Characteristics, Early Development and Outcome of Parent-Reported Regression in Autism Spectrum Disorder

Abstract

This study explored regression patterns in 100 children with ASD (3-11 years) using several approaches to enhance the validity of retrospective parent report. Both early development and outcome were examined in regression groups defined by 36 months age cut-off and two underlying empirical patterns based on type and onset age. Results over regression groups were generally consistent. During early development, children with regression showed a similar amount of social atypicalities and stereotyped behaviour as compared to children without regression. However, parents indicated less communication skills which could be a valuable predictor of regression. Development after regression was characterised by early language delay and more restricted and repetitive behaviour. The findings provide insight into the diagnosis and prognosis of regression in ASD.
The traditional literature indicates that behavioural signs of autism spectrum disorder (ASD) emerge through two distinct patterns of development: an early and a regressive onset. The early onset pattern is defined by delays and atypicalities in language and social-communicative development present in the first 12 months of life and is suggested to occur in the majority of children with ASD (Ozonoff, Heung, Byrd, Hansen & Hertz-Picciotto, 2008). The second onset pattern called “regression” is characterised by an initial period of apparently typical development followed by a substantial loss of previously developed language, social and/or other skills sometime in the second year of life (Barger, Campbell, & McDonough, 2013). Since a substantial subset of children showed early language delays and other developmental atypicalities before the start of the regression, an additional mixed pattern of early delays followed by later loss was also identified (Ozonoff, Williams, & Landa, 2005).

Furthermore, in some studies loss of skills can be attributed to stagnation of skills (“plateau”) as these could simply result from failure to progress acquired skills to a more developmentally advanced level (Shumway et al., 2011).

In a meta-analytic review of 85 studies by Barger and colleagues (2013) the overall prevalence of regression in children with ASD was estimated to be 32.1%, with an average onset at 21.4 months. Regression prevalence rates differed according to four categories of regression which could be extracted from the literature: language regression (24.9%), language/social regression (38.1%), mixed or other domains of regression such as loss of adaptive skills (32.5%), and unspecified regression when no operational definition of regression was provided (39.1%; Barger et al., 2013). Hence, it seems that most researchers report regression in language and/or social skills (Barger et al., 2013; Ozonoff, Heung, et al., 2008). In most studies, regression was assumed to occur before the age of 36 months (Barger et al., 2013) but different age cut-offs such as 24 months (Luyster et al., 2005) and 30 months (Ekinci, Arman, Melek, Bez, & Berkem, 2012) or no age cut-off (Gadow, Perlman & Weber, 2017) have been used as well. Different studies using various operational definitions and methodologies to measure regression reported that although most children (75-92%) seem to regain some or all of the lost skills, the duration of loss was variable, ranging from four to 26 months (e.g., Goin-Kochel, Esler, Kanne & Hus, 2014; Lord, Shulman & DiLavore, 2004; Ozonoff et al., 2005). The exact cause of regression in ASD is still largely unknown but is probably linked to a complex
interaction between biological and environmental factors leading to multiple etiological mechanisms (Barger, Campbell, & Simmons, 2017; Thurm, Powell, Neul, Wagner, & Zwaigenbaum, 2018).

The most common procedures to collect information on regression in ASD are retrospective parent report and analysis of early home-videos (for a review see Boterberg, Charman, Marschik, Bölte, & Roeyers, 2019). Although efficient and cost-effective, the parent report method has several limitations concerning validity including recall problems (Ozonoff, Li, Deprey, Hanzel, & Iosif, 2018). The most important form of recall bias is “forward telescoping” in which an event is reported as having occurred more recently than it actually took place (Janssen, Chessa, & Murre, 2006; Loftus & Marburger, 1983). As a result of this recall bias, parents of older children seem to report later ages of regression onset (Barger et al., 2013; Lord et al., 2004). Despite the advantage of home-video analysis to reduce reporting bias of parents, this method is labour-intensive and subject to other biases including lack of representativeness of the movie clips (Palomo, Belinchón, & Ozonoff, 2006).

Until now, only a limited number of prospective longitudinal studies, examining the development of high-risk siblings, revealed more information on the prevalence and onset, and types of regression (for a review see Ozonoff & Iosif, 2019; Pearson, Charman, Happé, Bolton, & McEwen, 2018). Although some of the prospective studies found that definite loss of language skills occurred in 17 to 42% of high-risk infants who received the diagnosis of ASD later on (Landa & Garrett-Mayer, 2006; Landa, Gross, Stuart, & Faherty, 2013) - prevalence numbers that are similar to retrospective studies - other studies did not detect clear losses in language, cognitive or motor skills (e.g., Ozonoff et al., 2010). On the other hand, prospective studies which conducted a very detailed analysis of social communication behaviour and social engagement skills in minute-by-minute segments through coding by trained clinicians, seemed able to detect earlier (between six and 18 months) and more gradual, subtle declines in the majority (up to 88% by examiner rating) of infant siblings who will later meet the criteria for ASD (Ozonoff et al., 2010; Ozonoff, Gangi, et al., 2018).

Thus, retrospective studies on regression using parent report seem to underestimate the prevalence of subtle social-communicative regression, which was also concluded in studies comparing parent report and home-video analysis (Ozonoff et al., 2011). However, in a clinical context, conducting a prospective assessment of behaviour through coding frequencies per minute would be very time-
consuming and expensive and thus hardly feasible (Goin-Kochel et al., 2014). Moreover, several methodological limitations of the current prospective studies such as representativeness of the subpopulation of infant siblings, small sample sizes and the possibility of skill loss and regaining between assessments, prevent us from drawing firm conclusions about regression in ASD (Jones, Gliga, Bedford, Charman, & Johnson, 2014; Pearson et al., 2018). Despite the importance of prospective follow-up and home-video analysis, retrospective parent report is still the most commonly used method to collect information about the early attainment and/or loss of skills in ASD in both research and clinical practice.

Although early development is assumed to be typical in the traditional definition of regression in children with ASD, a sizeable number of retrospective parent report studies found evidence for early delays and atypicalities in language and social-communication skills as well as repetitive behaviour in a substantial subset of children prior to loss of skills (ranging from 41-86%; Baird et al., 2008; Luyster et al., 2005; Ozonoff et al., 2005; Wiggins, Rice, & Baio, 2009). When compared to children with a typical development or developmental delay, children with ASD and regression showed more impairments before the age of 24 months (Luyster et al., 2005; Richler et al., 2006). In contrast, different home-video studies found that the development of social and communicative abilities seems to be similar between children with ASD and regression and typically developing children before the age of 12 months (Osterling, Dawson, & Munson, 2002; Werner & Dawson, 2005). Some studies even found that children with ASD and regression developed these abilities sooner than typically developing controls (Ozonoff et al., 2011; Werner & Dawson, 2005). When comparing the development of children with ASD and regression to children with ASD without regression, some parent report and home-video studies indicate that more typical early social-communicative and language skills and less behavioural atypicalities are found in children with regression (Baird et al., 2008; Luyster et al., 2005; Ozonoff et al., 2005). However, these differences seem to disappear after the age of 24 months (Werner & Dawson, 2005), which is also the mean onset age of regression.

Concerning the attainment of early milestones, in different studies it was found that children with ASD and regression developed their first words earlier as compared to children without regression (Jones & Campbell, 2010; Kalb, Law, Landa, & Law, 2010; Meilleur & Fombonne, 2009; Pickles et al., 2009).
However, with regard to the attainment of phrases, some studies found a later attainment (Kalb et al., 2010; Meilleur & Fombonne, 2009; Pickles et al., 2009), earlier attainment (Jones & Campbell, 2010) or no differences between children with and without regression (Baird et al., 2008). Further, most studies reported a typical or near typical motor development before loss of skills and no differences in achievement of motor milestones between children with and without regression (Bernabei, Cerquiglini, Cortesi, & D’Ardia, 2007; Jones & Campbell, 2010; Ozonoff, Young, et al., 2008).

With regard to the development after regression, several retrospective studies demonstrated that children with ASD and regression display more severe impairments in comparison with children without regression, as measured by average IQ (Bradley, Boan, Cohen, Charles, & Carpenter, 2016; Gadow, Perlman, & Weber, 2017), ASD characteristics (Estabillo, Matson, & Cervantes, 2018; Goin-Kochel et al., 2014), language skills (Kalb et al., 2010), adaptive behaviours (Goin-Kochel et al., 2014), and problem behaviours and psychiatric comorbidities (Estabillo et al., 2018; Gadow et al., 2017). However, in contrast, other studies reported a similar average IQ (Baird, Robinson, Boyd, & Charman, 2006; Goldberg et al., 2003; Kalb et al., 2010; Shumway et al., 2011), ASD characteristics (Mire et al., 2018), language skills (Pickles et al., 2009), adaptive behaviour (Malhi & Singhi, 2012; Shumway et al., 2011), and problem behaviour and psychiatric comorbidity outcomes (Hansen et al., 2008; Lance, York, Lee, & Zimmerman, 2014) among children with ASD with and without regression. For an overview of research findings comparing children with and without regression, see Barger and Campbell (2014) and Boterberg et al. (2019).

To date, research has not yet provided clear answers whether regression in ASD represents a distinct subtype (Rutter, 2006; Williams, Brignell, Prior, Bartak, & Roberts, 2015). Findings on regression rates, onset, aetiology, early development and later prognosis are inconsistent caused by lack of consensus and fundamental differences in specificity and inclusiveness of the definition of regression and other onset patterns, sampling strategies, and applied methods. It is most likely that prior retrospective studies underestimated the prevalence of regression because of different limitations related to the definition of regression such as only considering loss of productive language without including loss of other non-language skills, not including information on development before regression (Barger et al., 2013; Thurm, Manwaring, Luckenbaugh, Lord, & Swedo, 2014), not
distinguishing a plateau or stagnation in development from loss of skills (Kalb et al., 2010), and the
use of arbitrary age cut-offs (Hansen et al., 2008; Ozonoff, Heung, et al., 2008). Another limitation is
the use of unreliable and/or methods that have not been validated to measure regression.

While the regression categories of Barger et al. (2013) are useful for organizing the literature on
regression in ASD, it has not been investigated if they are also helpful for organizing regression types
of children with ASD. In other words, until now, none of the studies on regression in ASD has used a
quantitative approach in which regression types are empirically derived from individuals with ASD
rather than based on a qualitative organizational consideration of the regression literature.

It is our conviction that the greatest needs in the retrospective literature on regression in ASD
concerning the definition of regression are (1) a quantitative, empirical approach to examine as to
whether the ‘intuitive’ regression types that researchers commonly discuss actually reflect an
underlying empirical reality and (2) comparison of different regression groups based on different age
cut-offs and regression types. With regard to the methodology to measure regression there are still no
other cost-effective and methodological sound approaches available than parent report. Different
strategies to deal with the limitations of this method have to be developed and applied. In order to
measure regression in a reliable manner, more basic psychometric research is needed as well as
contrasting different retrospective regression measurements (see also Boterberg et al., 2019).

The first objective of the present study is to explore underlying, empirical patterns of regression in
children with ASD based on regression types and onset age as reported by parents.

A second objective is to examine differences in early development before regression and outcomes
after regression between children with and without regression, and different regression groups defined
by a 36 months age cut-off and empirically by regression type and onset age.

Lastly, a third objective is to investigate the reliability and validity of the use of different retrospective
parent report regression measuring instruments. In sum, the present study aims to provide an empirical
base for the definition of regression and enhance the validity of retrospective parent report to measure
regression.

Methods

Participants
Participants included 100 children with ASD between three and 11 years old ($M = 7.57$, $SD = 1.95$; 71% boys). All children had an official community diagnosis of ASD based on DSM-IV-TR or DSM-5 criteria and confirmed by a multidisciplinary team. We sought to recruit a community based sample via social media, parent associations of children with ASD, home guidance organisations and different multidisciplinary rehabilitation centres through online and newsletter advertisements. The primary purpose of the recruitment was to study the general development of children with ASD and there was no information presented with regard to regression. Children with a known genetic or neurological disorder linked to ASD, such as Fragile X syndrome or Landau-Kleffner syndrome were excluded for participation. Two children were excluded because of seizures and subsequent regression (in combination with a new medical treatment) during the research which impacted on different domains of functioning. Within our sample of 100 children, one twin, one triplet and 19 children had a sibling with ASD who also participated in the study. Most children (93%) were monolingual and raised in Dutch.

**Procedure**

At the beginning of the study, written consent was obtained from the parents. Each child was individually evaluated by one examiner with a professional background as a clinical psychologist who had received training in assessment and interpretation of the tests. The research consisted of two parts and the tests were always administered in the same order in each child. During the first part, the Autism Diagnostic Observation Scale – Second Edition (ADOS-2; Lord et al., 2012) was conducted. Subsequently, depending on the age and language level of the child, the Clinical Evaluation of Language Fundamentals, Fourth Edition (CELF-4; Semel, Wiig, & Secord, 2003) or the Clinical Evaluation of Language Fundamentals – Preschool, Second Edition (CELF preschool-2; Wiig, Secord, & Semel, 2004) was administered. When the language level of the child did not meet the requirements for the CELF preschool-2, the parents were asked to fill out the Dutch version of the Communicative Development Inventories (CDI; Fenson et al., 1993) to obtain an indication of the language level of the child. In the second part, the Wechsler Non-Verbal Scale of Ability (WNV; Wechsler & Naglieri, 2006) and the Movement Assessment Battery for Children – Second Edition (M-ABC-2; Henderson, Sugden, & Barnett, 2007) were administered. At the end of the research, items 1 to 28 of the Autism...
Diagnostic Interview-Revised (ADI-R; Rutter, Le Couteur, & Lord, 2008) together with a Dutch version of the Regression Supplemental Questions (RSQ; Thurm et al., 2014) were assessed. Since the interview was conducted at the end of the research, the examiner was blind for the type of onset pattern of ASD during the administration and scoring of the other tests. Further, the parents were asked to fill out several questionnaires: a Dutch version of the Early Development Questionnaire (EDQ; Ozonoff et al., 2005), the Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2002) and the Social Responsiveness Scale – Second Edition (SRS-2; Constantino & Gruber, 2012). Additionally, the SRS-2 was also filled out by the current teacher of the child.

*Measures*

**Early Development and Onset Patterns: Attainment and Loss of Skills**

The ADI-R is a semi-structured, 111-item, diagnostic parent interview which is administered to classify autism in children or adults with a mental age of two years or older. The ADI-R quantifies impairments in the reciprocal social interaction, communication and restrictive, repetitive and stereotyped patterns of behaviour. At the moment, the ADI-R is the most widely used instrument to measure regression in ASD. In the present study, the relevant items 1 to 28 about the early development and loss of skills were administered. With regard to language regression (items #11-19), the ADI-R requires a communicative use of at least five different words on a daily basis for at least three months prior to the reported loss (loss of the skill for at least three months). If parental report does not meet these criteria, the ADI-R criteria for language regression will not be met and these children would not be included in the regression group. Therefore, some previous studies included subthreshold loss groups (i.e., one month instead of three months; e.g., Goin-Kochel et al., 2014). Further, also potential losses in other skills such as motor, self-help, play, and social abilities are examined (items #20-28). However, these questions are open-ended and less specific which makes it difficult for parents to report for example subtle social-communicative losses, leading to an underestimation of regression in other than language skills. Since the ADI-R does not include detailed and follow-up questions about the nature and course of regression in non-language domains, in the present study a supplemental interview [RSQ; derived from the Regression Validity Interview (RVI; Lord et al., 2004)] which captures information about additional and more subtle skill losses in the
social-communicative domain (e.g., eye contact, social smiling and waving goodbye) was added. Within the RSQ, information on both full criteria and subthreshold losses is collected. The EDQ is a parent questionnaire which collects retrospective information about the onset of ASD characteristics and other aspects of early development. The questionnaire contains four parts and in the present study a fifth part was added by the authors to distinguish loss of skills from stagnation or plateau of skills. The first part includes 45 items about three different domains of behaviours (early social deficits, early communicative deficits and stereotyped behaviours) associated with ASD in the early years of life. On each item, parents have to decide how regularly their child demonstrated the behaviour during the first 18 months of life or, when the child experienced regression before this age, rate their child’s behaviour up to the point of the regression. The items in the Social and Communication subscales are scored in the same direction, with lower scores indicating the absence of age-appropriate behaviours. The items in the Repetitive Behaviour subscale are formulated in the opposite direction, with higher scores indicating the presence of atypical behaviours. The primary dependent variable derived from this section of the EDQ is the Early Development Summary Score, which is created by summing up the Social and the Communication scores, with higher scores indicating more typical development prior to 18 months of age. The second part of the questionnaire captures information on the age of acquisition of particular developmental milestones and the third part on the loss of different skills (i.e., communication, social, adaptive function and motor). The fourth part contains open-ended questions designed to collect qualitative information about onset, course and potential cause of regression. In the present study, the internal consistency of the scales of the EDQ was good to excellent with Cronbach’s alphas varying between .78 and .92. To minimize recall problems and enhance reliability of the reports of early development during the ADI-R, the RSQ as well as the EDQ, parents were asked to bring and consult their relevant records such as baby books or journals. The government of the country were this study has been conducted, provides a free consultation by a doctor and nurse during which there is a standardized follow-up of growth, health status and achievement of milestones of the child at 10 important developmental stages up to the age of 30 months. During each visit, the information is noted in a standardized booklet (Kind en Gezin, 2018). Most parents (72%) used these records during the research. Parents were always
asked to look up the information first within the booklet before answering the questions. Another approach that was used, were key events in the respondent’s life (such as the first birthday or a move) by creating a detailed timeline and context which helps to recall specific details (Ozonoff, Li, et al., 2018).

Outcomes in Cognitive Ability

The WNV is a nonverbal measure of ability for children and adolescents aged between four and 21 years, especially designed for children who have communicative disabilities. In the present study the WNV was selected over other traditional intellectual assessments of which the results may be questionable due to language-related difficulties in ASD. Since the WNV uses pictorial directions for informing the child on the demands of the test, it makes it very suitable for individuals with ASD, as was shown in previous studies (McPhillips, Finlay, Bejerot, & Hanley, 2014; Whyatt & Craig, 2012). Based on the results of the subtests, a single ability score can be derived. The reliability of the WNV was shown to be excellent (α = .91) and the correlations with traditional intelligence assessments ranged from .76 to .82 (Wechsler & Naglieri, 2006). In the present study, the internal consistency of the non-verbal IQ score was good (version 4;0-7;1: α = .83) and acceptable (version 8;0-21;11: α = .74).

Outcomes in ASD Characteristics and Severity

The ADOS-2 is a semi-structured, standardized assessment of communication and social interaction, play, and of restricted and repetitive behaviour. In the present study, either module one, two or three was administered based on the child’s age and language level. With regard to module 1, the internal consistency of Social Affect was acceptable (α = .79) but poor for the Repetitive and Restricted Behaviours (α = .56). With regard to module 2, the internal consistency of both Social Affect and the Repetitive and Restricted Behaviours was poor (α = .58 and α = .50, respectively). With regard to module 3, the internal consistency of Social Affect was good (α = .81), however, for Repetitive and Restricted Behaviours it was poor (α = .57). Further, the internal consistency of the total scores of the modules was questionable (module 2: α = .64) to good (module 1: α = .80 and module 3: .81). The poor internal consistency of the RRB scale is probably due to the fact that it only contains 4 items which are also very different in content. Furthermore, poor internal consistency for the RRB scale was
also found in previous studies which also had only limited variance in the scores on the four items (Bastiaansen et al., 2011; de Bildt et al., 2011). In line with previous research (e.g., Sheppard, Pillai, Wong, Ropar, & Mitchell, 2016) Calibrated Severity Scores (CSS) were used for Social Affect, Repetitive and Restricted Behaviours, and Total Score to account for variation in age, language level and module administration (Gotham, Pickles, & Lord, 2009; Hus, Gotham, & Lord, 2014).

The SCQ is a 40-item parent-report screening tool for measurement of ASD characteristics. The items are scored as yes/no and the first item indicates whether the child is able to speak at the moment. In the present study, the lifetime version of the SCQ was used and the internal consistency of the Total scale had excellent internal consistency ($\alpha = .85$).

The SRS-2 (Constantino & Gruber, 2012) is a 65-item rating scale measuring deficits in social behaviour associated with ASD. In the present study, the questionnaire was completed by both parents and current teacher. Items are scored on a 4-point Likert scale ranging from not true (=1) to always true (=4). In the present study, the internal consistency of the Total scale for both parent and teacher versions had excellent internal consistency ($\alpha = .93$ and $\alpha = .95$, respectively).

**Outcomes in Language Understanding and Production**

The CELF-4 and the CELF preschool-2 are individually administered tests for determining a language disorder or delay. The CELF-4 is used for children and adolescents between five and 21 years and the CELF preschool-2 for three to seven years. In the present study, depending on the age and language skills of the child, the appropriate version of the test was administered. For both tests, different subtests that comprise Core Language Score, Receptive Language Index and Expressive Language index were administered. The CELF-4 and CELF preschool-2 have a good reliability and validity (Semel et al., 2003; Wiig et al., 2004) and were also previously used in studies including children with ASD (Boucher, 2012; Lewis, Murdoch, & Woodyatt, 2007). With regard to language understanding in CELF-4, the internal consistency of the index score was good ($\alpha = .82$) for children between five and eight years and questionable ($\alpha = .66$) for children between nine and 11 years. With regard to language production in CELF-4, the internal consistency of the index score was good for both children between five and eight years ($\alpha = .87$) and for children between nine and 11 ($\alpha = .85$).
When the language level of the child did not meet the requirements for the CELF preschool-2, parents were asked to fill out the CDI. The *CDI* is a parent-report questionnaire of receptive and expressive vocabulary which provides raw counts of both word comprehension and word production. The CDI has adequate reliability and correlates with different language measures that use clinical observation such as the Dutch version of the Reynell Developmental Language Scales [RDLS (Edwards et al., 1997); Reynell Taalontwikkelingsschalen (RTOS; Schaerlaekens, Zink, & Van Ommeslaeghe, 2003)] and the Dutch Nonspeech Test (NNST; Zink & Lembrechts, 2000) and is also been used in populations with children with ASD (e.g., Luyster, Lopez, & Lord, 2007). Internal consistency was not calculated for the CELF preschool-2 and CDI because there were too few observations to obtain a reliable result. To account for variation in language test and age, age equivalents were calculated for both language production and language understanding levels. By subtracting the chronological age from the age equivalent, an indication of the language level was obtained. A positive value corresponded to a lead in language skills and a negative value corresponded to a delay in language skills.

**Outcomes in Motor Development**

The *M-ABC-2* assesses motor competence of children between three and 16 years old. In the present study, the appropriate age bands (three to six years and seven to 10 years) were used. The test includes eight subtests across three different domains: Manual Dexterity, Aiming and Catching, and Balance. The *M-ABC-2* was also used in previous studies with individuals with ASD (McPhillips et al., 2014; Whyatt & Craig, 2012). The *M-ABC-2* has good reliability and validity (Henderson & Sugden, 2007). In the present study, the component scores for each domain and total score were used. With regard to age band 1, the internal consistency of the Manual Dexterity domain was good ($\alpha = .82$) and for the Balance domain acceptable ($\alpha = .70$). However, the internal consistency of the Aiming and Catching domain was poor ($\alpha = .54$). Concerning age band 2, the internal consistency of the Balance domain was acceptable ($\alpha = .73$). However, the internal consistency of the Manual Dexterity domain was also poor ($\alpha = .57$) and for the Aiming and Catching domain even unacceptable ($\alpha = .41$). Although it is clear that the results of some of the subscales of the *M-ABC-2* have to be interpreted with caution in
the present study, it was found that both total scores of age bands 1 and 2 have an acceptable (age band 2: $\alpha = .76$) and good (age band 1: $\alpha = .84$) internal consistency.

**Data Analyses**

**Operationalization of the Regression and Non-Regression Group**

The inclusive regression group (ASD-R; n=36) includes the children with regression in language, social, motor and/or adaptive skills before, at, or after the age of 36 months. The group consists of 13 children who were reported to display a typical development followed by loss of skills together with 23 children who were reported to display already some developmental delays or atypicalities followed by loss of skills. At the moment there are only limited longitudinal data related to the potential causes of regression such as epilepsy (Barger & Campbell, 2014; Barger et al., 2017). Therefore, in the present study, an overly inclusive approach concerning the allocation of participants to the regression group was used. In this regard, within the regression group, there was one child with epilepsy (in which seizures happened before as well as after the regression) and three children in which parents reported regression after high fever caused by ear infections. There is also one case in which the child lost potty-training skills after urological surgery and we decided to not include this child in the regression group. Regarding life events causing a regression-like developmental pattern six children showed a regression of maximum two months after the start of school in combination with a move or birth of a sibling. In these cases, the regression most often involved adaptive skills and social withdrawal. The parents reported that these life events were clearly the cause of behavioural changes in their child and faded away when they became more adapted to the new situation (this could also be related to the ‘ups and downs’ in the development of children with ASD). Therefore, we decided to not include these children in the regression group.

The non-regression group (ASD-NR; n=64) consists of (i) 60 children who were reported to display characteristics of ASD and/or non-specific concerns related to ASD already during the first 12 months of life without loss of skills and (ii) 4 children who had a typical development followed by a plateau.

**Operationalization of Regression Groups Based on 36 months Cut-Off**

In the review article of Barger et al. (2013) it was found that most investigators conceptualise regression as a loss of previously acquired skills, typically before 36 months of age. Considering the
variation in age cut-offs in regression definitions and in line with results of recent previous retrospective studies on regression (Bradley et al., 2016; Gadow et al., 2017), we decided to distinguish two groups based on the age cut-off of 36 months: the regression before, or at 36 months group (ASD-R≤36M; n=24) and the regression after 36 months group (ASD-R>36M; n=12).

Operationalization of Regression Type Scales

The present study included both ‘full’ (i.e., duration of loss for 3 months, cf. definition of ADI-R) and ‘subthreshold’ losses (i.e., duration of loss for 1 month; cf. Goin-Kochel et al., 2014), two arbitrary guidelines that were often used in previous investigations. For analyses, the regression items on the ADI-R, RSQ and EDQ were scored binomial. This means that the answer categories on some of the ADI-R and RSQ items, of which the original answers were divided across three answer categories (no loss - probable loss - definite loss), were recoded so that ‘probable loss’ and ‘definite loss’ were merged. Based on the regression items from the ADI-R, RSQ and EDQ, four scales of regression within different developmental domains were distinguished:

Loss of language skills. Loss of language skills was defined as loss of language production (all or most babbling, meaningful words and/or phrases) and language understanding skills. This scale contains item #11 of the ADI-R and the four items of the EDQ on loss of communication skills. The internal consistency of the language regression scale in the present study was good (α = .85).

Loss of social skills. Loss of social skills was defined as loss of interest and involvement in others, social smiling, gaze, showing, reaction to name, reaching for caregiver and gestures or imitation behaviours such as pointing, clapping and waving goodbye. This also includes loss of play skills (as a non-linguistic social skill) defined as loss of pretend or imaginative play, puzzling, or interest in interactive games such as peek-a-boo. This scale consists of items #24 and #25 of the ADI-R, six items of the RSQ (reaction to name, social smiling, pointing, eye contact, waving bye-bye and showing) and six items of the EDQ on loss of social skills. The social regression scale has a good internal consistency (α = .84).

Loss of motor skills. Loss of motor skills was defined as loss of ability to manipulate objects, ability to carry, throw, kick or climb, or ability to physically move independently, or in posture and coordination


skills. This scale consists of items #21 and #22 of the ADI-R and the three items of the EDQ on loss of
motor skills. The motor regression scale has an acceptable internal consistency (α = .70).

Loss of adaptive skills. Loss of adaptive functioning was defined as loss of ability to feed self, to dress
self and toileting skills. This scale consists of item #23 of the ADI-R and the three items of the EDQ
on adaptive behaviours. The adaptive regression scale has an acceptable internal consistency (α = .70).

Statistical Analyses

Analyses were conducted with IBM SPSS (IBM Corp., 2017) and the statistical computing
environment R (R Core Team, 2013). Little’s MCAR test (Little, 1988) confirmed that missing data
were ‘missing completely at random’ (χ² (707) = 95.853, p = 1.000). Missing values were imputed
using the Expectation-Maximization technique (Schafer & Graham, 2002).

Latent class analysis (LCA) was used to characterise the underlying empirical regression groups,
based on regression type scales (i.e., language, social, motor and adaptive regression) and regression
onset age (before or after 36 months), displayed in the present sample of children with regression and
ASD. Because of the small sample size (n=36) of children with regression it was not possible to use
the original items of the ADI-R, RSQ and EDQ since the number of estimated parameters would
exceed the residual degrees of freedom. Therefore, the information from the original items of the ADI-
R, RSQ and EDQ was reduced into four binomial variables based on the four regression type scales.
LCA groups subjects into classes based on their item scores and subjects with comparable patterns of
item scores form one class. The primary objective of LCA in this study, is to find the smallest number
of classes of subjects with similar patterns of regression in ASD that are able to explain the
relationships among a set of observed variables (i.e., regression type scales and onset age). In the
analysis, classes were added stepwise until the model fits the data well. As a measure of how well the
model fits, the deviation of each individual from the average profile of its most likely class, given a
fixed number of classes, is used. As proposed by Nylund, Asparouhov, & Muthén (2007) the Bayesian
Information Criterion (BIC) was used to decide on the number of LCA classes. More specifically,
when comparing two estimated models with a different number of classes, the model with the lower
BIC value is the one to be preferred (Nylund et al., 2007). Additionally, the decision on how many
classes are preferred in the LCA, was also based on the interpretation of the content of the different
classes. In the present study, the software package poLCA version 1.4, implemented in the R statistical computing environment, was used to estimate latent class models for dichotomous and polytomous outcome variables (Linzer & Lewis, 2011, 2013). LCA results were reported according to the guidelines provided in Schreiber (2017).

With regard to the analyses on group differences, criteria for parametric testing were met, except for the ADOS calibrated severity scores (CSS) of which the data followed a non-normal distribution. Descriptive statistics were used to explore the characteristics of the regression groups that were distinguished. The family’s socioeconomic status (SES) was calculated by the Hollingshead’s four factor index based on both parents’ education level and occupation (Hollingshead, 1975). Group differences were examined using Chi square tests (categorical variables), one-way ANOVA (continuous variables) and non-parametric Mann-Whitney U or Kruskal-Wallis H tests (non-normally distributed variables). With regard to the one-way ANOVA’s, Levene’s tests were carried out and assumptions met. Because of the large variation in sample sizes, post hoc comparisons were carried out by Hochberg’s GT2. Bonferroni adjustments were applied to control for inflation of Type I error rate due to multiple comparisons (Bonferroni, 1936). Effect sizes were calculated using Cohen’s $d$ for continuous variables, odds ratio for binary variables within a 2 x 2 contingency table and $W$ for binary variables within a 3 x 3 contingency table. To assess the length of time needed to attain a skill after birth in the ASD-R and ASD-NR group, a non-parametric Kaplan-Meier survival analysis was used. A log rank test was conducted to compare survival curves or time to attain skills between groups. Because of significant differences in age between regression groups, correlations between age and outcome variables were analysed. No significant correlations were found. Moreover, since ADOS severity scores already take into account the age of the children to enhance comparability over different modules, an additional correction for age was not conducted within the analyses. Additional evidence on this decision can be found in the critical commentary by Miller and Chapman (2001) on “correcting” or “controlling for” real group differences on a potential covariate.

Concerning the agreement between regression measures (ADI-R, RSQ and EDQ) on the regression type scales, the kappa statistic (to measure agreement between 2 categorical measurements) and the Fleiss’ kappa statistic (to measure agreement between >2 categorical measurements) were used.
Results

Underlying Empirical Regression Groups Based on Type and Onset Age

The LCA analyses included the four regression type scales (language, social, motor and adaptive regression) together with the variable onset age of regression (before or after 36 months) as independent variables and identified two classes based on the lowest BIC index and the interpretation of the classes. An overview of the model fit evaluation information is presented in Table 1. The global maximum log-likelihood, -108.8985, was found in the second attempt at fitting the two-class model. The likelihood function of LCA is composed of two types of parameters. First the estimated item response probabilities were calculated as the percentage of subjects in each class reporting a particular type of regression or regression after 36 months of age (Figure 1). In this study, all items were binomial and scored in the same direction with a score 1 for no regression and 2 for regression. Concerning onset age of regression, onset before or at 36 months was scored as 1 and onset after 36 months was scored as 2. In this way, the estimated item response probabilities represent the percentage of subjects in each class reporting a particular type of regression or onset age of regression after 36 months. As a second parameter, the marginal proportions were calculated which are the percentages of subjects falling in each class (Table 2). Class 1 (75% of sample) had the most parents reporting a language (77.78%) and social (85.18%) regression, which was significantly more than class 2 (22.22% for both language and social regression; FET: $p < .01$ and FET: $p < .01$, respectively). Within class 1, 88.88% of the parents reported an onset age of regression before or at 36 months of age which was significantly more (FET: $p < .001$) than class 2 (0%). No significant differences were found regarding proportions of parent reports of adaptive and motor regression between class 1 and 2 (FET: $p = .652$ and FET: $p = .514$, respectively). However, within class 2, all parents reported an onset age of regression after the age of 36 months compared to only 11.11% in class 1 and this difference was significant (FET: $p < .001$). Hence, the scales language regression, social regression and onset age of regression were the best in discriminating between classes. Based on the LCA analyses it was decided to distinguish a group of children characterised by language and/or social and/or mixed regression (i.e., ASD-
R-L/S/M) and a group of children characterised by non-language or non-social (or adaptive and/or motor) regression (i.e., ASD-R-NL/NS).

Characteristics of Regression Groups

Regression Groups Based on 36 Months Age Cut-Off

See Table 3 for an overview of the characteristics of ASD-R≤36M and ASD-R>36M. Within the ASD-R≤36M group, all children lost language and/or social skills and in 50% of the children these losses were combined with loss of other skills such as motor and/or adaptive skills. Three children within the ASD-R≤36M group (12.50%) showed global regression in all domains of functioning. With regard to those who lost skills after 36 months, 58.33% (n=7) lost language and/or social skills, sometimes in combination with motor and/or adaptive skills. In five children only loss of motor and/or adaptive skills was reported. See the Appendix for an overview of skill loss domains in children with regression before and after 36 months.

Regression Groups Based on Type and Onset Age

See Table 3 for an overview of the characteristics of regression groups based on type and onset age. Within ASD-R-L/S/M, regression was reported to occur before or at the age of 36 months in 24 (88.89%) of the children and after the age of 36 months in three (11.11%) children. The ASD-R-NL/NS group only consisted of children with regression after 36 months (see also Table 2).

Group Differences Between ASD-NR and Regression Groups

Demographic and Clinical Differences

ASD-NR were significantly older ($M = 8.06\ years$, $SD = 1.85$) than the inclusive group ASD-R ($M = 6.71\ years$, $SD = 1.87$; $F(1,98) = 12.150, p < .007$). There was a significant difference in chronological age ($F(2,97) = 7.648, p < .007$) between ASD-NR, ASD-R≤36M and ASD-R>36M. Post hoc comparisons revealed that ASD-NR were significantly older ($p = .001$) than ASD-R≤36M ($M = 6.34\ years$, $SD = 2.02$). No significant differences were found between ASD-NR and ASD-R>36M ($p =$
and ASD-R≤36M and ASD-R>36M (p = .248). With regard to the empirical regression groups based on type and onset age, a significant difference in age (F(2,97) = 6.348, p < .007) was found between ASD-NR, ASD-R-L/S/M and ASD-R-NL/NS. Post hoc comparisons showed that ASD-NR were significantly older (p = .002) than ASD-R-L/S/M (M = 6.57 years, SD = 2.04). No significant differences were found between ASD-NR and ASD-R-NL/NS (p = .409) and, ASD-R-L/S/M and ASD-R-NL/NS (p = .824). Hence, children without regression had a chronological older age during participation in the present study compared to children with regression before or at 36 months of age or children with regression in language, social and/or mixed skills. Further, no significant differences were found in gender or socioeconomic status between ASD-NR and regression groups. Furthermore, there was a significant difference (F(2,97) = 5.743, p < .007) in the age at which the children received their diagnosis between ASD-NR, ASD-R≤36M and ASD-R>36M. Post hoc tests revealed a significant difference (p = .013) in age of diagnosis between ASD-NR (M = 62.03, SD = 22.83) and ASD-R≤36M (M = 46.67, SD = 19.24) and, a significant difference (p = .013) between ASD-R≤36M and ASD-R>36M (M = 69.33, SD = 21.84). No significant difference (p = .643) was found between ASD-NR and ASD-R>36M. Hence, children with regression before or at the age of 36 months received their diagnosis at an earlier age compared to children with a regression after the age of 36 months or children without regression. No significant differences (F(2,97) = 2.247, p = .111) between ASD-NR, ASD-R-L/S/M and ASD-R-NL/NS were found concerning age of diagnosis. After Bonferroni-correction, no significant differences between ASD-NR and the regression groups were found concerning the number of comorbidities, number of children who were following a special education program and/or who had ever followed a specific kind of therapy which focuses on ASD characteristics. See also Table 4.

Differences in Early Development Before Regression

Early ASD Characteristics. Based on the results of the EDQ, ASD-R showed significantly less early communicative skills (e.g., directed speech, use of words and phrases) before regression than ASD-NR (F(1,98) = 6.723, p < .013). ASD-R showed a similar amount of early social skills (e.g., interest in others, gaze, showing and interactive games) and were also reported to show the same number of early
repetitive and stereotyped behaviours as compared to ASD-NR. A significant difference between ASD-R and ASD-NR in the Early Developmental Summary Score disappeared after Bonferroni-correction. With regard to differences between ASD-NR and regression groups based on 36 months age cut-off and the empirical regression groups based on type and onset age, significant differences in the early communicative skills disappeared after Bonferroni-correction. See also Table 5.

Early Developmental Milestones. Because of the variation in the attainment of first steps (ADI-R item #5), first words (ADI-R item #9) and first two-word sentences (ADI-R item #10), a nonparametric Kaplan-Meier survival procedure was used to compare differences between ASD-NR and ASD-R. When a child did not attain the skill by the time of the participation in the research program, it was considered as a censored observation. No significant differences were found between the survival distributions of ASD-NR and ASD-R for attainment of first steps (median survival time ASD-NR = 14 months, SD = .41; median survival time ASD-R = 14 months, SD = .55; \(\chi^2(1) = .447, p = .504\); see Figure 2) and first words (median survival time ASD-NR = 15 months, SD = .93; median survival time ASD-R = 13 months, SD = .82; \(\chi^2(1) = .561, p = .454\); see Figure 3). However, a significant difference was detected for median survival time of first sentences between ASD-NR (24 months; SD = .15) and ASD-R (30 months; SD = 5.17; \(\chi^2(1) = 6.173, p < .05\); see Figure 4).

Differences in Later Functioning After Regression

Non-Verbal Intelligence. Although ASD-R showed a below average intelligence profile (\(M = 86.33, SD = 22.15\)) as compared to ASD-NR who had an average intelligence profile (\(M = 93.47, SD = 19.61\)), this difference was not significant (\(F(1,98) = 2.778, p = .099\)). Additionally, no significant differences in non-verbal intelligence scores were found between ASD-NR and regression groups based on 36 months age cut-off and the empirical regression groups based on type and onset age. See also Table 6. Further, although the inclusive regression group comprised nearly twice as much children with intellectual disability (ID; non-verbal IQ≤70) no significant differences (\(\chi^2(1) = 2.127, p = .145\)) were detected in the proportion of children with ID between ASD-NR (15.63%; n = 10) and ASD-R (27.78%; n = 10). Furthermore, no significant differences in the proportion of children with ID
were found between ASD-NR, ASD-R≤36M and ASD-R>36M ($\chi^2(2) = 3.516, p = .172$) and between ASD-NR, ASD-R-L/S/M and ASD-R-NL/NS ($\chi^2(2) = 2.358, p = .308$).

**ASD Characteristics and Severity.** Although no significant differences were found between ASD-NR and ASD-R in Calibrated Severity Score (CSS) of both the Social Affect domain and the Total Score on the ADOS, ASD-R showed a significantly higher CSS ($M = 8.31, SD = 2.07$) of the Restricted and Repetitive Behaviours (RRB) domain as compared to ASD-NR ($M = 6.73, SD = 2.47$; $U(100) = 1,629.00, p < .004$). More specifically, children with regression showed a high level of RRB symptoms as compared to children without regression who showed a moderate level of RRB symptoms (see also Lord et al., 2012). Significant differences in RRB ($H(2) = 19.604, p < .007$) were also found between ASD-NR, ASD-R≤36M and ASD-R>36M. Post hoc comparisons using the Mann-Whitney U-test revealed that ASD-R≤36M showed a significantly higher level of RRB ($M = 9.00, SD = 1.44$) compared to ASD-NR ($p = .000$) and ASD-R>36M ($M = 6.92, SD = 2.47; p = .006$). Furthermore, significant differences in RRB ($H(2) = 14.384, p < .007$) were also found between ASD-NR, ASD-R-L/S/M and ASD-R-NL/NS. Post hoc comparisons showed a significant higher level of RRB ($p = .000$) in ASD-R-L/S/M ($M = 8.67, SD = 1.69$) compared to ASD-NR. Although significant differences were found between ASD-R and regression groups concerning the ADOS Total CSS, none of these differences were still significant after Bonferroni-correction. Parent and teacher ratings seem to indicate higher ASD severity in children with regression, however, significant differences between groups disappeared after Bonferroni-correction. See also Table 6.

**Language and Motor Development.** ASD-R display greater productive language delays ($M = 12.70$ months, $SD = 28.95$) as compared to ASD-NR ($M = .40$ months, $SD = 25.94$). However, this difference disappeared after Bonferroni-correction. No significant differences in language delays were found between regression groups based on 36 months age cut-offs and the empirical regression groups based on type and onset age. Lastly, ASD-NR and the regression groups did not significantly differ in fine and gross motor skills as measured by the ABC-M-2. See also Table 6.

[Insert Table 6 about here.]
To enhance the reliability of parent report, at least one of the reported lost skills on the EDQ had to be confirmed during administration of the ADI-R and/or the RSQ. Only the report of the event of loss of skills was taken into account, regardless of specific restrictions on for example duration or age of regression. In 10% (n = 10) of the children who participated in the present study, parents reported loss of skills on the EDQ but not on the ADI-R and/or the RSQ. Concerning the added value of the RSQ and the EDQ upon the reports of the ADI-R, results show that in 13.89% of the cases with reported regression, the RSQ added information on the loss of specific social-communicative skills on top of the ADI-R. In 36.11% of the cases, the EDQ added information on the loss of language, social, motor or adaptive skills top of the ADI-R. Overall, in 44.44% of the cases either the RSQ or EDQ added valuable information on losses next to the ADI-R.

After excluding the cases in which parents only reported regression on the EDQ, analyses on the comparison between the different regression measures (i.e., ADI-R, RSQ and EDQ) show moderate agreement concerning parental reports on loss of language (k = .478, p < .01), loss of motor (k = .455, p < .01) and loss of adaptive (k = .463, p < .01) skills. With regard to the loss of social skills, only a slight agreement (Fleiss’ k = .094, p = .351) was found between parental reports on the ADI-R, RSQ and EDQ. This value was also non-significant which means that the agreement is not significantly better than would be expected by chance. An overview of the agreement between regression measures based on regression type scales is presented in the Appendix.

**Discussion**

The present study examined characteristics of regression in 100 children with ASD between three and 11 years old. To date, retrospective research on regression in ASD is characterised by inconsistent findings caused by lack of consensus on the definition of regression and use of various unvalidated methods. Novelties within this retrospective study were the use of an empirical, quantitative approach to distinguish regression patterns within children with ASD and different approaches to enhance the validity of retrospective parent report. To measure the attainment and loss of skills a combination of (i) traditional as well as more recent retrospective parent report measures, and (ii) a questionnaire and extensive interview with a mix of open-ended and detailed questions was used. To our knowledge, this
study was also the first to implement retrospectively ‘prospective’ information through standardized booklets filled out by professionals during consecutive consultations in the first 30 months of life. Based on a combination of three measurements of regression (the traditional ADI-R, a loss-supplement RSQ and the EDQ), 36% of the parents reported loss of skills in the development of their child at a mean age of 34 months (between eight and 96 months) in language, social, motor and/or adaptive skills. In 24% of the children with ASD, a regression mostly in language and/or social skills was reported before or at the age of 36 months with an average onset age at 21 months. Although a higher prevalence rate and younger onset age were expected based on the different strategies that were used in order to be more consistent with recent prospective research findings, current findings still correspond to previous parent report studies (Barger et al., 2013). However, a wider variation in onset age was seen in the present study with some parents already reporting the start of regression at the age of eight months. In line with recent studies (e.g., Bradley et al., 2016; Gadow et al., 2017), the prevalence of regression after 36 months was 12% with an average onset age of 5.1 years. The latter group of children demonstrated broader variation in the domains of skills loss (e.g., more losses in adaptive skills) as compared to those in whom skill loss started before or at 36 months. Consistent with prior studies (e.g., Goin-Kochel et al., 2014), a wide variation in duration of loss ranging from two to 44 months was seen and some children still did not regain their skills at the moment of the research. However, children who lost skills after 36 months seem to regain their skills sooner than children with regression before or at 36 months. Analysis of the underlying empirical regression patterns in the children with ASD revealed two groups. The first group characterised children with language and/or social regression in some cases combined with motor and/or adaptive regression and comprised 75% of the children with regression. In most of the children in this group regression was reported to occur before or at the age of 36 months with a mean onset age of 27 months. This group seems to correspond with a combination of the description of the theoretical categories of language (loss of meaningful verbalizations), social (loss of nonverbal social behaviours), language/social and mixed (loss of verbal and/or nonverbal abilities as well as the loss of some other ability without a clear communicative component) regression which could be extracted from the regression literature (Barger & Campbell, 2014; Barger et al., 2013). The
second group characterised children with non-language or non-social (or adaptive and/or motor) regression and comprised only 25% of the children with regression. All children in this group were reported to regress after the age of 36 months with a mean onset age of 4.7 years. In line with previous studies on factors affecting age at ASD diagnosis (e.g., Brett, Warnell, McConachie, & Parr, 2016; Mishaal, Ben-Itzchak, & Zachor, 2014), children who regressed before or at 36 months received their diagnosis at a younger age than children without regression and children with regression after 36 months. Further, as expected, regression was not related to any particular socio-economic status (Christopher, Sears, Williams, Oliver, & Hersh, 2004; Hansen et al., 2008). Remarkably, in contrast to prior studies (e.g., Gadow et al., 2017; Goin-Kochel et al., 2014) where regression in ASD was associated with a higher amount of later comorbidities, more special education services and ASD-related therapy, in our study significant differences between children who regressed and those who did not were not found. Most probably this is due to the methodological differences between studies and differences in arrangements of these services between countries.

Regarding early development, children with regression were reported to show similar impairments in their early social development and a similar amount of repetitive and stereotyped behaviours as compared to children without regression, which is in line with previous findings (e.g., Ozonoff et al., 2005). However, in contrast to previous studies, it was not confirmed that children with ASD and regression had less impairments prior to regression as compared to children with ASD without regression (e.g., Luyster et al., 2005; Ozonoff et al., 2005). This could be due to the age at which the early development was measured (in the present study prior to 18 months or prior to regression). Remarkably, children with regression were reported to show less communicative skills (e.g., less directed speech and use of words and/or phrases) before onset of regression than children without regression. On an individual level, almost half (45.83%) of the parents reported early atypicalities in the development of their child before the start of the regression. These findings are in line with previous results from both retrospective parent report (e.g., Ozonoff et al., 2005; Werner & Dawson, 2005) and prospective studies (e.g., Ozonoff et al., 2010) concluding that the development before the start of regression is not typical and that there is a common mixed early onset + regression pattern with both early delays and later losses (Ozonoff, Heung, et al., 2008). Although children with regression
show less communicative skills in general before the start of the regression as compared to children
without regression, no significant difference in the attainment of the first word milestone was found.
This finding is in contrast with previous findings indicating that children with regression say their first
words earlier than children without regression (e.g., Jones & Campbell, 2010; Kalb et al., 2010).
However, in most of the previous studies parent report on the attainment of first milestones was not
validated. In the present study, standardized retrospective ‘prospective’ information was used to
validate the information received by parent report. Additionally, the present study took into account
the variation in the attainment of first milestones as well as children who did not attain the skill by the
time of participation by using a more complex statistical technique (i.e. Kaplan-Meier survival
analysis) rather than comparing averages. Furthermore, the finding that children with regression attain
their first words earlier is probably also related to the fact that in most studies first words were
expected to be present prior to loss, a central requirement in most definitions of regression in ASD.
Similarly to previous research results (Kalb et al., 2010; Meilleur & Fombonne, 2009; Pickles et al.,
2009), children with regression were reported to acquire their first sentences at a later age (i.e. 30
months) than children without regression (i.e. 24 months). Since the average onset age of regression is
21 months, most children with regression fail to attain this skill at the expected age and show a
remarkable delay in the acquisition of their early language skills. Further, in accordance to previous
research (e.g., Bernabei et al., 2007; Ozonoff, Young, et al., 2008) no differences were found in the
attainment of the first steps.
Concerning development after regression, the findings in the present study are consistent with most
previous findings indicating that the average IQ scores of individuals with and without regression are
likely similar (Baird et al., 2006; Goldberg et al., 2003; Kalb et al., 2010; Rogers, Young, Cook,
Giolzetti, & Ozonoff, 2008; Shumway et al., 2011). However, in contrast with some previous studies
(Christopher et al., 2004; Wiggins et al., 2009), the present study found no differences in the
proportion of children with intellectual disability between the regression and non-regression group.
This could be related to the fact that in the present study only non-verbal intelligence was measured
instead of the full intelligence construct.
Based on clinical observation through the ADOS, we could confirm a higher level of repetitive and stereotyped behaviour in children with regression, more specifically in children with regression before or at the age of 36 months and children within the empirical group characterised by language and/or social regression sometimes in combination with motor and/or adaptive regression. These results are in line with most previous studies using parent report based on the ADI-R and medical records to measure repetitive and stereotyped behaviour (Bradley et al., 2016; Lam, Bodfish, & Piven, 2008; Meilleur & Fombonne, 2009; Wilson et al., 2003). No differences were found in parent (see also Jones & Campbell, 2010; Shumway et al., 2011; Werner, Dawson, Munson, & Osterling, 2005) or teacher (e.g., Mire et al., 2018) reported ASD characteristics. In line with research from Pickles et al. (2009), in which later expressive and receptive language skills in children between 10 and 14 years old were also measured using the CELF, no significant differences were found between the groups. However, it is important to mention that in the present study a substantial number of children in the regression group did not meet the required language level to conduct a standardized language test such as the CELF. Therefore, the results on language should be interpreted with caution. Further, in agreement with previous findings on parent report of fine motor skills (Chawarska et al., 2007), the present study did not find differences between children with and without regression by measuring fine motor skills through observation. Additionally, later gross motor development was equally impaired in children with and without regression.

In sum, in line with much of the research to date, only few differences between children with and without regression were found. Furthermore, since the regression groups based on 36 months age cut-off and empirical regression groups based on type and onset age largely overlap (only three children were differently ascertained), similar findings were detected except for the age of diagnosis, the post-hoc comparisons regarding RRB and some differences which disappeared after Bonferroni-correction. Additional analyses of the differences in early development and later outcomes between a theoretical group of children with language and/or social regression (n=15) and a group of children with mixed regression (language and/or social in combination with motor and/or adaptive skill loss; n=16), regardless of onset age of regression, showed similar results. Overall, analyses showed that a broad distinction between ASD-R and ASD-NR already revealed significant differences (e.g., in early
communication skills and first sentences milestone). Only in the case of differences in RRB symptoms, the distinction of regression groups based on 36 months age cut-off and regression types and onset age provided some additional information. In accordance with previous research by Gadow et al. (2017) results were generally consistent between the regression group before or at 36 months and the inclusive group, however, most of the significant differences related to the regression group before or at 36 months disappeared after Bonferroni-correction probably related to the small sample size. Furthermore, also only very few or no differences between children with regression before 36 months of age and those with regression at older ages were found in previous studies (Shinnar et al., 2001; Wiggins et al., 2009).

With regard to the agreement between regression measures and the added value of other measures on top of the ‘golden standard’ ADI-R, it is clear that the RSQ and EDQ are valuable instruments, with less arbitrary defined restrictions in the definition of regression, which clearly enhance the reliability of parent report on loss of more subtle social-communicative skills (cf. also Thurm et al., 2014).

In addition to the advanced empirical approach to define regression and the methodological improvements already mentioned, the present retrospective study also used well-validated standardized and observational assessments of a very broad range of developmental outcomes, including later motor development. In addition, a multi-method (reports and clinical observation) and multi-informant (clinicians, parents and teachers) approach were combined.

Even though regression is not a criterion for the diagnosis of ASD, monitoring the loss of skills in different developmental domains at multiple time points can be very important for early identification of ASD, particularly in children who may be at risk (Estabillo et al., 2018). However, since a substantial number of the children with ASD show an apparently typical development before regression according to their parents (54% in the present study), these children could be ‘missed’ during early screening for ASD (Carlsson et al., 2016). Further, regression can also occur after 36 months. However, to exclude other neurodegenerative conditions, an assessment by a paediatrician or paediatric neurologist is required in these cases (Yates & Le Couteur, 2016). Since most children with regression seem to go through a more impaired trajectory, a brief parent report of loss and attainment of skills obtained from an intake questionnaire may be a useful clinical indicator of later functioning
(Gadow et al., 2017). In order to reduce later problems, more therapy or a prevention-oriented approach can be provided.

There are several limitations which need further consideration. First, in 28% of the cases in the present study it was not possible to obtain standardized developmental booklets which could enhance the reliability of the parent reports on regression. In 68% of the missing cases, the children were seven years or older, which could be an explanation for the finding that the non-regression group consisted of a significantly larger number of older children. However, the finding that parents of younger children seemed more likely to report regression – because they are closer to the time of symptom onset – compared to parents of older children, was also found in prior cross-sectional studies and could also reflect a potential recall bias (Lord et al., 2004; Ozonoff, Li, et al., 2018; Tuchman & Rapin, 1997). Hence, future cross-sectional studies on regression using parent report should mainly focus on including younger children (e.g., pre-school children) to assure the reliability of the results.

Second, some of the regression groups consisted of a very small number of children which could have influenced the statistical significance of some of the differences between groups. Further, the total number of children with regression was rather small (n=36) which entailed that it was not possible to include all the information of the original items from the regression measurements. In future studies it would be interesting to use latent class analysis in a large group of children with regression in order to include specific skill losses (e.g., loss of social-communicative skills), full and/or subthreshold losses and to include onset age as a continuous variable instead of using a specific age cut-off.

Further, more attention and caution must be given on how regression is defined and operationalized since particular operational definitions could obscure important differences between children with and without regression (Barger & Campbell, 2014). In the present study there is little evidence that differences in the early development or later outcome are related to a specific type of regression. However, more research is needed to determine whether differences are unique to a particular regression type such as social or non-social and non-language regression. With regard to retrospective studies, it seems necessary to include supplemental questions to the regression items of the ADI-R such as the RSQ (Thurm et al., 2014) or the Regression Supplement Form (RSF; Goldberg et al., 2003). In order to validate parent report, additional video analysis could be used (e.g., Goldberg et al.,
In general, it would be very valuable to combine the retrospective and prospective approach to investigate characteristics of regression and other onset patterns (e.g., Ozonoff, Li, Deprey, Hanzel, & Iosif, 2018). The present results suggest that atypicalities in development of early communication could be valuable predictors of regression. This finding needs further investigation in prospective longitudinal studies. Such studies could also contribute to the examination of later outcomes based on early developmental characteristics and examine the hypothesis that the deleterious effects of regression would become more evident over time (Bernabei et al., 2007; Goin-Kochel et al., 2014; Lord et al., 2004).

Conclusions

Previous retrospective research on regression in ASD has produced conflicting results due to the use of divergent operational definitions. As there are no practical alternative approaches to retrospective parent report, it remains the most commonly used method to study early development. First, the present study offers a unique contribution to the retrospective literature on regression by using an empirical approach by which two underlying regression patterns based on regression type and onset age were characterised. Second, group differences between the non-regression group and regression groups based on 36 months age cut-off and empirical regression groups based on regression type and onset age, were generally consistent. Children with and without regression seem to develop in a similar way prior to regression. However, children with regression show less communication skills which could be valuable predictors for regression. Further, children who regress, turn out to experience a more deleterious outcome later in life, characterized by early language delays and more repetitive and stereotyped behaviour. Third, analysis of agreement between parent report regression measurements showed an added value of a combination of different interviews and questionnaires to measure loss of subtle social-communicative skills. The present retrospective results need further investigation through prospective longitudinal studies including high-risk siblings of children with ASD. Overall, a better understanding of developmental trajectories can provide more insight in the underlying biological process of ASD, and can lead to an earlier diagnosis and thus improve treatment services.
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