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Is There a 'Regressive Phenotype' of Autism Spectrum Disorder Associated with the Measles-Mumps-Rubella Vaccine? A CPEA Study

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A multi-site study of 351 children with Autism Spectrum Disorders (ASD) and 31 typically developing children used caregiver interviews to describe the children's early acquisition and loss of social-communication milestones. For the majority of children with ASD who had experienced a regression, pre-loss development was clearly atypical. Children who had lost skills also showed slightly poorer outcomes in verbal IQ and social reciprocity, a later mean age of onset of autistic symptoms, and more gastrointestinal symptoms than children with ASD and no regression. There was no evidence that onset of autistic symptoms or of regression was related to measles-mumps-rubella vaccination. The implications of these findings for the existence of a 'regressive phenotype' of ASD are discussed.

KEY WORDS: Autism spectrum disorder; language development; regression; Autism Diagnostic Interview - Revised (ADI-R); measles-mumps-rubella (MMR) vaccine; gastrointestinal disorders.

While most children with Autism Spectrum Disorders (ASD) are described as showing developmental differences from birth or early in infancy, a substantial minority (20–40%) of parents of children with ASD report that their children initially seemed to acquire some social and communicative skills that they subsequently lost, typically between 15 and 24 months of age (Davidovitch, Glick, Holtzman, Tirosh, & Safir, 2000; Goldberg *et al.*, 2003). These losses can occur in a range of skills, from using eye contact and gestures to producing meaningful words to participating in reciprocal games like "peek-a-boo."

In recent years, researchers have become interested in the question of whether children with ASD who experience a regression manifest a new variant or phenotype of the disorder. In order to address this question, investigators have examined whether

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children with ASD and regression differ from children with ASD and no regression in terms of skill development and severity of autistic symptoms, both in the early years and later on in life. Luyster *et al.* (2005) found that children with regression had superior social and communicative skills prior to loss compared to children with ASD and no regression. At the same time, however, studies have consistently found that children with ASD and regression were not developing like typical children prior to loss (Lord, Shulman, & DiLavore, 2004; Siperstein & Volkmar, 2004; Werner, Dawson, Munson, & Osterling, 2005).

Findings on social and communicative outcomes in children with ASD and regression have been less consistent. Kurita (1985) found that, at 38 months, children with autism and speech loss had a significantly lower developmental quotient than children without speech loss, suggesting that language loss may be related to poorer outcome, at least in the shorter term. Brown and Prelock (1995) found that individuals with ASD and a history of regression showed poorer social communication skills later in life than did individuals with ASD and no history of regression. Several studies have found that, at approximately 6 years of age, children with autism who had a history of regression had a lower IQ than those children who did not experience a regression (Burack & Volkmar, 1992; Kobayashi & Murata, 1998; Kurita, 1996). However, other studies have found no differences between children with ASD with and without regression on various outcome variables (Lord *et al.*, 2004).

Another way to examine the issue of whether regressive autism constitutes a distinct phenotype is to determine whether it is characterized by a distinct symptom profile. Some researchers have suggested that regressive autism is associated with an increased frequency of gastrointestinal (GI) disorders and symptoms (Wakefield *et al.*, 1998). Recent studies, however, have found no evidence for an increased risk of GI dysfunction among children with ASD and regression as compared to children with ASD and no regression (Fombonne & Chakrabarti, 2001; Molloy & Manning-Courtney, 2003).

Several years ago, Wakefield *et al.* (1998) suggested that both regression and GI dysfunction in children with ASD could be 'triggered' by the measles-mumps-rubella (MMR) vaccine. In one of the earliest studies on this topic, Wakefield *et al.* (1998) examined a group of 12 patients referred to a pediatric gastroenterology unit who were reported to have had a history of normal development followed by losses in language and other skills. Eight of the 12 children were described as having lost skills within days after being vaccinated; the interval ranged from 24 hours to 2 months. In most cases, parents and/or physicians attributed onset of symptoms to the MMR vaccine. All of the children had GI abnormalities (diarrhea, abdominal pain, bloating, and food intolerance) and most had received a clinical diagnosis of autism. The authors suggested that the MMR vaccine might have triggered bowel dysfunction; accompanying neurodevelopmental dysfunction, they posited, would have resulted from an excessive absorption of gut-derived peptides from food, which might disrupt normal brain development. It should be noted, however, that 10 of the 13 authors recently retracted this interpretation of the findings (Murch *et al.*, 2004).

More recently, researchers have begun to examine the evidence for a link between the MMR vaccine and autism. Chen, Landau, Sham, and Fombonne (2004) examined the association between the prevalence of autism and exposure to measles infection and the MMR vaccine in the UK and found no evidence for such a relationship. Wilson, Mills, Ross, McGowan, and Jadad (2003) reviewed four studies on the relationship between ASD and the MMR vaccine, none of which found any evidence for a link. For example, one study followed up 31 vaccinated children reported to have GI tract symptoms and found that none of the children went on to receive a diagnosis of ASD (Peltola *et al.*, 1998). Another study did not find an increased rate of GI symptoms or regression in children with autism after the MMR vaccine was introduced to a population in the UK (Taylor *et al.*, 2002).

One of the studies reviewed by Wilson *et al.* (2003), conducted by Fombonne and Chakrabarti (2001), provided the focus for the present study. The authors asked two questions: First, does regressive autism represent a new 'phenotype' of ASD? Second, is regressive autism associated with the MMR vaccine? If regressive autism truly is a new, MMR-induced phenotype of the disorder, Fombonne and Chakrabarti argued, then one would expect, among other things, that children with regressive autism would have different symptom and severity profiles and a higher rate of GI abnormalities than children with ASD and no regression. If a particular phenotype of autism were associated with the MMR vaccine, then the age of onset for these children (with ASD and regression) would follow age at vaccination and would differ from the age of onset for children without regression.

In the Fombonne and Chakrabarti (2001) study, children with pervasive developmental disorders (PDD) (including autism, atypical autism, Pervasive Developmental Disorder – Not Otherwise Specified, PDD-NOS, Asperger syndrome, and Childhood Disintegrative Disorder, CDD) and a history of regression were compared to a sample of children with PDD and no history of regression. No differences were found in any of the areas examined, leading Fombonne and Chakrabarti (2001) to conclude that there was no evidence for a new "regressive phenotype" of ASD associated with the MMR vaccine.

The Fombonne and Chakrabarti study used several different samples of children, in each case making the classification of children as regression or no-regression on the basis of parents' answers to the general questions regarding loss on the Autism Diagnostic Interview – Revised (ADI-R: Lord, Rutter, & Le Couteur, 1994). In order to be classified as having experienced a language regression on the ADI-R, it must be determined that the child had used at least 5 words (aside from "mama" and "dada") meaningfully on a daily basis for at least 3 months, followed by a period of at least 3 months in which s/he stopped using words completely. In order to be classified as having experienced a regression in other skills on the ADI-R, such as social reciprocity, it must be determined that the skill had been developing "normally" prior to loss. In the study by Fombonne and Chakrabarti, a child was classified in the regression group if s/he had shown a probable or definite loss of skills in at least one of seven possible domains on the ADI-R.

In a recent study of 2-year-olds referred for possible autism, Lord *et al.* (2004) found that many children with ASD whose parents described them as having lost words and/or social skills would not have met criteria for regression using the standard ADI-R questions, because the children had not had "normal development" prior to loss, or because they had not had at least five words prior to loss and/or did not stop talking for at least 3 months. It is possible, then, that children described by their parents as experiencing some loss would have been classified as no-regression in the study by Fombonne and Chakrabarti, who used the ADI-R loss questions as criteria for regression. As a result, the authors may have been less likely to detect group differences than they would have had they used slightly less stringent criteria.

Another factor to consider is that Fombonne and Chakrabarti, whose samples included parents of children 5 years old or older, used age of first parental concern from the ADI-R as the measure of onset. Most of the parents in the study, then, were reporting about events that had taken place many years ago; for example, of the three samples in the study, one consisted entirely of parents of individuals over 22 years old. Due to a "telescoping effect" observed in other studies (Cooper, Kim, Taylor, & Lord, 2001), it is possible that the mean age of first concern would have been lower had the participants (i.e. the "subjects" whose parents described them in the interviews) been younger at the time the parents were interviewed.

The present study addresses the same two questions posed in the study by Fombonne and Chakrabarti, using a large sample of children and a definition of regression that is both less restrictive and more specific, in the hope that this will provide the clearest possible distinction between children with ASD with regression and children with ASD and no regression. The following predictions were made:

(1) The children with ASD and regression should have more social and communicative skills prior to loss than the children with ASD and no regression, but still show signs of atypical early development
(2) If children with ASD and regression manifest a new phenotype of the disorder, they should show different outcomes, in terms of social and communicative skills, than children with ASD and no regression
(3) If regressive autism is associated with GI symptoms, then children with ASD and regression should have a greater tendency to have GI disorders and/or symptoms than children with ASD and no regression.
(4) If regressive autism is associated with the MMR vaccine, then age at onset of autistic symptoms should more closely follow age at MMR vaccination for children with ASD and regression than for children with ASD and no regression.

METHODS

Participants

This study is part of a larger project within the Collaborative Program for Excellence in Autism (CPEA), using data collected from 10 sites across the United States: the Albert Einstein College of

Medicine; Boston University; University of California – Irvine Medical Center; University of California – Los Angeles; University of Colorado; University of Pittsburgh – Western Psychiatric Institute and Clinics; University of Rochester Medical Center; University of Utah – Utah Autism Project; University of Washington; and the Yale Child Study Center. There are also several studies included in the Yale Program Project that recruited participants through the University of Chicago, the University of North Carolina, and the University of Michigan, bringing the total number of participating sites up to 13.

At the inception of this study, data had been collected for 1592 children diagnosed with ASD across all sites. These data include scores for the aforementioned ADI-R as well as the Autism Diagnostic Observation Schedule (ADOS; Lord *et al*., 1989), several standardized measures of verbal and non-verbal IQ, and demographic information. Each site used these previously collected data to identify potential participants. For children who had been evaluated more than once, information about the child's early history (e.g. language and other milestones) was obtained from the earliest parent report, because it was thought to be most accurate. Information about diagnosis and cognitive functioning was obtained from the most recent assessment, since later scores are generally more stable.

The following inclusion and exclusion criteria were used to determine which children from among this large sample were eligible to participate in this study: Children must have been born in westernized countries, have lived in the United States or Canada from birth to age 3, and must have received immunizations, for which records were available, in either of these countries. Children must have been at least 4 years of age and no more than 15 years of age at the time of the regression interview. Finally, all children were required to have complete ADOS and ADI-R scores, as well as verbal and non-verbal IQ scores from within the last 5 years.

Diagnostic criteria were also specified: Children must have received a best estimate diagnosis of autism, PDD-NOS or Asperger syndrome from a site clinician and met criteria for ASD on the ADOS and/or the ADI-R. Children with Rett syndrome or CDD, as well as children with identified genetic disorders, such as tuberous sclerosis and Fragile X syndrome, were excluded, as were subjects with visual, hearing, or motor impairments that would have precluded standard administration of study instruments.

Because previous work has indicated that word loss is the most easily measured aspect of regression in ASD (Goldberg *et al*., 2003), as well as the easiest for parents to remember (Lord *et al*., 2004; Shinnar *et al*., 2001), each site was asked to identify all children who had experienced word loss and met the criteria described above. Identification involved a two-step procedure intended to pinpoint an increasingly specific group of children with loss. First, investigators identified children whose parents had reported any kind of loss of skills on the initial ADI-R conducted at entry into the study. Any child who received a code of 1 or 2 on any of the loss items (indicating that the parent had reported some degree of loss in language and/or other skills) was screened at this stage. The second step was to identify those children within this any-loss group who met specific criteria for word loss. This was done by reviewing the child's ADI-R protocol, including interviewer notes. In cases where the notes were not clear, a brief follow-up telephone interview was conducted with the child's parent. A child was classified in the 'word loss' group if it was determined that s/he had spontaneously used at least three meaningful words (aside from 'mama' and 'dada') on a daily basis for at least 1 month, and then had stopped using *all* words for at least 1 month, prior to 36 months of age. If the child's ADI-R indicated that s/he had shown a repeated pattern of word gain and loss, s/he was also considered to be in the 'word loss' group. Whether or not children had experienced losses in other areas was not a factor in their inclusion in the 'word loss' group; if the child did not meet criteria for word loss, s/he was classified as ''no word loss,'' even if the ADI-R indicated s/he had experienced losses in other areas. Once children with ASD with and without word loss had been identified, parents were recruited to participate in the regression interview, in which they described their child's early skills in a number of social and communicative domains.

It is important to note, then, that ''no word loss'' is not synonymous with ''no-regression.'' In fact, a substantial minority of parents of children in the ''no word loss'' group reported that their child lost skills in several areas, such as gestures and pre-speech behaviors. Children who were reported on the regression interview to have lost at least 25% of skills in at least three skill areas, but did not meet criteria for word loss were designated as ''no-word loss regression.'' Because these children were found to have a pattern of skill acquisition and loss similar to that of the ''word loss'' children (see Luyster *et al*., 2005), both groups were combined into a more

general "regression" category; the remainder of the "no word loss" children were designated as the "no regression" group.

In total, data were analyzed for 351 children with ASD (163 regression, 188 no-regression) and 31 typically developing (TD) children. The same sample is used in a study by Luyster *et al.* (2005); see paper for a description of how typically developing children were recruited. Children with word loss were deliberately over-sampled; that is, we attempted to recruit all children with word loss and only a subset of other children with ASD who were similar in demographic variables. In the original design, each child with word loss was matched, within site, to a child without word loss on gender, ethnicity (Caucasian vs. non-Caucasian), approximate age at the time of parent interview, and approximate level of maternal education. However, because preliminary analyses, as described above, indicated that some children without word loss showed patterns of regression similar to those shown by the children in the "word loss" group (see Luyster *et al.*, 2005), we decided to recruit additional "no-word loss" participants. Also, because some of the smaller sites had difficulty matching, we decided to include subjects who could not be matched within site to increase our sample size. In the final sample, there were 101 matched pairs; that is, 202 out of the total 351 subjects were matched.

The demographics of the ASD and TD samples are provided in Table I. The level of maternal education in the TD sample was found to be significantly lower than that of the ASD sample ($\chi^2(3) = 9.27$, $p < .05$). There were also differences between the two groups on site, since the controls were recruited exclusively from Chicago and North Carolina. Within the ASD sample, there were no significant differences between the regression and no regression groups on ethnicity, gender, level of maternal education, or diagnosis. There was a significant difference between the groups in the age of the child at the time of the regression interview; the average age was significantly lower in the regression group ($M = 9.29$; $s.d. = 2.58$) than it was in the no-regression group ($M = 9.95$, $s.d. = 2.74$), ($t(343) = 2.28$, $p < .05$). The North Carolina and Chicago samples were compared to the remaining sample, since the former two comprised the majority of the total sample; group differences were found in level of maternal education, such that the North Carolina and Chicago groups had a greater proportion of mothers with a lower level of maternal education ($\chi^2(3) = 8.13$, $p < .05$)

Table I. Characteristics of Full Sample

	ASD $N = 351$	Typical $N = 31$
Gender		
Male	300 (85.4%)	22 (71.0%)
Female	51 (14.5%)	9 (29.0%)
Ethnicity[a]		
Caucasian	298 (84.9%)	22 (84.6%)
African American	33 (8.6%)	2 (7.7%)
Hispanic/Latino	8 (2.1%)	0 (0.0%)
Asian	7 (1.8%)	0 (0.0%)
Native American	3 (0.8%)	0 (0.0%)
Other	2 (0.5%)	2 (7.7%)
Diagnosis		
Autism	273 (77.8%)	–
ASD[b]	76 (21.7%)	–
Asperger syndrome	2 (0.6%)	–
Site		
Chicago/North Carolina/Michigan	211 (60.1%)	31 (100.0%)
Other	140 (39.9%)	0 (0.0%)
Maternal education [a]		
Graduate/professional degree or BA	206 (59.0%)	13 (43.3%)
Some college/ Associate's degree	101 (28.9%)	8 (26.6%)
High school graduate	31 (8.9%)	5 (16.7%)
GED/less than high school graduate	11 (3.2%)	4 (13.3%)
Age at time of interview (in years)	9.64 (2.68)	8.70 (3.04)

[a]Information about maternal education missing for two children with ASD and 1 typical child. Information about ethnicity missing for five children. Percentages for each variable are calculated excluding children for whom information on that variable is missing.

[b]The term 'ASD' refers to a broader diagnosis on the autistic spectrum and includes children with Pervasive Developmental Disorders-Not Otherwise Specified (PDD-NOS).

Procedure

Parents of the potential participants were sent a packet of information and contacted via telephone to request their permission for participation and to mail in consent forms. Once these forms were received, a telephone interview lasting approximately 1 hour took place. In the course of the interview, parents were asked to describe their child's early social and communication skills, as well as to provide details about various aspects of their own medical history and the medical histories of their child with ASD and other relatives. Compensation was only provided for parents of children in the TD group who received a $30 gift card.

Data indicating response rate was available for the ASD subjects at the North Carolina and Chicago

sites only: 428 families were initially contacted at these sites, 237 (55%) of whom were included in the final dataset. Some of the families contacted had a child diagnosed with a non-spectrum developmental disorder. Data from these participants are provided in a separate paper (see Luyster *et al.*, 2005). Forty-nine families (11.4%) were lost due to incorrect contact information and 58 (13.6%) refused; approximately half of these refusals were "soft" refusals, with the families expressing a willingness to be contacted but then repeatedly failing to be available at scheduled appointment times. The remaining 84 families (20%) were excluded for a variety of reasons that made them ineligible for participation (e.g. a child had been adopted after 12 months of age). Chi-square analyses indicated that the families who did and did not participate showed no differences in the child's gender, ethnicity, diagnosis, and age at interview, or in the mother's level of education. Twenty-five children (about 7% of the total sample), distributed approximately equally across the regression and no-regression groups, were part of a longitudinal sample described in a previous paper (Lord *et al.*, 2004).

Measures

The parent interview was developed specifically for the purposes of this study. Each of the four sections was adapted from published work in relevant areas. Interviewers were required to conduct a practice, audio-taped interview prior to telephoning actual participants. An experienced interviewer then listened to the interview and gave recommendations for improvement, as well as coded the interview a second time, pointing out any discrepancies in coding. Reliability of coding exceeded 90% exact agreement across all items for interviews that passed criteria. Maintenance of reliability was checked in Michigan for the Michigan, Chicago, and North Carolina participants, who comprised 60% of the total sample, and consistently exceeded 90% exact agreement for pairs of raters. (See Lord *et al.*, 2004 for the complete regression interview.)

When this interview was developed, the problem of accuracy of parent recall, especially for parents of older children, was carefully considered. To control for the telescoping effects described above, children were matched whenever possible on chronological age at the time of interview. Furthermore, the data collected were not based solely on parent report in the present interview; rather, current parent report was corroborated by the child's initial ADI-R, which was generally administered within 12 months of the time of loss for almost all of the children with regression at the North Carolina and Chicago sites, as well as children with regression at several other sites. Methods were also employed to help parents remember more accurately. For example, in order to determine the precise age at which the child lost words, the interviewer would ask if the child still had words at his/her second birthday; if so, s/he would then ask if the child still had words at the next major milestone, such as Christmas, the birth of another child, or a family move. Finally, parents were asked similar questions about loss at different points in the interview, as a way of checking whether they were answering consistently.

The first part of the telephone interview asked about the child's acquisition of major milestones in communication skills and about word loss. For instance, parents were asked at what age (in months) their child began to use words meaningfully, and, if their child had lost words, at what age this loss had occurred. These questions were adapted from the Toddler ADI-R, for which good test–retest and inter-rater reliability, discriminant and convergent validity, and internal consistency have been obtained (see Lord *et al.*, 2004).

The second part of the interview included questions adapted, with permission, from the MacArthur Communicative Development Inventory: Words and Gestures Form (CDI: Fenson, 1989), which is used to assess communication skills in typically developing 8- to 16-month olds and in older, developmentally delayed children. The CDI is divided into seven sections concerning different aspects of the child's early communication: pre-speech behaviors, games and routines, actions with objects, pretending to be a parent, phrase comprehension, early vocabulary, and early communicative gestures. It has been found to have excellent inter-rater reliability for totals within subscales as well as excellent validity (Stiles, 1994). Wording was changed slightly in order to administer this instrument orally and retrospectively, and the total number of items was reduced. Generally, the earliest communication items were selected, as well as those items especially likely to be related to autism (e.g. pointing) and those unlikely to be related to autism (e.g. actions with objects), which were included as a control. For each skill, we asked the parent if their child had acquired the skill prior to the age of 24 months, and if so, whether their child had ever become markedly worse at or completely lost that skill for at least 1 month

prior to the age of 36 months. The child received a score of 1 if s/he had the skill at 24 months and a 0 if s/he had not; s/he received a score of 1 if s/he had lost the behavior by 36 months and a 0 if s/he had not. Table II includes sample items adapted from the CDI.

Subsequent sections asked about the biological mother's prenatal, perinatal and neonatal history, as well as the child's immunizations. These items were adapted from the work of various authors (Deykin & MacMahon, 1980; Finegan & Quarrington, 1979; Gillberg & Gillberg, 1983; Lord, Molloy, Wendelboe, & Schopler, 1991). Questions about GI disorders and symptoms were selected on the basis of claims made about potential links with ASD and were based on the work of several authors (Pardi *et al*., 2000; Wakefield *et al*., 1998, 2000). Questions regarding immune function were included in order to examine the postulated link between certain autoimmune disorders and autism. These items were based on a study that used similar methods (Comi, Zimmerman, Frye, Law, & Peeden, 1999) and are the topic of a separate paper (Molloy *et al*., in press).

The interview was the primary measure for the current study. It included a mix of closed-end, open-end numeric and open-end codeable questions. Other measures included in analyses were the loss items from the initial ADI-R and algorithm scores from the most recent ADI-R and ADOS, as well as the standard scores from the Vineland Adaptive Behavior Scales (VABS: Sparrow, Balla, & Cicchetti, 1984), and verbal and non-verbal IQ scores obtained primarily from the Differential Abilities Scale (Elliott, 1990) or the Mullen Scales of Early Learning (Mullen, 1995). Complete medical records, including the dates of all vaccinations received, were also obtained whenever possible for the children in the ASD sample as well as their mothers.

Data Analysis

Group comparisons were carried out using chi-square analyses or ANOVAs. For some of the analyses of the timing of onset of autism relative to MMR vaccination, survival analysis was used in order to provide a more detailed picture than chi-square analyses could afford. On occasion, distributions of a given variable were generated for both the regression and no-regression groups, in order to obtain a clearer understanding of within-group variation in a given variable, such as verbal IQ. Finally, regression analysis was used to evaluate the degree to which early losses predicted certain outcome variables, such as IQ.

RESULTS

Before any analyses were conducted, parent responses to the regression telephone interview were compared to those from the original ADI-R, in order to check for discrepancies. If parent reports during the telephone interview differed from the loss history coded from the earlier ADI-R, the ADI-R protocols were re-checked. If it was determined that the loss had been miscoded in the ADI-R (e.g. if written notes confirmed the loss but the item was coded as 'no loss'), the child's loss grouping was changed. If, however, no basis for the report in the telephone interview was found in either the ADI-R notes or codes, the child maintained his or her original classification. Figure 1 shows how many children had conflicting information about loss on the ADI-R and the regression interview, and how these conflicts were resolved. As the figure indicates, over 80% of ASD cases fell into the same word loss classification based on parents' reports during their earliest ADI-R and the later telephone interview, and only approximately 3% were reclassified after the telephone

Table II. Sample Items Adapted from the MacArthur Communication Development Inventory

Skill area	Sample item
Prespeech behaviors	Responded when name was called (e.g. by turning and looking at source)
Games and routines	Played peek-a-boo
Actions with objects	Ate with a spoon or fork
Pretending to be a parent	Covered doll with blanket
Phrase comprehension	Understood 'Don't touch'
Early vocabulary	Said and/or understood 'juice'
First communicative gestures	Waved bye-bye on his/her own when someone left

Note: Respondents were asked if these items were present before 24 months of age and whether or not they were lost or significantly decreased for at least a month before 36 months of age.

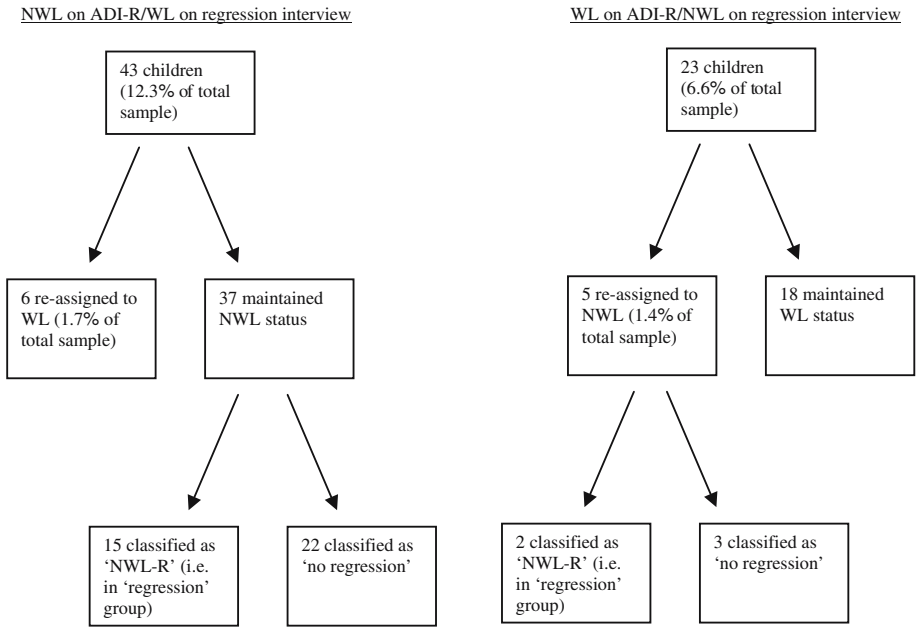

Fig. 1. Process for resolving conflicting information about loss on ADI-R and regression interview; *Note*: WL = word loss; NWL = no word loss; NWL-R = no word loss-regression; ADI-R = Autism Diagnostic Interview-Revised.

interview. All analyses were run with these changes and without them; because no differences between the two sets of findings were found, the latter are not reported separately.

Because various analyses required examinations of different subsets of the entire sample, the results section is divided according to analyses performed on different samples, each with a different size. As mentioned above, preliminary analyses found the 'no word loss regression' children to be similar to the children with word loss in terms of skill mastery and loss in the early years (Luyster *et al.*, 2005). For this reason, the following analyses combine both of these groups into a more general 'regression' group. Unless otherwise stated, all analyses compare children with ASD and regression to children with ASD and no regression. Analyses were also run comparing the 'word loss' and 'no word loss' groups, and very similar results were found; hence, the latter results are not reported separately.

Sample 1: Entire ASD Sample

The analyses in this section include the entire ASD sample (163 children with regression, 188 without regression). Some analyses also include the sample of 31 typically developing children used in the study by Luyster *et al.* (2005).

Skill Mastery of Children with Regression Prior to Loss

CDI area totals of children with regression were compared to those for the typically developing children in the study by Luyster *et al.* (2005). Results indicated that, before the age of 24 months, children with regression had significantly fewer skills than the typically developing children in all areas of the CDI. In the present study, in order to determine to what extent parental reports of the early history of the children with regression overlapped with those for the typically developing children on an individual level, data for each child with regression were analyzed to determine how many of the CDI area scores for each child fell within one standard deviation of the mean for the typical group. Figure 2 shows the distribution of number of areas falling in the ''typical range'' for children with regression, with zero being the minimum and seven being the maximum. As the graph indicates, the vast majority (i.e. 72%) of children with regression were described by their parents as falling in the 'typical range' for only a minority (i.e. at most 3 out of 7) of areas, even prior to experiencing a regression; however, this also means that nearly 30% of children with ASD and regression were reported to have skills in the 'typical range' in the majority of areas

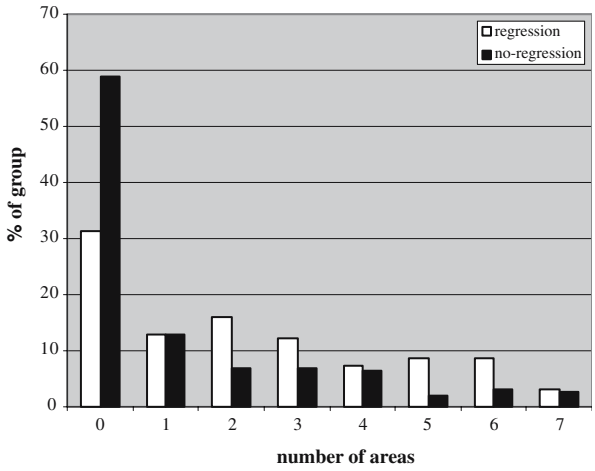

Fig. 2. Number of areas in 'typical range' by loss group; Note: 'Typical range' = within one s.d of mean score for typical children.

on the CDI. In the no-regression group, only about 15% of children were described as having skills in the 'typical range' on a majority of CDI areas. When divided into three groups—zero skills, 1–3, and 4–7 early skill areas in the typical range—the regression group had a greater proportion of children with the majority of early skill areas in the typical range compared to the no-regression group ($\chi^2 = 26.34$, $df = 2$, $p < .001$).

Social and Communicative Outcomes

In order to test the prediction that children with ASD and regression would have a different outcome, in terms of social and communicative skills, than those who did not, the two groups were compared on several measures of outcome, including verbal and non-verbal IQ scores; VABS standard scores in communication, daily living, socialization, and motor skills; ADOS domain scores; and ADI-R domain scores. As is shown in Table III, children in the regression group had lower verbal IQ (VIQ) scores and higher (i.e. more impaired) ADI-R social reciprocity domain scores than children without regression. The groups did not differ on any of the other outcome variables mentioned above.

A linear regression was then run using regression status as a predictor variable and VIQ as a dependent variable, with age at interview included as a covariate, because it was found to be significantly lower in the regression group, as mentioned above. Regression status was found to be a significant predictor of VIQ ($\beta = -8.79$, $p < .05$), controlling for age at interview.

In order to examine in more detail how the regression and no-regression groups differed on VIQ, distributions of VIQ for both groups were generated. As Fig. 3 indicates, the distribution of VIQ for the no-regression group is almost perfectly normal, with a mean of approximately 66. The distribution for the

Table III. Severity Measures by Regression Status

	Regression	No-regression
Verbal IQ[a]	56.74 (3.35)	66.28 (32.24)
Non-verbal IQ	72.51 (28.8)	77.69 (29.33)
ADI-R social reciprocity[b]	20.63 (6.59)	18.88 (6.49)
ADI-R verbal communication	14.71 (4.59)	14.62 (4.94)
ADI-R non-verbal communication	10.11 (3.4)	9.47 (3.65)
ADI-R restricted and repetitive behaviors	5.42 (2.41)	5.52 (2.41)
ADOS social	9.74 (3.13)	9.08 (2.99)
ADOS communication	5.63 (2.29)	5.53 (2.21)
ADOS play	1.97 (1.43)	1.85 (1.37)
ADOS restricted and repetitive behaviors	2.96 (1.88)	2.73 (1.97)
VABS socialization	65.2 (14.7)	60.4 (13.51)
VABS communication	61.6 (21.8)	61.01 (21.4)
VABS daily living	62.39 (20.43)	56.09 (18.47)
VABS motor skills	74.97 (17.37)	68.96 (20.31)

[a] F (1, 314) = 6.66, $p = .01$.
[b] F (1, 339) = 6.06, $p < .05$.
Note ADI-R = Autism Diagnostic Interview-Revised; ADOS = Autism Diagnostic Observation Schedule; VABS = Vineland Adaptive Behavior Scales. ADI-R and ADOS scores are summary scores within domains, whereby higher scores indicate a greater degree of impairment. VIQ scores were unavailable for 17 children with regression and 15 children without regression; ADI-R social scores were unavailable for four children with regression and six children without regression.

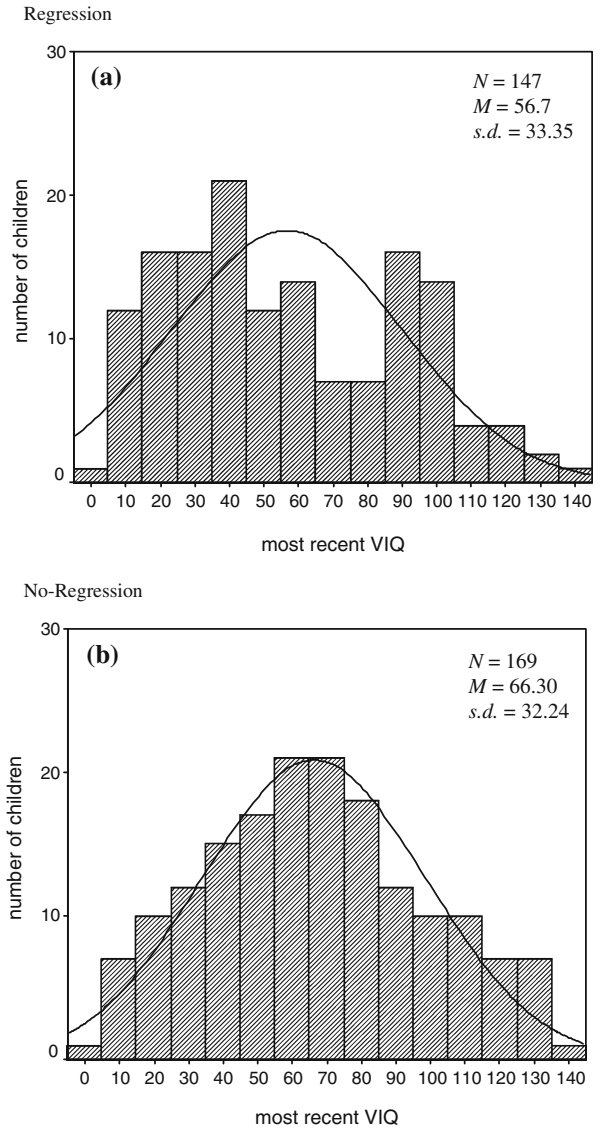

Fig. 3. Distributions of VIQ by regression status. (a) $N = 147$, $M = 56.7$, $s.d. = 33.35$. (b) $N = 169$, $M = 66.30$, $s.d. = 32.24$.

regression group looks strikingly different: it is bi-modal, with one peak occurring at about 40 and another close to 90. It is not surprising, then, that when the two groups were further subdivided into three VIQ groups—low (below 40), moderate (41–80), and high (above 80), a significantly greater proportion of children with regression had low VIQ scores, ($\chi^2 = 14.16$, $df = 2$, $p = .001$). However, similar proportions of children in the regression and no-regression groups had VIQ scores above 80, with about a third of the children in each group falling into this category.

Because VIQ was found to be associated with regression grouping and is generally associated with other measures, such as ADI-R and ADOS scores, it was included as a covariate in subsequent analyses of regression as a predictor of outcome. Controlling for age and VIQ, regression status was found to be a significant predictor of social reciprocity domain score on the ADI-R ($\beta = 1.47$, $p < .05$). Regression status did not predict any of the other outcome measures, controlling for age and VIQ.

As with VIQ, distributions of social reciprocity domain scores were generated for the two groups. As Fig. 4 indicates, the regression group had a significantly greater proportion of children with high scores, indicating a greater degree of impairment. When the regression and no-regression groups were further divided into three groups according to ADI-R social reciprocity score—low (0–10), moderate (11–20), and high (21–30), the regression group was found to have a significantly greater proportion of children in the "high" group as compared to the no-regression group ($\chi^2 = 6.60$, $df = 2$, $p < .05$). In other words, a greater percentage of children in the regression group were reported by their parents to be severely socially impaired, as compared to the no-regression group.

In order to examine whether the children with low VIQ scores were the same children who had high ADI-R social reciprocity scores, three groups were generated: children with VIQ scores above 50 and ADI-R social reciprocity scores below 20 (the "less impaired" group); children with VIQ scores below 50 and ADI-R social reciprocity scores above 20 (the "more impaired" group); and those who did not fall into either of these categories (the "other" group). The regression and no-regression groups were compared on the proportions of children that fell into each of these categories. Results indicated that the regression group had a significantly greater proportion of children with low VIQ scores and high ADI-R social reciprocity scores, compared to the no-regression group, ($\chi^2 = 10.24$, $df = 2$, $p < .01$). Approximately one-third of the children in both the regression and no-regression groups fell into the "other" category. These results indicate that the regression group had a greater proportion of children with *both* low VIQ scores and high ADI-R social reciprocity scores than the no-regression group.

Gastrointestinal Disorders and Symptoms

As outlined above, if there is a regressive phenotype of ASD associated with GI dysfunction,

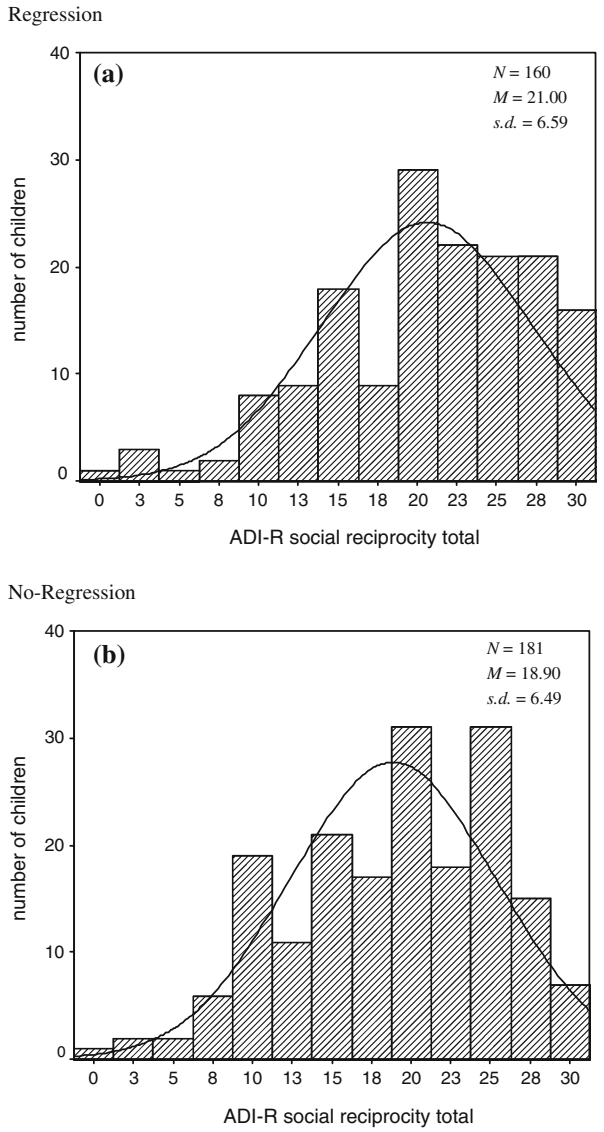

Fig. 4. Distributions of ADI-R social reciprocity domain scores by regression status. (a) *Note*: $N = 160$; $M = 21.00$; $s.d. = 6.59$. (b) *Note*: $N = 181$; $M = 18.90$; $s.d. = 6.49$.

then we would expect children with ASD and regression to have a higher frequency of specific GI disorders and/or symptoms than children with ASD and no regression. Chi-squares found no significant differences between the two groups in rates of GI *disorders* (e.g. Crohn's disease, colitis, irritable bowel syndrome), in part due to very low rates of GI disorders in general (i.e. no more than 4%, or 7 out of 164 children in the regression group and 2%, or 3 out of 187 children in the no-regression group). However, significant differences were found for frequency of GI *symptoms*.

Table IV shows the proportions of parents who reported that their child had experienced specific GI symptoms for 3 consecutive months at some point in his or her life. Significant differences were found between the regression and no-regression groups for the following GI symptoms: change in stool frequency ($\chi^2 = 9.57$, $df = 1$, $p < .01$); change in stool consistency ($\chi^2 = 8.95$, $df = 1$, $p < .01$); mucus in stool ($\chi^2 = 3.86$, $df = 1$, $p < .05$); long-lasting/recurrent diarrhea ($\chi^2 = 12.8$, $df = 1$, $p < .001$); and bloating ($\chi^2 = 4.51$, $df = 1$, $p < .05$). In all cases, the regression group had a higher rate of the symptom than the no-regression group. The total number of possible GI symptoms was then divided into ranges—zero, one to three, and four or more symptoms—because these represented distinct 'cut-points' in the overall distribution of number of GI symptoms. A significant group difference was found using these ranges ($\chi^2 = 7.53$, $df = 2$, $p < .05$). Where differences between the regression and no-regression groups were not significant, the regression group had a higher rate of the symptom for all but two symptoms (frequent diarrhea with vomiting and recurrent fever), where the no-regression group had a higher prevalence than the regression group, but the prevalence rates for both groups were very low (i.e. under 5%).

Sample 2: Analysis of Data for Children with Verified Dates of Vaccination and Onset

This set of analyses includes all children for whom we could verify dates of vaccination from medical records and ages of onset of autistic symptoms from the original ADI-R. The total number was 285 children (134 regression, 151 no-regression). The interviewer's judgment of onset from the ADI-R was used as the measure of onset. This judgment is made at the end of the ADI-R, allowing the interviewer to consider all the information provided by the caregiver, including both the absence of typically developing milestones (e.g., social smile) and the presence of unusual behaviors (e.g., lining up toys).

Age at Onset and Age at Vaccination

The regression and no-regression groups were compared on age of onset, in order to test the hypothesis that the regression group would have a different age of onset from the no-regression group, as one might expect if there is a "regressive phenotype"

Table IV. Rates of Gastrointestinal Symptoms

		Regression	No-regression
Change in stool frequenc y[b]	No	103 (63.20%)	144 (78.30%)
	Yes	60 (36.80%)	40 (21.70%)
Change in stool consistency[b]	No	102 (62.20%)	143 (76.90%)
	Yes	62 (37.80%)	43 (23.10%)
Mucus in stool[a]	No	141 (88.10%)	175 (94.10%)
	Yes	19 (11.90%)	11 (5.90%)
Long-lasting/recurrent diarrhea[c]	No	126 (76.80%)	168 (90.80%)
	Yes	38 (23.20%)	17 (9.20%)
Bloating[a]	No	131 (81.40%)	161 (89.40%)
	Yes	30 (18.60%)	19 (10.60%)
Abdominal pain/discomfort	No	120 (74.50%)	145 (82.50%)
	Yes	41 (25.50%)	31 (17.60%)
Mucus in stool	No	141 (88.10%)	175 (94.10%)
	Yes	19 (11.90%)	11 (5.90%)
Number of GI symptoms[a]	None	72 (47.10%)	103 (60.20%)
	One to three	61 (39.90%)	58 (33.90%)
	Four or more	20 (13.10%)	10 (5.80%)

[a]$p < .05$, [b]$p < .01$, [c]$p < .001$.

Note Data on GI symptoms were unavailable for several subjects. The numbers for unavailable data are as follows: stool frequency—1 regression, 3 no-regression; stool consistency—1 no-regression; mucus in stool—4 regression, 1 no-regression; diarrhea—2 no-regression; bloating—3 regression, 7 no- regression; number of GI symptoms—11 regression, 16 no-regression. Data for symptoms present in less than 10% of children in both groups are not reported.

of ASD characterized by a distinct course. The average age of onset for the children with regression ($M = 16.94$; $s.d. = 5.77$) was significantly later than it was for those without regression ($M = 13.70$; $s.d. = 8.17$), ($F(1, 283) = 14.60$, $p < .001$). The difference in age at MMR vaccination for those with regression ($M = 17.33$; $s.d. = 8.51$) as compared to those without regression ($M = 17.28$; $s.d. = 7.73$) was not significant.

Given that children with regression had a later age of onset of autistic symptoms than those without regression, but a similar age at MMR vaccination, one might predict that the two groups would differ in the timing of onset relative to vaccination; that is, a greater proportion of children with regression would have onset following vaccination than children without regression. In order to test this prediction, children with regression were compared to those without regression on timing of vaccination relative to onset. Table V shows the proportions of children in each group having onset before and after vaccination. Chi-square analyses yielded a significant difference between the groups in the proportions of children having onset before and after vaccination ($\chi^2 = 10.07$, $df = 1$, $p < .01$). As predicted, a significantly greater proportion of children with regression had onset following vaccination, as compared to children without regression.

Given parent reports of close temporal proximity between MMR vaccination and onset of autistic symptoms (Woo *et al.*, 2004), a second analysis examined the question of whether, among children who had onset of autistic symptoms after MMR vaccination, those with regression were more likely to have an onset that closely followed their age at vaccination than children without regression Children in both groups who had onset after vaccination were classified according to the interval between onset and vaccination: 0–3 months, 3–6 months, and more than 6 months. Chi-square analyses found no differences between the groups in the interval between vaccination and onset. A *t*-test was done to determine whether there was less variability in the interval between MMR immunization and onset of ASD in the regression group, as one might expect if regression in ASD were associated with the MMR vaccine; again, no group differences were found.

Table V. Age of Onset Relative to Age at MMR Vaccination

	Regression ($N = 134$)	No regression ($N = 151$)
Onset before vaccination	61 (45.5%)	97 (64.2%)
Onset after vaccination	73 (54.5%)	54 (35.8%)

Finally, survival analyses were run to obtain a more precise picture of the general timing of vaccination for the two groups, as well as the specific timing of onset of autistic symptoms relative to MMR vaccination. For these analyses, children with particularly late ages at MMR vaccination (i.e. after 60 months of age) were excluded. Figure 5 depicts the interval between time of birth and age at vaccination for both the regression and no-regression groups. As the graph indicates, the curves look similar. In both groups, most children received the MMR vaccine between 15 and 18 months. The longer tail on the curve for the no-regression group indicates that a few children in this group were vaccinated later than is typical, most likely because of parental concerns about their child's development. A logrank test found the difference between the two curves non-significant; the observed frequencies of regression ($n = 146$) and no-regression ($n = 164$) were close to those expected under equality of survival curves (142.68 and 167.32 for the regression and no-regression groups, respectively).

Figure 6 shows the Kaplan–Meier curves for the timing of onset relative to vaccination, using only the children who had onset after vaccination. As is shown in the figure, there is little difference between the two curves. A logrank test found no significant difference between the curves; the observed frequencies of regression ($n = 73$) and no-regression ($n = 54$) and were not significantly different from those expected under equality of survival curves (64.82 and 62.18 for the regression and no-regression groups, respectively).

Skill Mastery of Children with Possible 'Regressive Phenotype' Prior to Loss

Another way to examine whether there is a 'regressive phenotype' of ASD characterized by normal or near-normal skills before MMR vaccination is to compare the early development of the children who most closely match the 'phenotype' proposed to be associated with MMR vaccination to that of typically developing children. We selected those children in the sample who were reported to have had a regression, experienced onset of autistic symptoms after vaccination, and had at least one GI symptom for three consecutive months at some point in his/her life as the 'possible regressive phenotype' group. In the present sample, this group comprised 24 children. This sample was compared to the 'non-phenotype' group (i.e. the remaining ASD sample) on gender, ethnicity, diagnosis, and level of maternal education, as well as age at vaccination, age at interview, and age of onset of autistic symptoms as measured by the interviewer's judgment on the ADI-R, as explained above. As Table VI indicates, significant differences between the 'possible regressive phenotype' group and the remaining ASD sample were found for gender, such that the 'phenotype' group had a greater proportion of females than the no-regression group. Children in the 'possible regressive phenotype' group were also found to have significantly later ages of onset and significantly earlier ages at vaccination than the remaining ASD sample.

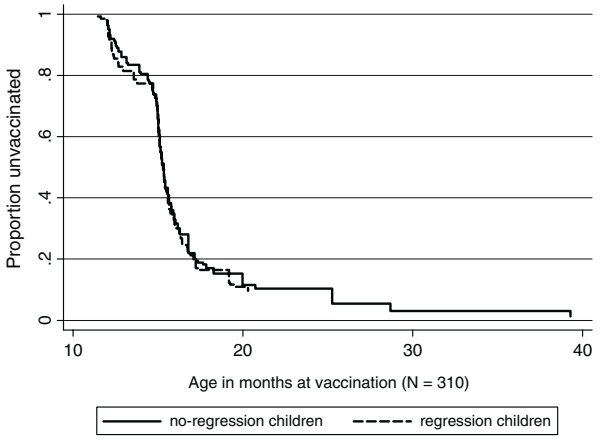

Fig. 5. Age at MMR vaccination by regression status; *Note*: 310 = number of children in the entire sample for whom verified dates of vaccination were available.

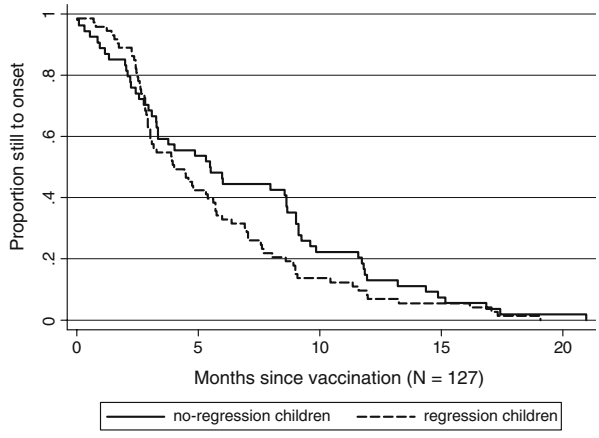

Fig. 6. Interval between onset of autistic symptoms relative and MMR vaccination by regression status; *Note*: 127 = number of children with onset after vaccination for whom verified dates of onset and vaccination were available.

Table VI. Demographics of 'Possible Regressive Phenotype' Group vs. Remaining ASD sample

	'Possible phenotype' ($N = 24$)	Remaining ASD sample ($N = 244$)
Gender[a]		
Male	16 (66.7%)	205 (84.0%)
Female	8 (33.3%)	39 (16.0%)
Age at onset (months)	19.00 (2.67)	14.55 (7.58)
Age at vaccination (months)	14.38 (1.59)	17.71 (8.62)

[a]$\chi^2(2) = 4.55$, $p < .05$.
Note: Children who did not have age at onset, age at vaccination determined from medical records, and complete information about GI symptoms were excluded from this analysis.

The CDI data for typically developing children were compared to that of the children in the 'possible regressive phenotype' group. Table VII provides the means for the 'phenotype' group, the 'remaining regression' group (i.e. children with regression who did not fit the 'phenotype' profile), the no-regression group, and the typically developing group. As the table shows, for the 'phenotype' group, the means for pre-speech behaviors, games and routines, and gestures fell within one standard deviation of the mean for the typically developing children, whereas none of the means for the other ASD groups fell in the typical range.

Since previous studies have reported that regressive autism is characterized by normal or near-normal development prior to loss, we then generated a distribution of the number of areas falling in the typical range for the possible regressive 'phenotype' group in order to address the issue. Exactly half of the children in this group had no scores falling in the typical range, and the maximum number of scores falling in the typical range for any child in this group was three. This suggests that the children who most closely fit the regressive 'phenotype' profile had abnormal development in the majority of areas on the CDI prior to loss.

Sample 3: Matched Pairs of Children with ASD with Word Loss and no Word Loss

Because word loss had been the original measure by which we had identified children with regression, and because we were interested in the relationship between MMR vaccination and autistic regression specifically, we decided to examine the association between MMR vaccination and word loss with all matched 'word loss-no word loss' pairs for whom we could verify vaccination data. In total, there were 86 matched pairs, i.e. 172 children. Each child in the NWL group was assigned a 'dummy' word loss age, the same age as the child in the WL group to whom s/he had previously been matched on gender, race, maternal education, and site.

Age at Word Loss Relative to Age at Vaccination

As is outlined above, if the MMR vaccination specifically 'triggers' word loss in children with ASD, independent of whether they are already showing delayed or abnormal development, then we would expect that, for the word loss group, age at word loss would closely follow age at vaccination. Such a pattern would not be expected for children with no word loss, for whom word loss age is an arbitrary

Table VII. Skill Mastery at 24 Months for 'Possible Regressive Phenotype' Group[a]

Sum of behaviors at 24 months by CDI section	'Phenotype' group ($N = 24$)	Regression remaining ($N = 78$)	No regression ($N = 166$)	Typical ($N = 31$)
Pre-speech behaviors	7.62[a] (1.84)	6.82 (2.30)	5.14 (2.55)	8.55 (0.96)
Games/routines	5.38[a] (1.84)	4.14 (1.91)	3.33 (2.09)	6.19 (1.17)
Actions with objects	6.83 (2.65)	6.17 (2.49)	5.12 (3.17)	10.45 (1.71)
Gestures	6.92[a] (2.17)	5.42 (2.81)	3.80 (2.81)	8.74 (1.99)
Pretending to be a parent	2.45 (1.40)	1.46 (1.77)	1.01 (1.53)	4.84 (1.61)
Phrase comprehension	16.33 (4.20)	13.10 (6.17)	9.81 (6.89)	19.29 (1.35)
Early vocabulary	11.25 (5.35)	8.01 (4.97)	6.77 (6.81)	16.77 (2.57)

[a]Within one standard deviation of typical score.
Note: This analysis includes only children for whom complete data about age at onset, age at vaccination, and GI symptoms were available.

number assigned from their matched pair. Figure 7 shows the Kaplan–Meier analysis for timing of word loss relative to age at vaccination, by word loss group. The analysis includes only those children for whom word loss followed vaccination.

As the figure shows, the curves look very similar. A logrank test found the difference non-significant; the observed frequencies of 'word loss' ($n = 67$) and 'no word loss' (n = 54) were close to those expected under equality of survival curves (68.77 and 52.23 for the 'word loss' and 'no word loss' groups, respectively). There is no sharp drop in the curve following vaccination for the word loss group, as would be expected if word loss were specifically associated with the MMR vaccine.

DISCUSSION

This study addressed two questions: First, is there evidence for a 'regressive phenotype' of ASD? Second, is regression in ASD associated with the MMR vaccine? The answer to the first question was mixed: Results from the CDI portion of the interview indicated that there was a small subgroup of children in the regression group who were described as showing near-normal development in the majority of CDI areas prior to loss. However, consistent with other studies, the majority of parents who reported a regression in their child also reported clearly atypical development prior to loss. Furthermore, it is important to note that the few children who showed near-normal development prior to loss were not the same children who manifested the 'possible regressive phenotype' (i.e. regression, GI symptoms, onset of autistic symptoms after vaccination). In fact, the results from the present study indicated that all those children who most clearly fit the 'possible regressive phenotype' showed abnormal development in the majority of areas on the CDI prior to loss. If there is a 'regressive phenotype' of ASD, then, it does not appear to be characterized by normal or near-normal early development.

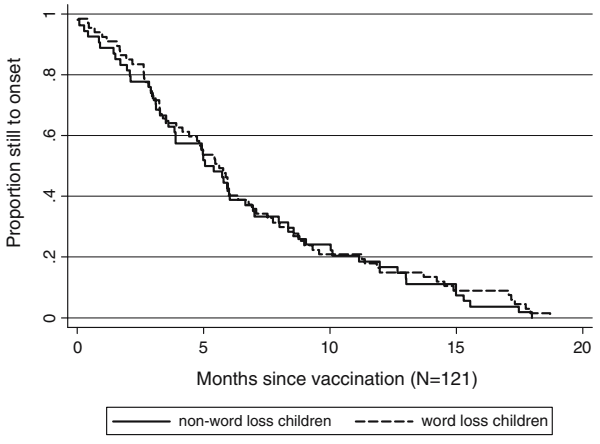

Fig. 7. Interval between MMR vaccination and word loss by loss group; *Note*: 121 = number of children in matched pairs for whom verified dates of vaccination and word loss were available.

Findings on developmental outcomes were also mixed. Children's most recent assessments (which in some cases were the same as the ones conducted upon entry into the studies) indicated that children with ASD and regression had lower VIQ scores and higher ADI-R social reciprocity domain scores than children with ASD and no regression; the latter finding is consistent with a recent study by Werner *et al.* (2005). It is important to note, however, that a subset of the regression group had a relatively high verbal IQ, as indicated by a peak in the distribution close to 90. Similarly, while a greater proportion of the regression sample had high ADI-R social reciprocity scores relative to the no-regression group, there was still a significant portion of the regression group that had moderate or low scores on this domain.

In the area of gastrointestinal dysfunction, the telephone interview conducted for this study indicated that parents of children with ASD reported higher rates of several GI symptoms than parents of children with ASD without regression. While this is certainly an important area for future study, it must be noted that the information about GI symptomology was based on parent report and was not corroborated by medical records. Furthermore, some of the group differences would have been considered non-significant had we corrected for the effect of multiple comparisons.

Taken together, the findings in the present study suggest that, much like children with ASD in general, children with ASD and regression are a heterogeneous group with varying trajectories of development. Moreover, even if there is a 'regressive phenotype' of ASD, there is no evidence that it is characterized by normal pre-loss development, as is often stated in papers about regression in children with ASD.

The answer to the second question is more definitive: the present study provides no evidence that regression in ASD is associated with MMR vaccination. The fact that a greater proportion of children in the regression group had onset of autistic symptoms

following vaccination is likely due to generally later ages at onset in this group. Furthermore, in *both* the regression and no-regression groups, most of the children who experienced onset after vaccination began showing signs of autism within a few months of vaccination. This tendency is likely related to the typical timing of onset of autism and of MMR vaccination in the U.S. Autism, by definition, must have its onset prior to the age of 3 years, and is typically described by parents in formal interviews as having its onset in the second year of life. The defining characteristics of autism include impairments in social behaviors and communication skills that develop in typical children between 9 and 18 months (Carter *et al*., 1998). For a child to meet diagnostic criteria for autism, then, s/he must fail to acquire behaviors typical of a 9- to 18-month-old, or develop such behaviors and then lose them by the age of 3 years. Thus, the ''window'' for onset of autism, at least as defined by the most well-documented social and communicative behaviors, is quite limited.

The ''window'' for vaccination is similarly constrained. In the present study, the majority of children with ASD, regardless of whether or not they had experienced a regression, were vaccinated by 18 months of age. De Stefano, Bhasin, Thompson, Yeargin-Allsopp, and Boyle (2004) found similar results in a recent study comparing ages at vaccination in children with and without autism. Consequently, even if onset of regressive autism and MMR vaccination are independent events, they are likely to occur within a narrow window of time. The use of regression in ASD as an indicator that MMR vaccination ''causes'' ASD is not warranted.

Similarly, the present study provides no evidence for an association between more narrowly defined regression associated with word loss and MMR vaccination. Survival analyses did not show an increased proportion of children with ASD and word loss experiencing regression soon after being immunized, as we would expect if word loss were linked to the vaccine. Instead, we observed a range of ages at which children lost words, with the maximum being approximately 20 months after vaccination.

Several factors may explain why differences were found between the regression and no-regression groups in the present study that were not found in the study by Fombonne and Chakrabarti (2001). First, the definition of language regression used in the present study was more liberal and based on more detailed information than the one used in their study. Thus, some children who were classified as 'no-regression' in their study would have been classified as 'regression' in the present research. This may have made it easier to detect group differences. Second, the children in the present study were, on the whole, much younger than those included in Fombonne and Chakrabarti's study, thereby increasing the likelihood of accurate parent report. Third, children with regression were over-sampled in the present study, allowing us to study a larger sample of children with regression than in previous studies. This may also explain why some differences were identified here that were not apparent when a subset of the North Carolina sample was analyzed on its own (see Lord *et al*., 2004).

Limitations and Directions for Future Research

The main limitations of the present study were design-related. In the interview, parents were asked if their child had acquired a given skill by the age of 24 months, and if so, whether s/he had lost that skill prior to 36 months of age. The way the question was structured necessarily made it impossible to know if the child had acquired a given skill *between* the ages of 24 and 36 months and whether a child who had lost a given skill had ever regained it. Incorporating these questions into an interview may provide further useful information about the nature of regression in children with ASD.

Another limitation of the present study was that information about children's early development was provided by retrospective parent report. Many of the original parent interviews were conducted when the children were approximately 2 years of age, and therefore not long after most losses would have occurred; however, we know that factors such as birth order affect parents' recognition of autistic behaviors in young children (De Giacomo & Fombonne, 1998). Information about GI symptoms, as mentioned above, was also provided through parent report. Further studies including a review of medical records and direct assessments are clearly needed.

It is also important to consider the potential influence of parents' beliefs about the causes of their child's autism (Woo *et al*., 2004). Lingam *et al*. (2003), for instance, found that parents who reported a regression in their child were more likely than parents of other children with ASD to speculate about the MMR vaccine and other possible 'causes' of autism. This could be due to the fact that parents' recognition of the regression is sometimes associated

with an event that calls attention to changes in their child's behavior (e.g., sickness, family move), making it easier to attribute it to a specific cause. On the other hand, it could be that parents who believe that the MMR vaccine or some other event "caused" their child's ASD are more likely to report that their child regressed. In the present study, however, the fact that the vast majority of parents were consistent in their reports of regression on the ADI-R and the regression interview, often several years apart and in most cases before there was widespread concern about the MMR vaccination "causing" ASD, suggests that parents' beliefs about the cause of their child's autism did not have a significant effect on their ability to report accurately.

A final factor to consider when interpreting the results of the present study is the effect of multiple comparisons. The significant findings regarding GI symptoms and certain outcome variables should be seen as preliminary and should be interpreted with caution. It will be important to see if future studies with larger samples can replicate these findings.

Similarly, the findings that the possible 'regressive phenotype' group had a higher proportion of girls, as well as later ages of onset and earlier ages of vaccination than the remaining ASD sample, should also be considered preliminary. Even larger samples (recalling that the children with regression in this study were identified from an original research population of nearly 1600 participants) may be necessary to examine these possible associations, as well as potential subgroups of children with regression, including those with unclear diagnostic profiles, children with GI disorders, those with relatively normal development prior to 2 years of age, and those with poorer outcome.

Overall, the findings from the present study provide no evidence of an MMR vaccination-induced regressive variant of ASD. It is important to note, however, that even with large numbers of children who were not vaccinated, we could not retrospectively rule out vaccination as a contributor to ASD in any individual child. While there was evidence of group differences between children with and without regression, these differences were not associated with particular patterns of timing of vaccination in this large sample of children with ASD. Differences were found, though, between children with ASD and regression and children with ASD and no regression in age of onset, GI symptomology, and certain outcome measures. If there is a 'regressive phenotype' of ASD, then, it was better characterized in our sample by the phenomenon of regression itself (i.e. stronger skills prior to loss and greater abnormality at least immediately after loss), a possible association with GI symptoms, and poorer outcome in a subgroup of children than by vaccination history.

The phenomenon of regression, or loss of social and communication skills, often including loss of words, is complex, and its meaning in terms of etiology and pathophysiology has not yet been determined. As we become better able to identify other risks for ASD in younger and younger children, regression in children with ASD may be able to be studied prospectively, with particular attention to possible links with other neurobiological changes in the first few years of life (Courchesne, Carper, & Akshoomoff, 2003).

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REFERENCES

Brown, J., & Prelock, P. A. (1995). The impact of regression on language-development in autism. *Journal of Autism and Developmental Disorders*, *25*(3), 305–309.

Burack, J. A., & Volkmar, F. R. (1992). Development of low- and high-functioning autistic children. *Journal of Child Psychology & Psychiatry & Allied Disciplines*, *33*(3), 607–616.

Carter, A. S., Volkmar, F. R., Sparrow, S. S., Wang, J. J., Lord, C., Dawson, G. *et al*. (1998). The vineland Adaptive Behavior Scales: Supplementary norms for individuals with autism. *Journal of Autism and Developmental Disorders*, *28*(4), 287–302.

Chen, W., Landau, S., Sham, P., & Fombonne, E. (2004). No evidence for links between autism, MMR and measles virus. *Psychological Medicine*, *34*(3), 543–553.

Comi, A. M., Zimmerman, A. W., Frye, V. H., Law, P. A., & Peeden, J. N. (1999). Familial clustering of autoimmune disorders and evaluation of medical risk factors in autism. *Journal of Child Neurology*, *14*(6), 388–394.

Cooper, J., Kim, P., Taylor, A., & Lord, C. (2001). *Early communication and social skills in children with autistic spectrum disorders, with and without early word loss*. San Diego, CA: Paper presented at the International Meeting for Autism Research (IMFAR).

Courchesne, E., Carper, R. A., & Akshoomoff, N. A. (2003). Evidence of brain overgrowth in the first year of life in autism. *JAMA*, *290*(3), 337–344.

Davidovitch, M., Glick, L., Holtzman, G., Tirosh, E., & Safir, M. P. (2000). Developmental regression in autism: Maternal perception. *Journal of Autism and Developmental Disorders*, *30*(2), 113–119.

De Giacomo, A., & Fombonne, E. (1998). Parental recognition of developmental abnormalities in autism. *European Child and Adolescent Psychiatry*, *7*(3), 131–136.

De Stefano, F., Bhasin, T. K., Thompson, W. W., Yeargin-Allsopp, M., & Boyle, C. (2004). Age at first measles-mumps-rubella vaccination in children with autism and school-matched control subjects: A population-based study in metropolitan Atlanta. *Pediatrics*, *113*(2), 259–266.

Deykin, E. Y., & MacMahon, G. (1980). Pregnancy, delivery, and neonatal complications among autistic children. *American Journal of Disease of Children*, *134*, 860–864.

Elliott, C. D. (1990). *Differential ability scales: Introductory and technical handbook*. New York: The Psychological Corporation.

Fenson, L. (1989). *The MacArthur Communicative Development Inventory: Infant and Toddler Versions*. San Diego: San Diego State University.

Finegan, J. A., & Quarrington, B. (1979). Pre-, peri-, and neonatal factors and infantile autism. *Journal of Child Psychology and Psychiatry & Allied Disciplines, 20*(2),119–128.

Fombonne, E., & Chakrabarti, S. (2001). No evidence for a new variant of measles-mumps-rubella-induced autism. *Pediatrics*, *108*, e58 .

Gillberg, C., & Gillberg, I. C. (1983). Infantile autism: A total population study of reduced optimality in the pre-, peri-, and neonatal period. *Journal of Autism and Developmental Disorders*, *13*(2), 153–166.

Goldberg, W., Osann, K., Filipek, P., Laulhere, T., Jarvis, K., Modahl, C. *et al*. (2003). Language and other regression: Assessment and timing. *Journal of Autism & Developmental Disorders*, *33*, 607–616.

Kobayashi, R., & Murata, T. (1998). Setback phenomenon in autism and long-term prognosis. *Acta Psychiatrica Scandinavica*, *98*(4), 296–303.

Kurita, H. (1985). Infantile-autism with speech loss before the age of 30 months. *Journal of the American Academy of Child and Adolescent Psychiatry*, *24*(2), 191–196.

Kurita, H. (1996). Specificity and developmental consequences of speech loss in children with pervasive developmental disorders. *Psychiatry and Clinical Neurosciences*, *50*(4), 181–184.

Lingam, R., Simmons, A., Andrews, N., Miller, E., Stowe, J., & Taylor, B. (2003). Prevalence of autism and parentally reported triggers in a north east London population. *Archives of Disease in Childhood*, *88*(8), 666–670.

Lord, C., Molloy, C., Wendelboe, M., & Schopler, E. (1991). Pre- and perinatal factors in high-functioning females and males with autism. *Journal of Autism and Developmental Disorders*, *21*(2), 197–209.

Lord, C., Rutter, M., Goode, S., Heemsbergen, J., Jordan, H., Mawhood, L. *et al*. (1989). Autism Diagnostic Observation Schedule – a standardized observation of communicative and social-behavior. *Journal of Autism and Developmental Disorders*, *19*(2), 185–212.

Lord, C., Rutter, M., & Le Couteur, A. (1994). The Autism Diagnostic Interview – Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders*, *24*(5), 659–685.

Lord, C., Shulman, C., & DiLavore, P. (2004). Regression and word loss in autism spectrum disorder. *Journal of Child Psychology and Psychiatry*, *45*, 1–21.

Luyster, R., Richler, J., Risi, S., Hsu, W. L., Dawson, G., Bernier, R. *et al*. (2005). Early regression in social communication in autistic spectrum disorders: A CPEA study. *Developmental Neuropsychology*, *27*(3), 311–336.

Molloy, C. A., Dawson, G., Dunn, M., Hyman, S. L., McMahon, W. M., & Minshew, N., et al. (in press). Familial autoimmune thyroid disease as a risk factor for regression in children with autism spectrum disorder. *Journal of Autism and Developmental Disorders*.

Molloy, C. A., & Manning-Courtney, P. (2003). Prevalence of chronic gastrointestinal symptoms in children with autism and autistic spectrum disorders. *Autism*, *7*(2), 165–171.

Mullen, E. (1995). *The Mullen Scales of Early Learning*. Circle Pines, MN: American Guidance Service.

Murch, S. H., Anthony, A., Casson, D. H., Malik, M., Berelowitz, M., Dhillon, A. P. *et al*. (2004). Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children (Retraction of vol 351, pg 637, 1998). *Lancet*, *363*(9411), 750–750.

Pardi, D. S., Tremaine, W. J., Sandborn, W. J., Loftus, E. V. Jr., Poland, G. A., Harmsen, W. S. *et al*. (2000). Early measles virus infection is associated with the development of inflammatory bowel disease. *American Journal of Gastroenterology*, *95*(6), 1480–1485.

Peltola, H., Patja, A., Leinikki, P., Valle, M., Davidkin, I., & Paunio, M. (1998). No evidence for measles, mumps, and rubella vaccine-associated inflammatory bowel disease or autism in a 14-year prospective study. *Lancet*, *351*(9112), 1327–1328.

Shinnar, S., Rapin, I., Arnold, S., Tuchman, R. F., Shulman, L., Ballaban-Gil, K. *et al*. (2001). Language regression in childhood. *Pediatric Neurology*, *24*(3), 183–189.

Siperstein, R., & Volkmar, F. (2004). Brief report: Parental reporting of regression in children with Pervasive Developmental Disorders. *Journal of Autism and Developmental Disorders*, *34*(6), 731–734.

Sparrow, S. S., Balla, D. A., & Cicchetti, D. V. (1984). *Vineland Adaptive Behavior Scales*. Circle Pines, MN: American Guidance Service.

Stiles, J. (1994). On the nature of informant judgements in inventory measures...and so what is it you want to know? In *Monographs for the Society for Research on Child Development* (Vol. 59, pp. 180–185). Chicago: Univ. of Chicago Press.

Taylor, B., Lingam, R., Simmons, A., Stowe, J., Miller, E., & Andrews, N (2002). Autism and MMR vaccination in North London; no causal relationship. *Molecular Psychiatry*, *7*, S7–S8.

Wakefield, A. J., Anthony, A., Murch, S. H., Thomson, M., Montgomery, S. M., Davies, S. *et al*. (2000). Enterocolitis in children with developmental disorders. *American Journal of Gastroenterology*, *95*(9), 2285–2295.

Wakefield, A. J., Murch, S. H., Anthony, A., Linnell, J., Casson, D. M., Malik, M. *et al*. (1998). Ileal-lymphoid-nodular -hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet*, *351*(9103), 634–641.

Werner, E., Dawson, G., Munson, J., & Osterling, J. (2005). Variation in early developmental course in autism and its relation with behavioral outcome at 3–4 years of age. *Journal of Autism & Developmental Disorders*,*35*(3), 337–350.

Wilson, K., Mills, E., Ross, C., McGowan, J., & Jadad, A. (2003). Association of autistic spectrum disorder and the measles, mumps, and rubella vaccine – A systematic review of current epidemiological evidence. *Archives of Pediatrics & Adolescent Medicine*, *157*(7), 628–634.

Woo, E. J., Ball, R., Bostrom, A., Shadomy, S. V., Ball, L. K., Evans, G. *et al*. (2004). Vaccine risk perception among reporters of autism after vaccination. *American Journal of Public Health*, *94*(6), 990–995.