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Prevalence and Onset of Regression within Autism Spectrum Disorders: A Meta-analytic Review

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Abstract Rates and onset of regression were meta-analyzed from 85 articles representing 29,035 participants with autism spectrum disorders (ASD). Overall prevalence rate for regression was 32.1, 95 % CI [29.5, 34.8] occurring at mean of 1.78 years, 95 % CI [1.67, 1.89]. Regression prevalence rates differed according to four types of regression: language regression, 24.9 %; language/social regression, 38.1 %; mixed regression, 32.5 %; and unspecified regression, 39.1 %. Regression prevalence also differed according to sampling method: population-based prevalence was 21.8 %, clinic-based prevalence was 33.6 %, and parent survey-based prevalence was 40.8 %. Risk of regression was equal for males and females, but higher for individuals diagnosed with autism versus another ASD. Later age of regression onset was predicted by older age of child.

Keywords Autism spectrum disorders · Regression · Meta-analysis

Authorship determined by alphabetical order. Brian D. Barger and Jonathan M. Campbell have contributed equally to all aspects of the study.

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Introduction

Autism spectrum disorders (ASD) are characterized by deficits in communication, socialization skills, and restricted, repetitive or stereotyped interests and behavior (American Psychiatric Association [APA] 2000). Although changes to the diagnostic definition of autism and related disorders loom, at present, ASD subtypes include autism, Asperger's disorder, and pervasive developmental disorder-not otherwise specified (PDD-NOS). Difficulties and delays are noted frequently by caregivers early in development for many children with ASD; however, a subset of children experience a period of apparently normal development for the first one to 2 years of life, followed by an abrupt or gradual loss of previously acquired skills, a phenomenon termed regression (Lainhart et al. 2002).

The phenomenon of developmental regression, or the loss of a previously established skill, has been discussed in the autism literature for approximately 50 years (e.g., Wolff and Chess 1964) and interest in the diagnostic utility and clinical significance of regression continues. Although formal diagnostic criteria for autism and other ASDs do not presently include regression, the presence of regression is required for diagnosis of Childhood Disintegrative Disorder (CDD). A diagnosis of CDD is considered if a child shows a period of "apparent normal development for at least the first 2 years after birth" which is followed by a "clinically significant loss of previously acquired skills (before age 10 years)" (p. 79, APA 2000). Skills must be lost in at least two of five areas, including language, social skills, and play, among others.

The significance of developmental regression vis-à-vis ASD, CDD, and formal diagnosis is not fully understood. In contrast to indicating the presence of a separate disorder, i.e., CDD, for example, some have suggested that the

presence of regression signals a particular etiology and prognosis within ASD that warrants consideration (e.g., Stefanatos 2008). The role and importance of developmental regression has also been discussed in conference proceedings examining proposed revisions to autism diagnosis for the fifth edition of the DSM (DSM-V). At present, the DSM-V workgroup on ASD proposes elimination of CDD as a separate category; however, regression may be retained as a specifier for the larger diagnosis of ASD (e.g., First 2008). At present, there is no consensus regarding the prevalence of regression within autism and other ASD diagnoses, and there is a clear need to better operationalize and define what is meant by the term developmental regression (First 2008).

Course, Clinical Outcome, and Etiology of Regression in Autism

Several comprehensive reviews have examined the phenomenon of regression in the last several years (e.g., Matson and Kozlowski 2010; Rogers 2004; Stefanatos 2008). Therefore, the literature on regression within ASD is only briefly highlighted prior to presentation of the meta-analysis. Investigations comparing the language and social abilities of children with ASD who have experienced regression (ASD-R) and children with ASD who have not (ASD-NR) yield mixed findings. According to some, children with ASD-R develop language abilities sooner than children with ASD-NR (e.g., Baird et al. 2008; Lord et al. 2004). Other reports, however, suggest that children with ASD-R are more impaired than non-regressed counterparts in regards to their communication skills (Bernabei et al. 2007). Investigations of home movies indicate that one-year-olds with ASD-R display higher levels of social and language development than those with ASD-NR, but not at age two (Werner and Dawson 2005). Similarly, home videos of infants with ASD-R reveal early typical social development, unlike children with ASD-NR (Maestro et al. 2006). Other studies, however, indicate that typical development is rare for children with ASD-R (Werner et al. 2005). Likewise, some report that ASD-R is negatively related to play activities (Bernabei et al. 2007) and positively related to severe behavioral problems when compared to ASD-NR (Hoshino et al. 1987). In contrast, other findings report similar behavioral and adaptive outcomes across groups (Jones and Campbell 2010).

There is limited evidence suggesting that ASD-R is associated with more severe cognitive problems, but relatively intact motor abilities. One investigation reported that children with lower cognitive functioning were more likely to experience regression than those with higher cognitive functioning (Tuchman and Rapin 1997). Likewise, another study reported that children with ASD-R have significantly lower IQ scores than children with ASD-NR (Kobayashi and Murata 1998). Interestingly, motor development was found not to be impaired for individuals with ASD-R (Bernabei et al. 2007) and some studies have reported that children with ASD-R begin walking *earlier* than children with ASD-NR (Jones and Campbell 2010).

The exact cause of regression is unknown; however, the literature proposes both environmental and biological etiological mechanisms. Environmental mechanisms considered to date include psychosocial stressors (Kobayashi and Murata 1998; Lainhart et al. 2002), prenatal and obstetric complications (Kurita 1985), vaccinations (Wakefield et al. 1998), and socioeconomic status or ethnicity (Rogers 2004). Biological factors considered to date include gender (Kobayashi and Murata 1998), epilepsy (Hansen et al. 2008; Tuchman and Rapin 1997), genetic vulnerability (Molloy et al. 2005), mitochondrial disorder (Plioplys 1998), and macrocephaly (Webb et al. 2007). Arguably, the most well-studied etiological factors are epilepsy and subclinical epileptiform activity. For example, Tuchman and Rapin (1997) found epilepsy or epileptiform activity to occur in a significant minority of children with autism and regression, but a smaller minority of children with autism without regression. In particular, 19 % of children with regression versus 10 % of children without regression showed epileptiform activity. Firm conclusions in regards to environmental and biological etiological mechanisms, however, are not yet established.

Prevalence Rates and the Operationalization of the Term "Regression"

The field has maintained an interest in examining the significance of regression, which has resulted in a range of reported prevalence rates in the research literature. For example, recent reviews cite the reported rate of regression as ranging from 12.5 to 50 % (e.g., Rogers 2004; Stefanatos 2008). Although published reports share a common understanding that the term "regression" refers to a loss of skills, variability exists in the literature regarding what kind of skills are central to ASD-R. The majority of researchers maintain that language is the central lost skill of concern (e.g., Jones and Campbell 2010); however, it is common for other researchers to expand the definition of regression to include the loss of non-linguistic social skills (e.g., play; Siperstein and Volkmar 2004). Some have been careful to delineate the relationship between language and social regression showing that a substantial proportion of individuals lose either language and social skills, yet many lose both (Hansen et al. 2008). Other investigators do not include a clear operational definition of regression or add other non-sociolinguistic skills that may be lost (e.g., cognitive or motor regression). Since operational definitions necessarily circumscribe the scope of any considered phenomenon, variability in definitions likely impact the reported prevalence of regression (e.g., Ozonoff et al. 2008).

Prevalence Rates, Sample Size, and Sampling Methods

Several researchers have noted an apparent trend in the regression literature indicating a sample size bias wherein studies with smaller samples tend to report higher prevalence rate than studies with larger sample sizes (Bernabei et al. 2007). For example, Rogers (2004) noted "…the percentage of children for whom regression occurs varies with the nature of the study group. Higher percentage estimates come from smaller samples and samples drawn from clinical referrals" (p. 140). Additionally, as noted by Rogers (2004), prevalence rates may also vary according to the type of sample used for data collection. For example, one sample drawn from a clinical population of children with atypical ASDs found almost half of the children to have experienced regression (Davidovitch et al. 2000) while another study using a population sample found only a 25 % prevalence rate of regression (Taylor et al. 2002). Therefore, examination of the potential influence of sample size or sampling approach (i.e., clinical or non-clinical) on prevalence rates is justified.

Prevalence Rates and Sample Characteristics

In addition to methodological characteristics, it is possible that particular sample characteristics might relate to the presence of regression. For example, it is possible that gender differences exist between ASD-R and ASD-NR, although little systematic research has explored this possibility (Stefanatos 2008). Another possibility is that ASD subtypes may differ in regards to the prevalence of regression. For example, Fombonne et al. (2004) reported that individuals with a diagnosis of autism had a higher prevalence of reported regression (24 %) than those with Asperger's syndrome and/or PDD-NOS (8 %). Therefore, characteristics of the investigated population with ASD could affect the reported prevalence of regression amongst individuals with ASD.

The age of the child at evaluation has also been shown to correlate with rates of regression. For example, Tuchman and Rapin (1997) found that parents of children who were evaluated closer to the time of regression were more likely to report the presence of regression when compared to parents presenting children for evaluation at older ages. Specifically, 40 % of children below the age of three (46/115) were reported to have regressed versus 28 % of children older than three (130/470).

Onset of Regression: Variability, Potential Moderator of Prevalence, and Outcome

Although reviews typically identify onset of regression to occur between 15 and 30 months of age (e.g., Stefanatos 2008), no systematic review has been conducted to provide a summary of onset data. Further, it is not clear if regression onset may relate to prevalence rates, such that earlier or later timing of regression may relate to lesser or greater rates of reported regression. Similarly, it is not known whether age of the child at evaluation may relate to a later reported onset of regression. The possibility has been termed the "telescoping effect" of parent recall by Lord et al. (2004) and others, whereby parents providing information about older children tend to report later onset of symptom recognition. In this case, parents of older children may report later ages of regression onset.

Finally, there may be systematic differences in age of onset across types of regression. For example, Goldberg et al. (2003) reported onset of non-language regression at roughly 18 months versus language regression at roughly 21 months for two subgroups of children with regression. Conversely, there is suggestion in the literature that loss of speech is the most easily detected form of regression and that language loss may be the most easily recognized by parents, who typically provide information regarding development (e.g., Stefanatos 2008). Given the extensive reliance on parent report to establish the onset of regression, it is difficult to separate age of regressive onset from age of parental recognition of regression (Goldberg et al.). Further, due to limitations of retrospective recall, it is difficult to collect information about the child's developmental functioning immediately prior to regression onset, and developmental attainment prior to regression may be a more salient predictor of outcome than the timing of regression.

Purpose of the Study

The present study implemented quantitative review methodology to address some of the questions and limitations identified in the literature on regression in ASD and, as such, served several purposes. First, authors synthesized published rates of regression and derived summary prevalence rates of regression. Calculating an aggregated average prevalence rate for regression across studies may be helpful in establishing an expected rate of regression within the autism spectrum generally. Significant deviations from the typical expected rates of regression may indicate the presence of unique characteristics for certain groups. Second, authors examined the relationship between sample size and regression prevalence rate to test the proposed statistical relationship between these factors. Third, we determined whether operational definitions of regression, sample type (i.e., population or clinical), and sample characteristics (i.e., gender, diagnosis, age of sample, and onset of regression) moderated reported prevalence rates of regression. Fourth, we calculated a weighted average of regression onset and examined if a relationship existed between regression onset and regression type as well as regression onset and age of sample. Ultimately, our purpose was to provide a reasonable estimate of the prevalence of regression and determine

factors that may moderate reports of regression and risks associated with experiencing regression.

Method

Literature Search

Authors conducted a literature search using the following search engines: MedLine, Web of Science, and PsycINFO. Search terms included each of the following terms: *autis**, *Asperger**, and *pervasive developmental disord** paired with *regress** and *setback*. Authors also conducted an ancestral search by locating and reviewing article reference lists, including several recent reviews of the regression literature: Matson and Kozlowski (2010), Ozonoff et al. (2008), Rapin (2006), Rogers (2004), and Stefanatos (2008). For the electronic database literature searches, authors limited the search to studies published from January 1980 to December 2010.

Inclusion and Exclusion Criteria

The following inclusion and exclusion criteria were utilized in selecting articles for the meta-analysis. First, studies that included data regarding prevalence rates of regression for individuals with ASD were included. Second, studies examining the phenomenon of regression comparing ASD-R and ASD from either clinical or population based samples were included. Third, studies with diagnoses rendered using the following classification systems: (1) DSM-III; DSM-III-R; DSM-IV; and DSM-IV-TR; and (2) International Classification of Disease 9th and 10th Revisions (ICD-9; ICD-10) were included. Fourth, only studies published in English in peer reviewed journals were included.

Studies published before 1980 (e.g., Creak 1963) were excluded from the review as this was the year of publication of the DSM-III, which introduced a codified and widely accepted definition of autism in the literature. Reviews (e.g., Stefanatos 2008), case studies, and studies that deliberately oversampled individuals with ASD (e.g., Richler et al. 2006) were excluded. Studies that matched roughly equal numbers of individuals with ASD-R and ASD were excluded (e.g., Luyster et al. 2005). Reports that included redundant data from previously reported findings were excluded (e.g., Ashwood et al. 2008; Autism and Developmental Disabilities Monitoring Network Year 2000 Principal Investigators 2007 [Arizona, Georgia, Maryland, South Carolina data]; Baird et al. 2008; Shattuck et al. 2009; Wiggins et al. 2009; see Fig. 1 for results of literature search as recommended by Moher et al. 2009).

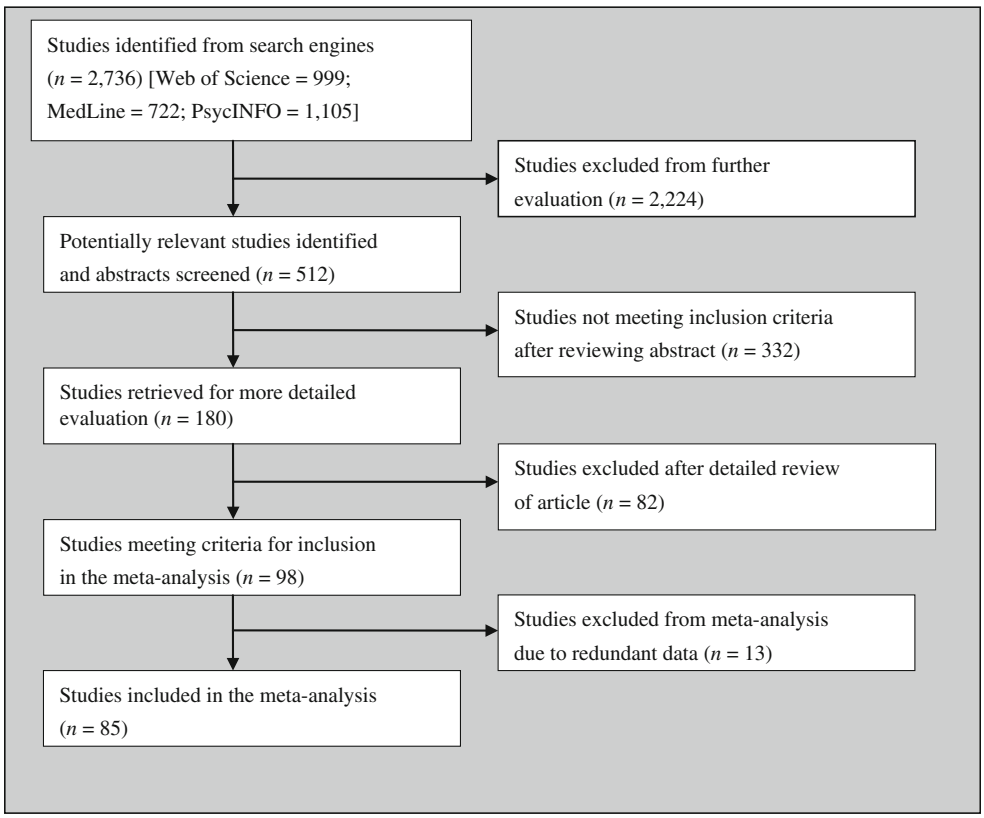

Fig. 1 Flow diagram showing progress through the literature search, study selection, and study inclusion for the meta-analysis

A complete reference list of articles is available upon request from the authors.

Coding

Regression Type

Upon reviewing the literature, it became apparent that researchers typically documented regression using four definitions: language, social, language/social, or mixed. Authors attempted to capture these definitions in the coding as follows. Language regression was defined as a definition that referenced loss of language and/or early verbalizations (e.g., babbling). Social regression was defined as a definition that referenced loss of social interaction skills (e.g., social smiling, joint attention, gestures). Language/social regression was defined as both (1) a mixture of both language and social skills loss and (2) either language or social skills loss if regression was not disaggregated. Mixed regression was defined as a definition that documented other domains of regression (e.g., loss of adaptive skills), most typically along with language and/or social regression. During piloting of the coding form, however, authors found that a number of studies did not provide an operational definition of regression. The final coding form, therefore, included a final category of unspecified regression to capture this reporting practice. Examples of unspecified regression included: "autistic regression," "developmental regression," "parent-reported regression," and "regression of autistic type."

In order to maintain statistical independence of regression rates, only one prevalence rate from each article was included in the meta-analysis, even if multiple rates could be derived from the article (see Lipsey and Wilson 2001). For the Fombonne and Chakrabarti (2001) study, an epidemiological sample and two clinical samples were available for coding; authors selected the epidemiological sample for inclusion in the analysis. Two Autism and Developmental Disabilities Monitoring Network reports were entered into the database; data were combined across multiple states where non-redundant data were reported ($n = 10$ state entries combined for the 2009 report; $n = 2$ state entries for the 2007 report). Given the few number of studies reporting only on social regression, social regression was given priority over all other regression types for inclusion in the final analysis. Language/social was prioritized over language regression, which was prioritized over mixed. Unspecified regression was the final category considered for coding. Although coding for social regression was prioritized over other types of regression, social regression was not included as a separate category for several reasons. First, studies describing regression as "social regression," included definitions and examples that captured social loss but also language and communication loss or other areas of regression. Such examples were coded as language/social regression or mixed regression. Second, social regression was described as present for individuals, but without excluding individuals with social regression plus other types of regression. As a result, unknown numbers of individuals experiencing social regression also experienced other types of regression (e.g., Siperstein and Volkmar 2004). As a result, authors found only two studies where social regression was clearly disambiguated from other types of regression (i.e., Hansen et al. 2008; Ozonoff et al. 2010), which left too few studies available for analysis of the social regression subgroup.

Sample Type and Sample Characteristics

Studies were coded according to whether the study utilized clinic- or population-based sampling. After locating several articles that involved parent survey methodology only, authors added a separate category to code parent survey sampling. Authors decided to include parent surveys in the meta-analysis despite the fact that the pre-established diagnostic inclusion criteria could not be verified in the reports. Authors coded data necessary to calculate odds ratios for comparing rates of regression for males and females as well as ASD diagnosis, which was coded as autism or non-autism ASD.

Data Management and Analysis

Comprehensive Meta-Analysis Software, Version 2 (CMA-2; Borenstein et al. 2005) was employed to calculate effect sizes, which were (1) proportions of the sample experiencing regression and (2) mean age of regression onset weighted by the inverse of within study variance and between study variance, i.e., τ^2. Mean weighted averages for regression prevalence rate and age of regression onset were derived using a random effects model.

Prevalence Rate Data

Consistent with Lipsey and Wilson's (2001) recommendations (pp. 39–40), proportions were converted to logits and all analyses performed using logits as effect sizes. Logit effect sizes, including confidence intervals, reported in the Results section were transformed into proportions using the following formula:

$$p = e^{\text{log it}} / e^{\text{log it}} + 1,$$

with e representing the base of the natural logarithm (i.e., roughly 2.7183) and raised to the power of the appropriate logit derived in the analysis (Lipsey and Wilson 2001, p. 40). The heterogeneity of logit effect sizes was tested using the

Q homogeneity statistic, which provided an indication of whether variability of proportions was greater than expected given sampling error. In the presence of a significant Q homogeneity statistic, authors tested for the moderating impact of variables identified in the literature review using random effects model derived Q_B values. For the comparisons between gender and ASD diagnostic group (i.e., autism vs. non-autism ASD), authors calculated odds ratios (*OR*) for studies that presented sufficient data. Authors utilized the meta-regression option in CMA-2 to test for relationships between age of onset of regression and sample age with prevalence rates of regression; meta-regression analyses utilized the method of moments procedure.

Mean age of Regression Onset

For age of regression onset, effect sizes were weighted by the inverse of within-study and between-study variance. For studies reporting median and ranges, means and standard deviations were estimated via procedures described by Hozo et al. (2005).

Data Analysis

First, authors tested for the presence of statistical relationship between sample size and unweighted prevalence rates via Pearson's r using SPSS software. Second, authors utilized the CMA-2 program to derive a weighted mean prevalence rate then test for differences in prevalence rates across moderator variables, if appropriate. Finally, the CMA-2 program was utilized to establish a weighted mean of regression onset followed by subgroup and meta-regression analysis of identified moderator variables, if appropriate. A random effects model was employed for subgroup and meta-regression moderator analyses for prevalence and onset data.

Results

Characteristics of studies included in the meta-analysis ($k = 85$) are presented in Table 1. The number of published studies examining the phenomenon of regression has increased across the past three decades, with 54 (63.5 %) of studies in the meta-analysis published between 2005 and 2010. On average, males were represented at a 4.56:1 ratio over females, which is consistent with the established rates of male to female representation within ASD. Across studies, the sample-size weighted average age of individuals with ASD was 7.53 years.

Coding Reliability

Data were coded by the second author. Prior to final coding decisions, authors piloted a coding form to evaluate reliability of coding decisions. Thirty-eight articles (44.7 %) were randomly identified and coded by the first author to establish initial inter-reliability agreement. Per Cicchetti's (1994) guidelines, good agreement was found for rating regression type ($\kappa = 0.73$) and excellent agreement ($\kappa = 0.94$) was found for rating studies as population, clinical, or parent-based survey. Authors also established excellent agreement for total sample size, $r(36) = 1.0$, and number of individuals regressed, $r(36) = 1.0$. Based on review of regression definitions and coding decisions, authors added a category to capture unspecified regression and conducted a final round of reliability coding with the final coding form. The second author coded all studies with the revised coding form and 34 studies (40 %) were selected randomly and coded by the first author. Coding decisions were found to be reliable across categories (see Table 2).

Overall Prevalence Rates of Regression

Overall, the mean weighted prevalence rate for any type of developmental regression was 32.1, 95 % CI [29.5, 34.8]. Pearson's correlation revealed no significant relationship between sample size and probit-transformed unweighted prevalence rate, $r(83) = -0.12$, *ns*. Prior to assessing the potential role of moderators, authors conducted a homogeneity analysis which revealed significant heterogeneity for prevalence rates, Q_{Total} $(84) = 1487.54$, $p < 0.001$; therefore, the possible moderating influences of variables identified in the literature review were evaluated using a random effects model.

Moderator Testing for Prevalence Rates

Impact of Regression Type and Sampling Method on Prevalence Rates

Significant differences were found between regression types ($Q_B = 14.20$, $p = 0.003$; Table 3). Studies reporting unspecified regression ($k = 18$) resulted in a prevalence rate of 39.1 %, language/social prevalence ($k = 12$) was 38.1 %, mixed regression prevalence ($k = 31$) was 32.5 %, and language only regression ($k = 24$) was 24.9 %. Significant differences were also found between population, clinic based, and parent-survey studies for regression rates ($Q_B = 14.63$, $p = 0.001$; Table 3). Across all types of regression, rates derived from parent surveys ($k = 7$) yielded an average prevalence of 40.8 %, clinical samples ($k = 66$) reported an average prevalence of 33.6 %, and prevalence rates derived from population samples ($k = 12$) reported an average prevalence of 21.8 %.

Relationship of Gender and Diagnosis with Prevalence Rates

In 22 studies, regression was reported separately for males and females allowing for calculation of odds ratios (*OR*).

Table 1 Characteristics of studies (N = 85) included in the meta-analysis

Variable	*N*	(%)	*M* (SD)
Journal			
J. of Autism & Developmental Disorders	18	21.2	
J. of Child Psychology & Psychiatry	5	5.9	
Pediatrics	5	5.9	
J. of Child Neurology	5	5.9	
Autism	4	4.7	
J. of the Amer Acad of Child & Adol Psychiatry	3	3.5	
Journals contributing fewer than three articles	45	52.9	
Years of publication			
1985–1989	3	3.5	
1990–1994	5	5.9	
1995–1999	8	9.4	
2000–2004	15	17.6	
2005–2010	54	63.5	
Diagnostic system			
DSM-IV/IV-TR	50	58.8	
ICD-9/ICD-10	11	12.9	
Multiple systems (e.g., DSM-IV or ICD-10)	8	9.4	
DSM-III	5	5.9	
DSM-III/III-R	5	5.9	
Parent reported diagnosis	5	5.9	
Diagnostic measure used			
ADI/ADI-R and ADOS	19	22.4	
Multiple combinations used	17	20.0	
Parent and/or child interview/child observation	12	14.1	
Childhood autism rating scale	8	9.4	
Other diagnostic measure (e.g., GARS, SCQ)	8	9.4	
Parent reported	6	7.1	
ADI/ADI-R	4	4.7	
ADOS	1	1.2	
Not reported	10	11.8	
Measure of regression			
ADI/ADI-R	20	23.5	
Other measure	14	16.5	
Parent reported	11	12.9	
Established via clinical interview	10	11.8	
Researcher designed questionnaire	8	9.4	
Multiple methods used	6	7.1	
Prospective observation	2	2.4	
Not reported	14	16.5	
Regression type			
Mixed	31	36.5	
Language	24	28.2	
Unspecified	18	21.2	
Language/social	12	14.1	
Sample type			
Clinical	66	77.6	
Population	12	14.1	

Table 1 continued

Variable	*N*	(%)	*M* (SD)
Parent survey	7	8.2	
Total sample size (range 10–7,103; *Mdn* = 104)			341.6 (865.5)
Total number regressed (range 4 – 1,980; *Mdn* = 34)			99.6 (253.6)
Age of sample[a] (*n* = 62; range 2.36–21.90; *Mdn* = 6.65; $M^{b}_{Weighted}$ = 7.53)			6.92 (3.13)
Age of regression[a] (*n* = 28; range 1.34–3.40; *Mdn* = 1.69; $M^{b}_{Weighted}$ = 1.71)			1.80 (0.42)
Percentage male (*n* = 69; range 0.52–1.0; *Mdn* = 0.81; $M^{b}_{Weighted}$ = 0.82)			.82 (0.07)
Percentage with autism (*n* = 66; range 0.00–1.0; *Mdn* = 0.74; $M^{b}_{Weighted}$ = 0.51)			.75 (0.23)

ADI autism diagnostic interview, *ADI-R* autism diagnostic interview-revised, *ADOS* autism diagnostic observation schedule, *DSM-III* diagnostic and statistical manual of mental disorders, third edition; *DSM-III-R* diagnostic and statistical manual of mental disorders, third edition—revised; *DSM-IV* diagnostic and statistical manual of mental disorders, fourth edition; *DSM-IV-TR* diagnostic and statistical manual of mental disorders, fourth edition—text revision; *GARS* Gilliam autism rating scale, *ICD*-9 international classification of diseases—9th revision, *ICD*-10 international classification of diseases—10th revision, *SCQ* social communication questionnaire

[a] Ages are reported in years, [b] weighted by sample size

Table 2 Results of reliability coding (n = 34; 40 % of studies)

Variable	*r*	% Agreement	κ
Publication year	1.0		
Total sample size	1.0		
Number of children regressed	.98		
Male total	1.0		
Number of males regressed	1.0		
Female total	1.0		
Number of females regressed	1.0		
Age of sample	1.0		
Age of regression	1.0		
Autism total	.98		
Autism regressed	.97		
ASD/PDDNOS total	.97		
ASD/PDDNOS regressed	1.0		
Regression type		94.12	.92
Sample type		97.06	.91
Diagnostic system used		88.24	.81
Diagnostic measure used		94.12	.93
Regression measure used		100.0	1.0

r = Pearson's correlation, % agreement = number of agreements/[number of agreements + number of disagreements], κ = kappa coefficient

Comparison of regression rates resulted in no significant difference in rates of regression for males and females (*OR* = 0.95; 95 % CI [0.76, 1.19]; $z = -0.43$, *ns*). For 23 studies, regression was reported separately for autism and non-autism ASDs. Comparison of regression rates resulted in a significantly greater risk for regression for individuals diagnosed with autism versus another ASD (*OR* = 1.83; 95 % CI [1.58, 2.11]; $z = 8.15$, $p < 0.001$). The test for heterogeneity of *OR*s was non-significant, $Q(22) = 27.09$, *ns*.

Relationships Between Age of Sample and Age of Onset of Regression with Prevalence Rates

As shown in Table 4, simple meta-regression analyses revealed no significant relationships between prevalence rates and either sample age or regression onset. We recoded age into groups corresponding with Tuchman and Rapin's (1997) categories (i.e., less than or equal to age three ($k = 5$) and greater than age three ($k = 57$) and found no between-group effect, Q_B (1) = 0.72, *ns*.

Age of Onset of Regression

Of the 28 studies reporting age of onset of regression, 17 reported means and standard deviations necessary for effect size calculations; 7 reported age of onset in median and ranges that were used to estimate means and standard deviations via Hozo et al.'s (2005) procedures. Overall, 24 studies were available for analysis of age of regression onset: 10 language, 9 mixed, 3 language/social, and 2 undefined. Weighted mean onset of regression was 1.78 years, 95 % CI [1.67, 1.89]. Due to the small numbers of language/social and unspecified regression groups, only between language and mixed regression groups contributed to the moderator analysis due to small numbers of studies in either of the remaining regression groups. Prior to assessing the potential role of moderators, authors conducted a homogeneity analysis which revealed significant heterogeneity for age of onset of regression, Q_{Total} (18) = 288.14, $p < 0.001$; therefore, the possible moderating influences of regression type and sample age were evaluated using a random effects model. Moderator analyses revealed no differences between regression types ($Q_B = 0.17$, $p = 0.68$; Table 5) with reported onset of language regression 1.82 years, 95 % CI [1.62, 2.01] and

Table 3 Subgroup analyses for regression prevalence rate

Variable and group	Q_B	*df*	*p*	*k*	*ES*	95 % CI
Regression type	14.20	3	0.003			
Unspecified				18	0.391	.324–.462
Language/social				12	0.381	.301–.467
Mixed				31	0.325	.278–.375
Language				24	0.249	.206–.298
Sample type	14.63	2	0.001			
Survey				7	0.408	.310–.513
Clinical				66	0.336	.305–.369
Population				12	0.218	.169–.277

Effect sizes are weighted proportions. *df* degrees of freedom; Q_B = between-group effect; *p* = probability; *k* = number of studies

Table 4 Summary of simple meta-regressions for prevalence rate

Predictor	*k*	*b*	*p*
Age of sample	62	−0.04	.15
Age of onset	28	0.04	.89

k = number of studies, *b* = unstandardized regression coefficient, *p* probability

Table 5 Test of regression type as moderator of age of onset of regression

Variable and group	Q_B	*df*	*p*	*k*	*ES*	95 % CI
Regression type	0.17	1	0.68			
Language				10	1.82	1.62–2.01
Mixed				9	1.76	1.62–1.90

Effect sizes are weighted means (years of age)

df degrees of freedom, Q_B = between-group effect, *p* probability, *k* = number of studies

onset of mixed regression 1.76 years, 95 % CI [1.62, 1.90]. A total of 21 studies reported information for both age of onset of regression and age of sample. Simple meta-regression using the CMS-2 method of moments procedure revealed a significant positive relationship between the age of regression onset and age of the sample [$b = 0.06$; $z = 2.61$, $p = 0.009$].

Discussion

Authors synthesized rates of developmental regression across 85 articles representing 29,035 individuals with ASD. A primary purpose of the review was to derive an average prevalence rate of regression in samples of individuals with ASD. Our analyses indicate that 32.1 % of individuals with an ASD experience some type of developmental regression, a rate that falls within typical ranges of 20–50 % reported in the literature. Variability in prevalence of regression was attributable to the operational definition of regression employed by researchers as well as sampling methods employed in primary studies. Contrary to suggestions in the literature, no inverse relationship was found between sample size and prevalence rates. Consistent with suggestions from the literature, however, population-based samples yielded regression rates that were lower than those reported for clinical samples.

Although the meta-analysis yielded an overall rate of developmental regression of 32.1 %, it is important to emphasize that rates of regression differed significantly depending on the definition utilized in the investigation. The findings indicate a general relationship between the degree of specificity and inclusiveness in the definition employed and the amount of regression found. For example, unspecified definitions of regression, such as "autistic regression" or "parent-reported regression," which would seemingly include any type of developmental regression, yielded the highest rates of regression. The most stringent definition of regression, i.e., language regression, yielded the lowest rates of the four coded definitions, roughly 14 % lower than the unspecified regression rate. The impact of specificity of regression on prevalence is illustrated clearly in several investigations that provide aggregated total and specific rates of regression (e.g., Hansen et al. 2008). In Hansen et al.'s investigation, for example, regression varied from a low of 25/333 (7.5 %) for language regression only to a high of 138/333 (41 %) for combined language and/or social regression. Variation in reported rates of regression in the literature is attributable, in part, to the inclusiveness or non-inclusiveness of the definition adopted.

Findings from the meta-analysis support the hypothesized relationship between regression prevalence and sampling strategy utilized in the investigation. Clinic-based studies reported significantly higher prevalence rates when compared to population-based studies. Clinic-based studies may be influenced by a number of factors including the severity of autism symptomology and socio-economic

status. Individuals with more severe symptomatology may be more likely to seek out professional help, as are families with the financial means to afford the services provided by clinics. On the other hand, population-based studies strive to account for a representative sample and are focused typically on accurately determining the prevalence of a given disorder in a certain catchment area. Prevalence of regression as reported in population-based studies (i.e., 21.8 %) may therefore provide a more accurate indicator than clinic-based studies.

Several recent investigations utilizing only parent-survey methodology produced higher prevalence rates (40.8 %) when compared to results from clinic (33.6 %) and population (21.8 %) sampling methods. The parent surveys included in the present study did not feature provision for documenting diagnosis or presence of developmental regression; that is, there was little quality control utilized in the investigations, which produced estimates that fell above the clinic and population-based estimates.

At present, parent report is almost universally employed to establish the presence of developmental regression. The quality of parent report utilized to establish regression ranges from formal criteria, such as those utilized in the ADI-R, to responses to single items asking if a child has ever regressed. The reliance on parent report is practical, but there is evidence that parent report may systematically yield underestimates of the presence of regression. Recent findings indicate that parents of children with ASD miss clinically observable declines in their children's social communication abilities, thereby under-reporting the presence of regression (Ozonoff et al. 2010). The rate of regression detected during prospective observation was 86 %, compared to a rate of 18 % based on parents' recall during structured interview (Ozonoff et al.). Given recent findings, the rates derived in the present analysis may present an underestimate of developmental regression, as the majority of investigations relied on parent report.

Risk of regression was found to be related to diagnosis, with greater risk associated with autism versus non-autism ASD. The findings are consistent with Meilleur and Fombonne's (2009) findings that indicated greater risk for non-language based regression for individuals with autism versus PDD-NOS. In contrast to our findings, Lord et al. (2004) found no difference in risk of language regression between children with autism and PDD-NOS. The homogeneity of risk documented in the present analysis, indicates that the risk for regression is greater for autism versus non-autism ASD across all types of regression, including language regression. The present authors included individuals with both Asperger's syndrome and PDD-NOS in the non-autism comparison group, which may account for the difference between the present findings and those of Lord et al. Although autism is acknowledged as a more severe form of ASD when compared to PDD-NOS, the significance of greater risk for regression in the autism group is not clear, as the presence of regression is not established universally with more severe symptomatology (e.g., Jones and Campbell 2010).

Contrary to findings reported in the literature regarding the relationship between child age and prevalence of regression, we did not find significant relationship between these variables. We did, however, detect a relationship between sample age and reported timing of regression, with parents of older children reporting later onset of regression. The retrospective report of regression onset is apparently susceptible to the "telescoping" effect described in others' reports of the relationship between increased age of children and increasingly older parent report of onset of symptoms and mastery of developmental milestones (e.g., Lord et al. 2004). As parents engage in retrospective recall of regression onset, later onset based on parent report is associated with older age of the child.

Another primary purpose of the review was to derive a mean age of regression onset, which was 1.78 years (21.35 months), a value that falls within the range of 15–30 months typically reported in reviews of the literature. Age of onset of regression did not differ according to whether regression was reported to be language or mixed. The findings run counter to those of Goldberg et al. (2003) who reported significantly earlier loss of non-language versus language regression. Definitions of regression reported in the literature are often not well specified; therefore, it may be the case that our groups of "language" and "mixed" share significant overlap. That is, language regression may very well be present for the mixed group along with other types of regression. Due to the reliance on parent report for establishing regression onset, however, we believed we might detect a difference due to parents' frequently reported earliest concerns being speech and language development (De Giacomo and Fombonne 1998) and the alleged easier parental task to report losses in speech versus other losses.

Potential Implications for DSM-V

As discussed in the DSM-V ASD conference planning papers, the significance and potential clinical implication of developmental regression is important. Findings from the meta-analysis provide at least partial answers to questions posed by the workgroup. First, developmental regression occurs for a large minority of children diagnosed with ASDs. Second, the wide array of definitions employed is problematic when attempting to produce estimates of how many children with ASD demonstrate a regression in development. The specificity of the proposed DSM-V regression specifier will clearly influence the

amount of regression detected in clinical and research settings. Third, and most important, the clinical implications for the presence of regression are not yet clearly established; the question of differential clinical outcomes for those with versus without regression was not addressed in the current meta-analysis.

Future Research

Relationships between developmental regression and (1) comorbid conditions and (2) developmental outcomes are not clearly documented. As noted in the introductory review, mixed findings exist in the literature when children with ASD-NR and ASD-R are compared across various measures; methods of quantitative review may help clarify some of the mixed reports in the literature. A meta-analysis that contrasts various outcomes between children who do and do not experience regression may better inform our understanding of the risk of comorbid problems, such as seizure disorders, for children with ASD-R as well as long-term developmental correlates. If reliable differences are established for children who regress versus those who do not via additional meta-analysis, the clinical usefulness of documenting early regression is better established. A subsequent meta-analytic review being conducted by the authors should provide information in this regard.

The present study has a number of notable limitations. Primarily, there is a lack of a standardized operational definition regarding regression. Although it appears that the ADI-R is the method most frequently used to document regression, roughly 25 % of the time in the present analysis, the lack of definitional specificity in 21 % of investigations is surprising. For the remaining investigations, definitions of regressions ranged widely and, in most cases, did not include disaggregated descriptions of regression documented in the study. In addition to varied topography, studies also differed in regards to the inclusion of a specific period for regression to occur; some investigators specified a time frame and others did not. As with any meta-analysis, the authors established inclusion and exclusion criteria and coding decisions that may have influenced the findings in undesirable ways. For example, authors' final inclusion of parent surveys in the analysis appears to have generated a slight over-estimate of the overall rate of developmental regression. Although the authors' coding strategy proved reliable, there exist various other approaches to code and capture the variability in the data set, such as coding and evaluating the impact of study quality on reported regression rates. As revealed in the moderator analyses, there is a large amount of heterogeneity that remains unexplained in the current analysis; other coded variables may have better explained this variation.

Despite study shortcomings, authors believe that the results advance knowledge about regression in autism in a number of ways. Primarily, the present findings yield a reasonable estimate of the rates of regression for individuals with ASD and illustrate the importance of the relationship between regression rate and operational definition employed. Second, by systematically organizing the autism regression literature according to regression type, coding procedures provide a useful initial organizing strategy by which to analyze the sizable literature on developmental regression. Third, the study delineates important differences between clinical and population based studies regarding reported prevalence rates. Fourth, study findings established relatively greater risk for regression for individuals with autism versus individuals with other non-autism ASD diagnoses. Finally, study findings identified a relationship between child's age and regression onset, which we attribute to the "telescoping effect."

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