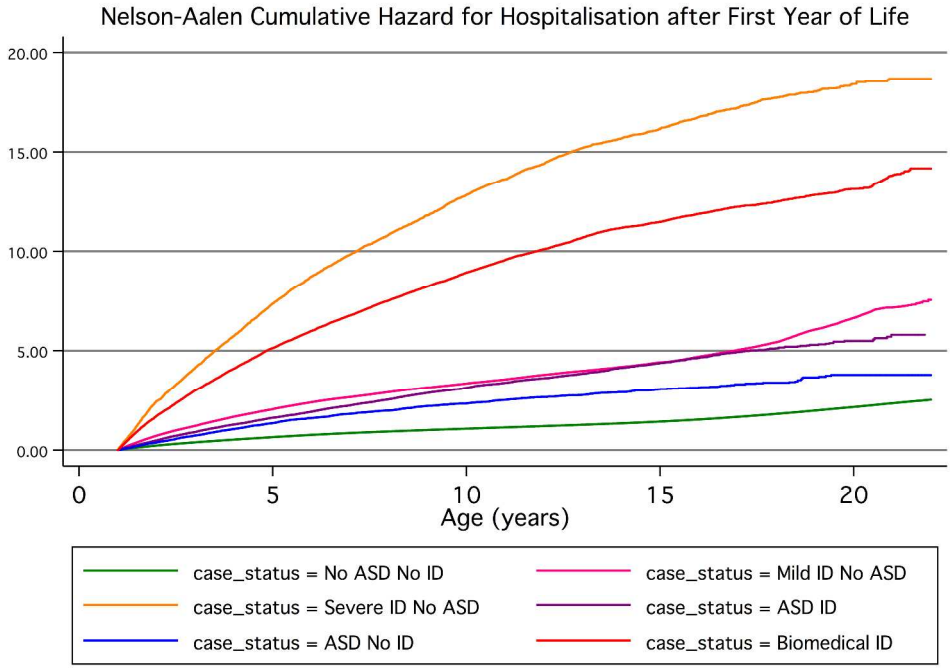


Figure 4 – Hazard Ratio for hospitalisation risk associated with birth year, pre-term birth and case group status from stratified model



Legend for figure 4





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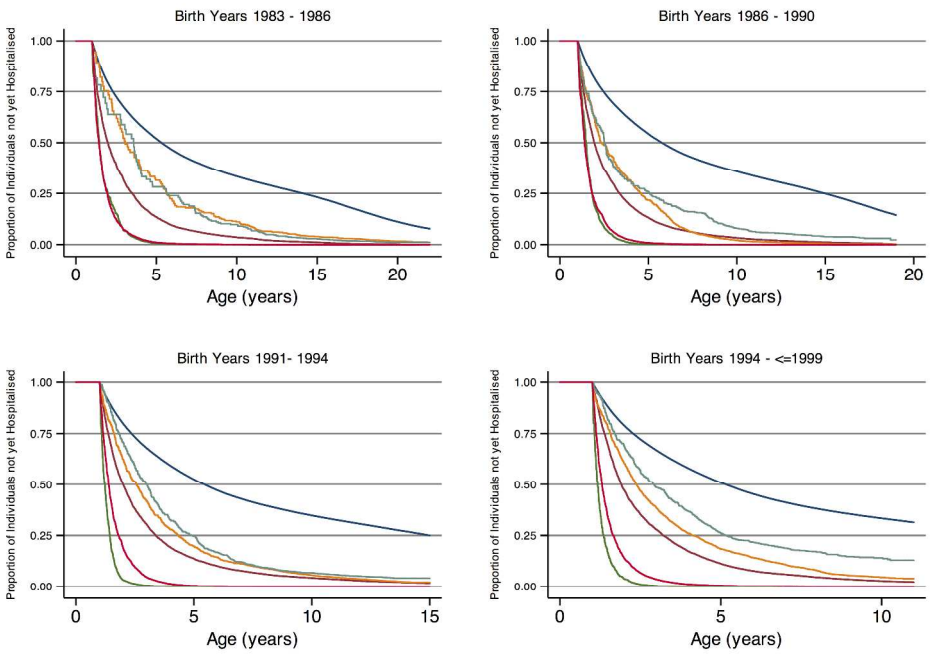

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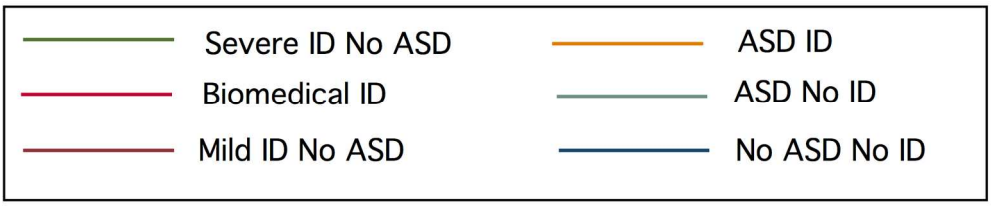

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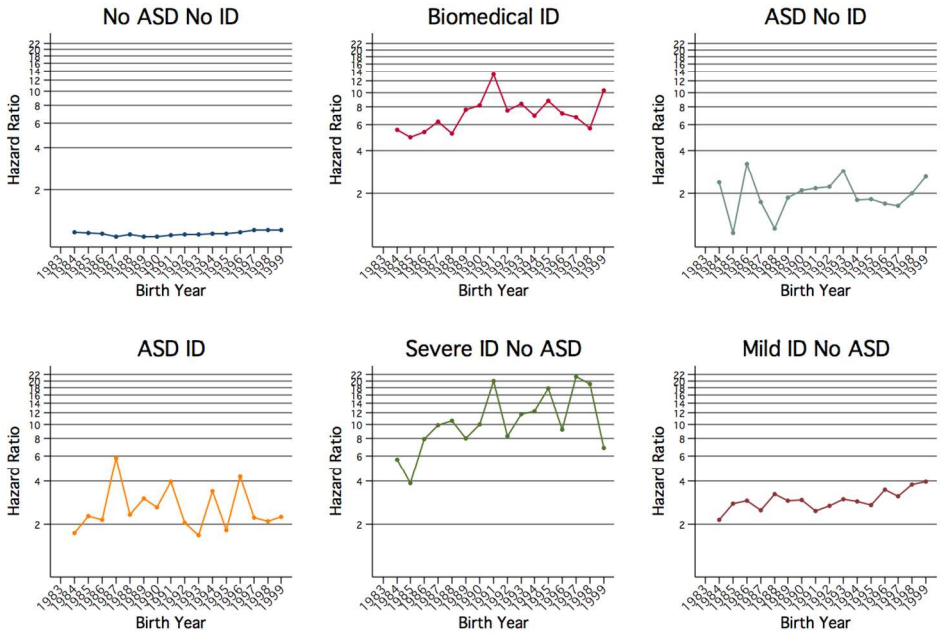

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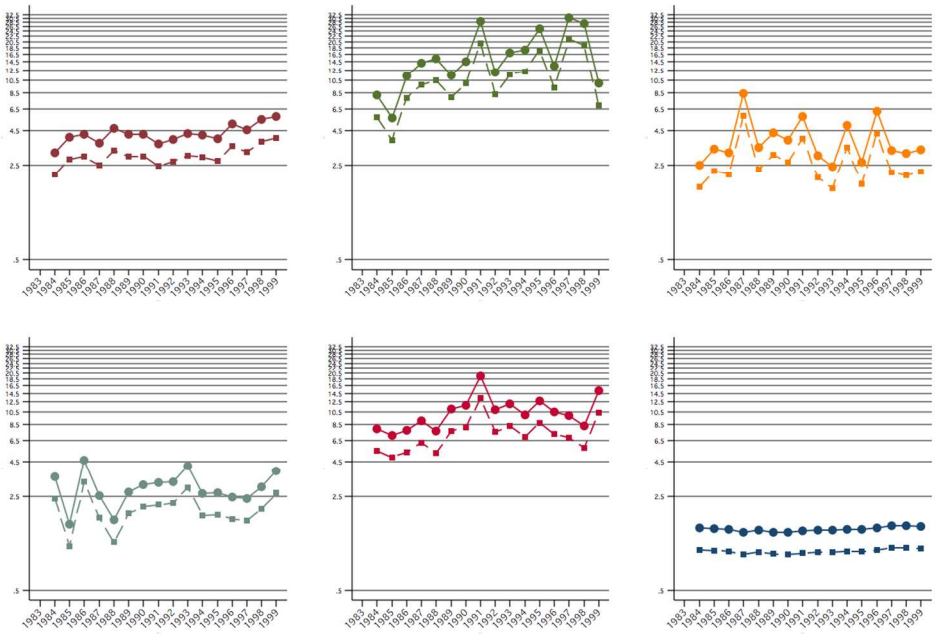

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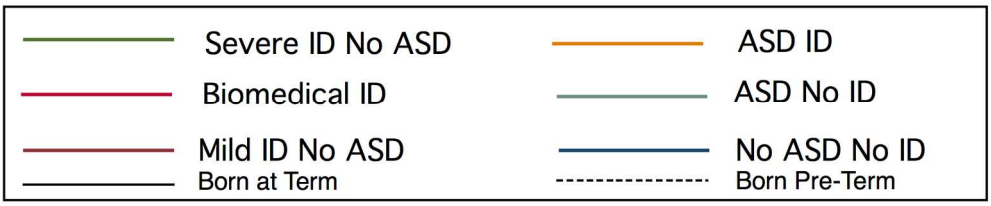

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			**3**
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4 – 5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
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	*6-7*
Bias	9	Describe any efforts to address potential sources of bias	4-7
Study size	10	Explain how the study size was arrived at	5-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	not applicable
		(*c*) Explain how missing data were addressed	not applicable
		(*d*) If applicable, explain how loss to follow-up was addressed	not applicable
		(*e*) Describe any sensitivity analyses	not applicable
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	7-8
		(b) Give reasons for non-participation at each stage	not applicable
		(c) Consider use of a flow diagram	not available
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	table 1
		(b) Indicate number of participants with missing data for each variable of interest	not applicable
		(c) Summarise follow-up time (eg, average and total amount)	7-8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9
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	9-10
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
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	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

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Hospitalisation rates for children with intellectual disability or autism born in Western Australia 1983 – 1999: a population-based cohort study

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Title: Hospitalisation rates for children with intellectual disability or autism born in Western Australia 1983 – 1999: a population-based cohort study

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Key Words**:** hospitalisation, intellectual disability, autism, utilisation

Word count: 3331

Article Summary

Focus:

- Children with an intellectual disability and/or autism often experience co-occurring morbidities.
- The rate of hospital admissions experienced by these children compared with the rest of the population has not been detailed previously.

Key Messages:

- The risk of hospitalisation for children with intellectual disability or autism is up to ten times that of those unaffected.
- The risk is greatest for those with severe intellectual disability without the presence of autism.
- Pre-term birth was a risk factor for later hospitalisation independently of year of birth or presence of intellectual disability or autism.

Strengths and Limitations:

- A strength of our study has been the ability to use population-based data on children's hospitalisations and link these to sources providing information on the presence of intellectual disability or autism spectrum disorders.
- One weakness in the study included the exclusion from our modelling of hospitalisation history in the first year of life.

There are no additional data available.

Contributor's Statements

Ami Bebbington has contributed to the paper through involvement in study design, statistical analysis and interpretation and manuscript preparation.
Emma Glasson has contributed to the paper through involvement in study design, manuscript editing and revision and final review.
Jenny Bourke has contributed to the paper through involvement in study design, manuscript editing and revision and final approval.
Nicholas de Klerk has contributed to the paper through statistical design and interpretation and final manuscript review.
Helen Leonard has contributed to the paper through involvement in study design, statistical interpretation, manuscript editing, revision and final approval.

ABSTRACT

Objectives: To describe the hospitalisation patterns in children with intellectual disability (ID) and/or autism spectrum disorder (ASD) after the first year of life and compare with those unaffected.

Design : Prospective cohort study using data linkage between health, intellectual disability and hospitalisation population-based data sets.

Setting : Western Australia

Participants : 416,611 individuals born between 1983 -1999 involving 1,027,962 hospital admission records. Five case categories were defined (mild/moderate ID, severe ID, biomedically caused ID, ASD with ID and ASD without ID) and compared with the remainder of children and young people

Primary and Secondary Outcome Measures: Time to event analysis was used to compare time to hospitalisation and rate of hospitalisation between the different case-groups by estimating hazard ratios, accounting for birth year and pre-term birth status.

Results: ID and/or ASD were found to be associated with an increased risk of hospitalisation compared with the remainder of the population. The increase in risk was highest in those with severe ID and no ASD (HR=10.33, 95% CI 8.66 – 12.31). For those with ID of known biomedical cause or mild ID of unknown cause, the risk of hospitalisation was lower (HR=7.36, 95% CI 6.73 – 8.07 and HR=3.08, 95% CI 2.78 – 3.40, respectively). Those with ASDs had slightly increased risk (HR=2.82, 95% CI 2.26- 3.50 for those with ID and HR=2.09, 95% CI 1.85 – 2.36 for those without ID).

Conclusions: Children with an ID or ASD experience an increased risk of hospitalisation after the first year of life which varied from two to ten times that of the rest of the population. Findings can inform service planning or resource allocation for these children with special needs.

Introduction

Intellectual disability (ID) affects 143 per 10,000 children[1] and is associated with a range of co-morbid health conditions.[2-4] It is heterogeneous,[5] and clustering of some medical conditions may be associated with particular disorders such as Down syndrome [6] or Prader-Willi syndrome.[7] Whilst epilepsy and sensory impairments often occur in association with specific syndromes or more severe cognitive impairment, conditions such as fractures or obesity, may develop as secondary to medication use, nutritional deficiency or lack of mobility.[2] Consequently, children with ID may face greater health challenges than typically developing children and use health care systems more frequently.[8 9] Mental health problems are also common in people with ID.[10] For instance, in a Canadian adolescent and adult population with ID a high proportion of hospitalisations were attributed to the presence of psychiatric conditions.[11]

Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by difficulties in communication and social interaction and associated with repetitive or unusual behaviours.[12] ASD was reported to affect 30 and 60 per 10,000 children in 2003. [13] However a more recent report from the US Autism and Developmental Disabilities Monitoring (ADDM) Network suggests a higher prevalence of 113 per 10,000.[14] Moreover nearly two thirds of children with ASDs also have ID.[15] Therefore, it is not surprising that children with ASD also often experience medical conditions such as epilepsy, bowel dysfunction and autoimmune disorders[16] and that their burden of hospitalisation is considered to be high.[17]

Differences in health care policies and pathways of care may impact on hospitalisation rates and service use for children with developmental disorders over time.[8, 18] For example, a recent Canadian study using administrative data [19] found that those with intellectual or developmental disabilities were more likely than those without to use emergency department services. Families with children affected by ID and/or ASDs may have particular difficulty in accessing primary and

specialist health care services, leading to emergency department presentations and hospitalisation rates greater than those not affected by these disorders. A further Canadian study[20] found that admissions to an emergency department for people with ID were more likely to be for a psychobehavioural rather than a medical reason. However there is little population-based data describing the pattern of hospitalisation among children with ID or ASD. This study uses data linkage between health and disability data sets to investigate temporal trends in hospitalisation risk for children with ID and children with ASD in Western Australia (WA) born 1983-1999. The aim was to compare hospitalisation rates between children with ID and/or ASD to children without these diagnoses, taking into account type of ID, birth cohort and preterm birth.

Methods

Cases of ID were ascertained from the Intellectual Disability Exploring Answers (IDEA) database, [21] a population-based register of individuals in WA with intellectual disability with or without an autism spectrum disorder (ASD). The IDEA database receives information from the Disability Services Commission (DSC) and from the Department of Education on individuals accessing services or educational support for an intellectual disability in WA. The inclusion criteria for the IDEA database are an indication of developmental delay before 18 years of age, a full IQ score below 70, and significant deficits in adaptive behaviour. Cases are categorised into mild ID (IQ between 55 and 69), moderate ID (IQ 40-54) and severe ID (IQ <40) but for the purposes of this study, the mild and moderate ID groups were combined.

As detailed previously [15] individuals with a diagnosis of an ASD (which includes autism, Asperger syndrome or Pervasive Developmental Disorder not otherwise specified) were again identified for this study from three sources; DSC, the Western Australian Register for Autism Spectrum Disorders (a prospective data collection system for diagnostic information for cases diagnosed since

1999), and/or from a case group born 1983-1995 and diagnosed by 1999 as identified by a developmental paediatrician through case-note review. Using record linkage to the IDEA database, individuals identified with an ASD were sub-divided into those with or without an additional ID. Those for whom an ID status could not be determined were grouped with those with ID, so that the ASD without ID group contained only those definitively known not to have an ID. Individuals were further classified according to whether there was a known biomedical cause for the ID (such as a congenital or genetic condition e.g. Down syndrome) or otherwise. This categorisation is based on the information in the Intellectual Disability (IDEA) Database[21] 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 our own[15, 22] and previous published research.[23] 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). However we excluded diagnostic categories (e.g. preterm birth) that are associated with but are not necessarily a sufficient cause of ID and those where a genetic diagnosis might be suspected but not clinically or genetically confirmed. Therefore five case categories were defined (mild/moderate ID, severe ID, biomedically caused ID, ASD with ID and ASD without ID) and compared with the remainder of children and young people born in WA between 1983 and 1999 who, at the time of case extraction, were unaffected by ID or ASD.

Information on hospitalisations from 1 January, 1983- 31 December, 2004 was obtained from the WA Hospital Morbidity Data System, which is a statutory collection of data relating to all inpatient episodes to public, private and freestanding day hospitals in WA since 1970.[24] It contains ICD-coded diagnosis and procedure information. WA also has a statutory collection of pregnancy, birth and maternal data, recorded at the time of birth, known as the Midwives Notification System. [24] Linkage of all birth records 1983 to 1999 to hospital and death data was undertaken independently

at the WA Data Linkage Branch, where these data sets and others are linked regularly for the purposes of approved research projects.[24] A de-identified dataset was provided for this analysis in which all individuals were followed from birth through to either death or the censoring date of 31 December, 2004. Pre-term birth was defined as being born at less than 37 weeks gestation with gestational age obtained from the Midwives Notification System.

The analysis was restricted to hospitalisations occurring after the first year of life, thereby excluding individuals who did not survive to this age. The focus of this paper was on hospitalisations occurring in childhood and adolescence, an area lacking in quantitative, population-based research, rather than on the hospitalisations occurring peri-natally or in infancy, where our group has already quantified the increased burden of hospital care in children with ID (particularly biomedically-caused ID).[8] Hospitalisations occurring on the same day as another recorded hospitalisation, as well as those occurring as part of a nested transfer (the patient moves to another hospital during a stay in hospital) or a transfer sequence (the patient moves between hospitals successively without return home) were considered as a single event.

While we refer to case and comparison groups throughout, this is a cohort study where the different case groups can be thought of as different 'exposures'. Thus time to event analysis (which allows for varying individual time at risk) was used to compare time to hospitalisation and rate of hospitalisation between the groups, accounting for birth year and pre-term birth status. Hospitalisation rates were represented by incidence rates (IR) in terms of number of admissions per person per year. Group status was used as a categorical predictor of time to hospitalisation, producing Nelson-Aalen cumulative hazard estimates (which in this case represent expected number of hospitalisations experienced by a particular age). Hazard ratios from the Cox proportional hazards model were also used to investigate differences in risk of hospitalisation for the different case groups, with robust standard errors estimated to account for the multiple

hospitalisations per individual. The effect of birth year was considered by stratifying year of birth into four eras being 1983- 1985, 1986-1989, 1990-1993 and 1994-1999, such that each group has equal number of records, using STATA's **egen cut** command. In more specific modelling, birth year was included as an indicator variable for each individual year from 1983 to 1999 rather than banded. Ethical approval for this study was granted by the UWA Human Research Ethics Committee.

Results

A dataset of 1,027,962 records representing the time at risk of hospitalisation for 416,611 children (Table 1) and young people born in WA from 1983 to 1999 was created. The total time at risk of hospitalisation in the cohort was 5,146,927.5 person years, while 3,818.6 person years were spent in hospital (when not on the risk set for hospitalisation). Individual time at risk varied from 5 years (for those born in 1999) to 21 years (for those born in 1983). The dataset contained 611,816 admissions to hospital with a median of one hospitalisation per subject, giving an incidence rate (IR) of 0.12 admissions per person per year and median time to hospitalisation of 5.09 years (inter-quartile-range (IQR) 2.26 years – 13.65 years). By the age of ten years, 67.7% (95% CI 67.6% - 67.8%) of individuals had been hospitalised at least once, increasing to 85.0% (95% CI 84.9% - 85.1%) by the age of 18 years. On average, a child of 10 years in this cohort had been hospitalised 1.13 times (cumulative hazard) and a young person of 18 years, 1.90 times.

The highest rate of hospitalisation was observed for cases with severe ID but without an ASD (1.16 hospitalisations/person-year, median time to hospitalisation 1.27 years) followed by cases with a biomedical cause of ID (0.84 hospitalisations/person year, median age of 1.37 years at first hospitalisation), mild or moderate ID without ASD (IR 0.34, median age 1.95 years), and ASDs with ID (IR 0.33, median age of 2.43 years at first hospitalisation). Those children with ASD and no ID had the lowest rate of hospitalisation of the case groups (IR 0.24, median age of 2.89 years at

first hospitalisation) however their rate was still higher than that of the general population (IR 0.11, median age of 5.37 years at first hospitalisation). The highest rates of hospitalisation over time were experienced by those with severe ID and those with ID with a known biomedical cause with both groups experiencing five or more hospitalisations by five years of age (Figure 1). The similarity of curves between those with mild/moderate ID and ASD with ID can also be seen. All case groups experienced a higher estimated risk of hospitalisations than the unaffected individuals (Table 2).

Figure 2 shows the time to hospitalisation curves by case status for the four birth cohorts. The curves for the severe ID and the biomedically caused ID groups separate increasingly with advancing age and shows that the difference between these two groups has amplified over time. Table 3 shows the differences in rate estimates for the different birth year bands over the different case status groups, compared with all other groups. This shows that there is an increase in difference in hospitalisation rate over time in the severe ID (no ASD) groups and the biomedical ID groups much greater than the rate differences of the other groups, and that the severe ID group's risk increases more steeply than that of the biomedical ID group. To measure this more precisely, interaction effects between case status and birth year were included in the Cox proportional hazards modelling and demonstrated that a significantly greater proportion of the variability in time to hospitalisation was explained by the interaction model than by the main effects model ($p < 0.001$).

Figure 3 shows the hazard ratios over birth year from this interaction model in all six groups. These hazard ratios and their confidence intervals are also shown in Table 4. The great increase in risk for all groups compared with the general population is clear, as is the change in hospitalisation relative risk over time both within each group and differing patterns between the groups. In all groups, an increase in risk of hospitalisation was associated with a more recent birth year, however, a small but steadily upwards trend was only observed in the general population and the mild/moderate ID

groups. Risk of hospitalisation per birth year fluctuated for those with ASDs (with or without an ID) and for those with severe ID (though from a higher rate).

There were 30,850 births before 37 weeks gestation (7.42% of all births in the cohort) who survived the first year of life. Univariate comparison of time to hospitalisation for those born pre-term vs. full term suggests that those born pre-term are admitted to hospital more frequently (IR 0.17 per person-year for pre-term, 0.11 for full term), and earlier (median time to hospitalisation 3.01 years for pre-term, 5.37 years for full-term) than those born full term. Including birth year and case status factors in the Cox proportional hazards model showed that the hazard ratio for pre-term birth was 1.45 (95% CI 1.39 – 1.51, $p<0.001$), indicating the independent effect of pre-term birth on hospitalisations for each case group (Figure 4).

Discussion

This study quantified the rate of hospitalisations for children with an ID and/or ASD compared with the general population. Children diagnosed with ID and/or ASD experienced more hospitalisations than children with neither condition, and this effect persisted after taking into account birth year and pre-term birth status. Whilst overall hospitalisation rates differ by age, the rate of hospitalisation appears to decline with increasing age, particularly for the groups with a known biomedical cause and with severe ID of unknown cause, in contrast to the general population where the rate appears more constant. We also showed that the independent effect of pre-term birth on hospitalisation rates after one year of age is both an increase in frequency and earlier median age at hospitalisation, and this is consistent across all case groups.

Recent studies in the US[17] and Denmark[22] have investigated the hospitalisation burden for children with autism, and found that individuals with autism had significantly higher lengths of stay and that costs were considerably more than for those without autism. The Danish study also found that

children with ASD had an increased rate of contact with hospital, regardless of the cause of their hospital admission. However, unlike our study neither of these two studies were able to compare the hospitalisation patterns of children with ASD with those of children with ID. What we found was that the highest rate of hospitalisations occurred among the severe ID group, followed by those with a known biomedical cause for their ID, mild/moderate ID, ASD with ID, ASD without ID and then the comparison population. Thus the rate of hospitalisation was positively correlated with the severity of ID. Our study was able to demonstrate the gradient of risk between the groups over the study period using the same data methods, whole-of-population sampling and controlling for interaction variables. We have also shown an increasing discrepancy in hospitalisations over time between those with severe ID and no ASD and those with a biomedical cause, particularly at younger ages. One possible explanation is that in more recent years the aetiology of severe intellectual disability is being increasingly identified through new genetic techniques[25, 26] and thus there has been a diagnostic transfer from those with severe ID of unknown cause to those with a biomedical cause over time. Another explanation may be the improved survival in those with severe ID of unknown cause which is associated with ongoing high medical needs.

Various comorbid health conditions affect children with ID, including epilepsy, skin conditions, sensory loss, fractures and psychiatric disorders.[2-4] However apart from individual conditions such as Down syndrome,[6] Rett syndrome,[27] Tuberous Sclerosis [28] and Angelman syndrome [29] and a recent paper describing the increase over time in resource utilisation by children with neurological impairment,[30] there is a dearth of population-based data on medical co-morbidities associated with ID. Our results would suggest that, although ID may be under-recognised and under-researched in comparison to autism, its associated health burden should not be underestimated. In Canada it has been shown that for ambulatory care sensitive (ACS) conditions, people with an ID are hospitalised at six times the rate of those without an ID, with the rate ratio peaking at double this for those aged 30-39 years.[31] This may reflect a lack of appropriate and accessible primary care for people with

ID, particularly for those transitioning from the paediatric health care system. The highest hospitalisation rate ratio was for epilepsy, known to be a common co-morbid condition for people with ID [3], and a condition with a high level of impact on the life of the individual and their family.[32]

As with ID, various comorbid health conditions including gastrointestinal disorders, sleep disturbances, sensory impairments , diabetes mellitus type 1 and epilepsy also occur in ASD.[9, 16, 33, 34] Although the hospitalisation burden for children with ASD[17, 35] has previously been reported to be high we have clearly shown in our present study that for children with ID the burden is considerably greater. Behaviour and communication difficulties are reported to be significant barriers to utilising hospital care for children with developmental disabilities [19, 36] and may increase the overall burden and amount of family support necessary.[37, 38] Such challenging behaviours are known to be more frequent in children with ASD than in those with ID and thus may increase the difficulty in their accessing hospital care. Comorbid psychopathology is particularly common in children with ASD [39] and the specific types of behaviours associated with ASD may discourage hospitalisation and also shorten the length of stay.[40] More detailed research on the patterns of primary and secondary health care use for people with an ID and/or ASD, according to health burden and sociodemographic status is needed to unpack the associations between these disorders and increased hospitalisation. Because of the increased risk of hospitalisations of children with ID and ASD resource planners need to prioritise specialised care allocation for these populations. Lack of medical and nursing staff trained in developmental disability management skills may have in the past led to negative experiences, inadequate care and compounded problems.[41, 42] Qualitative information from parents would help to understand these relationships and identify specific factors that may affect or modify the risk of hospitalisation in these children. Such research would be important in helping to inform resource planning. We concur with the plea made by Berry and colleagues to ensure that the current health care system is adequately educated and equipped to care for this growing proportion of vulnerable children within the hospital population.[30]

A strength of our study has been the ability to use population-based data on children's hospitalisations and link these to sources of disability diagnosis (i.e. presence of ID or ASD). By including birth year in the model we were able to account for these changes over time and show how the patterns of risk of hospitalisation changed for individuals in the different categories. We also accounted for possible confounding by pre-term birth status, known to be associated with increased childhood hospitalisations[43] and demonstrated the consistent effect of pre-term birth on hospitalisation rates across all case groups and the rest of the population. Weaknesses in our study included exclusion from our modelling of hospitalisation history in the first year of life, which may indeed change later risk of hospitalisation. This was lack of access to birth date data (for privacy reasons) and to a change in coding practises in the WA healthcare system that occurred in the mid-1990s.

Children with developmental disabilities have an increased risk of hospitalisation, the extent of which varies according to the type of disability and level of intellectual functioning. Future research should investigate how hospitalisations relate to underlying morbidities, common in intellectual disability and less so in autism, and also consider the role of access to primary care in preventing unnecessary hospitalisation. A better understanding of the patterns of hospitalisation for these children will help establish resource planning opportunities for the specific services required to meet their increasing needs.[44]

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References

1. Leonard H, Petterson B, Bower C, et al. Prevalence of intellectual disability in Western Australia. Paediatr Perinat Epidemiol. 2003;17:58-67.
2. Jansen DE, Krol B, Groothoff JW, et al. People with intellectual disability and their health problems: a review of comparative studies. J Intell Disabil Res. 2004;48(Pt 2):93-102. Epub 2004/01/16.
3. Oeseburg B, Dijkstra GJ, Groothoff JW, et al. Prevalence of chronic health conditions in children with intellectual disability: a systematic literature review. Intellect Dev Disabil. 2011;49(2):59-85.
4. van Schrojenstein Lantman-de Valk HMJ. Health in People with Intellectual Disabilities: Current Knowledge and Gaps in Knowledge. J Appl Res Intellect Disabil. 2005;18(4):325-33.
5. Leonard H, Wen X. The epidemiology of mental retardation: challenges and opportunities in the new millennium. Ment Retard Dev D R. 2002;8(3):117-34.
6. Thomas K, Girdler S, Bourke J, et al. Overview of Health Issues in School-aged Children with Down Syndrome. In: Urbano R, C., editor. Int Rev Res Ment Ret: Academic Press; 2010. p. p. 67-106.
7. Cassidy SB, Schwartz S, Miller JL, et al. Genet Med. 2012;14(1):10-26. Epub 2012/01/13.
8. Williams K, Leonard H, Tursan d'Espaignet E, et al. Hospitalisations from birth to 5 years in a population cohort of Western Australian children with intellectual disability. Arch Dis Child. 2005;90(12):1243-8.
9. Schieve LA, Gonzalez V, Boulet SL, et al. Concurrent medical conditions and health care use and needs among children with learning and behavioral developmental disabilities, National Health Interview Survey, 2006-2010. Res Dev Disabil. 2012;33(2):467-76. Epub 2011/11/29.
10. Einfeld SL, Tonge BJ. Population prevalence of psychopathology in children and adolescents with intellectual disability: II. Epidemiological findings. J Intell Disabil Res. 1996;40(Pt 2):99-109.
11. Balogh RS, Hunter D, Ouellette-Kuntz H. Hospital Utilization among Persons with an Intellectual Disability, Ontario, Canada, 1995–2001. J Appl Res Intellect Disabil. 2005;18(2):181-90.
12. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Health Disorders 4th Edition. Washington DC: American Psychiatric Association; 1994.
13. Leonard H, Dixon G, Whitehouse A, et al. Unpacking the complex nature of the autism epidemic. Res Autism Spect Dis. 2010;4(4):548-54.

14. Baio J. Prevalence of autism spectrum disordres-Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States 2008. MMWR CDC Surveill Summ. 2012;61(3):1-19.
15. Leonard H, Glasson E, Nassar N, et al. Autism and intellectual disability are differentially related to sociodemographic background at birth. PLoS One. 2011;6(3):e17875. Epub 2011/04/12.
16. Kohane IS, McMurry A, Weber G, et al. The co-morbidity burden of children and young adults with autism spectrum disorders. PLoS One. 2012;7(4):e33224. Epub 2012/04/19.
17. Lokhandwala T, Khanna R, West-Strum D. Hospitalization burden among individuals with autism. J Autism Dev Disord. 2012;42(1):95-104. Epub 2011/03/16.
18. Thomas K, Bourke J, Girdler S, et al. Variation over time in medical conditions and health service utilization of children with Down syndrome. J Pediatr. 2011;158(2):194-200 e1.
19. Lunsky Y, Lin E, Balogh R, et al. Are adults with developmental disabilities more likely to visit EDs? Am J Emerg Med. 2011;29(4):463-5.
20. Lunsky Y, Balogh R, Khodaverdian A, et al. A Comparison of Medical and Psychobehavioral Emergency Department Visits Made by Adults with Intellectual Disabilities. Emerg Med Int. 2012;2012:6.
21. Petterson B, Leonard H, Bourke J, et al. IDEA (Intellectual Disability Exploring Answers): a population-based database for intellectual disability in Western Australia. Ann Hum Biol. 2005;32(2):237-43.
22. Leonard H, Petterson B, De Klerk N, et al. Association of sociodemographic characteristics of children with intellectual disability in Western Australia. Soc Sci Med. 2005;60(7):1499-513.
23. Yeargin-Allsopp M, Murphy CC, Cordero JF, et al. Reported biomedical causes and associated medical conditions for mental retardation among 10-year-old children, metropolitan Atlanta, 1985 to 1987. Dev Med Child Neurol. 1997;39(3):142-9. Epub 1997/03/01.
24. Holman CD, Bass AJ, Rosman DL, et al. A decade of data linkage in Western Australia: strategic design, applications and benefits of the WA data linkage system. Aust Health Rev. 2008;32(4):766-77. Epub 2008/11/05.
25. Jaillard S, Drunat Sv, Bendavid C, et al. Identification of gene copy number variations in patients with mental retardation using array-CGH: Novel syndromes in a large French series. Eur J Med Genet. 2010;53(2):66-75.
26. Koolen DA, Pfundt R, de Leeuw N, et al. Genomic microarrays in mental retardation: A practical workflow for diagnostic applications. Hum Mutat. 2009;30(3):283-92.
27. Young D, Bebbington A, de Klerk N, et al. The relationship between MECP2 mutation type and health status and service use trajectories over time in a Rett syndrome population. Res Autism Spect Dis. 2011;5(1):442-9.
28. Osborne JP, Merrifield J, O'Callaghan FJ. Tuberous sclerosis--what's new? Arch Dis Child. 2008;93(9):728-31. Epub 2008/05/06.
29. Williams CA, Driscoll DJ, Dagli AI. Clinical and genetic aspects of Angelman syndrome. Genet Med. 2010;12(7):385-95. Epub 2010/05/07.
30. Berry JG, Poduri A, Bonkowsky JL, et al. Trends in resource utilization by children with neurological impairment in the United States inpatient health care system: a repeat cross-sectional study. PLoS Med. 2012;9(1):e1001158. Epub 2012/01/25.
31. Balogh R, Brownell M, Ouellette-Kuntz H, et al. Hospitalisation rates for ambulatory care sensitive conditions for persons with and without an intellectual disability--a population perspective. J Intell Disabil Res. 2010;54(9):820-32. Epub 2010/08/14.

32. Bowley C, Kerr M. Epilepsy and intellectual disability. J Intell Disabil Res. 2000;44 (Pt 5):529-43. Epub 2000/11/18.
33. Lauritsen MB, Mors O, Mortensen PB, et al. Medical disorders among inpatients with autism in Denmark according to ICD-8: a nationwide register-based study. J Autism Dev Disord. 2002;32(2):115-9.
34. Bolton PF. Medical conditions in autism spectrum disorders. J Neurodev Disord. 2009;1(2):102-13. Epub 2009/06/01.
35. Atladottir HO, Schendel D, Lauritsen M, et al. Patterns of Contact with Hospital for Children with an Autism Spectrum Disorder: A Danish Register-Based Study. J Autism Dev Disord. 2012;42(8):1717-28.
36. van Schrojenstein Lantman-de Valk HMJ, van den Akker M, Maaskant MA, et al. Prevalence and incidence of health problems in people with intellectual disability. J Intell Disabil Res. 1997;41(1):42-51.
37. Hemsley B, Balandin S, Togher L. Narrative analysis of the hospital experience for older parents of people who cannot speak. J Aging Stud. 2007;21(3):239-54.
38. Iacono T, Davis R. The experiences of people with developmental disability in Emergency Departments and hospital wards. Res Dev Disabil. 2003;24(4):247-64.
39. Brereton AV, Tonge BJ, Einfeld SL. Psychopathology in children and adolescents with autism compared to young people with intellectual disability. J Autism Dev Disord. 2006;36(7):863-70. Epub 2006/08/10.
40. Scarpinato N, Bradley J, Kurbjun K, et al. Caring for the child with an autism spectrum disorder in the acute care setting. J Spec Pediatr Nurs. 2010;15(3):244-54. Epub 2010/07/14.
41. Lennox N, Diggens J. Knowledge, skills and attitudes: Medical schools' coverage of an ideal curriculum on intellectual disability. J Intellect Dev Dis. 1999;24(4):341.
42. Ouellette-Kuntz H. Understanding Health Disparities and Inequities Faced by Individuals with Intellectual Disabilities. J Appl Res Intellect Disabil. 2005;18(2):113-21.
43. Petrou S, Mehta Z, Hockley C, et al. The impact of preterm birth on hospital inpatient admissions and costs during the first 5 years of life. Pediatrics. 2003;112(6 Pt 1):1290-7.
44. Brownell MD, Derksen SA, Jutte DP, et al. Socio-economic inequities in children's injury rates: has the gradient changed over time? Can J Public Health. 2010;101 Suppl 3:S28-31. Epub 2011/03/22.

Table 1 – Distribution of individuals in different case groups

Case-comparison group status	Frequency	Percent	Cumulative
No ASD No ID	409,454	98.28	98.28
Mild/mod ID No ASD	4,667	1.12	99.4
Severe ID No ASD	293	0.07	99.47
ASD & ID	767	0.18	99.66
ASD No ID	475	0.11	99.77
Biomedical ID	955	0.23	100
Total	416,611	100	

Table 2 - Cox Proportional Hazard Ratios for Hospitalisation by Case Group

Case group	Hazard Ratio	Robust Standard Error	p-value*	95% Confidence Interval	
No ASD No ID	1.0	-			
Mild/mod ID No ASD	3.1	0.16	<0.001	2.8	3.4
Severe ID No ASD	10.3	0.93	<0.001	8.7	12.3
ASD & ID	2.8	0.31	<0.001	2.3	3.5
ASD No ID	2.1	0.13	<0.001	1.8	2.4
Biomedical ID	7.4	0.34	<0.001	6.7	8.1

*Wald test

Table 3 – Rate Estimate comparison (using margins, dydx**) for birth year band trend over the different case-status groups.**

Birth Year Band	Case-Status	Rate Estimate difference	95% Confidence Interval		P-value
1983 - 1986	Affected	Baseline for Affected status Rate Estimate			
	No ASD No ID	Baseline for No ASD No ID Rate Estimate			
1986 - 1990	Affected	0.573	0.445	0.701	<0.001
	No ASD No ID	-0.046	-0.053	-0.039	<0.001
1990 - 1994	Affected	0.056	0.010	0.102	0.017
	No ASD No ID	-0.266	-0.811	0.278	0.338
1994 - 1999	Affected	0.075	0.028	0.122	0.002
	No ASD No ID	0.263	-0.388	0.913	0.429
1983 - 1986	All other Groups	Baseline for All other groups Rate Estimate			
	Mild ID no ASD	Baseline for Mild ID No ASD Rate Estimate			
1986 - 1990	All other Groups	-0.014	-0.023	-0.005	0.001
	Mild ID no ASD	-0.210	-0.328	-0.091	0.001
1990 - 1994	All other Groups	0.042	0.032	0.052	<0.001
	Mild ID no ASD	-0.332	-0.452	-0.212	<0.001
1994 - 1999	All other Groups	0.081	0.070	0.091	<0.001
	Mild ID no ASD	0.084	-0.056	0.224	0.239
1983 - 1986	All other Groups	Baseline for All other groups Rate Estimate			
	Severe ID no ASD	Baseline for Severe ID no ASD Rate Estimate			
1986 - 1990	All other Groups	-0.035	-0.043	-0.026	<0.001
	Severe ID no ASD	3.570	2.905	4.236	<0.001
1990 - 1994	All other Groups	-0.001	-0.010	0.009	0.841
	Severe ID no ASD	7.901	7.042	8.760	<0.001
1994 - 1999	All other Groups	0.040	0.030	0.050	<0.001
	Severe ID no ASD	9.399	8.312	10.487	<0.001

Birth Year Band	Case-Status	Rate Estimate difference	95% Confidence Interval		P-value
1983 - 1986	All other Groups	Baseline for All other groups Rate Estimate			
	ASD & ID	Baseline for ASD & ID Rate Estimate			
1986 - 1990	All other Groups	-0.021	-0.030	-0.012	<0.001
	ASD & ID	1.488	1.115	1.862	<0.001
1990 - 1994	All other Groups	0.046	0.034	0.057	<0.001
	ASD & ID	0.855	0.467	1.242	<0.001
1994 - 1999	All other Groups	0.079	0.068	0.090	<0.001
	ASD & ID	0.835	0.502	1.168	<0.001
1983 - 1986	All other Groups	Baseline for All other groups Rate Estimate			
	ASD no ID	Baseline for ASD & no ID Rate Estimate			
1986 - 1990	All other Groups	-0.016	-0.025	-0.008	<0.001
	ASD no ID	0.104	-0.321	0.530	0.631
1990 - 1994	All other Groups	0.048	0.036	0.059	<0.001
	ASD no ID	0.493	0.057	0.929	0.027
1994 - 1999	All other Groups	0.082	0.071	0.093	<0.001
	ASD no ID	-0.064	-0.463	0.335	0.754
1983 - 1986	All other Groups	Baseline for All other groups Rate Estimate			
	Biomedical ID	Baseline for Biomedical ID Rate Estimate			
1986 - 1990	All other Groups	-0.031	-0.039	-0.023	<0.001
	Biomedical ID	1.439	1.100	1.777	<0.001
1990 - 1994	All other Groups	-0.005	-0.015	0.005	0.340
	Biomedical ID	5.307	4.828	5.786	<0.001
1994 - 1999	All other Groups	0.055	0.044	0.065	<0.001
	Biomedical ID	2.731	2.322	3.140	<0.001

Table 4

Hazard Ratios, 95% Confidence Intervals and p-values compared to individuals without ASD or ID born in 1993 as shown in Figure 3.

Case Status	Birth Year	Hazard Ratio	95% Confidence Interval		P-value (compared to baseline)
No ASD or ID	1983	baseline			
	1984	0.997	0.985	1.009	0.587
	1985	0.994	0.982	1.007	0.352
	1986	0.974	0.962	0.987	<0.001
	1987	0.930	0.918	0.943	<0.001
	1988	0.960	0.947	0.973	<0.001
	1989	0.934	0.921	0.947	<0.001
	1990	0.929	0.915	0.942	<0.001
	1991	0.946	0.932	0.960	<0.001
	1992	0.960	0.946	0.974	<0.001
	1993	0.968	0.954	0.982	<0.001
	1994	0.972	0.958	0.987	<0.001
	1995	0.975	0.960	0.990	0.001
	1996	0.999	0.984	1.015	0.943
	1997	1.036	1.019	1.052	<0.001
	1998	1.041	1.024	1.058	<0.001
	1999	1.031	1.014	1.049	<0.001
Mild ID no ASD	**1983**	**4.626**	**4.418**	**4.844**	**<0.001**
	1984	**2.192**	**2.061**	**2.332**	**<0.001**
	1985	**2.852**	**2.704**	**3.009**	**<0.001**
	1986	**2.958**	**2.811**	**3.112**	**<0.001**
	1987	**2.558**	**2.436**	**2.686**	**<0.001**
	1988	**3.328**	**3.175**	**3.488**	**<0.001**
	1989	**3.014**	**2.869**	**3.166**	**<0.001**
	1990	**3.019**	**2.875**	**3.170**	**<0.001**
	1991	**2.539**	**2.408**	**2.678**	**<0.001**
	1992	**2.736**	**2.601**	**2.879**	**<0.001**
	1993	**3.079**	**2.904**	**3.266**	**<0.001**
	1994	**3.017**	**2.848**	**3.197**	**<0.001**
	1995	**2.821**	**2.632**	**3.024**	**<0.001**
	1996	**3.662**	**3.421**	**3.920**	**<0.001**
	1997	**3.254**	**2.960**	**3.577**	**<0.001**
	1998	**3.896**	**3.498**	**4.339**	**<0.001**
	1999	**4.001**	**3.549**	**4.510**	**<0.001**

Case Status	Birth Year	Hazard Ratio	95% Confidence Interval		P-value (compared to baseline)
Severe ID no ASD	1983	6.813	6.046	7.676	<0.001
	1984	5.783	5.052	6.620	<0.001
	1985	4.619	4.014	5.314	<0.001
	1986	8.095	7.252	9.038	<0.001
	1987	10.362	9.257	11.599	<0.001
	1988	11.129	10.030	12.348	<0.001
	1989	8.089	7.245	9.033	<0.001
	1990	11.263	10.049	12.625	<0.001
	1991	20.315	18.789	21.965	<0.001
	1992	8.552	7.491	9.763	<0.001
	1993	11.824	10.050	13.909	<0.001
	1994	12.425	10.556	14.626	<0.001
	1995	17.095	14.755	19.806	<0.001
	1996	9.998	8.007	12.485	<0.001
	1997	20.663	17.483	24.422	<0.001
	1998	20.499	18.260	23.013	<0.001
	1999	7.245	5.612	9.353	<0.001
ASD & ID	**1983**	**1.352**	**0.945**	**1.934**	**0.099**
	1984	**1.743**	**1.313**	**2.313**	**<0.001**
	1985	**2.206**	**1.745**	**2.789**	**<0.001**
	1986	**2.081**	**1.664**	**2.602**	**<0.001**
	1987	**5.996**	**5.353**	**6.715**	**<0.001**
	1988	**2.246**	**1.838**	**2.744**	**<0.001**
	1989	**3.081**	**2.665**	**3.563**	**<0.001**
	1990	**2.642**	**2.227**	**3.134**	**<0.001**
	1991	**4.074**	**3.579**	**4.638**	**<0.001**
	1992	**2.039**	**1.696**	**2.450**	**<0.001**
	1993	**1.762**	**1.428**	**2.175**	**<0.001**
	1994	**3.448**	**3.021**	**3.936**	**<0.001**
	1995	**1.821**	**1.516**	**2.186**	**<0.001**
	1996	**4.367**	**3.872**	**4.925**	**<0.001**
	1997	**2.225**	**1.927**	**2.568**	**<0.001**
	1998	**2.102**	**1.800**	**2.454**	**<0.001**
	1999	**2.264**	**1.936**	**2.647**	**<0.001**

Case Status	Birth Year	Hazard Ratio	95% Confidence Interval		P-value (compared to baseline)
ASD no ID	1983	2.048	1.508	2.782	<0.001
	1984	2.321	1.773	3.038	<0.001
	1985	1.095	0.671	1.787	0.718
	1986	3.387	2.661	4.312	<0.001
	1987	1.720	1.338	2.211	<0.001
	1988	1.104	0.712	1.712	0.657
	1989	1.936	1.527	2.456	<0.001
	1990	2.088	1.690	2.580	<0.001
	1991	2.139	1.777	2.575	<0.001
	1992	2.207	1.843	2.645	<0.001
	1993	2.928	2.471	3.469	<0.001
	1994	1.819	1.477	2.239	<0.001
	1995	1.874	1.524	2.305	<0.001
	1996	1.691	1.384	2.066	<0.001
	1997	1.638	1.293	2.074	<0.001
	1998	2.080	1.562	2.768	<0.001
	1999	2.728	2.001	3.720	<0.001
Biomedical ID	**1983**	**4.812**	**4.443**	**5.211**	**<0.001**
	1984	**5.748**	**5.328**	**6.200**	**<0.001**
	1985	**5.012**	**4.615**	**5.444**	**<0.001**
	1986	**5.480**	**5.041**	**5.958**	**<0.001**
	1987	**6.311**	**5.832**	**6.829**	**<0.001**
	1988	**5.369**	**4.900**	**5.883**	**<0.001**
	1989	**7.738**	**7.095**	**8.438**	**<0.001**
	1990	**8.700**	**8.089**	**9.358**	**<0.001**
	1991	**13.724**	**12.984**	**14.505**	**<0.001**
	1992	**7.796**	**7.161**	**8.488**	**<0.001**
	1993	**8.786**	**8.127**	**9.497**	**<0.001**
	1994	**7.086**	**6.355**	**7.902**	**<0.001**
	1995	**8.710**	**8.017**	**9.463**	**<0.001**
	1996	**7.535**	**6.798**	**8.353**	**<0.001**
	1997	**7.182**	**6.403**	**8.057**	**<0.001**
	1998	**6.102**	**5.370**	**6.935**	**<0.001**
	1999	**10.575**	**9.584**	**11.667**	**<0.001**

FIGURE LEGENDS

Figure 1 – Nelson-Aalen Cumulative Hazard for Hospitalisation (number of hospitalisations expected by Age shown on x-axis)

Figure 2 – Kaplan-Meier Curves showing proportion of individuals in each case group who have not been hospitalised by age, for each birth cohort

Figure 3 – Hazard Ratios from multivariate interaction model by birth year and case group status

Figure 4 – Hazard Ratio for hospitalisation risk associated with birth year, pre-term birth and case group status from stratified model

Title: Hospitalisation rates for children with intellectual disability or autism born in Western Australia 1983 – 1999: a population-based cohort study

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Word count: ~~2980~~3331

Article Summary

Focus:

- Children with an intellectual disability and/or autism often experience co-occurring morbidities.
- The rate of hospital admissions experienced by these children compared with the rest of the population has not been detailed previously.

Key Messages:

- The risk of hospitalisation for children with intellectual disability or autism is up to ten times that of those unaffected.
- The risk is greatest for those with severe intellectual disability without the presence of autism.
- Pre-term birth was a risk factor for later hospitalisation independently of year of birth or presence of intellectual disability or autism.

Strengths and Limitations:

- A strength of our study has been the ability to use population-based data on children's hospitalisations and link these to sources providing information on the presence of intellectual disability or autism spectrum disorders.
- One weakness in the study included the exclusion from our modelling of hospitalisation history in the first year of life.

There are no additional data available.

Contributor's Statements

Ami Bebbington has contributed to the paper through involvement in study design, statistical analysis and interpretation and manuscript preparation.
Emma Glasson has contributed to the paper through involvement in study design, manuscript editing and revision and final review.
Jenny Bourke has contributed to the paper through involvement in study design, manuscript editing and revision and final approval.
Nicholas de Klerk has contributed to the paper through statistical design and interpretation and final manuscript review.
Helen Leonard has contributed to the paper through involvement in study design, statistical interpretation, manuscript editing, revision and final approval.

ABSTRACT

Objectives: To describe the hospitalisation patterns in children with intellectual disability (ID) and/or autism spectrum disorder (ASD) after the first year of life and compare with those unaffected.

Design : Prospective cohort study using data linkage between health, intellectual disability and hospitalisation population-based data sets.

Setting : Western Australia

Participants : 416,611 individuals born between 1983 -1999 involving 1,027,962 hospital admission records. Five case categories were defined (mild/moderate ID, severe ID, biomedically caused ID, ASD with ID and ASD without ID) and compared with the remainder of children and young people

Primary and Secondary Outcome Measures: Time to event analysis was used to compare time to hospitalisation and rate of hospitalisation between the different case-groups by estimating hazard ratios, accounting for birth year and pre-term birth status.

Results: ID and/or ASD were found to be associated with an increased risk of hospitalisation compared with the remainder of the population. The increase in risk was highest in those with severe ID and no ASD (HR=10.33, 95% CI 8.66 – 12.31). For those with ID of known biomedical cause or mild ID of unknown cause, the risk of hospitalisation was lower (HR=7.36, 95% CI 6.73 – 8.07 and HR=3.08, 95% CI 2.78 – 3.40, respectively). Those with ASDs had slightly increased risk (HR=2.82, 95% CI 2.26- 3.50 for those with ID and HR=2.09, 95% CI 1.85 – 2.36 for those without ID).

Conclusions: Children with an ID or ASD experience an increased risk of hospitalisation after the first year of life which varied from two to ten times that of the rest of the population. Findings can inform service planning or resource allocation for these children with special needs.

Introduction

Intellectual disability (ID) affects 143 per 10,000 children[1] and is associated with a range of co-morbid health conditions.[2-4] It is heterogeneous,[5] and clustering of some medical conditions may be associated with particular disorders such as Down syndrome [6] or Prader-Willi syndrome.[7] Whilst epilepsy and sensory impairments often occur in association with specific syndromes or more severe cognitive impairment, conditions such as fractures or obesity, may develop as secondary to medication use, nutritional deficiency or lack of mobility.[2] Consequently, children with ID may face greater health challenges than typically developing children and use health care systems more frequently.[8 9] Mental health problems are also common in people with ID.-[10] ~~and~~ For instance, in a Canadian adolescent and adult population with ID a high proportion of hospitalisations were attributed to the presence of psychiatric conditions.[11]

Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by difficulties in communication and social interaction and associated with repetitive or unusual behaviours.[12] ASD ~~affects between~~was reported to affect 30 and 60 per 10,000 children in 2003. [13] However a more recent report from the US Autism and Developmental Disabilities Monitoring (ADDM) Network suggests a higher prevalence of 113 per 10,000.[14] ~~but~~ Moreover nearly two thirds of children with ASDs also have ID.[15] Therefore, it is not surprising that children with ASD also often experience medical conditions such as epilepsy, bowel dysfunction and autoimmune disorders[16] and that their burden of hospitalisation is considered to be high.[17]

Differences in health care policies and pathways of care may impact on hospitalisation rates and service use for children with developmental disorders over time.[8, 18] For example, a recent Canadian study using administrative data [19] found that those with intellectual or developmental disabilities were more likely than those without to use emergency department services. Families with children affected by ID and/or ASDs may have particular difficulty in accessing primary and

specialist health care services, leading to emergency department presentations and hospitalisation rates greater than those not affected by these disorders. A further Canadian study[20] found that admissions to an emergency department for people with ID were more likely to be for a psychobehavioural rather than a medical reason. However there is little population-based data describing the pattern of hospitalisation among children with ID or ASD. This study uses data linkage between health and disability data sets to investigate temporal trends in hospitalisation risk for children with ID and children with ASD in Western Australia (WA) born 1983-1999. The aim was to compare hospitalisation rates between children with ID and/or ASD to children without these diagnoses, taking into account type of ID, birth cohort and preterm birth.

Methods

Cases of ID were ascertained from the Intellectual Disability Exploring Answers (IDEA) database, [21] a population-based register of individuals in WA with intellectual disability with or without an autism spectrum disorder (ASD). The IDEA database receives information from the Disability Services Commission (DSC) and from the Department of Education on individuals accessing services or educational support for an intellectual disability in WA. The inclusion criteria for the IDEA database are an indication of developmental delay before 18 years of age, a full IQ score below 70, and significant deficits in adaptive behaviour. Cases are categorised into mild ID (IQ between 55 and 69), moderate ID (IQ 40-54) and severe ID (IQ <40) but for the purposes of this study, the mild and moderate ID groups were combined.

As detailed previously [15] individuals with a diagnosis of an ASD (which includes autism, Asperger syndrome or Pervasive Developmental Disorder not otherwise specified) were again identified for this study from three sources; DSC, the Western Australian Register for Autism Spectrum Disorders (a prospective data collection system for diagnostic information for cases diagnosed since

1999), and/or from a case group born 1983-1995 and diagnosed by 1999 as identified by a developmental paediatrician through case-note review. Using record linkage to the IDEA database, individuals identified with an ASD were sub-divided into those with or without an additional ID. Those for whom an ID status could not be determined were grouped with those with ID, so that the ASD without ID group contained only those definitively known not to have an ID. Individuals were further classified according to whether there was a known biomedical cause for the ID (such as a congenital or genetic condition e.g. Down syndrome) or otherwise. This categorisation is based on the information in the Intellectual Disability (IDEA) Database[21] 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 our own[15, 22] and previous published research.[23] 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). However we excluded diagnostic categories (e.g. preterm birth) that are associated with but are not necessarily a sufficient cause of ID and those where a genetic diagnosis might be suspected but not clinically or genetically confirmed.

~~Individuals were further classified according to whether there was a known biomedical cause for the ID (such as a congenital or genetic conditions e.g. Down syndrome) or otherwise, since, if so there is most probably a greater likelihood of additional comorbidities and need for hospitalisation.~~

Therefore five case categories were defined (mild/moderate ID, severe ID, biomedically caused ID, ASD with ID and ASD without ID) and compared with the remainder of children and young people born in WA between 1983 and 1999 who, at the time of case extraction, were unaffected by ID or ASD.

Information on hospitalisations from 1 January, 1983- 31 December, 2004~~5~~ was obtained from the WA Hospital Morbidity Data System, which is a statutory collection of data relating to all inpatient episodes to public, private and freestanding day hospitals in WA since 1970.[24] It contains ICD-

coded diagnosis and procedure information. WA also has a statutory collection of pregnancy, birth and maternal data, recorded at the time of birth, known as the Midwives Notification System. [24] Linkage of all birth records 1983 to 1999 ~~(collected via the Midwives Notification System, a statutory collection of pregnancy, birth and maternal data, recorded at the time of birth,[21])~~ to hospital and death data was undertaken independently at the WA Data Linkage Branch, where these data sets and others are linked regularly for the purposes of approved research projects.[24] ~~and a~~A de-identified dataset was provided for this analysis in which all individuals were followed from birth through to either death or the censoring date of 31 December, 2004. Pre-term birth was defined as being born at less than 37 weeks gestation with gestational age obtained from the Midwives Notification System.

The analysis was restricted to hospitalisations occurring after the first year of life, thereby excluding individuals who did not survive to this age. The focus of this paper was on hospitalisations occurring in childhood and adolescence, an area lacking in quantitative, population-based research, rather than on the hospitalisations occurring peri-natally or in infancy, where our group has already quantified the increased burden of hospital care in children with ID (particularly biomedically-caused ID).[8] Hospitalisations occurring on the same day as another recorded hospitalisation, as well as those occurring as part of a nested transfer (the patient moves to another hospital during a stay in hospital) or a transfer sequence (the patient moves between hospitals successively without return home) were ~~excluded~~considered as a single event.

While we refer to case and comparison groups throughout, this is a cohort study where the different case groups can be thought of as different 'exposures'. Thus time to event analysis (which allows for varying individual time at risk) was used to compare time to hospitalisation and rate of hospitalisation between the groups, accounting for birth year and pre-term birth status. Hospitalisation rates were represented by incidence rates (IR) in terms of number of admissions per

person per year. Group status was used as a categorical predictor of time to hospitalisation, producing Nelson-Aalen cumulative hazard estimates (which in this case represent expected number of hospitalisations experienced by a particular age). Hazard ratios from the Cox proportional hazards model were also used to investigate differences in risk of hospitalisation for the different case groups, with robust standard errors estimated to account for the multiple hospitalisations per individual. The effect of birth year was considered by stratifying year of birth into four eras being 1983- 1985, 1986-1989, 1990-1993 and 1994-1999, such that each group has equal number of records, using STATA's **egen cut** command. In more specific modelling, birth year was included as an indicator variable for each individual year from 1983 to 1999 rather than banded. Ethical approval for this study was granted by the UWA Human Research Ethics Committee.

Results

A dataset of 1,027,962 records representing the time at risk of hospitalisation for 416,611 children (Table 1) and young people born in WA from 1983 to 1999 was created. The total time at risk of hospitalisation in the cohort was 5,146,927.5 person years, while 3,818.6 person years were spent in hospital (when not on the risk set for hospitalisation). Individual time at risk varied from 5 years (for those born in 1999) to 21 years (for those born in 1983). The dataset contained 611,816 admissions to hospital with a median of one hospitalisation per subject, giving an incidence rate (IR) of 0.12 admissions per person per year and median time to hospitalisation of 5.09 years (inter-quartile-range (IQR) 2.26 years – 13.65 years). By the age of ten years, 67.7% (95% CI 67.6% - 67.8%) of individuals had been hospitalised at least once, increasing to 85.0% (95% CI 84.9% - 85.1%) by the age of 18 years. On average, a child of 10 years in this cohort had been hospitalised 1.13 times (cumulative hazard) and a young person of 18 years, 1.90 times.

The highest rate of hospitalisation was observed for cases with severe ID but without an ASD (1.16 hospitalisations/person-year, median time to hospitalisation 1.27 years) followed by cases with a biomedical cause of ID (0.84 hospitalisations/person year, median age of 1.37 years at first hospitalisation), mild or moderate ID without ASD (IR 0.34, median age 1.95 years), and ASDs with ID (IR 0.33, median age of 2.43 years at first hospitalisation). Those children with ASD and no ID had the lowest rate of hospitalisation of the case groups (IR 0.24, median age of 2.89 years at first hospitalisation) however their rate was still higher than that of the general population (IR 0.11, median age of 5.37 years at first hospitalisation). The highest rates of hospitalisation over time were experienced by those with severe ID and those with ID with a known biomedical cause with both groups experiencing five or more hospitalisations by five years of age (Figure 1). The similarity of curves between those with mild/moderate ID and ASD with ID can also be seen. All case groups experienced a higher estimated risk of hospitalisations than the unaffected individuals (Table 2).

Figure 2 shows the time to hospitalisation curves by case status for the four birth cohorts. The curves for the severe ID and the biomedically caused ID groups separate increasingly with advancing age and shows that the difference between these two groups has amplified over time. Table 3 shows the differences in rate estimates for the different birth year bands over the different case status groups, compared with all other groups. This shows that there is an increase in difference in hospitalisation rate over time in the severe ID (no ASD) groups and the biomedical ID groups much greater than the rate differences of the other groups, and that the severe ID group's risk increases more steeply than that of the biomedical ID group. To measure this more precisely, interaction effects between case status and birth year were included in the Cox proportional hazards modelling and demonstrated that a significantly greater proportion of the variability in time to hospitalisation was explained by the interaction model than by the main effects model ($p < 0.001$).

Figure 3 shows the hazard ratios over birth year from this interaction model in all six groups. These hazard ratios and their confidence intervals are also shown in Table 4. The great increase in risk for all groups compared with the general population is clear, as is the change in hospitalisation relative risk over time both within each group and differing patterns between the groups. In all groups, an increase in risk of hospitalisation was associated with a more recent birth year, however, a small but steadily upwards trend was only observed in the general population and the mild/moderate ID groups. Risk of hospitalisation per birth year fluctuated for those with ASDs (with or without an ID) and for those with severe ID (though from a higher rate).

There were 30,850 births before 37 weeks gestation (7.42% of all births in the cohort) who survived the first year of life. Univariate comparison of time to hospitalisation for those born pre-term vs. full term suggests that those born pre-term are admitted to hospital more frequently (IR 0.17 per person-year for pre-term, 0.11 for full term), and earlier (median time to hospitalisation 3.01 years for pre-term, 5.37 years for full-term) than those born full term. Including birth year and case status factors in the Cox proportional hazards model showed that the hazard ratio for pre-term birth was 1.45 (95% CI 1.39 – 1.51, p<0.001), indicating ~~that indeed,~~the independent effect of pre-term birth ~~was a risk factor for later hospitalisation independently of ID/ASD group or birth year~~ on hospitalisations for each case group (Figure 4). ~~Including pre-term birth in the model with case group and birth year interaction resulted in the hazard ratio curves shown in Figure 4 where the pre-term and at term lines are separated by a fixed distance which is the independent effect of pre-term birth. The birth year and case-status differences persist after including this pre-term birth effect.~~

Discussion

This study quantified the rate of hospitalisations for children with an ID and/or ASD compared with the general population. Children diagnosed with ID and/or ASD experienced more hospitalisations

than children with neither condition, and this effect persisted after taking into account birth year and pre-term birth status. Whilst overall hospitalisation rates differ by age, the rate of hospitalisation appears to decline with increasing age, particularly for the groups with a known biomedical cause and with severe ID of unknown cause, in contrast to the general population where the rate appears more constant. We also showed that the independent effect of pre-term birth on hospitalisation rates after one year of age is both an increase in frequency and earlier median age at hospitalisation, and this is consistent across all case groups.

~~The highest rate of hospitalisations occurred among the severe ID group, followed by those with a known biomedical cause for their ID, mild/moderate ID, ASD with ID, ASD without ID and then the comparison population. Thus the rate of hospitalisation was positively correlated with the severity of ID. Although r~~Recent studies in the US[17] and Denmark[22] have investigated the hospitalisation burden for children with autism, and found that individuals with autism had significantly higher lengths of stay and that costs were considerably more than for those without autism. The Danish study also found that children with ASD had an increased rate of contact with hospital, regardless of the cause of their hospital admission. However, ~~this is the first~~unlike our study neither of these two studies ~~to~~ were able to compare the hospitalisation patterns of children with ASD- with those of children with ID~~and ID with the rest of a total population over an extended time period~~. What we found was that the highest rate of hospitalisations occurred among the severe ID group, followed by those with a known biomedical cause for their ID, mild/moderate ID, ASD with ID, ASD without ID and then the comparison population. Thus the rate of hospitalisation was positively correlated with the severity of ID. ~~The current~~Our study was able to ~~show~~ demonstrate the gradient of risk between the groups over the study period using the same data methods, whole-of-population sampling and controlling for interaction variables. We have also shown an increasing discrepancy in hospitalisations over time between those with severe ID and no ASD and those with a biomedical cause, particularly at younger ages. One possible explanation is that in more recent

years the aetiology of severe intellectual disability is being increasingly identified through new genetic techniques[25, 26] and thus there has been a diagnostic transfer from those with severe ID of unknown cause to those with a biomedical cause over time. Another explanation may be the improved survival in those with severe ID of unknown cause which is associated with ongoing high medical needs.

Various comorbid health conditions affect children with ID, including epilepsy, skin conditions, sensory loss, fractures and psychiatric disorders.[2-4] However apart from individual conditions such as Down syndrome,[6] Rett syndrome,[27] Tuberous Sclerosis [28] and Angelman syndrome [29] and a recent paper describing the increase over time in resource utilisation by children with neurological impairment,[30] there is a dearth of population-based data on medical co-morbidities associated with ID. Our results would suggest that, although ID may be under-recognised and under-researched in comparison to autism, its associated health burden should not be underestimated. In Canada it has been shown that for ambulatory care sensitive (ACS) conditions, people with an ID are hospitalised at six times the rate of those without an ID, with the rate ratio peaking at double this for those aged 30-39 years.[31] This may reflect a lack of appropriate and accessible primary care for people with ID, particularly for those transitioning from the paediatric health care system. The highest hospitalisation rate ratio was for epilepsy, known to be a common co-morbid condition for people with ID [3], and a condition with a high level of impact on the life of the individual and their family.[32]

As with ID, various comorbid health conditions including gastrointestinal disorders, sleep disturbances, sensory impairments ~~and~~ , diabetes mellitus type 1 and epilepsy also occur in ASD.[9, 16, 33, 34] Although the hospitalisation burden for children with ASD[17, 35] has previously been reported to be high we have clearly shown in our present study that for children with ID the burden is considerably greater. Behaviour and communication difficulties are reported to be significant barriers to utilising hospital care for children with developmental disabilities [19, 36] and may increase

the overall burden and amount of family support necessary.[37, 38] Such challenging behaviours are known to be more frequent in children with ASD than in those with ID and thus may increase the difficulty in their accessing hospital care. Comorbid psychopathology is particularly common in children with ASD [39] and the specific types of behaviours associated with ASD may discourage hospitalisation and also shorten the length of stay.[40] More detailed research on the patterns of primary and secondary health care use for people with an ID and/or ASD, according to health burden and sociodemographic status is needed to unpack the associations between these disorders and increased hospitalisation. Because of the increased risk of hospitalisations of children with ID and ASD resource planners need to prioritise specialised care allocation for these populations. Lack of medical and nursing staff trained in developmental disability management skills may have in the past led to negative experiences, inadequate care and compounded problems.[41, 42] Qualitative information from parents would help to understand these relationships and identify specific factors that may affect or modify the risk of hospitalisation in these children. Such research would be important in helping to inform resource planning. We concur with the plea made by Berry and colleagues to ensure that the current health care system is adequately educated and equipped to care for this growing proportion of vulnerable children within the hospital population.[30]

A strength of our study has been the ability to use population-based data on children's hospitalisations and link these to sources of disability diagnosis (i.e. presence of ID or ASD). By including birth year in the model we were able to account for these changes over time and show how the patterns of risk of hospitalisation changed for individuals in the different categories. We also accounted for possible confounding by pre-term birth status, known to be associated with increased childhood hospitalisations[43] and demonstrated the consistent effect of pre-term birth on hospitalisation rates across all case groups and the rest of the population. Weaknesses in our study included exclusion from our modelling of hospitalisation history in the first year of life, which may indeed change later risk of hospitalisation. This was lack of access to birth date data (for privacy

reasons) and to a change in coding practises in the WA healthcare system that occurred in the mid-1990s.

Children with developmental disabilities have an increased risk of hospitalisation, the extent of which varies according to the type of disability and level of intellectual functioning. Future research should investigate how hospitalisations relate to underlying morbidities, common in intellectual disability and less so in autism, and also consider the role of access to primary care in preventing unnecessary hospitalisation. A better understanding of the patterns of hospitalisation for these children will help establish resource planning opportunities for the specific services required to meet their increasing needs.[44]

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References

1. Leonard H, Petterson B, Bower C, Sanders R. Prevalence of intellectual disability in Western Australia. Paediatr Perinat Epidemiol. 2003;17:58-67.

2. Jansen DE, Krol B, Groothoff JW, Post D. People with intellectual disability and their health problems: a review of comparative studies. J Intell Disabil Res. 2004;48(Pt 2):93-102. Epub 2004/01/16.
3. Oeseburg B, Dijkstra GJ, Groothoff JW, Reijneveld SA, Jansen DE. Prevalence of chronic health conditions in children with intellectual disability: a systematic literature review. Intellect Dev Disabil. 2011;49(2):59-85.
4. van Schrojenstein Lantman-de Valk HMJ. Health in People with Intellectual Disabilities: Current Knowledge and Gaps in Knowledge. J Appl Res Intellect Disabil. 2005;18(4):325-33.
5. Leonard H, Wen X. The epidemiology of mental retardation: challenges and opportunities in the new millennium. Ment Retard Dev D R. 2002;8(3):117-34.
6. Thomas K, Girdler S, Bourke J, Deshpande A, Bathgate K, Fehr S, Leonard H. Overview of Health Issues in School-aged Children with Down Syndrome. In: Urbano R, C., editor. Int Rev Res Ment Ret: Academic Press; 2010. p. p. 67-106.
7. Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader-Willi syndrome. Genet Med. 2012;14(1):10-26. Epub 2012/01/13.
8. Williams K, Leonard H, Tursan d'Espaignet E, Colvin L, Slack-Smith L, Stanley F. Hospitalisations from birth to 5 years in a population cohort of Western Australian children with intellectual disability. Arch Dis Child. 2005;90(12):1243-8.
9. Schieve LA, Gonzalez V, Boulet SL, Visser SN, Rice CE, Braun KV, Boyle CA. Concurrent medical conditions and health care use and needs among children with learning and behavioral developmental disabilities, National Health Interview Survey, 2006-2010. Res Dev Disabil. 2012;33(2):467-76. Epub 2011/11/29.
10. Einfeld SL, Tonge BJ. Population prevalence of psychopathology in children and adolescents with intellectual disability: II. Epidemiological findings. J Intell Disabil Res. 1996;40(Pt 2):99-109.
11. Balogh RS, Hunter D, Ouellette-Kuntz H. Hospital Utilization among Persons with an Intellectual Disability, Ontario, Canada, 1995–2001. J Appl Res Intellect Disabil. 2005;18(2):181-90.
12. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Health Disorders 4th Edition. Washington DC: American Psychiatric Association; 1994.
13. Leonard H, Dixon G, Whitehouse A, Bourke J, Aiberti K, Nassar N, Bower C, Glasson E. Unpacking the complex nature of the autism epidemic. Res Autism Spect Dis. 2010;4(4):548-54.
14. Baio J. Prevalence of autism spectrum disordres-Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States 2008. MMWR CDC Surveill Summ. 2012;61(3):1-19.
15. Leonard H, Glasson E, Nassar N, Whitehouse A, Bebbington A, Bourke J, Jacoby P, Dixon G, Malacova E, Bower C, Stanley F. Autism and intellectual disability are differentially related to sociodemographic background at birth. PLoS One. 2011;6(3):e17875. Epub 2011/04/12.
16. Kohane IS, McMurry A, Weber G, MacFadden D, Rappaport L, Kunkel L, Bickel J, Wattanasin N, Spence S, Murphy S, Churchill S. The co-morbidity burden of children and young adults with autism spectrum disorders. PLoS One. 2012;7(4):e33224. Epub 2012/04/19.
17. Lokhandwala T, Khanna R, West-Strum D. Hospitalization burden among individuals with autism. J Autism Dev Disord. 2012;42(1):95-104. Epub 2011/03/16.
18. Thomas K, Bourke J, Girdler S, Bebbington A, Jacoby P, Leonard H. Variation over time in medical conditions and health service utilization of children with Down syndrome. J Pediatr. 2011;158(2):194-200 e1.

19. Lunsky Y, Lin E, Balogh R, Klein-Geltink J, Bennie J, Wilton AS, Kurdyak P. Are adults with developmental disabilities more likely to visit EDs? Am J Emerg Med. 2011;29(4):463-5.
20. Lunsky Y, Balogh R, Khodaverdian A, Elliott D, Jaskulski C, Morris S. A Comparison of Medical and Psychobehavioral Emergency Department Visits Made by Adults with Intellectual Disabilities. Emerg Med Int. 2012;2012:6.
21. Petterson B, Leonard H, Bourke J, Sanders R, Chalmers R, Jacoby P, Bower C. IDEA (Intellectual Disability Exploring Answers): a population-based database for intellectual disability in Western Australia. Ann Hum Biol. 2005;32(2):237-43.
22. Leonard H, Petterson B, De Klerk N, Zubrick SR, Glasson E, Sanders R, Bower C. Association of sociodemographic characteristics of children with intellectual disability in Western Australia. Soc Sci Med. 2005;60(7):1499-513.
23. Yeargin-Allsopp M, Murphy CC, Cordero JF, Decoufle P, Hollowell JG. Reported biomedical causes and associated medical conditions for mental retardation among 10-year-old children, metropolitan Atlanta, 1985 to 1987. Dev Med Child Neurol. 1997;39(3):142-9. Epub 1997/03/01.
24. Holman CD, Bass AJ, Rosman DL, Smith MB, Semmens JB, Glasson EJ, Brook EL, Trutwein B, Rouse IL, Watson CR, de Klerk NH, Stanley FJ. A decade of data linkage in Western Australia: strategic design, applications and benefits of the WA data linkage system. Aust Health Rev. 2008;32(4):766-77. Epub 2008/11/05.
25. Jaillard S, Drunat Sv, Bendavid C, Aboura A, Etcheverry A, Journel H, Delahaye Ae, Pasquier L, Bonneau D, Toutain A, Burglen L, Guichet As, Pipiras E, Gilbert-Dussardier B, Benzacken B, Martin-Coignard D, Henry C, David A, Lucas J, Mosser J, David Vr, Odent S, Verloes A, Dubourg Cl. Identification of gene copy number variations in patients with mental retardation using array-CGH: Novel syndromes in a large French series. Eur J Med Genet. 2010;53(2):66-75.
26. Koolen DA, Pfundt R, de Leeuw N, Hehir-Kwa JY, Nillesen WM, Neefs I, Scheltinga I, Sistermans E, Smeets D, Brunner HG, van Kessel AG, Veltman JA, de Vries BBA. Genomic microarrays in mental retardation: A practical workflow for diagnostic applications. Hum Mutat. 2009;30(3):283-92.
27. Young D, Bebbington A, de Klerk N, Bower C, Nagarajan L, Leonard H. The relationship between MECP2 mutation type and health status and service use trajectories over time in a Rett syndrome population. Res Autism Spect Dis. 2011;5(1):442-9.
28. Osborne JP, Merrifield J, O'Callaghan FJ. Tuberous sclerosis--what's new? Arch Dis Child. 2008;93(9):728-31. Epub 2008/05/06.
29. Williams CA, Driscoll DJ, Dagli AI. Clinical and genetic aspects of Angelman syndrome. Genet Med. 2010;12(7):385-95. Epub 2010/05/07.
30. Berry JG, Poduri A, Bonkowsky JL, Zhou J, Graham DA, Welch C, Putney H, Srivastava R. Trends in resource utilization by children with neurological impairment in the United States inpatient health care system: a repeat cross-sectional study. PLoS Med. 2012;9(1):e1001158. Epub 2012/01/25.
31. Balogh R, Brownell M, Ouellette-Kuntz H, Colantonio A. Hospitalisation rates for ambulatory care sensitive conditions for persons with and without an intellectual disability--a population perspective. J Intell Disabil Res. 2010;54(9):820-32. Epub 2010/08/14.
32. Bowley C, Kerr M. Epilepsy and intellectual disability. J Intell Disabil Res. 2000;44 (Pt 5):529-43. Epub 2000/11/18.
33. Lauritsen MB, Mors O, Mortensen PB, Ewald H. Medical disorders among inpatients with autism in Denmark according to ICD-8: a nationwide register-based study. J Autism Dev Disord. 2002;32(2):115-9.
34. Bolton PF. Medical conditions in autism spectrum disorders. J Neurodev Disord. 2009;1(2):102-13. Epub 2009/06/01.

35. Atladottir HO, Schendel D, Lauritsen M, Henriksen T, Parner E. Patterns of Contact with Hospital for Children with an Autism Spectrum Disorder: A Danish Register-Based Study. J Autism Dev Disord. 2012;42(8):1717-28.
36. van Schrojenstein Lantman-de Valk HMJ, van den Akker M, Maaskant MA, Haveman MJ, Urlings HFJ, Kessels AG, Crebolder HFJK. Prevalence and incidence of health problems in people with intellectual disability. J Intell Disabil Res. 1997;41(1):42-51.
37. Hemsley B, Balandin S, Togher L. Narrative analysis of the hospital experience for older parents of people who cannot speak. J Aging Stud. 2007;21(3):239-54.
38. Iacono T, Davis R. The experiences of people with developmental disability in Emergency Departments and hospital wards. Res Dev Disabil. 2003;24(4):247-64.
39. Brereton AV, Tonge BJ, Einfeld SL. Psychopathology in children and adolescents with autism compared to young people with intellectual disability. J Autism Dev Disord. 2006;36(7):863-70. Epub 2006/08/10.
40. Scarpinato N, Bradley J, Kurbjun K, Bateman X, Holtzer B, Ely B. Caring for the child with an autism spectrum disorder in the acute care setting. J Spec Pediatr Nurs. 2010;15(3):244-54. Epub 2010/07/14.
41. Lennox N, Diggens J. Knowledge, skills and attitudes: Medical schools' coverage of an ideal curriculum on intellectual disability. J Intellect Dev Dis. 1999;24(4):341.
42. Ouellette-Kuntz H. Understanding Health Disparities and Inequities Faced by Individuals with Intellectual Disabilities. J Appl Res Intellect Disabil. 2005;18(2):113-21.
43. Petrou S, Mehta Z, Hockley C, Cook-Mozaffari P, Henderson J, Goldacre M. The impact of preterm birth on hospital inpatient admissions and costs during the first 5 years of life. Pediatrics. 2003;112(6 Pt 1):1290-7.
44. Brownell MD, Derksen SA, Jutte DP, Roos NP, Ekuma O, Yallop L. Socio-economic inequities in children's injury rates: has the gradient changed over time? Can J Public Health. 2010;101 Suppl 3:S28-31. Epub 2011/03/22.

Table 1 – Distribution of individuals in different case groups

Case-comparison group status	Frequency	Percent	Cumulative
No ASD No ID	409,454	98.28	98.28
Mild/mod ID No ASD	4,667	1.12	99.4
Severe ID No ASD	293	0.07	99.47
ASD & ID	767	0.18	99.66
ASD No ID	475	0.11	99.77
Biomedical ID	955	0.23	100
Total	416,611	100	

Figure 1 – Nelson-Aalen Cumulative Hazard for Hospitalisation (number of hospitalisations expected by Age shown on x-axis)

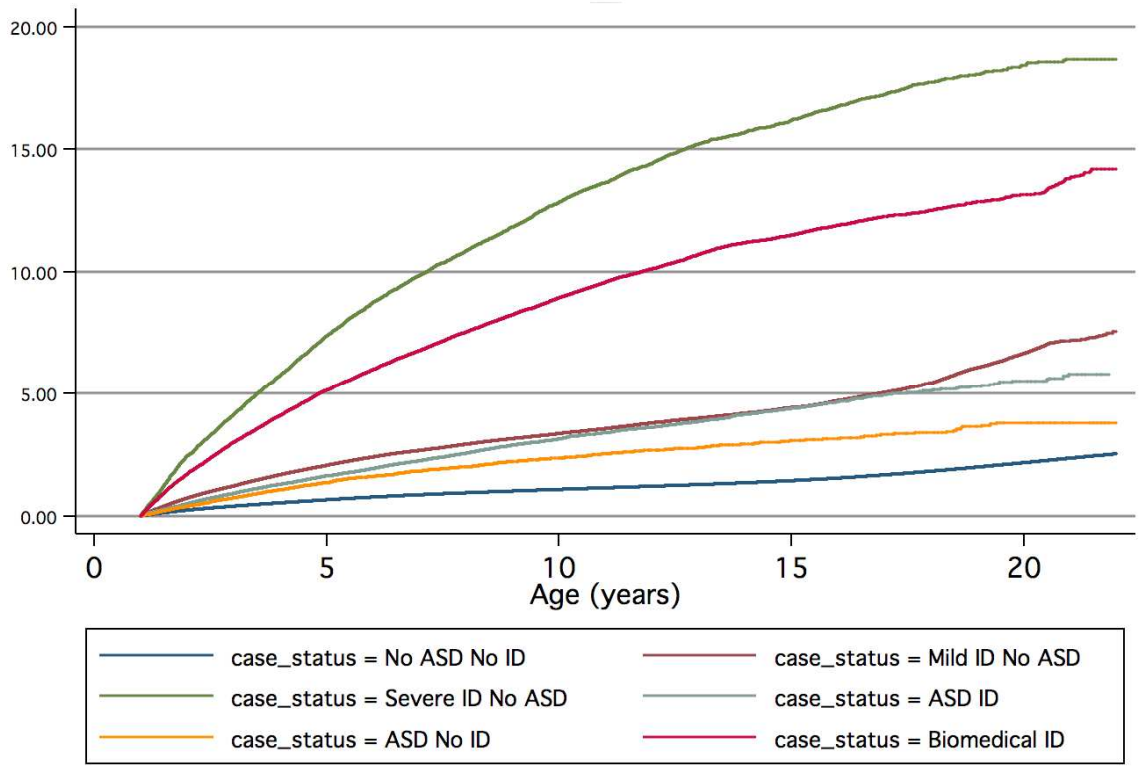


Table 2 - Cox Proportional Hazard Ratios for Hospitalisation by Case Group

Case group	Hazard Ratio	Robust Standard Error	p-value*	95% Confidence Interval	
No ASD No ID	1.0	-			
Mild/mod ID No ASD	3.1	0.16	<0.001	2.8	3.4
Severe ID No ASD	10.3	0.93	<0.001	8.7	12.3
ASD & ID	2.8	0.31	<0.001	2.3	3.5
ASD No ID	2.1	0.13	<0.001	1.8	2.4
Biomedical ID	7.4	0.34	<0.001	6.7	8.1

*Wald test

Figure 2 – Kaplan-Meier Curves showing proportion of individuals in each case group who have not been hospitalised by age, for each birth cohort

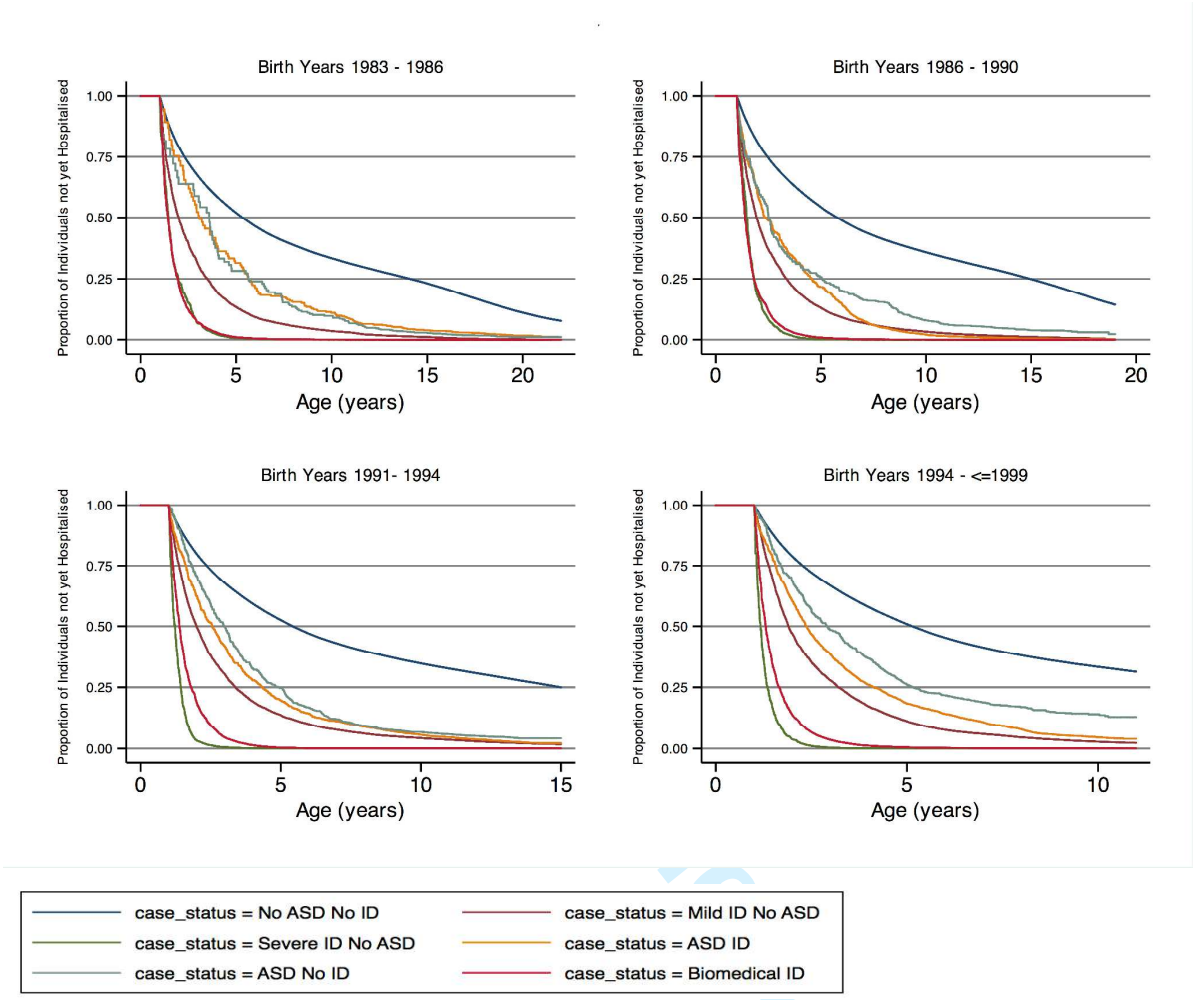


Table 3 – Rate Estimate comparison (using **margins, dydx**) for birth year band trend over the different case-status groups.

Birth Year Band	Case-Status	Rate Estimate difference	95% Confidence Interval		P-value
1983 - 1986	Affected	Baseline for Affected status Rate Estimate			
	No ASD No ID	Baseline for No ASD No ID Rate Estimate			
1986 - 1990	Affected	0.573	0.445	0.701	<0.001
	No ASD No ID	-0.046	-0.053	-0.039	<0.001
1990 - 1994	Affected	0.056	0.010	0.102	0.017
	No ASD No ID	-0.266	-0.811	0.278	0.338
1994 - 1999	Affected	0.075	0.028	0.122	0.002
	No ASD No ID	0.263	-0.388	0.913	0.429
1983 - 1986	All other Groups	Baseline for All other groups Rate Estimate			
	Mild ID no ASD	Baseline for Mild ID No ASD Rate Estimate			
1986 - 1990	All other Groups	-0.014	-0.023	-0.005	0.001
	Mild ID no ASD	-0.210	-0.328	-0.091	0.001
1990 - 1994	All other Groups	0.042	0.032	0.052	<0.001
	Mild ID no ASD	-0.332	-0.452	-0.212	<0.001
1994 - 1999	All other Groups	0.081	0.070	0.091	<0.001
	Mild ID no ASD	0.084	-0.056	0.224	0.239
1983 - 1986	All other Groups	Baseline for All other groups Rate Estimate			
	Severe ID no ASD	Baseline for Severe ID no ASD Rate Estimate			
1986 - 1990	All other Groups	-0.035	-0.043	-0.026	<0.001
	Severe ID no ASD	3.570	2.905	4.236	<0.001
1990 - 1994	All other Groups	-0.001	-0.010	0.009	0.841
	Severe ID no ASD	7.901	7.042	8.760	<0.001
1994 - 1999	All other Groups	0.040	0.030	0.050	<0.001
	Severe ID no ASD	9.399	8.312	10.487	<0.001

Birth Year Band	Case-Status	Rate Estimate difference	95% Confidence Interval		P-value
1983 - 1986	All other Groups	Baseline for All other groups Rate Estimate			
	ASD & ID	Baseline for ASD & ID Rate Estimate			
1986 - 1990	All other Groups	-0.021	-0.030	-0.012	<0.001
	ASD & ID	1.488	1.115	1.862	<0.001
1990 - 1994	All other Groups	0.046	0.034	0.057	<0.001
	ASD & ID	0.855	0.467	1.242	<0.001
1994 - 1999	All other Groups	0.079	0.068	0.090	<0.001
	ASD & ID	0.835	0.502	1.168	<0.001
1983 - 1986	All other Groups	Baseline for All other groups Rate Estimate			
	ASD no ID	Baseline for ASD & no ID Rate Estimate			
1986 - 1990	All other Groups	-0.016	-0.025	-0.008	<0.001
	ASD no ID	0.104	-0.321	0.530	0.631
1990 - 1994	All other Groups	0.048	0.036	0.059	<0.001
	ASD no ID	0.493	0.057	0.929	0.027
1994 - 1999	All other Groups	0.082	0.071	0.093	<0.001
	ASD no ID	-0.064	-0.463	0.335	0.754
1983 - 1986	All other Groups	Baseline for All other groups Rate Estimate			
	Biomedical ID	Baseline for Biomedical ID Rate Estimate			
1986 - 1990	All other Groups	-0.031	-0.039	-0.023	<0.001
	Biomedical ID	1.439	1.100	1.777	<0.001
1990 - 1994	All other Groups	-0.005	-0.015	0.005	0.340
	Biomedical ID	5.307	4.828	5.786	<0.001
1994 - 1999	All other Groups	0.055	0.044	0.065	<0.001
	Biomedical ID	2.731	2.322	3.140	<0.001

Figure 3 – Hazard Ratios from multivariate interaction model by birth year and case group status

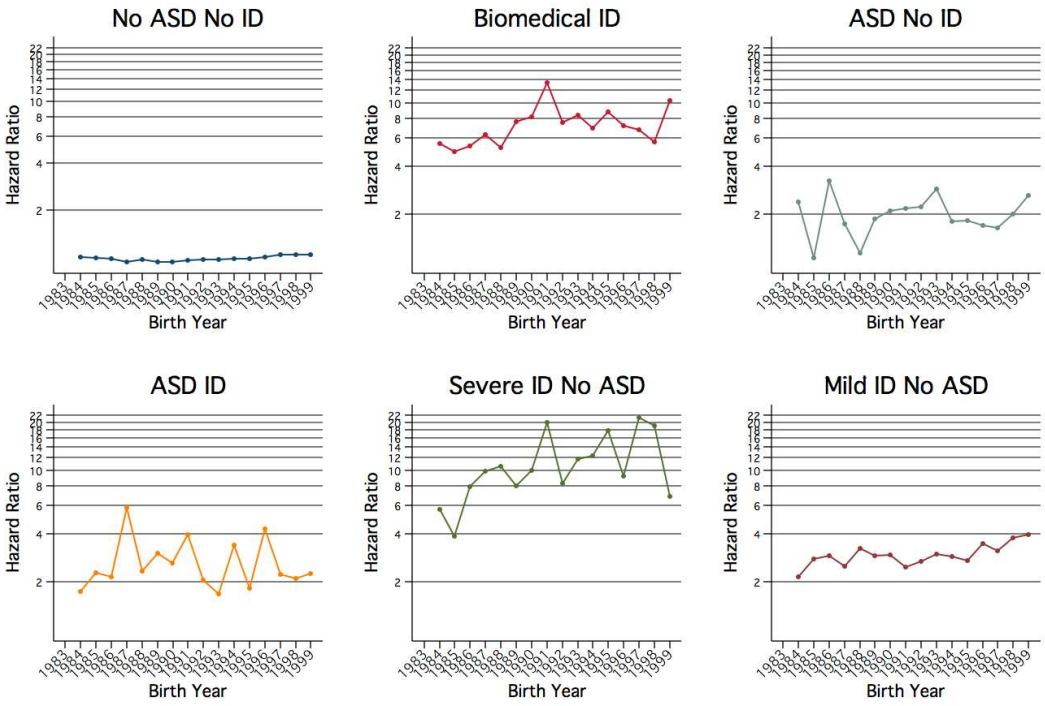


Table 4

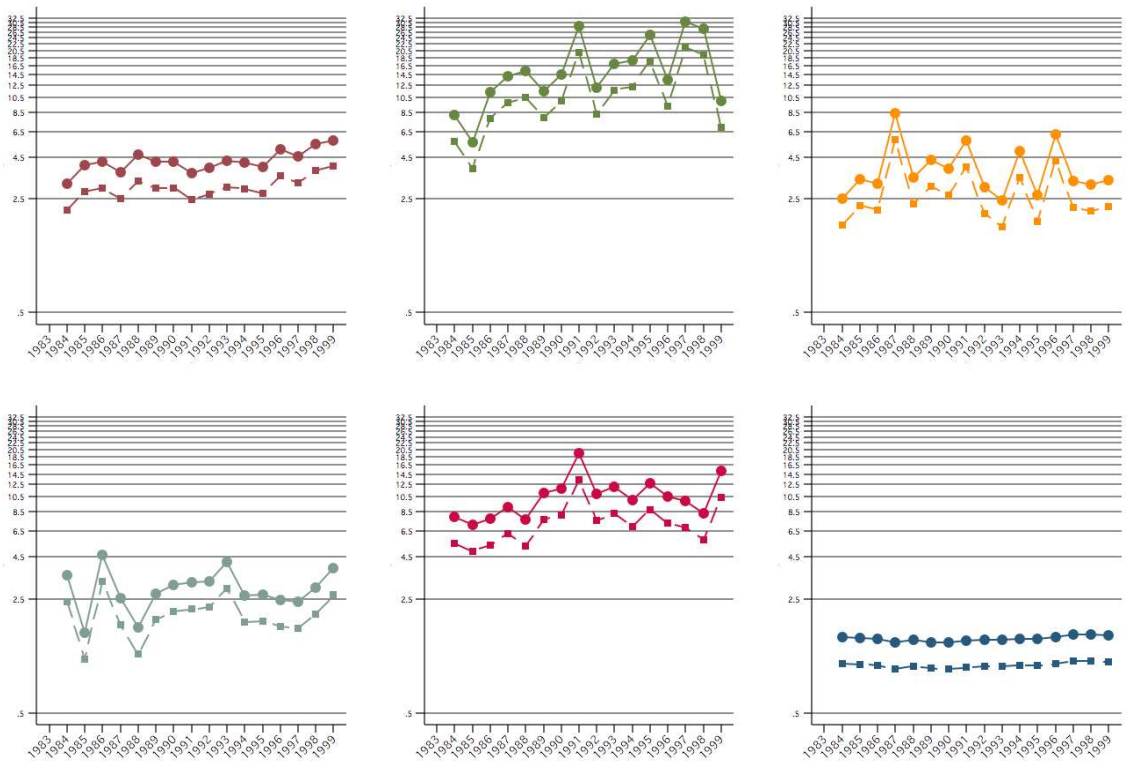
Hazard Ratios, 95% Confidence Intervals and p-values compared to individuals without ASD or ID born in 1993 as shown in Figure 3.

Case Status	Birth Year	Hazard Ratio	95% Confidence Interval		P-value (compared to baseline)
No ASD or ID	1983	baseline			
	1984	0.997	0.985	1.009	0.587
	1985	0.994	0.982	1.007	0.352
	1986	0.974	0.962	0.987	<0.001
	1987	0.930	0.918	0.943	<0.001
	1988	0.960	0.947	0.973	<0.001
	1989	0.934	0.921	0.947	<0.001
	1990	0.929	0.915	0.942	<0.001
	1991	0.946	0.932	0.960	<0.001
	1992	0.960	0.946	0.974	<0.001
	1993	0.968	0.954	0.982	<0.001
	1994	0.972	0.958	0.987	<0.001
	1995	0.975	0.960	0.990	0.001
	1996	0.999	0.984	1.015	0.943
	1997	1.036	1.019	1.052	<0.001
	1998	1.041	1.024	1.058	<0.001
	1999	1.031	1.014	1.049	<0.001
Mild ID no ASD	**1983**	**4.626**	**4.418**	**4.844**	**<0.001**
	1984	**2.192**	**2.061**	**2.332**	**<0.001**
	1985	**2.852**	**2.704**	**3.009**	**<0.001**
	1986	**2.958**	**2.811**	**3.112**	**<0.001**
	1987	**2.558**	**2.436**	**2.686**	**<0.001**
	1988	**3.328**	**3.175**	**3.488**	**<0.001**
	1989	**3.014**	**2.869**	**3.166**	**<0.001**
	1990	**3.019**	**2.875**	**3.170**	**<0.001**
	1991	**2.539**	**2.408**	**2.678**	**<0.001**
	1992	**2.736**	**2.601**	**2.879**	**<0.001**
	1993	**3.079**	**2.904**	**3.266**	**<0.001**
	1994	**3.017**	**2.848**	**3.197**	**<0.001**
	1995	**2.821**	**2.632**	**3.024**	**<0.001**
	1996	**3.662**	**3.421**	**3.920**	**<0.001**
	1997	**3.254**	**2.960**	**3.577**	**<0.001**
	1998	**3.896**	**3.498**	**4.339**	**<0.001**
	1999	**4.001**	**3.549**	**4.510**	**<0.001**

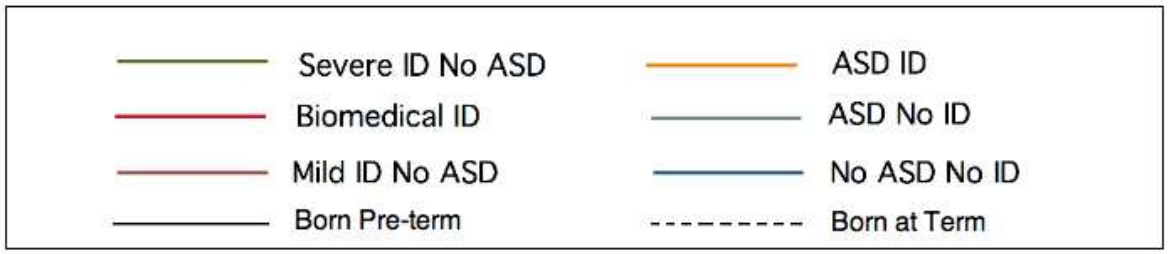
Case Status	Birth Year	Hazard Ratio	95% Confidence Interval		P-value (compared to baseline)
Severe ID no ASD	1983	6.813	6.046	7.676	<0.001
	1984	5.783	5.052	6.620	<0.001
	1985	4.619	4.014	5.314	<0.001
	1986	8.095	7.252	9.038	<0.001
	1987	10.362	9.257	11.599	<0.001
	1988	11.129	10.030	12.348	<0.001
	1989	8.089	7.245	9.033	<0.001
	1990	11.263	10.049	12.625	<0.001
	1991	20.315	18.789	21.965	<0.001
	1992	8.552	7.491	9.763	<0.001
	1993	11.824	10.050	13.909	<0.001
	1994	12.425	10.556	14.626	<0.001
	1995	17.095	14.755	19.806	<0.001
	1996	9.998	8.007	12.485	<0.001
	1997	20.663	17.483	24.422	<0.001
	1998	20.499	18.260	23.013	<0.001
	1999	7.245	5.612	9.353	<0.001
ASD & ID	**1983**	**1.352**	**0.945**	**1.934**	**0.099**
	1984	**1.743**	**1.313**	**2.313**	**<0.001**
	1985	**2.206**	**1.745**	**2.789**	**<0.001**
	1986	**2.081**	**1.664**	**2.602**	**<0.001**
	1987	**5.996**	**5.353**	**6.715**	**<0.001**
	1988	**2.246**	**1.838**	**2.744**	**<0.001**
	1989	**3.081**	**2.665**	**3.563**	**<0.001**
	1990	**2.642**	**2.227**	**3.134**	**<0.001**
	1991	**4.074**	**3.579**	**4.638**	**<0.001**
	1992	**2.039**	**1.696**	**2.450**	**<0.001**
	1993	**1.762**	**1.428**	**2.175**	**<0.001**
	1994	**3.448**	**3.021**	**3.936**	**<0.001**
	1995	**1.821**	**1.516**	**2.186**	**<0.001**
	1996	**4.367**	**3.872**	**4.925**	**<0.001**
	1997	**2.225**	**1.927**	**2.568**	**<0.001**
	1998	**2.102**	**1.800**	**2.454**	**<0.001**
	1999	**2.264**	**1.936**	**2.647**	**<0.001**

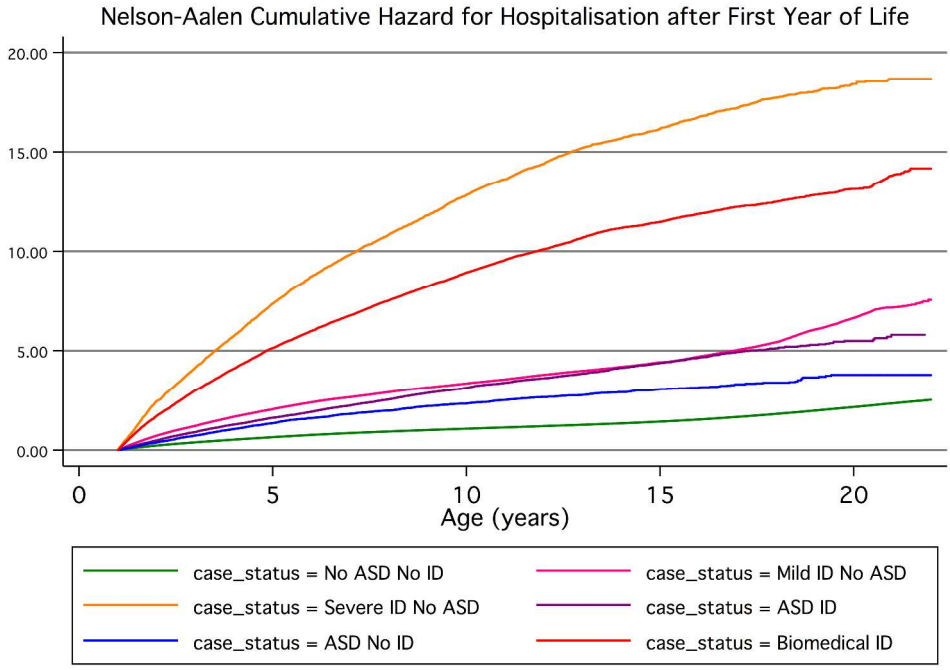
Case Status	Birth Year	Hazard Ratio	95% Confidence Interval		P-value (compared to baseline)
ASD no ID	1983	2.048	1.508	2.782	<0.001
	1984	2.321	1.773	3.038	<0.001
	1985	1.095	0.671	1.787	0.718
	1986	3.387	2.661	4.312	<0.001
	1987	1.720	1.338	2.211	<0.001
	1988	1.104	0.712	1.712	0.657
	1989	1.936	1.527	2.456	<0.001
	1990	2.088	1.690	2.580	<0.001
	1991	2.139	1.777	2.575	<0.001
	1992	2.207	1.843	2.645	<0.001
	1993	2.928	2.471	3.469	<0.001
	1994	1.819	1.477	2.239	<0.001
	1995	1.874	1.524	2.305	<0.001
	1996	1.691	1.384	2.066	<0.001
	1997	1.638	1.293	2.074	<0.001
	1998	2.080	1.562	2.768	<0.001
	1999	2.728	2.001	3.720	<0.001
Biomedical ID	**1983**	**4.812**	**4.443**	**5.211**	**<0.001**
	1984	**5.748**	**5.328**	**6.200**	**<0.001**
	1985	**5.012**	**4.615**	**5.444**	**<0.001**
	1986	**5.480**	**5.041**	**5.958**	**<0.001**
	1987	**6.311**	**5.832**	**6.829**	**<0.001**
	1988	**5.369**	**4.900**	**5.883**	**<0.001**
	1989	**7.738**	**7.095**	**8.438**	**<0.001**
	1990	**8.700**	**8.089**	**9.358**	**<0.001**
	1991	**13.724**	**12.984**	**14.505**	**<0.001**
	1992	**7.796**	**7.161**	**8.488**	**<0.001**
	1993	**8.786**	**8.127**	**9.497**	**<0.001**
	1994	**7.086**	**6.355**	**7.902**	**<0.001**
	1995	**8.710**	**8.017**	**9.463**	**<0.001**
	1996	**7.535**	**6.798**	**8.353**	**<0.001**
	1997	**7.182**	**6.403**	**8.057**	**<0.001**
	1998	**6.102**	**5.370**	**6.935**	**<0.001**
	1999	**10.575**	**9.584**	**11.667**	**<0.001**

~~Fig~~Figure 4 – Hazard Ratio for hospitalisation risk associated with birth year, pre-term birth and case group status from stratified model



Legend for figure 4





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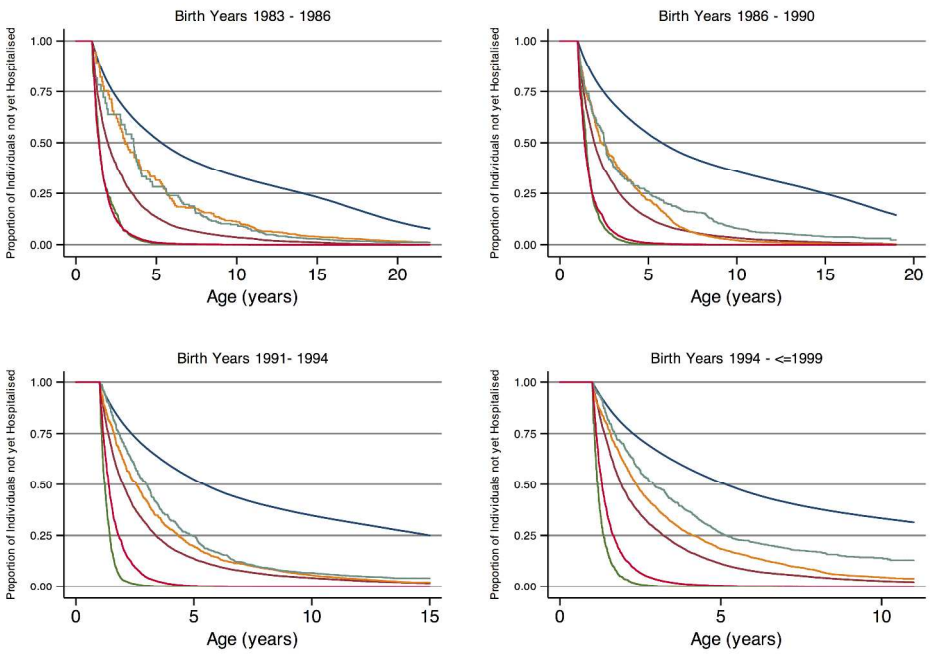

see attached legend file.
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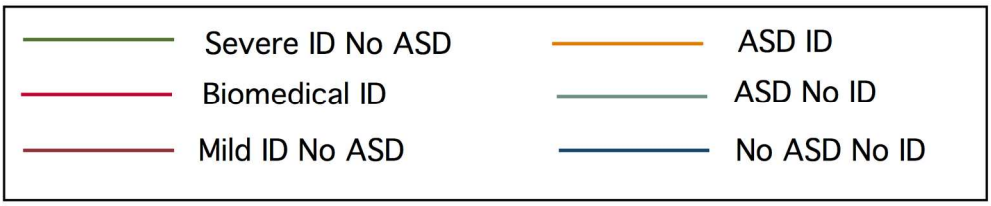

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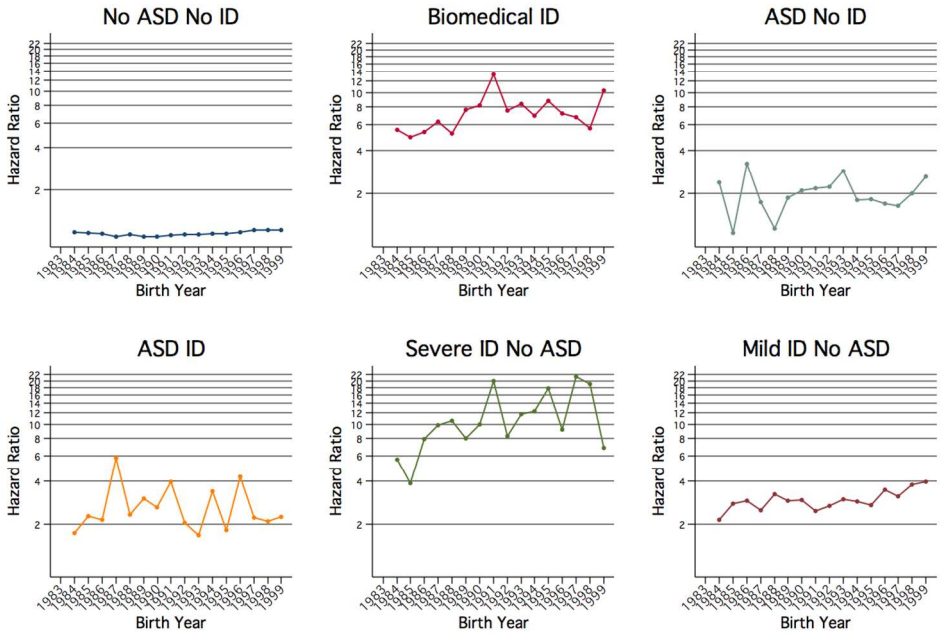

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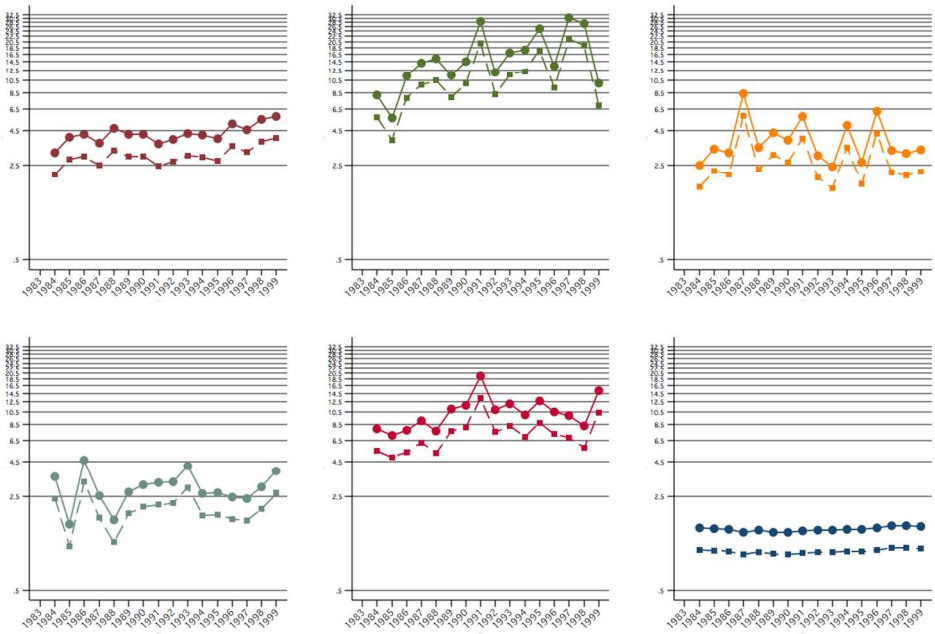

see attached Legend file.
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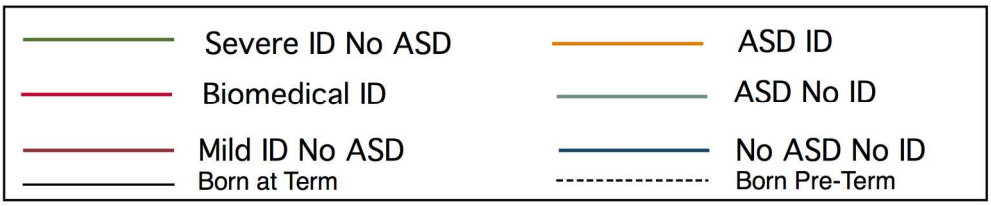

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			**3**
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4 – 5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
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	*6-7*
Bias	9	Describe any efforts to address potential sources of bias	4-7
Study size	10	Explain how the study size was arrived at	5-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	not applicable
		(*c*) Explain how missing data were addressed	not applicable
		(*d*) If applicable, explain how loss to follow-up was addressed	not applicable
		(*e*) Describe any sensitivity analyses	not applicable
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	7-8
		(b) Give reasons for non-participation at each stage	not applicable
		(c) Consider use of a flow diagram	not available
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	table 1
		(b) Indicate number of participants with missing data for each variable of interest	not applicable
		(c) Summarise follow-up time (eg, average and total amount)	7-8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9
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	9-10
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
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	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.