Baird, G., **Charman, T.**, Pickles, A., Chandler, S., Loucas, T., Meldrum, D., Carcani-Rathwell, I., Serkana, D., & Simonoff, E. (2008). Regression, developmental trajectory and associated problems in disorders in the autism spectrum: the SNAP study. *Journal of Autism and Developmental Disorders, 38*, 1827-1836.

Regression, developmental trajectory and associated problems in disorders in the autism spectrum: the SNAP study

Gillian Baird[1], Tony Charman[2], Andrew Pickles[3], Susie Chandler[1], Tom Loucas[4], David Meldrum[5], Iris Carcani-Rathwell[6], Devanitha Serkana[7], Emily Simonoff[8]

1 Guy's & St Thomas' NHS Foundation Trust

2 UCL Institute of Child Health, London

3 Biostatistics, Health Methodology Research Group, University of Manchester

4 School of Psychology and Clinical Language Sciences, University of Reading

5 Chatswood Assessment Centre

6 Greenwich Neurodevelopmental CAMHS, Oxleas NHS Trust

7 Cheyne Child Development Centre, Chelsea & Westminster Hospital

8 Department of Child and Adolescent Psychiatry, Institute of Psychiatry, King's College London

Running Head**:** Regression in ASD

Abstract

We report rates of regression and associated findings in a population derived group of 255 children aged 9-14 years, participating in a prevalence study of autism spectrum disorders (ASD); 53 with narrowly defined autism, 105 with broader ASD and 97 with non-ASD neurodevelopmental problems, drawn from those with special educational needs within a population of 56,946 children. Language regression was reported in 30% with narrowly defined autism, 8% with broader ASD and less than 3% with developmental problems without ASD. A smaller group of children were identified who underwent a less clear setback. Regression was associated with higher rates of autistic symptoms and a deviation in developmental trajectory. Regression was not associated with epilepsy or gastrointestinal problems.

Key words: SNAP**,** Autism, Regression, Outcome, Epilepsy, Gastro-intestinal problems

Retrospective histories from parents and analysis of home videotapes have shown that for most children with autism, abnormalities in development become clear prior to 2 years of age (Adrien et al., 1991; Dahlgren & Gillberg, 1989; Losche, 1990; Osterling & Dawson, 1994; Rogers & DiLalla, 1990; Werner et al., 2005; Werner & Dawson, 2005) and often within the first year of life. However, a feature of autistic development that remains a puzzle is that some children present with apparently normal development as perceived by parents followed by quite marked cessation of skill acquisition and frequent loss of, or failure to use, acquired language and social skills. Commonest in the second year of life, this has been termed 'autistic regression', and occurs in 15-40% of children with autism (Fombonne & Chakrabarti 2001; Kurita, 1985; Lord et al., 2004; Luyster et al., 2005; Prizant 1996; Richler et al., 2006; Tuchman & Rapin, 1997).

Some parents report that there is a very abrupt change in their child's development and behaviour, others report a much more gradual change lasting weeks. In some cases parents report that development has been normal prior to the regression (although more detailed examination and retrospective videos may indicate some subtle impairment), others report that although there was some delay in acquiring skills they still note significant regression. Even in those children where there is no obvious loss of skills, stasis of cognitive and social development may be reported by parents and has now been found in studies of at risk infants-the siblings of children with autism (Landa & Garrett-Mayer, 2006; Landa, Holman & Garrett-Mayer, 2007).

A common operational definition of regression is a loss of spoken language after the first 3-5 word stage of acquisition (Le Couteur et al, 1989; Lord et al., 1994; Lord et al., 2004; Tuchman & Rapin, 1999). There is also usually loss of non-verbal communication (e.g. gestures such as waving bye-bye) frequently decreased use of eye gaze to regulate social interaction, some social withdrawal and lack of social interest, and sometimes a loss of play skills (Ozonoff et al., 2005; Werner et al., 2005). Gross motor development is not usually affected although some

parents note a change in fine manipulative skills (Davidovitch et al., 2000). However, in children who have not reached the 3-5 word stage of language development, parents may note regression of babble and proto-words with or without regression in social interest, gestures etc. The period of developmental stasis or loss of skill-use is usually followed by a regaining of skills but at varying rates. Some children never regain lost skills (Evans-Jones & Rosenbloom, 1978; Lord et al., 2004).

Several reports have suggested that the eventual outcome in children with regression is that of a lower language level, lower IQ and lower adaptive level compared with those who do not regress (Kurita, 1985; Hoshino et al., 1987; Kobayashi & Murata, 1998; Rogers & DiLalla, 1990). However, other studies have found no difference in outcome (Chakrabarti & Fombonne 2001; Davidovitch et al., 2000; Lord et al., 2004) or mixed results with the regressed group showing a bimodal outcome in verbal IQ and social reciprocity (Richler et al., 2006) which may be a result of inclusion of differing groups within the autism spectrum.

Regression to autism in older children following a period of clearly normal development up to the age of at least 2 years is classified separately in ICD-10 (WHO, 1993) and DSM-IV (APA, 1994) as Developmental or Other Childhood Disintegrative Disorder (CDD). Previously titled Heller's syndrome, regression is in language, communication, social play, curiosity in the environment, sometimes loss of bowel/bladder function and the onset of stereotyped skills. This is a rare phenomenon. Fombonne (2002) estimates a prevalence of CDD of no more than 0.2/10,000. In several studies the CDD group have a poorer outcome in terms of cognitive and functional skills (Malhotra & Gupta 2002; Volkmar & Cohen, 1989), though Kurita et al. (2004) found no such difference.

The process underlying regression and stasis is unknown. There has been speculation that the anatomical remodelling of the brain with synaptic growth and pruning during the second year

of life is impaired in autism due to gene-based mechanisms (Carper & Courchesne, 2005) resulting in variable effect on function. Also a suggestion that regression constitutes a genetically different disorder (Molloy et al., 2005), unconfirmed in the IMGSAC sample where in families in which more than one child has autism, regression occurred in one sib and not another (Parr et al., 2006 and in preparation), although newer genetic techniques may cast further light on possible genetic contributions (Marshall et al., 2008; Weiss et al., 2008). Whether the regressive process is influenced by environmental factors is also unknown. There has been concern that the number of children with regressive autism has increased but recent reviews (Fombonne & Chakrabarti, 2001; Taylor et al., 2002) have shown no such increase. Considerable research has failed to support an association between one suggested environmental factor, MMR immunisation, postulated to be linked with enterocolitis and the risk of a regressive autistic disorder (Baird et al. 2008; DeStefano, 2002; Honda et al., 2005; Richler et al. 2006). Other suggestions have included epilepsy as a causative factor in regression allied to Landau-Kleffner syndrome, an aphasia due to localised peri-sylvian epilepsy, (Robinson et al., 2001), although most children with regression of language who have autism do not have epileptic seizures and language regression with autism is not more common in those with epilepsy than those without epilepsy (Shinnar et al., 2001; Tuchman & Rapin, 1997).

As part of a prevalence study of autism and related pervasive developmental disorders (commonly called ‘autism spectrum disorders’; ASDs) we assessed a group of 255 9-to-14 year old children with and without ASD drawn from a geographically defined population rather than a clinically referred group. A sample weighting procedure enabled us to estimate characteristics of the total population of children with autism and ASD. This study provided us with the opportunity to examine the following questions regarding the nature, timing, consequences and associated features of regression in children with autism, other ASDs and children without ASD

with mental retardation, learning difficulties and behavioural disorders: a) Does regression affect developmental trajectory and outcome?; b) Does regression occur in non ASD cases?; c) Is there a greater prevalence of gastro-intestinal problems or epilepsy in the regressed versus non-regressed groups?

Methods

Participants

The population studied is a cohort of 56,946 children born between July 1st 1990 and December 31st 1991 from 12 districts in the South Thames region of the UK. Children with a statement of special educational needs (SEN) (1733; 218 of whom had a local ASD diagnosis) or a local diagnosis of ASD but no SEN statement (37) were screened using the Social Communication Questionnaire (SCQ; Rutter et al., 2003). The mean (SD) age at SCQ screening in the whole cohort was 10.3 (0.4) years.

A subset of children, stratified by local diagnosis and high, medium and low SCQ score (255) received an in-depth diagnostic assessment (see Figure 1 in Baird et al., 2006). The diagnostic assessment included standardized clinical observation (Autism Diagnostic Observation Schedule – Generic (ADOS-G; Lord et al., 2000)) parent interview assessments of autism symptoms (Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994)) and assessment of IQ. Children were classified using ICD-10 research criteria as ASD or no ASD by clinical consensus using all sources of information. The ASD group was divided into a 'broad ASD' (105) and 'narrow autism' (53) group, the latter defined as meeting autism criteria on the ADI-R, the ADOS-G and clinical consensus of ICD-10 childhood autism and the broad ASD defined as all other cases meeting clinical consensus of any ASD. The total number of ICD-10 autism symptoms was recorded. The 'no ASD' group (97) had a variety of diagnoses: intellectual disability (mental retardation), specific language or literacy impairments, ADHD/ODD, cerebral

palsy, deafness and visual impairment. Collectively they form a control group for some of the analyses.

Measures

The ADI-R has specific questions (Items 11-15) about regression of language and other skills. Regression was defined in two ways. The first adopted the ADI-R definition of strict language regression as 'loss of 5 words used communicatively for 3 months before loss' with or without loss of skills in other areas, a group called 'definite language regression'. An additional group was defined where the parent described stasis or loss of words or babble, but where the child had not reached the 5-word stage or there was regression of skills other than language (Q20 in ADI 2000), called the 'lower level regression' group.

A systematic enquiry was additionally made of early development using items based on the Diagnostic Interview for Social and Communication Disorders (with permission) (DISCO; Wing et al., 2002) that supplemented the ADI items on language acquisition. The DISCO was developed for systematic enquiry about a range of normal and abnormal behaviours but does not have population 'norms'. 17 questions about the normality of development of sucking, babble, gesture, play and social responsiveness in the first year were used and scored as described by the authors yielding a range of scores from 0 to 34 to give a single figure as proxy for normal early development, a higher score indicating greater abnormality. Both the ADI-R and DISCO questions rely on retrospective memory. Contemporaneous child health records were available in the majority of cases (79%) and were systematically searched to look for age of concern, age of referral, medical problems and any contemporaneous note of developmental problems or regression to validate the parental history. No case met criteria for Rett syndrome or CDD.

Epilepsy was enquired about twice, once during the ADI-R and at subsequent interview about medical conditions. Seizures were classified as febrile only, epileptic past or current (on

treatment) and non-epileptic (e.g. reflex anoxic seizures). Medical notes were checked for corroboration of epilepsy. Gastrointestinal (GI) symptoms, reflecting the presentation of GI symptoms in general clinical paediatric practice, for the last three months (current) and at any point in the past, , were assessed using a questionnaire completed by the main caregiver (Circani-Rathwell et al., in preparation). Current symptoms elicited were of vomiting (occurring at least once per day or more than five times in a week); diarrhoea (defined as loose/watery stools three or more times a day >14 days); persistent abdominal pain (three or more episodes severe enough to interfere with activity) constipation (defined as a bowel action<three times per week); weight loss; blood in stools and soiling. Past symptoms of vomiting, diarrhoea, abdominal pain (defined as above) and stool withholding were also elicited. The four symptoms of vomiting, diarrhoea, abdominal pain and constipation were summated to give a possible score of 0-4 either of past or current GI symptoms. A 'possible enterocolitis' group was constructed from the presence of 2 or more of the following 5 current gastro intestinal symptoms: persistent diarrhoea, persistent vomiting, weight loss, persistent abdominal pain; blood in stool; plus past diarrhoea >14 days duration and excluding current constipation. 87 children were screened for coeliac antibodies (in whom a sufficient blood sample was obtained) and the single child (from the control group) found to be positive, but asymptomatic, was excluded from the gastro-intestinal analysis together with eight children with cerebral palsy who might be expected to have motility or upper GI problems.

Measures used were IQ, adaptive behaviour on the Vineland Scales (Sparrow et al., 1984) and severity of autism symptoms using an ICD-10 ASD symptom score (0-12). IQ was measured using the Wechsler Intelligence Scale for Children (N=209; WISC-III- UK; Wechsler, 1992), Raven's Standard Progressive Matrices (SPM) or Coloured Progressive Matrices (CPM; Raven, 1990a,b), depending on the child's ability. For the 35 cases where SPM or CPM but not WISC

full scale IQ's were available, imputed full-scale IQ's were obtained using the regression relationship of full to SPM/CPM IQ within each diagnostic group (conversion to IQ from Catherine Lord, personal communication February 2008). For the 11 cases where no direct cognitive testing was possible all cases had Adaptive Behaviour Composite on the Vineland Adaptive Behaviour Scales (Sparrow et al., 1984) below 20 and these cases were assigned an IQ score of 19 to reflect their profound level of mental retardation.

Statistical analysis

The text includes data on the exact numbers of children with and without regression seen in the study. All subsequent analyses presented in the tables and text are adjusted using stratification weights. Stratification of the ASD/SEN sample was based on whether or not a child had a locally recorded ASD diagnosis (yes/no) and 4 levels of SCQ score (low score (<8), moderately low score (8-14), moderately high score (15-21), high score (≥22); see Baird et al., 2006,Figure 1, p.212 for details). Use of weights allowed all statistics such as proportions, means, group differences and screen performance measures to be presented as target population estimates, taking account not only of the differences in sampling proportions according to SCQ score and local ASD diagnosis, but also the differential response to the SCQ associated with a prior local ASD diagnosis, health district and child's sex. Standard errors of simple means and regression, logistic regression and proportional hazards regression coefficients and contrasts, Wald test statistics and p-values were calculated using the linearisation version of the robust parameter covariance matrix as implemented by the svy procedures of Stata 9 (Stata, 2005). Confidence intervals for the rate of regression were estimated at the 2.5th and 97.5th percentiles from 1000 bootstrap samples.

Results

In the 255 cases assessed, regression was reported in 38 cases, 28 with definite language regression and 10 with lower level regression who are reported separately. Table 1 shows the number of cases, weighted rates and 95% confidence intervals (CIs) according to regression category and diagnosis.

The definite language regression group

Of the 28 children who met criteria for 'definite language regression', 26 had ASD and 2 did not. The rate of definite language regression was significantly higher (30.2%) in the narrow autism group than in the broad ASD group (8%, p=.01) and the no ASD group (2.8%, p=.003). The rate of definite language regression did not significantly differ between the (combined) ASD group (12.6%) and the no ASD group (p=.08). 16.3% regressed in one or more area other than language: 5.5% were reported to have lost purposive hand movements (but did not follow a trajectory typical of Rett syndrome), 10.5% motor skills, 2.4% self-help skills, 19.4% constructive or imaginative play and 19.4% were reported to have regressed in the area of social engagement/responsiveness. Association with illness (regression reported by parents as occurring within 7 days of an illness) was reported in 11 children: non-encephalopathic illness in 8 with ASD (two parents reported that illness and regression followed within 2 weeks of the MMR); 1 ASD case presented aged 1 year with frequent epileptic seizures and had a left temporal tumour subsequently removed. Of the 2 remaining non-ASD cases, one had a definite encephalitis, the other was a child with Down's syndrome who developed leukaemia.

Table 1 about here

Age at regression

The mean weighted age of regression was 25.0 (SE 1.5) months for the cases with definite language regression. For the two non-ASD cases with clear language regression the age of loss was 20 months and 48 months, respectively. The only other case with age of language loss greater than 33 months was one case with autism whose parents, on the ADI-R, reported plateauing of development at 24 months and then loss of language at 69 months of age, although contemporaneous health records indicated parental report of language loss at 24 months of age and they also reported that development prior to language loss was not normal The pattern of development was thus not consistent with CDD.

Outcome at 9-14 years of definite language regression compared with no regression

Outcome was examined in terms of IQ, Vineland composite scores, and ICD-10 ASD symptom score. Table 2 shows mean differences and pair-wise comparisons. The effects of regression controlling for diagnosis were tested in multivariate regression models. With regard to IQ and Vineland scores, there was no significant difference between regression and non regression once diagnostic category was taken into account. The ICD-10 ASD symptom score was significantly greater in the regression group than the no regression (non-standardized B =3.25, $p<.001$). The effect remained significant when diagnosis (broad ASD or narrow autism) was accounted for. Age at regression was not significantly associated with outcome IQ, Vineland scores or ICD-10 ASD symptom score.

Table 2 about here

Validation of parental history of regression

Contemporaneous casenote information was available for 16 of the 28 cases with clear regression. Loss of skills or stasis/plateau was documented by paediatricians (from parental

report) in 11/16 cases (69%). For these 11 cases the age of regression recorded in casenotes was 25.1 (SE=1.9) months compared to 28.4 (4.7) reported by parents in the ADI-R, a difference that was not significant (paired t-test; t=0.65, p>.10). The discrepancy between the reported ages was 12 months or less in N=8 cases and greater than 12 months in N=3 cases, including the case where contemporaneous casenotes indicated a parent-reported loss of language from more than 20 words at age 24 months but loss was subsequently reported at age 69 months in the ADI-R.

Language development and regression

Age of first words and age of first phrases (weighted) as reported by parents during the ADI-R are shown in Table 3. At the time of our assessment, amongst those with autism or ASD, only 1 child with an ASD had not attained single words. The age of acquiring first words in the definite language loss group is significantly younger than the no regression group (B=-30.6, p=.03); these findings remained significant when diagnosis was accounted for. There was no significant difference between the definite language regression and no regression groups in age of acquiring phrase speech, either on its own, or with diagnosis added as a covariate.

We examined whether the failure to achieve phrase speech varied according to regression group. Twelve children with a ASD had not achieved phrase speech by the time of the assessment, of whom 2 had a ASD diagnosis and 10 an autism diagnosis representing 8% of the non-regression group, and 9% of the definite language regression group. A Cox proportional hazards model of the time to phrase speech that took into account the censored times from those who had not achieved phrase speech, confirmed the absence of significant regression group differences, particularly when controlling for delay in phrase acquisition due to diagnosis (hazard ratio 0.61, p=.03).

Early developmental skills, developmental trajectory and regression

The definite language regression group had lower DISCO total scores (indicating less abnormality) than the no regression group (B=-3.7, p=.003) and remained so after diagnosis was accounted for (B=-4.4, p<.001).

Table 3 about here

The relationship between outcome (symptom severity), regression and early development, was then explored by predicting in a linear regression model symptom severity from early development score, level of regression and interaction between the two independent variable A significant interaction (t=-2.17, p= 0.03) was found, such that the early development score was significantly positively related to later symptom severity in the no regression and lower level regression groups but unrelated in the definite regression group (Wald test F(1,150)=1.12, p= 0.29).

'Lower level' regression in ASD

Parents of 10 children reported symptoms that met the criteria for 'lower level' regression. The rate of lower-level regression was significantly higher (8.4%) in the narrow autism group than in the broad ASD group (2.6%, p=.04) and the no ASD group (0.4%, p=.002). The (combined) ASD group was significantly more likely to show lower level regression (p=.02). Of the 10 children with lower-level regression, 9 had ASD. Regression was not associated with illness in the 9 with ASD; the one child without ASD regressed in motor skills only having had a cerebrovascular event complicating an ear infection and resulting in cerebral palsy. Of the 9 with ASD, two (20%) lost babble or words, 6 (60%) lost social engagement or play skills, 1 lost hand and self-help skills. Contemporaneous casenote information was available on 7/10 of the lower-level regression cases. Five of these 7 (71%) have a note of some type of regression or stasis. The age

at regression was 25.0 (SE 3.3) months for cases with lower level regression (not different to definite language regression).

Prior to regression, the score for DISCO items in the lower level regression group (mean 10.6) was similar to that in the no regression group (mean 10.3). Hence, there was greater developmental impairment than in the definite regression group (mean 6.6), although this difference was not significant due to small sample size in the lower level regression group. The lower level regression group had a significantly higher ICD-10 ASD symptom score than the no regression group. (B=2.06, p=.003) and the definite language regression group (B=2.31, p=.01). 36% of the low-level regression group had not developed phrase speech at the time of assessment (compared with 8% and 9 % of the no regression and language regression groups, respectively).

Both regression groups combined

The outcome of both definite language and lower level regression combined is similar to each in that the main effect is on increase in ICD10 symptoms and thus a diagnosis of autism rather than ASD.

Association of regression with epilepsy or bowel problems

The weighted rates of epilepsy are shown in Table 4. 18% had a past or current history of epilepsy. 8% have current epilepsy. There was no evidence suggestive of differential rates of febrile seizures, past or current epilepsy when comparing the definite and no regression groups. Although past and current epilepsy are highest in the group with lower level regression, the difference is not statistically significant due to the small sample size in this cell. .

Table 4 about here

Table 5 shows the weighted mean symptom count for current and past gastrointestinal problems. Current symptoms varied across regression groups ($F(2,122)=11.96$, $p=.001$), but the rate was higher in the no-regression group than the lower ($F(1,122)=7.09$, $p=0.0007$) or definite regression ($F(1,122)=4.70$, $p=0.03$) groups . No significant group difference was found in past gastro-intestinal symptoms ($F(2,121)=2.84$, $p=0.6$). 'Possible enterocolitis', as defined above was reported in one child who did not have ASD, also did not regress. No child had a previous diagnosis of inflammatory bowel disorder.

Table 5 about here

Regression in non ASD SEN cases

Clear language regression occurred in 2 non-ASD cases at ages 20 months and 48 months, one had encephalitis, the other was a child with Down's syndrome severely ill with leukaemia . The one non-ASD case with lower level regression had the cerebral incident at age 9 months.

Discussion

In this study, regression is confirmed as a feature of ASD development. It is rare in children who do not have ASD and in these cases if it occurs is likely to be in association with a neurological illness. We have found that the main effect of a history of regression in autism is an outcome of increased symptom score and more severe autism as shown by diagnostic category. This is true for both definite language regression and 'lower level' regression. To investigate the important question of whether regression as a feature of autism presentation exerts an additional effect on potential developmental outcome, we have used a measure of development in the first year as a proxy for developmental competence and compared the predicted trajectory from the DISCO score in non regressed and regressed groups. The accuracy of parental recall in the DISCO items

is unknown. However, the early DISCO score does predict outcome in the non-regressed group and our results suggest that there is an expected continuity in development which is displaced by regression. Thus, despite the definite language regression group showing more typical development in infancy evidenced by earlier first words and less abnormal social communication in the first year (lower DISCO scores), that early trajectory is not maintained (cf. Landa et al., 2007; Pickles et al., under review). The neurodevelopmental abnormality that underlies this deviant developmental trajectory remains to the determined.

This study has used two levels of regression, one clearly defined, the other looser but based on clear parental report of stasis and loss of babble or 1-2 words plus or minus loss in other areas. It remains unclear whether the aetiological or pathological process differs between definite language regression and 'lower level' regression. Although reported here separately to enable comparison with other studies, our results show that the two regression groups show common trends in association with diagnostic group and effects on outcome.

Recent studies reporting the development of siblings of children with autism who go on to develop autism suggests that there is stasis and plateauing of the rate of development in the second year (Landa & Garrett-Mayer, 2006; Landa et al., 2007). Thus, overt regression may lie on a continuum of no arrest in developmental progress through plateauing to frank regression and the manifestation of the regressive process appears to depend on the stage of brain maturation and of development the child has reached rather than their chronological age (Pickles et al., under review). No case in this study met full criteria for Rett syndrome or CDD. The one case that by parental report on the ADI-R regressed at 69 months was not totally normal prior to language loss, plateauing was reported at 24 months and indeed examination of contemporaneous health records indicated parent report of loss of language at 2 years of age.

Fombonne and Chakrabarti (2001), using a similar definition of `clear language regression', found no differences in outcome between regressed and non-regressed. Richler et al. (2006) did find lower VIQ scores and higher (more impaired) social reciprocity ADI-R scores following regression but also found a bimodal distribution of VIQ scores in their regression group. That study had much larger numbers than ours (163 with regression and 188 without) and hence greater power to detect differences. However, there were also differences in methods: Richler et al (2006) used a less stringent diagnostic criterion for autism and a broader definition of regression. Neither of these studies attempted to predict developmental trajectory from reported developmental status prior to regression.

We defined gastro-intestinal problems in a standard way. Several studies have found high reported rates of gastro-intestinal symptoms in ASD (CPEA study, Richler et al., 2006, Valicentini-McDermott et al., 2006). The choice of 14 days for diarrhoea symptoms chosen in this study may be regarded as too short and reflective of acute illness rather than chronic GI disorder, however we found no evidence of more current or past gastrointestinal problems in regressed versus non-regressed groups. This finding is in contrast with the larger CPEA study although there are differences in the questions asked. For example, the CPEA study enquired about 'change in stool frequency and consistency' rather than the specific stool frequency indicating constipation as in the present study. The conclusions in their paper point out that had corrections been made for multiple comparisons of data, the differences would have no longer been significant.

We found no evidence for excess epilepsy in regressed versus non-regressed groups past or current, which is consistent with Tuchman (1999). Neither did regression signal increased epilepsy with age (to 11-14 years). No child had a diagnosis of Landau-Kleffner syndrome. The

reported age of language regression in this study (25 months) is slightly later than in some other studies. There is variation from a mean 16 months in Lord et al. (2004) and Ozonoff et al. (2005) to around 20 months in many studies. Tuchman (1999) noted the age of regression to be 12 to 48 months. Some variation in age of reported regression may be accounted for by age at reporting. The sample of Lord et al. (2004) was 4-5 years old at their most recent ADI-R) but the large CPEA study (Luyster et al., 2005) were interviewed at a mean of 9 years and mean age of reported word loss was 20 months.

Importantly, regression of social, language or motor development rarely occurred in children with non-ASD neurodevelopmental problems (see also Pickles et al., under review who show that regression is rare in children with language disorder), and then in association with encephalopathic illness.

Strengths and limitations of the study

The present study reported on a carefully ascertained and assessed population derived sample and thus free of the bias usually associated with a clinically referred sample. It included non ASD as well as narrow autism and broader ASD cases. The use of a statistical weighting procedure enables generalisation of the findings to the unselected population, though at the expense of precision (note the wide confidence intervals for some estimates). Another strength of the present study was to be able to corroborate parental reporting of regression and medical problems from contemporaneous health records although with only 57% of records available, and only 69% of those documenting regression, positive corroboration exists for <40% of the reported regression cases. The limitations are the relatively small number of cases with regression and in common with most other studies investigating regression in ASD, the reliance on parental report regarding the nature and timing of regression as well as pre-regression development.

Clinical implications

In young children presenting to child health services with concerns about development, the spectrum of autistic disorders are among the commonest of the developmental disorders. One feature of the history that is particularly important to take note of is regression. In the absence of an acute neurological event or neurological signs including epilepsy, regression in a child of 1- 3 years should be a ‘red alert’ for assessment of autism and signals an altered trajectory of development (Filipek et al., 2000).

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Author Note

Gillian Baird, Guy's & St Thomas' NHS Foundation Trust, London, UK; Tony Charman, Behavioural & Brain Sciences Unit, UCL Institute of Child Health, London, UK; Andrew Pickles, Biostatistics, Health Methodology Research Group, University of Manchester, UK; Susie Chandler, Guy's & St Thomas' NHS Foundation Trust, London, UK; Tom Loucas, School of Psychology and Clinical Language Sciences, University of Reading, UK; David Meldrum, Chatswood Assessment Centre, Sydney, New South Wales, Australia; Iris Carcani-Rathwell, Greenwich Neurodevelopmental CAMHS, Oxleas NHS Trust, London, UK; Devanitha Sirkana, Cheyne Child Development Centre, Chelsea & Westminster Hospital, London, UK; Emily Simonoff, Department of Child and Adolescent Psychiatry, Institute of Psychiatry, King's College London, UK.

Susie Chandler is now at Behavioural & Brain Sciences Unit, UCL Institute of Child Health, London, UK

Acknowledgments: The study was funded by the Wellcome Trust and the Department of Health. We thank the expert group, Patrick Bolton, Antony Cox, Ann Gilchrist, Rebecca Landa, Ann Le Couteur, Catherine Lord, Lennart Pedersen and Michael Rutter. Thanks also to Greg Pasco, Samantha Ross, Vicky Slonims, Emma Rowley and Martha Turner for their help with assessments.

Correspondence concerning this article should be addressed to: Dr G Baird, Newcomen Centre, Guy's & St Thomas' NHS Foundation Trust, St. Thomas's Street, London SE1 9RT, UK. Tel: 0207 188 9662; email: gillian.baird@gstt.nhs.uk

Table 1

Presence of Regression according to Diagnostic Category

	No ASD	Broad ASD	Narrow Autism
No Regression			
N	94	93	30
Rate	.97	.89	.61
95% CIs	.91 – 1.00	.79 - .97	.45 - .76
Lower-lever Regression			
N	1	4	5
Rate	.00	.03	.08
95% CIs	0 - .02	.01 - .06	.02 - .17
Language Regression			
N	2	8	18
Rate	.03	.08	.30
95% CIs	0 - .09	.02 - .18	.18 - .45

Rates and confidence intervals (CIs) are weighted. Rates are given for proportion of each regression classification within each diagnostic group

Table 2

Outcome in IQ, Vineland Adaptive Behaviour Scale and ICD-10 ASD Symptom Severity according to Regression and Diagnostic Classification

		Mean Score (95% confidence Intervals)		
		No Regression	Lower-Level Regression	Definite language regression
IQ	Combined ASD	70.3	60.6	65.0
		(63.1 – 77.5)	(41.9 – 79.3)	(57.6 – 70.3)
	Broad ASD	72.8	72.2	64.1
		(64.1- 81.6)	(58.5 – 86.0)	(55.5 – 72.8)
	Narrow autism	55.2	43.9	63.8
		(50.6 – 61.8)	(14.6 – 73.0)	(54.7 – 73.0)
Vineland	Combined ASD	46.7	37.5	42.3
		(42.0 – 51.4)	(25.9 – 49.2)	(34.7 – 49.8)
	Broad ASD	49.1	45.1	47.7
		(44.1 – 54.1)	33.8 – 56.4	(39.2 – 56.0)
	Narrow autism	38.5	26.5	37.7
		(26.8 – 40.2)	(13.8 – 39.3)	31.0 – 44.4
ICD-10 symptom score	Combined ASD [a,b]	7.00	10.15	8.07
		(6.41 – 7.52)	(9.14 – 11.17)	(5.53 – 10.61)
	Broad ASD [a,b,c]	6.31	9.69	5.69
		(5.86 – 6.76)	(8.16 – 11.24)	(3.19 – 8.19)
	Narrow autism	10.55	10.81	10.12
		(9.99 – 11.11)	(10.46 – 11.16)	(9.23 – 11.01)

F tests for significant differences within diagnostic category across regression groups, $p < .05$
[a] overall test between all three groups; [b] no regression vs. lower level regression; [c] lower-level regression vs. definite language regression

Table 3

Early Development according to Regression Classification

Diagnoses combined	Mean Score, (95% Confidence Intervals)		
	No regression	Lower level regression	Definite language regression
Age of first words[a,b,c]	26.1 (22.0 – 30.2)	46.7 (17.5 – 75.8)	15.9 (13.6 – 19.0)
Age of phrase speech	43.5 (37.2 – 49.7)	51.6 (30.0 - 73.2)	49.7 (39.4 – 70.0)
Early development problems[a,b]	10.3 (8.6 – 12.1)	10.7 (4.8 – 16.5)	6.6 (4.8 – 8.3)

F tests for significant differences within diagnostic category across regression groups, $p < .05$
[a] overall test between all three groups; [b] definite language regression vs. no regression; [c] definite language regression vs. lower-level regression

Table 4

Rate of Febrile Convulsions and Epilepsy according to Regression Group

	Rate (95% confidence intervals) and *N affected*		
	No regression	Lower-level regression	Definite language regression
Febrile Convulsions	.03	.07	.05
	(0 - .07)	(.01 - .07)	(0 - .31)
	N=5	*N=1*	*N=1*
Epilepsy Ever	.12	.33	.07
	(05 - .21)	(0 - .71)	(0 - .25)
	N=15	*N=2*	*N=2*
Current Epilepsy	.07	.33	0
	(.02 - .15)	(0 - .75)	(N/A)
	N=8	*N=2*	*N=0*

Table 5

Mean Number of Gastrointestinal Symptoms[1]

	Mean number of symptoms (95% Confidence Intervals) *Total subjects included*		
	No regression	Lower level regression	Definite language regression
Current problems	.50	0	.13
	(321- .7890)	N/A	(0 - .341)
	N=100	*N=7*	*N=17*
Past problems	.54	.21	.81
	(.27- .80)	(0 - .61)	(.51 – 1.11)
	N=102	*N=7*	*N=17*

[1] Mean scores range from 0-4