Language development in autism spectrum disorder: longitudinal comparison with a community cohort of children with language impairment and typical development

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Abstract

Background

Autism spectrum disorder (ASD) is a lifelong developmental disability that affects more than 1 in 50 children in Australia. Language difficulties are common in ASD with up to 30% of children unable to communicate using words. Despite a substantial number of studies examining language outcomes in individuals with ASD, it is difficult for families and clinicians to interpret study findings. This is because many studies use; selected clinical samples that may not generalise to the broader population, heterogeneous methodology, and the quality of studies varies. Rarely do studies use standardised language-specific tools. In addition, few studies have compared development in children with ASD to children without ASD, which means it is difficult to place differences in children with ASD within a developmental context. As a consequence, we do not yet fully understand how language develops in children with ASD and we are not able to accurately predict language outcomes. Parents and clinicians need evidence about language trajectories in ASD to inform decision-making and understand prognosis. Service providers and policy makers also require information for appropriate resource allocation for current and future needs.

Aims

The overall aim of this thesis was to examine trajectories of language development in individuals diagnosed with ASD. To achieve this aim, three main studies were conducted. Study 1 systematically reviewed and synthesised the extant literature on language outcomes in individuals with ASD. Studies 2 and 3 examined individual and mean trajectories of language development in children with ASD from 1 to 2 years and 4 to 7 years, respectively, and compared these trajectories to large samples of children
with language impairment (LI) and typical language development (TD). Study 3 described language trajectories for children with ASD and investigated predictors of language outcomes from 4 to 7 years in children with and without ASD.

Method
Children in studies 2 and 3 were recruited from a prospective longitudinal community-based study of 1910 children in Victoria (the Early Language in Victoria Study; ELVS). Individual and mean trajectories were mapped from 1 to 2 years (ASD; n=41, LI: n=119, TD: n=861) and 4 to 7 years (ASD; n=27, LI n=110, TD: n=831). In Study 2, individual and mean communication trajectories were mapped using scores from two parent checklists, namely the Communication Symbolic Behaviour Scales Infant Toddler Checklist and the MacArthur Bates Communicative Development Inventories. We compared the proportion of children who lost specific communication skills between the three groups (ASD, LI, TD) and the spread of loss across different communication domains. In Study 3 we used the Clinical Evaluation of Language Fundamentals data collected in ELVS (preschool second edition and fourth edition) to map individual and mean language trajectories from 4 to 7 years. The proportion of children who had declined, remained stable or accelerated in language skills was compared across groups. Putative predictors of language outcomes were also investigated.

Results
Language ability was heterogeneous, however, mean scores for children with ASD and LI were lower than scores for children with TD and reference norms, in all studies included in the systematic review and Studies 2 and 3 in the community sample.
From 1 to 2 years, the gap between children with ASD and TD/LI grew larger in all communication domains except in the areas of speech and expressive vocabulary, which was similar for children with LI and ASD.

From 4-7 years, despite having lower language ability on average compared with the typically developing group, most children with ASD were developing language at the same pace as the LI and TD children. A diagnosis of ASD did not predict a greater gap between receptive and expressive language ability. The child’s early language ability and IQ were most important in predicting language ability at a later age.

Conclusion
Systematic review and synthesis of existing studies showed that children with ASD in all studies (with one exception) had lower scores at baseline when compared with reference norms but children tracked in parallel to reference norms. The limited amount of data available from studies investigating children over 9 years made it difficult to draw accurate conclusions on trajectories beyond this age, however the few studies that had presented data suggest rate of language progress may slow from around 10 years.

In Studies 2 and 3 that utilised the ELVS, children with ASD demonstrated communication abilities that were not significantly different to other children at 12 months of age in most areas. However, on average their language and social communication progressed at a slower rate than other children from around 12 months to 2 years in most areas of communication. Findings from children in the ELVS aged 4 to 7 years were consistent with the systematic review findings. In Study 3 children with ASD who were verbal and had IQ in the normal range demonstrated lower language scores at baseline and follow up on average, but tracked in parallel to reference norms
over time. The knowledge gained from this thesis will help guide prognostic
information to be provided to parents. It will also assist with planning for future support
needs of individuals with ASD.
**Declaration**

This is to certify that

1. The thesis comprises only my original work towards the Doctor of Philosophy except where indicated in the preface

ii. Due acknowledgement has been made in the text to all other material used

iii. This thesis is fewer than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

Amanda Brignell
Preface

I acknowledge the contribution of the following co-authors to the published and unpublished work in Studies 1-3 (Chapters 6, 7 & 8). A description of the contribution of each author is outlined below.

Study 1. A systematic review of language outcomes in autism spectrum disorder.
Prof Katrina Williams, A/Prof Angela Morgan, Kim Jachno, Dr Susan Woolfenden, Dr Tamara May, Dr Felicity Klopper, Dr Vanessa Sarkozy.

Protocol development and modification: KW, SW, VS, AB; database search development and modifications; Katy Sterling-Levis, AB; sifting articles: AB, SW, VS, FK, TM, KW; data extraction: AB, FK; risk of bias assessments: AB, AM, TM; statistical analysis: AB, KJ; manuscript preparation: AB; manuscript review and editing: KW, AM, SW, TM, FK, VS, KJ.

Study 2. Parent reported patterns of loss and gain in communication in 1 to 2 year old children are not unique to autism spectrum disorder. A/Prof Angela Morgan, Prof Katrina Williams, Prof Margot Prior, A/Prof Susan Donath, Prof Sheena Reilly, Prof Edith Bavin, Dr Patricia Eadie.

Study conceptualisation and design: AB; data management: AB, statistical analysis: AB, SD; manuscript preparation and submission: AB; manuscript review, response to reviewers and manuscript revisions: AB; editing and manuscript revision: AM, KW, MP, SR, EB, PE, SD.
Study 3. Language trajectories and predictors of language outcome from 4 to 7 years in children with and without autism spectrum disorder. A/Prof Angela Morgan, Prof Katrina Williams, Kim Jachno, Prof Margot Prior, Prof Sheena Reilly.

Study conceptualisation and design: AB; data management: AB, statistical analysis: AB, KJ; manuscript preparation: AB; manuscript review and editing: AM, KW, MP, SD, SR, KJ.
Publications and presentations arising from this thesis

Peer reviewed publication


Conference presentations


Other presentations


Translation/media


Produced and presented a webinar and podcast on social communication and autism spectrum disorder. This was run through the Developmental Medicine department, Royal Children’s Hospital. Target audience: parents and clinicians. Oral presentation. One hour.

Note. All presentations were selected from abstract except those marked with a star (*)
Related publications during candidature


Related conference presentations during candidature


# Presentation was given by a co-author
Acknowledgements

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I extend special thanks to Kim Jachno and A/Prof Susan Donath for their statistical support. Kim has a special talent for explaining complex things in simple ways, which has greatly strengthened my knowledge of statistics and has been much appreciated. Thank you to Poh Chua for assistance with the search strategies for the systematic review.
I would like to express my gratitude to Prof Sheena Reilly for her great foresight in establishing the ELVS. I was very fortunate to have been given access to such a valuable resource. I would also like to thank the ELVS research assistants for data collection and Sandra Novakovic, Eileen Cini, Dr Fallon Cook and Dr Kathryn Harker for their assistance.

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I am very grateful to my family; Lyn, Barry and Georgie and to Maurice for their ever constant patience, love, kindness and support from afar.

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I acknowledge the financial support I have received from an Australian Post Graduate Award, the William Collie Trust and The University of Melbourne and Murdoch Childrens Research Institute travelling scholarships. These scholarships allowed me to present my work at conferences in Brisbane, Perth, Shanghai and Edinburgh.
This PhD is dedicated to all the children with ASD, and their families who participated in the studies within this thesis. It is only through their generosity that we will continue to develop our knowledge of ASD.
Table of Contents

Abstract .................................................................................................................................. iii
Declaration .............................................................................................................................. vi
Preface ................................................................................................................................... vii
Publications and Presentations ......................................................................................... viii
Acknowledgements ............................................................................................................ xv
Table of Contents ............................................................................................................... xvii
List of Figures ....................................................................................................................... xxii
List of Tables ......................................................................................................................... xxiii
Abbreviations ...................................................................................................................... xxiv
Glossary of Terms ................................................................................................................. xxv
Thesis Outline ....................................................................................................................... xxvi
Setting ................................................................................................................................... xxvii
Methodological Issues .......................................................................................................... xxvii

Chapter 1 Autism spectrum disorder ............................................................................. 1
  Epidemiology of ASD ......................................................................................................... 1
  Diagnosis ............................................................................................................................ 1
  Prevalence ......................................................................................................................... 2
  Causes of ASD .................................................................................................................. 3
  Cognitive theories of ASD .............................................................................................. 5
  Onset, development and life course of ASD ................................................................. 6
  Associated clinical features and comorbidities ............................................................ 7
  Summary ............................................................................................................................ 9

Chapter 2 Communication development in autism spectrum disorder ......................... 11
  Communication difficulties in ASD ................................................................................ 11
  The long-term impacts of communication disorders for children with ASD .............. 12
  Neurobiological underpinnings of communication difficulties in ASD ................. 13
  Overlap between children with ASD and language impairment ......................... 17
  Communication phenotypes in ASD ....................................................................... 21
  Links between cognitive impairment and language ............................................. 22
  Regression (loss) of communication skills ............................................................ 24
  Receptive-expressive language discrepancy ....................................................... 27
Children with ASD who fail to develop verbal speech .......................................................... 30

Chapter 3 Communication trajectories ........................................................................... 33
Social communication development in children with and without ASD .................. 33
Language development in children with and without ASD ........................................ 37
  Language development in children without ASD .................................................. 37
  Language development in ASD ........................................................................ 40
Predictors of language outcomes in children with and without ASD ....................... 45
  Predictors of language outcomes in children without ASD .............................. 45
  Predictors of language outcomes in children with ASD ..................................... 49

Chapter 4 This thesis ................................................................................................ 57
  Rationale for the thesis .......................................................................................... 57
  Challenges in understanding communication outcomes in ASD ...................... 57
  A review of the current evidence on language outcomes is required ............. 57
  Existing data from a community-based sample provide new opportunities .... 58
Summary ..................................................................................................................... 61
Thesis aims ............................................................................................................... 62

Chapter 5 Study 1. A systematic review and meta-analysis of language outcomes in autism spectrum disorder .............................................................. 66
  Abstract ................................................................................................................. 67
  Introduction .......................................................................................................... 69
  Methods ................................................................................................................ 71
    Inclusion/exclusion criteria .............................................................................. 71
    Types of studies ................................................................................................ 71
    Types of outcome measures .......................................................................... 72
  Search strategy for identification of studies ...................................................... 72
  Review of studies .............................................................................................. 73
  Quality Assessment ............................................................................................ 73
  Data management .............................................................................................. 74
  Statistical analysis ............................................................................................. 76
Results ..................................................................................................................... 77
  Search results .................................................................................................... 77
  Risk of bias assessment ...................................................................................... 81
  Language outcome measures ........................................................................... 85
  Characteristics of studies ................................................................................. 87
# Table of Contents

Participants ............................................................................................................ 150  
Measures ............................................................................................................... 150  
Procedures ............................................................................................................. 151  
Identification of subgroups ................................................................................... 151  
Outcome measures ................................................................................................. 153  
Predictor measures ................................................................................................. 153  
Statistical Analysis ................................................................................................. 154  
Results....................................................................................................................... 155  
   Individual trajectories ............................................................................................ 155  
   Trajectory types ..................................................................................................... 158  
   Mean trajectories ................................................................................................... 160  
Receptive-expressive language profiles ..................................................................... 164  
Predictors of receptive and expressive language outcomes at 7 years .................. 166  
Discussion ................................................................................................................. 168  

**Chapter 9 Discussion** ............................................................................................... 173  
   Summary of principle findings ................................................................................. 174  
   Communication trajectories from 1 to 2 years of age ............................................ 174  
   Language trajectories from 4 to 9 years of age ..................................................... 177  
   Language trajectories beyond 9 years of age ....................................................... 180  
   Predictors of language outcomes ............................................................................ 182  
   Expressive and receptive language discrepancy .................................................... 184  
   Children with ASD who are minimally verbal ..................................................... 185  
Strengths and Limitations ......................................................................................... 187  
   Methodology .......................................................................................................... 187  
   Sample ................................................................................................................ 190  
   Measures ............................................................................................................... 191  
   Loss to follow up .................................................................................................... 193  
Clinical implications .................................................................................................. 194  
Future directions ....................................................................................................... 197  
Concluding remarks .................................................................................................. 199  

**Bibliography** ....................................................................................................... 201  

**Appendices** ....................................................................................................... 226  
   Appendix A. Published article on regression in autism spectrum disorders .......... 227  
   Appendix B. Databases and search terms used for the systematic review .......... 232
# List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 1</td>
<td>Structure of the thesis by study, chapter and age investigated</td>
<td>xxvi</td>
</tr>
<tr>
<td>Figure 2</td>
<td>Simplified model of the causal pathways to ASD (adapted from, Loke, Hannan, &amp; Craig, 2015)</td>
<td>4</td>
</tr>
<tr>
<td>Figure 3</td>
<td>Model of factors that may interplay to predict language outcomes</td>
<td>45</td>
</tr>
<tr>
<td>Figure 4</td>
<td>Results of the literature search and study selection</td>
<td>78</td>
</tr>
<tr>
<td>Figure 5</td>
<td>Number of studies that used each type of language measure</td>
<td>85</td>
</tr>
<tr>
<td>Figure 6</td>
<td>Standard scores in receptive (a) and expressive syntax (b) at baseline and follow-up with 95% confidence intervals for studies using the MSEL and PLS</td>
<td>92</td>
</tr>
<tr>
<td>Figure 7</td>
<td>Random effects meta-analysis on seven studies using PLS or MSEL as a scoring system for receptive syntax outcomes</td>
<td>94</td>
</tr>
<tr>
<td>Figure 8</td>
<td>Random effects meta-analysis on seven studies using PLS or MSEL as a scoring system for expressive syntax outcomes</td>
<td>95</td>
</tr>
<tr>
<td>Figure 9</td>
<td>Combined receptive/expressive syntax language and receptive vocabulary language age relative to chronological age</td>
<td>96</td>
</tr>
<tr>
<td>Figure 10</td>
<td>Standard scores on the VABS at baseline and follow-up.</td>
<td>101</td>
</tr>
<tr>
<td>Figure 11</td>
<td>Random effects meta-analysis using VABS standard scores</td>
<td>104</td>
</tr>
<tr>
<td>Figure 12</td>
<td>Proportion of individuals with ASD were verbal aged ≤5 years (preschool) (a) and &gt; 5 years (b)</td>
<td>107</td>
</tr>
<tr>
<td>Figure 13</td>
<td>Proportion of individuals with ASD who used phrases (and longer) at baseline and follow-up</td>
<td>109</td>
</tr>
<tr>
<td>Figure 14</td>
<td>Inclusion and exclusion criteria.</td>
<td>128</td>
</tr>
<tr>
<td>Figure 15</td>
<td>Individual language trajectories from 4 to 7 years of children with ASD. Standard scores on the CELF are presented</td>
<td>157</td>
</tr>
<tr>
<td>Figure 16</td>
<td>Mean language trajectories (CELF standard scores) for male and female subgroups of children with ASD, TD, LI</td>
<td>162</td>
</tr>
<tr>
<td>Figure 17</td>
<td>Distribution of the receptive-expressive difference scores for non-ASD and ASD children at 4 (a) and 7 years (b)</td>
<td>165</td>
</tr>
</tbody>
</table>
List of Tables

Table 1  Co-occurring developmental, psychiatric, medical, neurological and genetic diagnoses (adapted from Levy et al., 2010) ........................................... 9
Table 2  Longitudinal studies of children 2 years and under at baseline .......... 43
Table 3  Longitudinal studies investigating predictors of language outcomes in ASD ........................................................................................................... 51
Table 4. Structure, aims and hypotheses of the thesis ..................................... 63
Table 5  Clinical information collected from included studies ...................... 74
Table 6  Studies with two or more publications and overlapping participants .... 79
Table 7  Risk of bias rating on included publications ................................... 82
Table 8  Language outcome domains and tools ............................................. 86
Table 9  Language outcome measures used by each study ................................ 88
Table 10  Key messages for clinicians ........................................................... 118
Table 11  Language and communication measures ....................................... 122
Table 12  Nonverbal IQ measures ................................................................. 124
Table 13  Social communication measures .................................................. 125
Table 14  Mean scores for the CELF-P and CELF-4 at each year the tool was administered ................................................................. 127
Table 15. Characteristics of those children with ASD included and not included in Study 3 .......................................................................................... 129
Table 16  Trajectory types (decline, maintain and accelerate) for children with ASD, LI and TD ................................................................. 159
Table 17  Predictors of language outcomes ................................................... 167
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD</td>
<td>Autism Spectrum Disorder</td>
</tr>
<tr>
<td>BPVS</td>
<td>British Picture Vocabulary Scales</td>
</tr>
<tr>
<td>CDI</td>
<td>MacArthur Bates Communicative Development Inventories</td>
</tr>
<tr>
<td>CELF-4</td>
<td>Clinical Evaluation of Language Fundamentals-Fourth Edition</td>
</tr>
<tr>
<td>CELF-P2</td>
<td>Clinical Evaluation of Language Preschool- Second Edition</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CSBS-ITC</td>
<td>Communication Symbolic Behaviour Scales-Infant Toddler Checklist</td>
</tr>
<tr>
<td>ELVS</td>
<td>Early Language in Victoria Study</td>
</tr>
<tr>
<td>EOWVT</td>
<td>Expressive One Word Vocabulary Test</td>
</tr>
<tr>
<td>EVT</td>
<td>Expressive Vocabulary Test</td>
</tr>
<tr>
<td>GEE</td>
<td>Generalised estimating equations</td>
</tr>
<tr>
<td>KBIT-2</td>
<td>Kaufman Brief Intelligence Test-second edition</td>
</tr>
<tr>
<td>LI</td>
<td>Language impairment</td>
</tr>
<tr>
<td>MSEL</td>
<td>Mullen Scale of Early Learning</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>Peds-QL</td>
<td>Pediatric Quality of Life Inventory 4.0</td>
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<tr>
<td>PLS</td>
<td>Preschool Language Scales</td>
</tr>
<tr>
<td>PPVT</td>
<td>Peabody Picture Vocabulary Test</td>
</tr>
<tr>
<td>RDLS</td>
<td>Reynell Developmental Language Scales</td>
</tr>
<tr>
<td>SCQ</td>
<td>Social Communication Questionnaire</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SDQ</td>
<td>Strengths and Difficulties Questionnaire</td>
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<tr>
<td>SEIFA</td>
<td>Socio-Economic Indexes for Areas</td>
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<tr>
<td>SICD</td>
<td>Sequenced Inventory of Communication Development</td>
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<tr>
<td>TD</td>
<td>Typical development</td>
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<tr>
<td>TOLD</td>
<td>Test of Oral Language</td>
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<tr>
<td>VABS</td>
<td>Vineland Adaptive Behaviour Scales</td>
</tr>
<tr>
<td>WASI</td>
<td>Wechsler Abbreviated Scale of Intelligence</td>
</tr>
</tbody>
</table>
## Glossary of Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adaptive language</td>
<td>Communication skills used to interact functionally with the environment</td>
</tr>
<tr>
<td>Communication</td>
<td>Expressive/receptive language and social communication (pragmatics and social interaction)</td>
</tr>
<tr>
<td>Developmental Delay</td>
<td>Development is delayed in two or more areas (e.g., IQ and language)</td>
</tr>
<tr>
<td>Expressive syntax</td>
<td>The ability to express structural language (e.g., using sentences, grammar and words). In the context of this thesis this term involves the expression of structural language more broadly i.e. beyond only vocabulary</td>
</tr>
<tr>
<td>Expressive vocabulary</td>
<td>The words that can be expressed</td>
</tr>
<tr>
<td>Language</td>
<td>Receptive and expressive vocabulary and syntax (words and sentences)</td>
</tr>
<tr>
<td>Language delay</td>
<td>Language that is slower to progress than typical language development but is not deviant in quality</td>
</tr>
<tr>
<td>Language disorder</td>
<td>Language that is deviant in trajectory and/or in quality compared with typical language development</td>
</tr>
<tr>
<td>Language impairment</td>
<td>Language that on formal testing is 1.33 standard deviations below the age-expected mean</td>
</tr>
<tr>
<td>Non-specific language impairment</td>
<td>Language and nonverbal IQ are below the average range</td>
</tr>
<tr>
<td>Receptive syntax</td>
<td>The ability to understand structural language (e.g., sentences, grammar and words). In the context of this thesis this term involves the understanding of structural language more broadly i.e. beyond only vocabulary</td>
</tr>
<tr>
<td>Receptive vocabulary</td>
<td>The words that can be understood</td>
</tr>
<tr>
<td>Social communication</td>
<td>Language that is used in social situations. Includes pragmatics and social interaction</td>
</tr>
<tr>
<td>Specific language impairment</td>
<td>Language is below the average range (-1.33 to -1.25 standard deviations below mean), nonverbal IQ is &gt;85</td>
</tr>
<tr>
<td>Minimally verbal</td>
<td>Children who use 30 words or less</td>
</tr>
</tbody>
</table>
Thesis outline

This thesis is divided into three sections. The first section provides a review of the literature on the epidemiology of ASD, communication development in children with and without ASD and predictors of language outcome. This section also reviews the literature on trajectories of language development (Chapters 1-3). The rationale and aims of the thesis are outlined in Chapter 4. Section 2 describes the methods and findings of the three main studies of the thesis, depicted in Figure 1. Study 1 is a systematic review of language outcomes and examines individuals with ASD across all ages (Chapter 5). Studies 2 and 3 utilise data from a community-based longitudinal study of language development, the Early Language in Victoria Study (Chapters 7-8). These studies examine trajectories of language development in children with and without ASD from 1 to 2 years (Study 2) and 4 to 7 years (Study 3). The thesis concludes with Section 3, which is a discussion of the main findings from the three studies. This final section outlines the clinical significance and implications of the findings from Studies 1-3 and highlights suggestions for future directions, specifically around recommendations for filling the evidence gaps (Chapter 9).

Figure 1 Structure of the thesis by study, chapter and age investigated
Setting

Studies 2 and 3 in this thesis included data from the Early Language in Victoria Study (ELVS). This is a longitudinal, community-based study of children living in Victoria, Australia. The ELVS has tracked the development of the children’s language (and related areas) from 8 months to 7 years of age and the children have been followed up almost yearly. A proportion of the 1910 children in the ELVS have been reported by their parents to have a diagnosis of ASD (n=44). Further details on the ELVS are provided in the methodology chapter (Chapter 6) and in the chapter relevant to the study (Chapters 7-8).

Methodological issues

The methods of each study are outlined chapter by chapter, however, since Study 2 and 3 both utilised data from the same broader study (ELVS) the methods were consistent. Rather than repeat the same methodology across several chapters, only the methods not described in the relevant chapter are outlined in the methodology chapter (Chapter 6).
Chapter 1  Autism spectrum disorder

Chapter 1 provides an overview of autism spectrum disorder (ASD). This chapter discusses the epidemiology (diagnosis, prevalence, causes) and the cognitive theories that have been proposed to explain the condition. The onset and development of the condition over the life course are also described, along with commonly associated co-morbidities.

Epidemiology of ASD

Diagnosis

Autism Spectrum Disorder (ASD) is a highly heterogeneous neurodevelopmental disability characterised by a dyad of impairments that include social communication difficulties and repetitive and restricted interests and behaviours (American Psychiatric Association, 2013). With each new edition of the Diagnostic Statistical Manual of Mental Disorders (DSM), attempts have been made to improve the reliability and validity of the diagnosis of ASD. However, ongoing debate about the validity of the current diagnostic criteria remains (Brignell, Morgan, Woolfenden, & Williams, 2014; Buxbaum & Baron-Cohen, 2013).

More recently there has been movement towards describing psychological and neurodevelopmental disorders such as ASD by their dimensions or cognitive profiles (Cuthbert, 2014; Cuthbert & Insel, 2013). For example, ASD could be described using the dimensions of social communication and repetitive behaviours. It has been argued that this approach will better facilitate the convergence of the genetic, environmental,
neurobiological, cognitive and behavioural factors involved in the development of ASD and move research into ASD beyond its current borders (Cuthbert, 2014).

**Prevalence**

The estimated prevalence of ASD has increased over the past two decades, with recent estimates from the United States being one in 68 children affected (Centers for Disease Control and Prevention, 2014) and estimates from Australia of around one in 50 (Randall et al., 2015). These slightly higher estimates from Australia may be due to the methods used to collect prevalence data (e.g., Randall et al., 2015 used parent-reported ASD rather than clinically confirmed cases). Males are around 4.5 times more likely to be identified with ASD than girls (Centers for Disease Control and Prevention, 2014). A number of factors are likely to have contributed to the increase in prevalence, including improved awareness of ASD, changes to the criteria used to diagnose ASD (e.g., DSM-5), diagnostic drift (e.g., children with intellectual disability now receiving dual diagnoses) and changes to funding specifically available for ASD in some countries (Coo et al., 2008; Hansen, Schendel, & Parner, 2015; King & Bearman, 2009; Lundstrom, Reichenberg, Anckarsater, Lichtenstein, & Gillberg, 2015; Polyak, Kubina, & Girirajan, 2015).

Along with the increase in estimated prevalence, there have been changes to the types of children diagnosed with ASD. In the 1980s it was estimated that 50% of children did not develop spoken language, or were considered nonverbal (Kobayashi, Murata, & Yoshinaga, 1992; Tager-Flusberg, Paul, & Lord, 2005). More recently, however, it has been estimated between 25 to 30% of children with ASD are not able to use words to communicate functionally (Norrelgen et al., 2014). Likewise, the proportion of children
with ASD and co-occurring intellectual disability has decreased over the years from around 80% in 1990s (Fombonne, 1999) to more recent estimates of around 33% (Connolly, Mackay, & Boyle, 2016). It has been hypothesised that greater awareness of the heterogeneity of ASD, as well as better detection of milder cases, may have contributed to these changes in profile (Keyes et al., 2012).

**Causes of ASD**

The exact cause of ASD is unknown although both genetics and the environment are thought to play a role (Chaste & Leboyer, 2012). To date standard genetic methods have not been able to identify autism-specific genes (Hallmayer et al., 2011; Krishnan et al., 2016), however with the emergence of more advanced analytic techniques promising, preliminary findings are emerging. A number of genes (e.g., SCN2A, STXBP1 TRIO, LRP1, CNTNAP2, 16p11.2) have been identified that have conveyed susceptibility to ASD however these genes have been implicated in other conditions such as schizophrenia, severe intellectual disability, epileptic encephalopathies, as well as ASD (Ciuladaite et al., 2011; Tager-Flusberg, 2015; Zhu, Need, Petrovski, & Goldstein, 2014).

Several putative environmental risk factors have been investigated during the pre- and postnatal period of development. While some risk factors have been associated with ASD (e.g., advanced parental age, gestational diabetes, prenatal medication use) their individual contribution to the development of ASD has been found to be small (Gardener, Spiegelman, & Buka, 2009). Given the complexity and heterogeneity of ASD, it is unlikely a single causative factor at the genetic, environmental, neurological
or cognitive level will fully explain the behavioural symptoms of ASD. Figure 2 shows a simplified theoretical model of the potential causes pathways to ASD.

Figure 2  Simplified model of the causal pathways to ASD (adapted from, Loke, Hannan, & Craig, 2015).

Social communication skills: mild________________________severe impairment

Repetitive, restricted interests: mild________________________severe impairment

+/- Associated difficulties and comorbidities (e.g. anxiety, language impairment, intellectual disability, attention deficit hyperactivity disorder, executive functioning difficulties)
Cognitive theories of ASD

A range of cognitive theories has been proposed to explain how the brain systems and pathways in individuals with ASD influence the behavioural characteristics of ASD (Baron-Cohen et al., 2011; Brunsdon et al., 2015; Brunsdon & Happe, 2014; Happe & Frith, 1996). Three major cognitive theories have been proposed: executive dysfunction, weak central coherence and theory of mind difficulties. Executive functions are cognitive processes such as attention and inhibitory control, working memory, problem solving and planning. Central coherence refers to the ability to understand context or ‘the big picture’. Theory of mind is the ability to attribute mental states such as beliefs and intentions to oneself and others. Around one third of individuals are reported to have multiple cognitive atypicalities in these three areas of cognition and a higher proportion of children with ASD experience difficulties in these areas relative to individuals without ASD (Brunsdon et al., 2015). However, difficulties with these cognitive functions are not a universal feature of individuals with ASD and none of the theories, individually or together, fully explain the behavioural manifestation of ASD (Brunsdon et al., 2015). More recently it has been suggested specific profiles of ASD may result from different combinations of these cognitive deficits. For example, theory of mind deficits may explain social communication behaviours, executive dysfunction may explain restricted and repetitive behaviours and interests and weak central coherence may explain the splintered profiles of strength and weakness that result from being detail focused (Brunsdon et al., 2015).
Onset, development and life course of ASD

Up until the last decade, ASD has traditionally been described as having two patterns of onset: regressive onset, which is a loss of previously acquired skills, and early onset, which is symptom emergence within the first year without a clear loss of skills (Stefanatos, 2008; K. Williams, Brignell, Prior, Bartak, & Roberts, 2015). In recent years, with the advent of high-risk sibling studies closely monitoring early development in younger siblings of children with ASD, more detailed descriptions of the onset of ASD and unfolding of symptoms have emerged. This research will be discussed in more detail in Chapter 2, under ‘Regression (loss) of communication skills’.

A systematic review of 42 studies that had investigated the average age of ASD diagnosis found mean age of diagnosis ranged from 38 to 120 months, even though the features of ASD may appear years prior to a diagnosis (Daniels & Mandell, 2014). In Australia, the mean age of diagnosis in children was around four years in children aged under seven (Bent, Dissanayake, & Barbara, 2015). ASD is described as a lifelong disability, yet a proportion of children with ASD will experience a change in the severity of their autism behaviours and some children may even “move off” the spectrum altogether, no longer meeting diagnostic criteria (Fein et al., 2013; Gotham, Pickles, & Lord, 2012; Perry et al., 2011; Sutera, 2010; Woolfenden, Sarkozy, Ridley, & Williams, 2012). The diagnosis of ASD is less stable for children who have been diagnosed younger and for children with fewer ASD symptoms (e.g., those with the previous diagnostic category of pervasive developmental disorder- not otherwise specified compared with autistic disorder) (Rondeau et al., 2011; Woolfenden et al., 2012).
Our knowledge about how ASD develops across the lifespan and the outcomes of individuals with ASD remains limited because few studies have followed children beyond childhood (Magiati, Tay, & Howlin, 2014). A systematic review of studies that have investigated long-term outcomes in ASD found outcomes to be highly variable between studies (Magiati et al., 2014). There was a reduction in severity of ASD symptoms over time in most studies included in the systematic review. However, some studies reported relative stability in language, IQ and adaptive functioning and others reported deterioration in ability over time (Magiati et al., 2014). Several studies of adults diagnosed with ASD found most were dependent on their families or alternate support services, few lived independently or had close friendships and communication and literacy difficulties were common (Howlin, Goode, Hutton, & Rutter, 2004; Howlin & Moss, 2012; Howlin, Moss, Savage, & Rutter, 2013). It is important to note that the aforementioned adult studies may not reflect the outcomes of individuals being diagnosed with ASD in more recent years. Ongoing changes to the diagnostic criteria and better identification of milder cases may result in different adult outcomes to those reported in currently published studies.

**Associated clinical features and comorbidities**

Children with ASD frequently have associated clinical features and co-occurring conditions. The prevalence rates of these co-occurring conditions in ASD vary according to the types of samples, with population based studies generally showing lower rates than clinical samples. In one clinically-derived study for example, 95% of individuals with ASD had three or more comorbid psychiatric disorders (Joshi et al., 2010). In another population-derived study, the prevalence of having at least one co-
A morbid psychiatric disorder was 70%, with at least 41% of individuals with ASD having two or more co-occurring conditions (Simonoff et al., 2008).

These co-occurring conditions may impact an individual’s participation, functioning and quality of life as significantly as the ASD symptoms. Furthermore, they may overlap with symptoms of ASD to the extent that they delay or prevent a diagnosis of ASD. Appropriate management of associated conditions is important and interventions are available, however further research is required to understand how effective these interventions are specifically for individuals with ASD (Joshi et al., 2010; Nadeau et al., 2011).

Some comorbidities now need to be specified when making a diagnosis of ASD under DSM-5 such as intellectual disability and language impairment (American Psychiatric Association, 2013). In this thesis we focus on the comorbidity of language impairment, which is one of the most common co-occurring conditions in ASD (Levy et al., 2010). A deeper understanding of how and why conditions such as language impairment and intellectual disability often co-occur with ASD and their genetic, neurobiological and behavioural overlap will be important in helping us understand ASD. The table below lists some of the co-occurring conditions associated with ASD.
Table 1  Co-occurring developmental, psychiatric, medical, neurological and genetic diagnoses (adapted from Levy et al., 2010).

<table>
<thead>
<tr>
<th>Developmental diagnoses</th>
<th>Language impairment, intellectual disability, sensory integration disorder, attention deficit hyperactivity disorder, learning difficulties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric diagnoses</td>
<td>Anxiety, oppositional defiant disorder, emotional disorder, mood disorder, visual impairment, tic disorders</td>
</tr>
<tr>
<td>Medical, neurological and genetic diagnoses</td>
<td>Epilepsy, encephalopathy, hearing loss, cerebral palsy, chromosome disorders, down syndrome, tuberous sclerosis, fragile X syndrome, velocardiofacial syndrome, neurofibromatosis</td>
</tr>
</tbody>
</table>

Summary

The diagnosis and estimated prevalence of autism spectrum disorder have changed over the past few decades. Along with these changes, there has been an abundance of theories around the neurobiological and neuropsychological underpinnings of ASD. Research into ASD has increased over the past decade and this has advanced our understanding of the condition, yet our knowledge about the causes, onset patterns and the way ASD develops across the lifespan remains limited. Further to this, our knowledge of how ASD interacts with co-morbid conditions such as language impairment, including how language develops over time in children with ASD, how different language development is to other children and what predicts which children will have better or worse outcomes remains very limited. In this context we need to identify opportunities for ways to improve our knowledge to facilitate important discoveries and improved support for individuals with ASD.
### Key points

Autism is a highly heterogeneous, lifelong condition

The cause of autism unknown but is likely to be a combination of the environment and genetics

The estimated prevalence of ASD has increased over past decade. A variety of factors has likely influenced this increase

An abundance of cognitive theories have tried to explain the characteristics of ASD but none fully explain the disorder

Onset of ASD can vary between individuals.

ASD is associated with a variety of adverse outcomes in adulthood

A high proportion of individuals with ASD have comorbidities such as language impairment and psychiatric disorders
Chapter 2  Communication development in autism spectrum disorder

Communication difficulties in ASD

Communication presents as one of the greatest challenges to children with ASD. It has been estimated that up to 63% of children have some difficulties with language development (Levy et al., 2010) and around 60% of individuals with ASD have accessed speech and language services (Pringle, Colpe, Blumberg, Avila, & Kogan, 2012). Observed problems with language development are often the primary reason for referral for diagnostic assessment (Chakrabarti & Fombonne, 2001; De Giacomo & Fombonne, 1998; Herlihy, Knoch, Vibert, & Fein, 2015; Noterdaeme & Hutzelmeyer-Nickels, 2010). Language impairment can result in a number of significant adverse sequelae even without the additional impact of social communication difficulties that are common in ASD. In ASD language difficulties can result in both primary effects from the initial neurobiological disruption and secondary effects that result from the child’s atypical ability to shape their learning experiences (Mundy & Jarrold, 2010). In other words, the effects of ASD can be additive or interactional with cumulative or even multiplied impact on outcomes.

To meet current ASD diagnostic criteria (DSM-5), children are required to have impairment in three areas within the social communication domain, namely: 1) the use of nonverbal communication, 2) developing and maintaining relationships and 3) social-emotional reciprocity. These social communication difficulties can vary considerably in type, severity and quality for each individual. In addition, a number of communication behaviours that were previously categorised under qualitative impairments in communication in DSM IV (American Psychiatric Association, 2000) have been re-
classified to the *repetitive and restricted interests and behaviours* domain. These
behaviours include stereotyped and repetitive speech, incessant questioning, echolalia,
reversal of pronouns and perseverative or tangential speech (American Psychiatric
Association, 2013).

While social communication difficulties are a defining feature in children with ASD, the
structural language skills (including vocabulary, use of grammar, syntax and
phonology) are remarkably variable. A substantial number of individuals with ASD
never develop the use of verbal (25%; Norrelgen et al., 2014) or fluent language (53%;
Wodka, Mathy, & Kalb, 2013), whilst others have well-preserved (or even superior)
language skills on formal testing (Bishop, 2003; Boucher, 2012; Kjelgaard & Tager-
Flusberg, 2001; Tager-Flusberg & Caronna, 2007). To this end, some researchers have
described this heterogeneity as a ‘structural language spectrum’ (Grzadzinski, Huerta, &
Lord, 2013).

**The long-term impacts of communication disorders for children with ASD**

Communication is an intrinsic human experience and an important life skill. Functional
language is a key ingredient for an individual to participate and function within his or
her family and community. There is consensus in the literature that early verbal skills
play a critical role in predicting long-term outcomes for children with ASD in areas
such as adaptive functioning, psycho-social adjustment and wellbeing (Billstedt,
Gillberg, & Gillberg, 2007; Gillespie-Lynch et al., 2012; Hofvander et al., 2009;
Howlin, Mawhood, & Rutter, 2000; Howlin & Moss, 2012; Howlin, Savage, Moss,
Tempier, & Rutter, 2014; Szatmari, Bryson, Boyle, Streiner, & Duku, 2003). Language
skills are critical to school placements and academic performance as well as the ability
to participate in social opportunities and have successful interactions with peers (Thurm, Lord, Lee, & Newschaffer, 2007; Venter, Lord, & Schopler, 1992).

Social communication impairments are a hallmark of ASD and have been associated with emotional and behavioural problems (Ketelaars, Cuperus, Jansonius, & Verhoeven, 2010), high rates of referral to educational psychology services (Mackie & Law, 2010) and difficulties forming adult relationships (Whitehouse, Watt, Line, & Bishop, 2009). Given social communication difficulties are central to a diagnosis of ASD, it is not surprising that studies comparing children with ASD to other neurodevelopmental disabilities such as specific language impairment and developmental delay, consistently report poorer outcomes for the children with ASD in areas such as general communicative competence, social engagement and quality of peer interactions (Mawhood & Howlin, 2000; Sigman et al., 1999).

Whilst the real-world impacts of communication disorders are clear, there is continuing debate over the aetiology and conceptual theoretical models of early social-communication and language development in ASD and whether the two are connected in some, if not all, individuals with ASD. In trying to disentangle this, it is important to understand the neurobiological mechanisms that may underlie the social communication and language impairments in ASD.

**Neurobiological underpinnings of communication difficulties in ASD**

In recent years high-risk younger siblings of children with ASD have been studied closely to gain a better understanding of the early development of ASD. These studies have indicated a broad range of predictors are likely to play a role in social
communication development in ASD. No primary theory of underlying cognitive deficit or neurobiological account in ASD has been able to account for the breadth of the findings (see Jones, Gliga, Bedford, Charman, & Johnson, 2014 for a review). This presents researchers with a substantial challenge trying to identify the neurobiological underpinnings of communication development in ASD. What follows here is an outline of some of the key areas of neurobiological investigation over recent years.

(1) Abnormal brain growth

This theory stems from findings of abnormal brain growth in some children with ASD within the first 2 years of life (Courchesne, Carper, & Akshoomoff, 2003). Abnormal early brain growth, as seen by measuring head circumference, is reported to particularly affect the frontal cortex and is associated with abnormal synaptic pruning (Courchesne et al., 2011; Rubenstein & Merzenich, 2003). It has been theorized that these abnormalities in brain growth may interfere with the normal progression of language, although the exact mechanism involved remains unclear. It is important to note that the findings have primarily come from one research group (Courchesne et al., 2003). To date increased head circumference is only reported in a subset of children with ASD (59%) and some healthy controls have also shown this increase in head circumference (6%). Moreover, a systematic review of early brain overgrowth and head circumference in ASD found inconsistent support for a subgroup of children with ASD who experience early brain overgrowth (Raznahan et al., 2013) and studies of high-risk siblings have found head growth to be uninformative as an ASD risk marker (Zwaigenbaum et al., 2014).
(2) **Over pruning hypothesis**

This hypothesis is an extension of a study that developed a neurocomputational model of the regressive subtype of ASD (M. S. Thomas, Knowland, & Karmiloff-Smith, 2011). M. S. Thomas, Davis, Karmiloff-Smith, Knowland, and Charman (2016) broadened their original study to include a more general version of the hypothesis to account for the heterogeneity in onset types and developmental trajectories (early onset, regressive onset and late onset) seen in ASD. This hypothesis suggests there is over-aggressive synaptic pruning in brain connectivity in infants with ASD, which is an exaggeration of normal pruning that occurs in infancy. The authors argue that trajectories of development (including language and social communication) in ASD may be explained by this single pathological mechanism. They propose unaffected siblings of children with ASD may inherit milder versions of the pathological mechanism or they may inherit risk factors without the pathological mechanism. The authors claim this hypothesis is consistent with findings from high-risk sibling studies and may explain why children with ASD do not show overt differences to those without ASD in the first few months of development (M. S. Thomas et al., 2016). This hypothesis is based on theory and computational modelling, not neurobiological findings and hence warrants further exploration and demonstration in humans.

(3) **Reduced connectivity in the social brain**

Findings of anomalies in the modulation of neural activity in the superior temporal sulcus (STS) in response to social stimuli have emerged from magnetic resonance imaging (MRI) studies in adolescents and adults (Pelphrey & Carter, 2008; Pelphrey, Shultz, Hudac, & Wyk, 2011). Further, functional MRI studies have shown that aberrant neural activity is associated with reduced functional connectivity between the “social
brain” areas (i.e. fusiform gyrus, superior temporal sulcus, prefrontal cortex) (Jann et al., 2015; Minshew & Williams, 2007; Pitskel et al., 2011). This has led to the theory that children with ASD may develop typically until this critical “interconnection”, required to facilitate normal social communication development and subsequent language development fails to progress.

(4) Reduced brain activity in response to speech

One study examined the development of language in infants aged 12-24 months by combining neurological and behaviour markers (Lombardo et al., 2015). Of the 60 children who went on to be diagnosed with ASD, 36 went on to develop age appropriate language and 24 were minimally verbal. Brain activity during speech tasks was assessed in infancy using functional magnetic resonance imaging (fMRI). The children’s development and behaviour was monitored every 6 months. This study found reduced brain activation on fMRI in response to speech, combined with behavioural markers of ASD, predicted later language outcomes with 80% accuracy. There was 68% accuracy when either measure was used alone. Most of the children with ASD who did not go on to develop language difficulties demonstrated similar patterns on the fMRI to the controls.

Parallel to these findings, it has been demonstrated in high-risk siblings that some children with ASD experience a heightened response to their name compared with typically developing children in the first 6 months of life followed by an under response to their name at around 12 months of age (Nadig et al., 2007; Yirmiya & Charman, 2010). It has been theorised that this abnormal response to name may be an early symptom of ASD and may mark the beginning of underlying language difficulties.
All four of the abovementioned neurobiologically informed accounts go some way to explain the regression in social communication development reported in a substantial minority of children with ASD. They also go some way to explain why the detection of clinical differences between children with ASD and those with typical development occurs after 12 months of age (Jones et al., 2014; Landa, Holman, & Garrett-Mayer, 2007; Macari et al., 2012; Szatmari et al., 2016; Zwaigenbaum, Bryson, & Garon, 2013; Zwaigenbaum et al., 2005).

At the present time the exact neurodevelopmental abnormality underpinning the different social communication and language trajectories in ASD remains unclear. It seems more likely that multiple, rather than one, mechanism will be at play and that this will explain some, if not most, of the heterogeneity between individuals. It is generally held that the social communication difficulties that emerge in early childhood are most likely to be related to the interactional effects of a combination of biological (including genetic) and environmental vulnerabilities and protective factors (Chaste & Leboyer, 2012; Krishnan et al., 2016; Rubenstein, 2010). These mechanisms may combine to produce disruption in the normal development of multiple systems in the brain, particularly those involved in social development and language (Happé, Ronald, & Plomin, 2006). Developing ways to identify these differences in a way that will benefit individuals will be the next challenge.

**Overlap between children with ASD and language impairment**

**Language impairment terminology**

There has been ongoing debate about the most appropriate terminology to use to identify children who present with language difficulties (Bishop, Snowling, Thompson,
Traditionally two main types of language impairment have been described in the literature: specific language impairment (SLI) and non-specific language impairment (NLI). Children with SLI are usually described as having delayed language (e.g., 1.25-1.33 standard deviations below the mean) and a nonverbal IQ of more than 85. Children with NLI are usually described as having delayed language (e.g., 1.25-1.33 standard deviations below the mean) and a nonverbal IQ below 85 (Bishop, Snowling, Thompson, Greenhalgh, et al., 2016; Reilly et al., 2014; Tomblin, Zhang, Buckwalter, & O'Brien, 2003).

More recently, the terms ‘language disorder’ and ‘developmental language disorder’ (specifically for children that have language disorder of unknown biomedical cause) have been proposed. It has been argued these terms better encapsulate the functional impairment of language disorder and its prognosis (Bishop, Snowling, Thompson, & Greenhalgh, 2016).

Alongside developing agreed terminology there have been attempts to gain consensus on the most appropriate criteria to use to identify language disorder (Bishop, Snowling, Thompson, Greenhalgh, et al., 2016). Through use of a Delphi survey which surveyed experts in the field, it was recommended that criteria for language disorder should include children with low nonverbal ability and not solely those with a verbal-nonverbal discrepancy. There were several rationales for this decision including that adaptive behaviour is equally as important as IQ but was not included in previous descriptions of SLI and furthermore, children with a verbal-nonverbal discrepancy do not respond differentially to intervention and they do not have unique language profiles (Bishop, Snowling, Thompson, Greenhalgh, et al., 2016).
In this thesis we use the term ‘language impairment’ to describe children with impaired language without intellectual disability. The decision to use this terminology was based on accepted terms at the time, before the abovementioned papers (Bishop, Snowling, Thompson, & Greenhalgh, 2016; Bishop, Snowling, Thompson, Greenhalgh, et al., 2016) were published.

Examining the way language develops in ASD has the potential to shed light on our knowledge about communication in the general population. Language difficulties are common to many neurodevelopmental disabilities and there is substantial overlap in features for young children with ASD, language disorder/delay and developmental delay (Ellis Weismer, Lord, & Esler, 2010; Kjelgaard & Tager-Flusberg, 2001; Lord, 1995; Paul, Chawarska, & Volkmar, 2008; Rapin, Dunn, Allen, Stevens, & Fein, 2009; Veness et al., 2012) as well as shared risk factors such as demographic, neurobiological and behavioural factors (Tager-Flusberg, 2016).

**Language impairment in children with and without ASD**

Traditionally language impairment and ASD have been considered to be aetiologically distinct with some describing the overlap as superficial and proposing distinct aetiological mechanisms, as evidenced by differences in cognitive and language profiles (Norbury & Sparks, 2013; L. J. Taylor, Maybery, Grayndler, & Whitehouse, 2013; Whitehouse, Barry, & Bishop, 2007; D. L. Williams, Botting, & Boucher, 2008).

An alternative account leading to the same conclusion, known as ‘phenomimicry’ has also been hypothesied (Bishop, 2010). Phenomimicry is when the causal pathways for one condition leads to an outcome resembling another condition. In ASD this would operate with ASD risk factors leading to language impairment as the consequence. As
such the language impairment in ASD can be thought of as different to that in children without ASD (Bishop, 2010).

Countering these hypotheses, some authors have argued specific language impairment is comorbid to ASD and children with language impairment are likely to be a specific subgroup of ASD with the two conditions sharing aetiological underpinnings (Kjelgaard & Tager-Flusberg, 2001; Tager-Flusberg, 2015). In support of this theory, children with ASD and co-occurring language impairment and children with specific language impairment were found to have similar patterns of performance in non-word repetition (a task usually difficult for children with language impairment) while children with ASD without language impairment and children with typical language development did not present with such difficulties (Tager-Flusberg, 2015).

Although some genetic and neurobiological evidence has suggested an overlap between specific language impairment and autism (D. L. Williams et al., 2008), this overlap has been challenged on the grounds that a generalized learning disability might contribute to the poor performance of lower functioning individuals with ASD leading to language impairment as assessed using standardized language measures (Boucher, 2012).

A notable distinction between ASD and other developmental disabilities is that social communication difficulties are central to ASD whereas in other developmental delays and language delays/disorders, social communication difficulties tend to be secondary, or consequential to language problems (Rice, Warren, & Betz, 2005). Admittedly, in both practice and research this is often hard to disentangle, especially if research is cross-sectional in type or when longitudinal research does not include early life.
Communication phenotypes in ASD

There are multiple described communication phenotypes of children with ASD emerging primarily from studies using cross-sectional methodologies (Loucas et al., 2008; Paul, Orlovski, Marcinko, & Volkmar, 2009; Rice et al., 2005; Tager-Flusberg, 2015; Tager-Flusberg & Caronna, 2007). In the interest of space these phenotypes will not be described in detail here, however a brief summary of the characteristics more typical of children with ASD follows. Further attention will be given to the first two characteristics later in this Chapter.

i. A profile where receptive language skills are more impaired than expressive language skills (Barbaro & Dissanayake, 2012; Charman, Drew, Baird, & Baird, 2003; Ellis Weismer & Kover, 2015; Ellis Weismer et al., 2010; Kover, McDuffie, Hagerman, & Abbeduto, 2013; Luyster, Kadlec, Carter, & Tager-Flusberg, 2008; Paul & Roth, 2011; Pickles, Anderson, & Lord, 2014; Volden et al., 2011).

ii. Regression (loss) in social communication and/or language around the second year of life (Baird et al., 2008; Barger, Campbell, & McDonough, 2013; Lord, Shulman, & DiLavore, 2004; Ozonoff, Williams, & Landa, 2005).

iii. Reduced use of gestures, especially to compensate for limited language (Charman, Drew, et al., 2003; Mundy, Sigman, & Kasari, 1990).

iv. Joint attention difficulties (initiating and responding) (Anderson et al., 2007; Charman, Baron-Cohen, et al., 2003; Mundy & Jarrold, 2010; Mundy et al., 1990).


Links between cognitive impairments and language

In addition to the above communication characteristics, cognitive impairments (specifically weak central coherence, difficulties with theory of mind and executive dysfunction) are reported to be more common in individuals with ASD (described in Chapter 1). Neuroconstructivist theories of development propose that one developmental domain can have a constraining or facilitating influence on other developmental domains. To this end, researchers have also attempted to understand how the cognitive impairments seen in individuals with ASD may be associated with communication and more specifically, language development (e.g., Baron-Cohen, Campbell, Karmiloff-Smith, Grant, & Walker, 1995; Charman et al., 2000; Pellicano, 2010a, 2010b, Tager-Flusberg & Joseph, 2005).

The topic of the link between language and theory of mind has grown substantially over the past two decades and the amount of research is far too great to cover comprehensively in this chapter of the thesis. Hence, a summary will be provided.

Theory of mind is understood to develop from early joint attention skills and has long been associated with pragmatic language ability, a core deficit for those with ASD (Tager-Flusberg & Joseph, 2003). However, some researchers have argued theory of mind may also have an important interaction with linguistic ability (e.g. syntax, grammar, semantics, narrative), which is often impaired in ASD. Evidence suggests the relationship between theory of mind and lexical and structural language may be more complex than previously thought (Tager-Flusberg, 2000, Pellicano, 2010). For example, Tager-Flusberg (2000) argues theory of mind is a prerequisite for learning language yet children with ASD also come to understand theory of mind by using their language.
skills. We are also yet to fully understand how different aspects of theory of mind and language interact during different developmental periods. In order to do this longitudinal studies are required so relationships can be studied over time. One longitudinal study of language, theory of mind and adaptive functioning (n=39) found theory of mind mediated an association between language and adaptive functioning but did not mediate social skills and adaptive functioning in children with ASD and IQ>70 (Bennett et al., 2013).

Studies have also investigated the relationship between executive dysfunction and language in ASD. To date, despite both structural language difficulties and executive dysfunction being common in ASD, studies are yet to find a clear and direct association between the two domains (Robert, McGrath & Tager-Flusberg, 2005). It has been proposed the co-occurrence of these two conditions may be related to common genetic factors that produce the neuropathology (Robert, McGrath & Tager-Flusberg, 2005).

The link between language and central coherence (the processing of local information compared with the whole) has been explored, mainly in relation to understanding the cognitive differences between children with language impairment and those with ASD. On the whole, children with language impairment and no ASD have been found to have relatively better ability in processing the whole picture rather than detail, an opposite pattern to children with ASD with and without language impairment (L. J. Taylor, Maybery, Grayndler, & Whitehouse, 2013). One might expect if there was a link between language and central coherence some differences would be seen between children with ASD with language impairments and those without language impairments. In studies to date these two groups of children have not performed significantly differently on central coherence tasks (L. J. Taylor, Maybery, Grayndler, &
Whitehouse, 2013). Further research will be required to elucidate conclusively whether there is a relationship between language and central coherence in ASD.

In addition to the above specific cognitive abilities, children with ASD are described as having difficulty with tasks that involve abstract or symbolic concepts and the use of language to infer meaning from a situation (Brunsdon et al., 2015; Happé & Frith, 2006). From these findings we may infer that language and some, perhaps particular and specific, cognitive impairments are closely linked but the nature of this relationship is yet to be established and the centrality of language difficulties remains unclear.

**Regression (loss) of communication skills**

As well as enhancing our understanding of the interrelation of early social communication and language domains, studies that have closely monitored development from infancy also have the potential to shed light on the phenomenon of regression that is reported to occur in around 30% of children with ASD (Barger et al., 2013). Regression in ASD is typically defined as the loss of skills that have been previously established (most commonly this loss involves language and social skills). The onset of regression has been reported to occur usually around 2 years of age in children with ASD (Lord, Shulman, et al., 2004; Stefanatos, 2008; Thurm, Manwaring, Luckenbaugh, Lord, & Swedo, 2014).

While not pervasive in ASD, regression has rarely been reported to occur in other types of common neurodevelopmental disorders such as language disorder and idiopathic developmental delay (Baird et al., 2008; Lord, Shulman, et al., 2004; Pickles et al., 2009), although these studies have been limited by a lack of comparison groups with
information collected prospectively. There are some rare metabolic and neurological conditions that involve the loss of skills with biological mechanisms that are well understood (e.g., Landau-Kleffner syndrome, infantile spasms).

The way regression had been described in the literature has evolved over time. By far the most common description has been by dichotomous categories (regression being present or absent) using questions from the Autism Diagnostic Interview (ADI; Barger et al., 2013). However, over the years other ways of describing the onset of regression have been proposed. For example, Shumway et al. (2011) has argued that 4 categories may be a more useful way to describe the onset of regression (plateau; delay prior to 12 months then loss; no delay prior to 12 months then loss; and early onset).

High-risk sibling studies have reported regression to be far more common and widespread across developmental skills than originally thought (Ozonoff et al., 2010) and some have described loss of skills as a ‘process’ rather than a single event (M. S. Thomas et al., 2016). A continuum of onset has been proposed where some children experience substantial, catastrophic regression and others far less loss of skills or no skill loss at all (Chawarska, 2016; Landa, Gross, Stuart, & Faherty, 2013). Findings from high-risk sibling studies have described the onset of regression as variable and gradual in the majority of children with a dramatic loss of skills occurring only in a minority (Bryson et al., 2007; Landa et al., 2007; Lord, Luyster, Guthrie, & Pickles, 2012; Ozonoff et al., 2010; Rozga et al., 2011). Very recent research has also identified a ‘recovery group’ of children who show early signs of ASD in the first 18 months followed by a reduction of ASD symptoms over time (Chawarska, 2016), implying potentially protective factors in this subgroup of children or different underlying biological mechanisms.
More recently studies have started to investigate loss and gain of different components of communication skills. Loss of eye contact and gaze to faces has been reported to be the most common social communication skill lost in a number of retrospective studies e.g., Ozonoff et al. (2005). Eye gaze, social interest, shared positive affect, smiling and initiating interactive games have shown declining trajectories in prospective high-risk sibling studies (Landa et al., 2013; Landa et al., 2007; Ozonoff et al., 2010) and word loss, although it occurs, was found to be less common than social skill loss (Landa et al., 2013; Ozonoff et al., 2010).

One of the primary reasons for slow progress in our understanding of regression is the limited methodologies that can be applied to study regression. The most widely published means of studying regression has been retrospective parent report. This method relies heavily on the accuracy of parents reporting on an event that may have occurred several years prior the child’s diagnosis. In particular the accuracy of parent report has been found to be quite low compared with direct observation in the area of social communication development (Ozonoff et al., 2010) and a ‘telescoping effect’ has been reported to occur when there has been a substantial period of time between the event and recall of the event (Lord, Shulman, et al., 2004)

Retrospective home video footage has also been used to study regression and has the advantage of allowing direct observation of skills. However, this method also has limitations. For example, the footage tends to be bookended by special events and may not represent situations that allow assessment of the full picture of ASD.

High-risk sibling studies are probably the most promising for studying regression because they are able to closely monitor very early development in children who later
go on to receive a diagnosis of ASD. However, sibling studies also have a number of methodological limitations. It has been argued, for example, that growing up with an older sibling with ASD may create a different environment to growing up with typically developing siblings and there is evidence the phenotypes of high-risk children are different to other children with ASD, including those later diagnosed (Pandey et al., 2008; Pinto et al., 2010; Sebat et al., 2007; L. J. Taylor et al., 2015). Further detail on regression in ASD in the form of a review co-authored by the author of this thesis is provided in Appendix A.

To date only four published studies have prospectively studied regression in ASD from infancy (Bryson et al., 2007; Landa et al., 2007; Ozonoff et al., 2010; Rozga et al., 2011) and the majority of participants in these studies have been high-risk siblings with ASD.

Community-based studies where children’s social and communication development have been monitored since infancy, and where parents can report concurrently on skills as they are observed without yet knowing their child’s developmental outcome, offer a useful supplement to high-risk studies on regression. Community-based studies are likely to provide a more representative picture of children with ASD as they contain children who are at high-risk of ASD, as well as those without a family history of ASD.

**Receptive-expressive language discrepancy**

There has been mixed evidence about whether children with ASD have a relative weakness in receptive compared with expressive language. Some authors propose this discrepancy may be a characteristic of ASD (Hudry et al., 2013) and others have
reasoned receptive language difficulties may more reflect the reduced overall social responsiveness in ASD rather than specific language processing deficits (Tager-Flusberg, 2015, 2016). Findings from previous studies on the topic have not been definitive mainly due to heterogeneous methodology including different language measures, age ranges and few studies using clearly-defined comparison groups within the same cohort.

Three studies have made direct comparisons with children who have typical development. Of these, two used parent report measures (Charman, Drew, et al., 2003; Hudry et al., 2010) and one used measures of receptive/expressive vocabulary (Kover et al., 2013). An additional study compared children with ASD with developmentally delayed children (Ellis Weismer et al., 2010). To our knowledge, no studies have compared receptive-expressive language discrepancy in children with ASD to large groups of children with typical development and language impairment using a comprehensive measure of language.

Studies of children with ASD under 4 years using direct assessments of language (Ellis Weismer & Kover, 2015; Ellis Weismer et al., 2010; Luyster et al., 2008; Mitchell et al., 2006; Volden et al., 2011) and parent report tools (Hudry et al., 2010) have consistently reported discrepancies between mean receptive and expressive language scores, although not all children with ASD demonstrate this characteristic (e.g., only 30% of children in Hudry et al., 2010 reported a significant gap between receptive and expressive language).

Studies of children with ASD aged between 4-14 years have noted less consistent differences between receptive and expressive language on vocabulary in children with
ASD (Kjelgaard & Tager-Flusberg, 2001; Kover et al., 2013) with the latter of these two studies reporting 18% of children with ASD had significantly lower receptive than expressive vocabulary scores compared with 8% of children with typical language development showing the same profile. There has been some suggestion that the gap between receptive and expressive vocabulary may grow larger with increasing nonverbal IQ ability, although this finding has yet to be replicated (Kover et al., 2013). The receptive-expressive discrepancy also appears to depend on the type of tool used to assess language, with some studies finding a discrepancy on direct formal assessments administered by clinicians but not on parent report measures such as the MacArthur Communicative Development Inventories (Ellis Weismer et al., 2010; Luyster, Qiu, Lopez, & Lord, 2007). A meta-analysis of studies investigating receptive-expressive language studies (n=74) found that although some children demonstrated this discrepancy there was no evidence of an expressive advantage over receptive language in children with ASD (Kwok, Brown, Smyth, & Oram Cardy, 2015).

Relative receptive language weakness profiles have been identified in some subgroups of children with specific language impairment (Conti-Ramsden, St Clair, Pickles, & Durkin, 2012) suggesting this profile is not unique to ASD. Also, there have been reports with subgroups of children with ASD, language impairment and typical development that share common features in their language profiles (Kover et al., 2013; Tager-Flusberg, 2006; Tomblin, 2011). Without large samples of clearly delineated children with typical development and language impairment within the same cohort, the specificity of the receptive-expressive discrepancy to ASD remains unclear.
Children with ASD who fail to develop verbal speech

A subgroup of children with ASD remain minimally verbal (use less than 30 words) throughout childhood (Norrelgen et al., 2014; Tager-Flusberg & Kasari, 2013). Theories that have tried to explain the phenomenon of lack of speech have included: a failure of cognitive ability; a more specific failure of symbolic capacity; failure to understand the value of communication or a lack of motivation to communicate; social communication deficits that impact the ability to learn language; failure to develop affective bonds that lead to a desire to communicate and lastly, an apraxic deficit in speech motor planning (Anderson et al., 2007; Kasari, Brady, Lord, & Tager-Flusberg, 2013; Paul, Campbell, Gilbert, & Tsiouri, 2013; Pickett, Pullara, O'Grady, & Gordon, 2009; Shriberg, Paul, Black, & van Santen, 2011). Research to prove or disprove these theories has failed to produce conclusive answers, likely due to methodological constraints in studying such complex, highly interactive domains.

The source of the failure to develop functional verbal communication has fundamental implications for the type of intervention approach engaged. A child with apraxia may benefit from a speech intervention, a child with poor symbolic capacity will need intervention focused on building these skills (e.g., Kasari, Paparella, Freeman, & Jahromi, 2008).

While attempts are made to understand the causal underpinnings of children with ASD who remain minimally verbal, empirical research which examines the phenotypes of those children who benefit from certain interventions and those who don’t will also be important (Paul et al., 2013; Trembath & Vivanti, 2014). Furthermore, elucidating the genetic underpinnings for specific speech and language disorders and their neurological
bases will inform which children are more at risk of not developing speech and the most appropriate approach for these children, whether it be specific strategies for speech or augmentative communication options. In addition to informing intervention and prognosis, such findings will assist us to understand the theories and mechanisms that may be at play in preventing the development of language.

Prior to the past 5 years children who were minimally verbal were often neglected from research, in part because there were not adequate tools to assess them and they did not respond to interventions as other children might. The establishment of a special workshop on the topic of minimally verbal children with ASD organised by the National Institutes of Health (National Institute of Health, 2010) has seen a flurry of research into language development specifically dedicated to these children (e.g., Kasari et al., 2014; Paul et al., 2013; Tager-Flusberg & Kasari, 2013; Thurm, Manwaring, Swineford, & Farmer, 2015).
<table>
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<tr>
<th><strong>Key points</strong></th>
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<tr>
<td>Language difficulties occur in around 60% of children with ASD</td>
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<tr>
<td>There is substantial heterogeneity in language ability in ASD</td>
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<td>It remains under debate whether language impairment is part of the cognitive/language profile in ASD or whether it is a co-occurring condition with ASD.</td>
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<tr>
<td>Language ability in childhood is an important predictor of long term outcome in a range of areas such as employment, social relationships and adaptive functioning</td>
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<tr>
<td>A range of neurobiological explanations has been proposed to explain ASD but none have fully been able to explain the condition</td>
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<tr>
<td>It has been proposed that some aspects of communication development appear to be more characteristic of ASD than other conditions including relative weakness in receptive versus expressive language and loss of communication skills in the first few years of life.</td>
</tr>
<tr>
<td>Up to 30% of children with ASD remain minimally verbal. The reasons why some children with ASD do not develop verbal language is yet to be explained.</td>
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Chapter 3  Communication trajectories

ASD is a spectrum of behaviours and to understand communication development in ASD in its entirety it is also important to understand communication development in children without ASD.

Social communication development in children with and without ASD

It has been known for some time that early social-communication skills play an important role in the development of language in typically developing children (Bates, Benigni, Bretherton, Camaioni, & Volterra, 1979; Carpenter & Nagell, 1998; Charman et al., 2000; Mundy, Henderson, Inge, & Coman, 2007; Tomasello & Farrar, 1986). Specifically, Bates et al. (1979) have argued that symbolic capacity may lay the foundations for early joint attention, imitation and play to subsequent language development. Social communication skills undergo particularly rapid development between one and two years of life (Carpenter & Nagell, 1998; Crais, Douglas, & Campbell, 2004).

Moreover, children who are typically developing show relatively predictable patterns of emergence of social cognition in the early years of life. In a study by Carpenter et al. (1998) joint engagement, communicative gestures, attention following, imitative learning and referential learning were found to follow in sequence in the majority of typically developing children (87%). Such patterns were also seen in the majority of children with developmental delays (90%). The remaining children tended to have less predictable patterns of development.
While social cognition appears to be an equally important predictor of language outcomes for children with ASD (Brooks & Meltzoff, 2008; Charman, Baron-Cohen, et al., 2003; Mundy et al., 1990), some studies have shown that the development of such skills is highly variable in ASD and that they do not develop chronologically or predictably in the same way that they do in typically developing children. For example, using similar methods as those used with typically developing children, Carpenter, Pennington, and Rogers (2002) found that only 50% of children with ASD followed the same pattern of emergence.

Rather, the children with ASD tended to develop skills in an alternate order: imitative learning, referential language, joint engagement, attention following and communicative gestures. Carpenter et al. (2002) argued that such findings may go some way to explain why some children with ASD learn language differently to typically developing children. For instance, children with ASD may use imitation as an alternate route to learning words (i.e. to learning via social interaction, symbolism, joint attention and toddler equivalents of theory of mind/executive function) and this may explain why many children have extensive vocabularies but lack an understanding of the meaning of these words or how to use such words within a social context (Carpenter et al., 2002; Rogers & Pennington, 1991).

It is worth noting that the Carpenter et al. (2002) study had a number of limitations, including that: the children studied were 4 years of age on average, well beyond the age many of the early social-communication skills are expected to develop; the study was cross-sectional in design which makes the assumption that cross-sectional results which represent one point in time reflect developmental patterns; there were potential problems with the way tools were used to assess skills in children with ASD (e.g., not
all children were able to complete all tasks and there were ceiling and floor effects), a broad range of ages were included and the sample size was small. While these factors limit interpretation and generalization of the findings, the study was an important first step towards understanding the developmental sequence of the emergence of and interrelation of social communication in children with ASD compared with other populations.

Since the publication of Carpenter et al. (2002) limited progress has been made regarding our understanding of the sequence of development of early social-communication skills in ASD relevant to language growth (Pry, Petersen, & Baghdadli, 2009; Thurm et al., 2007). Most studies that have tried to investigate early social communication development have reported on individual skills rather than the interrelation of multiple skills (Dereu, Roeyers, Raymaekers, & Warreyn, 2012). Some authors have described the core early communication skills such as imitation, joint attention and play as “interactive competencies” (Pry et al., 2009).

Other authors have speculated from their findings that joint attention and imitation may be an important “starter set” of skills that lay the foundation for later language development, and that representational skills such as play and deferred imitation are important in helping children extend their language once it has started to develop (Toth, Munson, Meltzoff, & Dawson, 2006). In infants at high and low risk for ASD, response to joint attention at 15 months has been found to mediate the association between motor imitation at 12 months and expressive vocabulary at 18 months (Edmunds, Ibanez, Warren, Messinger, & Stone, 2016). A recent longitudinal study examining the associations between social and language pathways in preschoolers with ASD (time of diagnosis) found a pattern where the two domains appeared strongly associated at time
of diagnosis but appeared to become more independent over the following 12 months (Bennett et al., 2015).

In the past five years, a small number of longitudinal studies has begun to investigate individual trajectories of social communication behaviours in children with ASD. This allows the examination of how such skills may relate to each other and the sequence of development (Dereu et al., 2012; Paparella, Goods, Freeman, & Kasari, 2011). Paparella et al. (2011) assessed the sequence of development in a range of social communication domains in 53 children with and without ASD aged 12 to 60 months. This study had findings that were largely consistent with those of Carpenter et al. (2002) in that the children with ASD were found to acquire joint attention skills in a different sequence to typical children. For example, following eye gaze, which usually emerges mid-sequence for typically developing children, was the last nonverbal skill to emerge in children with ASD. The skill of showing was also found to develop later in children with ASD in this study compared with typically developing children. Interestingly, there was no difference between children with ASD and typical development in nonverbal requesting gestures.

Dereu et al. (2012) studied a range of domains of development in toddlers with ASD compared with children who were typically developing. In this study the sample size was small (n=9) which limited the conclusions that could be drawn but in general Dereu et al. (2012) found that there was great variability in skill development even within individuals (i.e. different skills developed at different paces), particularly in the skill of imitation. Likewise, several other studies have found variability in trajectory for different aspects of social communication such as gesture compared with use of eye contact (e.g., Lord, 2014; Thurm et al., 2014). Interestingly, Dereu et al. (2012) also
noted substantial variability between children with ASD with some demonstrating a deviant trajectory and others demonstrating a delay in development. Much work is still to be done in this area in terms of describing the development of, and interrelation of early social communication skills and language.

**Language development in children with and without ASD**

**Language development in children without ASD**

Trajectories of language development in pre-school aged children are considerably variable (Reilly et al., 2010; Rice, Taylor, & Zubrick, 2008; Ukoumunne et al., 2012) and prediction of language outcome is especially difficult in children aged under 3 years. In one study around 70% of late-talking 2 year olds (without comorbid developmental conditions) had ‘caught up’ by 4 years of age (Reilly et al., 2010). Other studies report similar findings, estimating around 75% of late-talkers demonstrate language within the normal range on standardised language testing by 3 years (Rice et al., 2008; Roos & Weismer, 2008). However, there are some reports late-talkers have weaker language than non-late-talkers throughout childhood and are at greater risk for difficulties with literacy and high-order language tasks (Rescorla, 2005, 2009).

There has been wide variability in findings on the persistence of language outcomes with a review of published studies reporting between 11-92% of children had ongoing language difficulties (Tomblin et al., 2003). In a sample of 196 kindergarten children Tomblin et al. (2003) found 66% of children with receptive-expressive delays had persistent language impairment after 2 years and 62% after 4 years. Among children with NLI 75% had persistent language impairment after 2 years and 67% after 4 years.
Another study found 92% of children with SLI at 6 years of age remained language impaired after one year and 88.5% remained after 4 years when children were 11 years of age (Conti-Ramsden & Botting, 1999; Conti-Ramsden, Botting, Simkin, & Knox, 2001). In a large population-based study of younger children conducted in Norway (n=10,587) 3%, 5% and 6.5% of the children demonstrated persistent, transient and late-onset language impairment, respectively from 3 to 5 years (Zambrana, Pons, Eadie, & Ystrom, 2014). A number of factors may have produced the variability in study findings. This includes the age at which children were assessed, type of sample (e.g. population versus clinical sample) and criteria used to define language impairment.

When language ability has been investigated in more detail, different growth trajectories have been found for different language domains. For example, different trajectories on specific language measures such as grammatical markers (e.g., verb tenses) have been explored. In one study it was found children with and without SLI demonstrated similar developmental trajectories for specific language abilities with both groups experiencing periods of acceleration over time (Rice, Wexler, & Hershberger, 1998). In a later study Rice, Redmond, and Hoffman (2006) found no difference in trajectories of growth in mean length of utterance between children with and without SLI over 5 years. The finding that language trajectories in school aged children tend to be more stable and predictable (i.e. children retain their language status) than preschool children has been described in several studies (Law, Tomblin, & Xuyang, 2008) and it has also be found children with SLI follow a similar developmental pattern to typically developing children (e.g., Beitchman et al., 1996; Johnson et al., 1999; Law et al., 2008; Rice, 2004; Rice et al., 1998; Tomblin et al., 2003).
Consistent with the above findings, Law et al have proposed that despite children with SLI having lower scores than typically developing children, they tend to track in parallel over time. In other words they maintain the same rate of progress. In their study of 184 children with SLI followed at 3 time points (7, 8, and 11 years), children with SLI developed at a similar pace to typically developing children over time, regardless of subgroup (e.g., combined receptive-expressive language delay, expressive language delay only etc.). In this study the majority of children demonstrated stability and predictability in receptive language growth. Although some children did fall behind and others caught up, there was an overall pattern of language growth and consistency. The primary difference between children was not their trajectory of development but their initial severity of language impairment (Law et al., 2008).

Finally, trajectories of language development have been examined in a large sample of children with a history of SLI (n=242) from 7 to 17 years (Conti-Ramsden et al., 2012). Trajectories were examined for the whole group and a multidimensional approach involving a variety of language and cognitive measures was used to ascribe subgroups. There was variability in language ability and seven subgroups were identified based on language functioning. Expressive language was found to be more stable in growth than receptive language, which accelerated from 7 to 8 years of age. On the whole, the majority of children with SLI had stable language growth regardless of subgroup over the 10 year period (Conti-Ramsden et al., 2012), consistent with findings from previous studies (e.g., Law et al., 2008).

Several studies have now shown children with more severe delays and those with delays in more than one module (e.g., combined receptive and expressive delay or lower nonverbal IQ) have more persistent impairments than children with specific deficits.
(Beitchman et al., 1996; Bishop & Edmundson, 1987; Cole, Schwartz, Notari, Dale, & Mills, 1995; Tomblin et al., 2003). Other studies have reported accelerated language development in some subgroups such as preschool aged children (Bishop & Edmundson, 1987).

**Language development in ASD**

Studies that have investigated language outcomes in children with ASD are not discussed in detail here but are presented in Chapter 5 (systematic review). The exception to this will be studies that have examined individual trajectories and studies that have followed children in first few years of life. This is because few studies of children under 2 years met inclusion criteria for the systematic review due to their small sample sizes and the methods used in studies investigating individual trajectories have informed the methods used in this thesis.

**(1) Individual language trajectories in ASD**

The vast majority of studies that have examined language trajectories have attempted to develop subgroups (or classes) of children or have presented information on the group as a whole using mean scores (e.g., Landa, Gross, Stuart, & Bauman, 2012; Pickles et al., 2014). While this may have been appropriate 30 years ago when children diagnosed with ASD were, perhaps, more homogeneous, there has been increasing dissatisfaction with this approach because it fails to capture important individual differences in children with ASD (Dereu et al., 2012). We know that children with ASD have vastly different trajectories of development (Baghdadli et al., 2012; Chawarska, 2016; Lord et al., 2012). Some children regress in their development, some make gradual
improvements and others may demonstrate dramatic improvement (Anderson et al., 2007).

When groups are combined to form a mean trajectory we lose the nuanced differences in development. In fact, the individual variability in children with ASD may indeed be the most telling and interesting aspect of development. A number of studies have been published over recent years that have reported on individual trajectories of language and social communication development (Anderson, Oti, Lord, & Welch, 2009; Dereu et al., 2012; Lord et al., 2012; Paparella et al., 2011). It is hoped that by examining individual trajectories a more detailed picture of development and the heterogeneity in ASD can be better understood and clinically meaningful subgroups formed that may assist in tailoring interventions and prognostication. However, reporting individual trajectories is still new to the literature on ASD and to date no clear patterns have emerged, other than substantial variability in language ability and direction of change.

(2) Longitudinal studies of children with ASD from infancy

Five studies have prospectively investigated communication trajectories in children under 2 years of age (Barbaro & Dissanayake, 2012; Landa et al., 2012; Lombardo et al., 2015; Lord et al., 2012; Paul, Chawarska, Cicchetti, & Volkmar, 2008). In all but two of the aforementioned studies children had their ASD diagnosis confirmed at 3-5 years of age. Barbaro & Dissanayake (2012) and Lord et al., (2012) were the exceptions and these studies provided a best estimate diagnostic status at 24 months and 30 months respectively.

Landa et al. (2012) found that changes in development were not evenly distributed across the time span and that children tended to have periods of accelerated growth and
slow growth at different periods during development. Lord et al. (2012) found the children with ASD fitted different 4 verbal trajectories classes based on social and language development (severe persistent (21%), worsening (21%), improving (19%) and nonspectrum (40%)). Interestingly, in this study few children experienced actual loss of skills (regression) although a number of children did plateau in their development and therefore appeared to be worsening relative to age norms.

Behavioural measures were described separately for those with good and poor language outcomes in one study. In this study the children in each language group (n=36 good n=24 poor) demonstrated improving or declining trajectories respectively based on standard scores over time (Lombardo et al., 2015). This study did not investigate regression of communication skills. Lastly, standard scores on a language tool were found to increase over time in a study of children with ASD aged 15-25 months at baseline and followed for 2 years (Paul, Chawarska, Cicchetti, et al., 2008). Table 2 shows further detail on studies that have investigated children with ASD aged 2 years and under at baseline. There are several limitations that apply to studies that that have included children who have been diagnosed under 3 years. In addition to a diagnosis of ASD being less stable and reliable in younger children (Woolfenden et al., 2012), the autism symptoms in these children are likely to be more severe. Hence the study may not include children who have milder symptoms and therefore may not be representative of the broader population of children with ASD.
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<th>Author</th>
<th>Relevance</th>
<th>Overall findings</th>
<th>Comments</th>
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<tr>
<td>Barbaro (2012)</td>
<td>Community-based study</td>
<td>Enrolled at 12, 18 and 24 months and measured at each time point. Diagnosed ASD: 24 months.</td>
<td>Used MSEL to measure language. Mean receptive language scores found to be lower than expressive language scores at 12 and 18 and 24 months for ASD. Children with AD had lower mean scores, followed by children with ASD and children with developmental delay/language impairment at 12, 18 and 24 months. At 18 months there were significant difference between ASD, AD, DD/LI for receptive and expressive language ability. Small sample size at lower age levels limits interpretation of change over time. Diagnosis performed when children young so may be less stable/reliable. 12 months ASD n=9; 18 months ASD/AD n=37 DD/LI n=8; 24 months AD/ASD n=79, DD/LI n=20</td>
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<tr>
<td>Landa (2012)</td>
<td>Assessed at 27 months, 35 mo., 41mo., 72 mo.</td>
<td>Enrolled &lt;2 years Multiple time points measured Diagnosed ASD: 21-33 months</td>
<td>A significant mean increase in communication scores was found between 27 and 35 and 41 and 72 months. No difference was found between 35 and 41 mo. However, mean overall gains in communication found between 27 mo. and 72 mo. were large. Changes in trajectory were not evenly distributed across the time intervals. Trajectories taken over a period of short-term intervention. Study unclear regarding details of this intervention. No comparison group</td>
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<tr>
<td>Lombardo (2015)</td>
<td>ASD n=60, DD/LD n=19; TD n=24</td>
<td>Enrolled at mean age &lt;2 years. Diagnosed ASD: 3-4 years. Followed every 6 mo. for one year</td>
<td>Divided children into ‘poor’ and ‘good’ outcome. Behaviour measures (language adaptive behaviour and ADOS) and fMRI findings taken early in development predicted language outcome with 80% accuracy. Variable trajectories seen. Children in poor group had lower standard scores at follow up and those in high group had higher standard scores. Combined mean for whole cohort showed improved standard scores but not significant ‘catch up’. Interventions received unclear. Did not report on ‘loss of skills’. Used two comparison groups (TD/DD) but don’t describe how recruited/ language characteristics. Do not describe loss to follow up. Used MSEL at outcome, not a specific language tool.</td>
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<td>Lord (2012)</td>
<td>Enrolled&lt;2 years. Assessed using diagnostic instruments every visit (6 monthly). Variety of measures taken prospectively. Investigates regression.</td>
<td>Used MSEL to measure language. Four trajectory classes. About one third of children consistently showed clear severe and persistent deficits in social-affect from 12–36 months- slower gains in receptive and expressive language skills than the improving group. Second group improved in social-affect and improved more in verbal (both receptive and expressive language) skills compared with the severe persistent group. Early ADI-R scores didn’t differentiate between these trajectory classes. Worsening group not differentiable from severe persistent group or the improving group by change in language scores. Some children in the worsening and severe persistent group and some in the DD group made little/no progress in language over 2 years.</td>
<td>Children in DD group may not have been representatively ‘typical’ (referred for ASD diagnosis but did not get one). Tools repeated every two months- may have resulted in a ‘practice effect’. Children very young for ASD diagnosis-stability of diagnosis at this age?</td>
</tr>
<tr>
<td>Paul (2008)</td>
<td>Enrolled between 18-25 months. Diagnosed ASD: 15-25 months.</td>
<td>Mean standard scores increased for whole group over the 2-year period although a better and worse expressive language groups were identified. Repetitive behaviour, higher nonverbal IQ, better receptive language, symbolic play, response to joint attention and sounds and words predicted better expressive language outcomes.</td>
<td>No comparison group. Used Mullen Scales of Early Learning to assess language outcomes. All retained their diagnosis at each time point.</td>
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Predictors of language outcomes in children with and without ASD

Language develops as a complex interaction of a broad range of factors, both genetic and environmental (Figure 3). The factors that influence language development may be shared across conditions such as ASD or language impairment or they may be unique to individual conditions.

Figure 3  Model of factors that may interplay to predict language outcomes

Predictors of language outcomes in children without ASD

Predicting language outcomes in children is of key importance to inform clinical decision-making, such as whether direct intervention or close monitoring is required. Known risk factors include congenital conditions such as genetic disorders (e.g., Down syndrome), metabolic disorders and severe sensory impairment (e.g., deafness, blindness). Medical risk factors for language difficulties include foetal alcohol syndrome, cerebral palsy and brain damage. Several environmental factors have also been identified such as chemical poisoning and parental abuse/neglect (Paul & Roth,
While the risk of language delay for children with the abovementioned conditions is better understood, it has been difficult to identify reliable predictors for children with language impairment of unknown cause, particularly for children aged under 3 years.

Study 3 in this thesis will focus primarily on the child (intrinsic) and environmental (extrinsic) that may influence outcome rather than exploring the full range of factors that may influence outcome, shown in Figure 3. A range of predictors (both intrinsic and extrinsic) has been investigated in an effort to understand which children are likely to have persisting language impairment, which may have late-onset language impairment and which may ‘grow out’ of their language impairment. Predictors have been assessed at a range of ages through childhood and will be presented as two separate sections below.

**Predictors of language outcomes in preschoolers**

In typically developing toddlers one of the most important predictors of later language development has been language ability at preschool age (Chiat & Roy, 2008; Watt, Wetherby, & Shumway, 2006). That is, if children have good language early in life they were more likely to have good language later on. Furthermore, it has been found receptive language is an important predictor of both expressive and receptive language outcome (Chiat & Roy, 2008; Ellis & Thal, 2008; Watt et al., 2006). The use of gestures has also been found to predict receptive language outcomes, and acts for joint attention and range of consonants were found to predict expressive language (Ellis & Thal, 2008; Watt et al., 2006). Other child factors found to predict later language ability include delayed speech sound development (Law, Boyle, Harris, Harkness, & Nye, 2000; Rice et al., 2008), being late to combine words (Carson, Klee, Carson, & Hime, 2003; Dale,
Price, Bishop, & Plomin, 2003) and having less advanced sentence structures than expected for a child’s age (Hadley & Holt, 2006; Thal, Reilly, Seibert, Jeffries, & Fenson, 2004).

**Predictors of language outcomes in children aged 4 years and older**

In a community-based study mutable-proximal factors (factors that have the potential to be modified through parent or child interventions e.g. reading to the child) and mutable-distal factors (factors that have the potential to be modified through indirect interventions e.g. social policy) were examined to investigate whether they predicted language growth and language outcome from 4 to 7 years of age. Neighbourhood disadvantage, family income and family literacy were identified as important distal predictors of language outcomes and proximal factors such as number of books in the home, TV viewing, shared book reading were associated with language growth over time (McKean et al., 2015). In another study by the same authors a ‘risk model’ was developed using seven factors measured at 12 months (family factors, parenting characteristics and child communication skills). This risk model predicted language outcomes at 4 years with about the same accuracy as measures of vocabulary measured by the CDI at 24 months (McKean et al., 2016). Examining the factors that may influence language development has important implications for the types of interventions that may be important at different ages. In some cases, a universal broad-brush prevention approach (such as parent education on language development or attendance at high quality preschool) may be most effective and in others a targeted treatment approach may be the best approach.

A similar Australian population-based study included children around the same age (4 years at baseline) who were followed up over time (C. Taylor, Christensen, Lawrence,
Mitrou, & Zubrick, 2013). In this study important predictors of receptive vocabulary delays were maternal non-English speaking background, low school readiness, child wasn’t read to at home, four or more siblings, low family income, low birthweight, low maternal level of education, maternal poor mental health, low maternal parenting consistency and high reactivity in the child. These factors were important in predicting language outcomes, however, they did not predict change in language ability over time. Rather, socio-economic disadvantage was the only significant predictor of language growth from 4 to 8 years with the authors suggesting the impact of social determinants may increase with child age (C. Taylor et al., 2013).

**Risk factors for language impairments**

To date no single risk factor has been identified to explain language impairment in its entirety, however, a family history of speech language delay or literacy problems, prematurity, low birth weight or slow growth, being male, and low maternal education appear to play some role (Law et al., 2000; Stanton-Chapman, Chapman, Bainbridge, & Scott, 2002; Zubrick, Taylor, Rice, & Slegers, 2007). Specifically, a large population-based study based in Norway found the odds for persistent language impairment were doubled for boys and the odds for children with poor receptive language at 1.5 years were tripled if there was a family history of late talking. Family history of literacy difficulties increased the odds of late-onset and persistent language impairment and family history of speech difficulties increased the risk of transient language impairment (Zambrana et al., 2014).

A broad range of prognostic and risk factors, both intrinsic and extrinsic have been examined over different developmental periods and it is likely these predictors interact with each other in different ways to compound or protect against risk for language
difficulties. While some factors appear to be more important than others (e.g., family history of language impairment, receptive vocabulary and use of gesture) currently it is not possible reliably to predict who will have persisting or resolving language difficulties.

**Predictors of language outcomes in children with ASD**

A number of studies has used cross-sectional designs to investigate social communication predictors of language in children with ASD (e.g., Charman et al., 2000; Charman, Drew, et al., 2003; Dawson et al., 2004; Ellis Weismer et al., 2010; Luyster et al., 2008; Mitchell et al., 2006; Wetherby & Woods, 2006). These studies have shed light on the interactions between social communication skills and language. However, to better understand causal relations it is important to study how early social communication skills impact language development over time. Longitudinal studies investigating language outcomes of children with ASD have found some early developmental domains to be more important predictors than others. Table 3 below outlines 10 key predictors identified across the ASD literature: play, speech sounds, gesture, joint attention, imitation, early language, parent-child interaction, socio-economic disadvantage, ASD symptoms, and IQ. To our knowledge, no studies have specifically focused on gender as a potential predictor of language outcome in ASD.

The decision-making around which predictors to include and the approach taken in this thesis is based on social-interactionist theory. Social-interactionist theory proposes that rather than development being modular and static (where the brain has individual components that when impaired act independently and do not impact other functions in development), the processes are dynamic and evolve through social experience and
interaction between the child’s linguistic and cognitive capacities with the child’s social-language environment. In this view, biological organization of the brain directly impacts thinking and experience which then shapes learning (Bishop, 1997; Greenough, Black, & Wallace, 1987; Karmiloff-Smith, 2013).
<table>
<thead>
<tr>
<th>Predictors</th>
<th>Studies</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Play</strong></td>
<td>Paul, Chawarska, Cicchetti, et al. (2008) n=37; age: 15-25 mo.</td>
<td>Symbolic play predicted language ability at 4 years but functional play did not.</td>
</tr>
<tr>
<td></td>
<td>Poon, Watson, Baranek, and Poe (2012) n=29; age: 4-5 yrs</td>
<td>Object play at 18 months predicted language ability at 7 years</td>
</tr>
<tr>
<td></td>
<td>Sigman et al. (1999) n=42; age: 2-6 yrs age, Sigman and McGovern (2005) n=48; age: 3;11 yrs</td>
<td>Functional play at 4 years predicted expressive but not receptive language ability. Functional play also predicted rate of language change from 12-18 years</td>
</tr>
<tr>
<td><strong>Early sounds</strong></td>
<td>Paul et al. (2011) n=48; age: 6-12 mo.</td>
<td>Lack of diminishing of abnormal sounds predicted social communication behaviours and ASD diagnosis.</td>
</tr>
<tr>
<td></td>
<td>Wetherby, Watt, Morgan, and Shumway (2007) n=50; age: 30 mo.</td>
<td>Inventory of consonants at 18 months predicted receptive language at 3 years</td>
</tr>
<tr>
<td><strong>Gesture</strong></td>
<td>Bopp and Mirenda (2011) n=44; age: 3;11 yrs</td>
<td>No association between gesture and later language ability</td>
</tr>
<tr>
<td></td>
<td>Charman, Baron-Cohen, et al. (2003) n=18; age: 20 mo.</td>
<td>Mastery of gesture remained stable once child learned 20 words</td>
</tr>
<tr>
<td></td>
<td>Luyster et al. (2007) n=62; age: 29 mo.</td>
<td>There was a steady increase in early and late gestures with increase in expressive vocabulary.</td>
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<tr>
<td>Predictors</td>
<td>Studies</td>
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<td></td>
<td>n=83; age: 2 yrs, Toth et al. (2006) n=60; age: 34-52 mo.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bopp and Mirenda (2011) n=44; age: 3:11 yrs; Luyster et al. (2007) n=62; age: 29 mo.</td>
<td>Imitation abilities did not predict later language ability</td>
</tr>
<tr>
<td>Motor imitation</td>
<td>Edmunds et al. (2016)</td>
<td>15 month response to joint attention mediated the association between 12 month motor imitation and 18 month expressive vocabulary</td>
</tr>
<tr>
<td></td>
<td>Sigman and McGovern (2005) n=48; age: 3;11 yrs</td>
<td>Responding to and initiating joint attention at 4 years associated with expressive language gain one year later. Response to joint attention at 4 years resulted in greater expressive language at 12 years. Neither initiating nor responding to joint attention predicted receptive language gains.</td>
</tr>
<tr>
<td>Language</td>
<td>Bopp and Mirenda (2011) n=44; age: 3:11 yrs, Pry et al. (2009) n=132; age: 5.5yrs, Thurm et al., 2007 n=83; age: 2 yrs, Paul, Chawarska, Cicchetti, et al., 2008 n=37; age: 15-25 mo., Mawhood and Howlin (2000) n=19; age: 24 yrs, Venter et al. (1992) n=58; age: 14.7 yrs, Ellis Weismer and Kover (2015) n=129; age: 2.5 yrs,</td>
<td>Early language ability predicted later language ability</td>
</tr>
<tr>
<td>Predictors</td>
<td>Studies</td>
<td>Main findings</td>
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<tr>
<td>Wetherby et al. (2007) n=50; age: 30 mo.</td>
<td>Found language to be strongest predictor of all social communication predictors of later language outcome</td>
<td></td>
</tr>
<tr>
<td>Parent-child interaction</td>
<td>Siller and Sigman (2002) n=48; age: 3;11 yrs, Maternal behaviours, such as synchrony associated with increases in both response to joint attention and initiating joint attention and language for many of the children. Higher levels of synchronization and less demanding quality of parent language associated with superior communication skills over all time periods (1, 10, 16 years).</td>
<td></td>
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<tr>
<td>Parent-child interaction</td>
<td>Siller and Sigman (2008) n=28; age: 31-64 mo. Pre-schoolers who were more responsive to their parent’s bids for joint attention made greater gains in language development and parents who were more responsive had children with better language compared with those who had lower levels of synchrony.</td>
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</tr>
<tr>
<td>McDuffie and Yoder (2010) n=32; age: 18-60 mo.</td>
<td>At the 6 mo. follow up the number of parent utterances that followed child’s focus of attention and number of parent utterances that responded to child’s communicative acts predicted vocabulary.</td>
<td></td>
</tr>
<tr>
<td>Haebig, McDuffie, and Ellis Weismer (2013b) n=40; age: 24-39 months</td>
<td>Parent directives that followed child’s focus of attention predicted comprehension and expressive language one year later (unique variance)</td>
<td></td>
</tr>
<tr>
<td>McDuffie and Yoder (2010) n=32; age: 18-60 mo.</td>
<td>Baseline nonverbal cognition/IQ predicted later language outcomes</td>
<td></td>
</tr>
<tr>
<td>Predictors</td>
<td>Studies</td>
<td>Main findings</td>
</tr>
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</tr>
<tr>
<td></td>
<td>Charman, Baron-Cohen, et al. (2003) n=18; age: 20 mo.</td>
<td>Nonverbal IQ at 20 months not associated with language outcomes at 42 months</td>
</tr>
<tr>
<td>ASD symptoms</td>
<td>Ellis Weismer and Kover (2015) n=129; age: 2.5 yrs, Baghdadli et al.</td>
<td>Severity of ASD symptoms predicted language outcomes</td>
</tr>
<tr>
<td></td>
<td>(2012) n=152; age: 4.9 yrs, Magiati, Moss, Charman, and Howlin (2011) n=36; age: 3.4 yrs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sigman and McGovern (2005) n=48; age: 3;11 yrs, Thurm et al. (2015)</td>
<td>Severity of ASD symptoms did not predict language outcome when other important factors (e.g., IQ)</td>
</tr>
<tr>
<td></td>
<td>n=70; age: 1-5 yrs</td>
<td>taken into account</td>
</tr>
<tr>
<td>Socioeconomic disadvantage</td>
<td>Ellis Weismer and Kover (2015) n=129; age: 2.5 yrs</td>
<td>Socioeconomic status predicted expressive but not receptive vocabulary</td>
</tr>
</tbody>
</table>
The extant body of literature on the predictive associations between early social communication and language outcomes present a complex picture. While the evidence suggests that some predictors (e.g., IQ and language) are more consistently important than others, each study has used different tools, different time periods, a combination of different predictors and different methods. Moreover, even those studies that have used the same tools and methods have produced conflicting findings (Bopp & Mirenda, 2011; Charman et al., 2005; Ellis Weismer & Kover, 2015; Luyster et al., 2007).

Some studies have found different predictors to have relative importance at different time periods. For example, Toth et al. (2006) found initiating proto-declarative joint attention and immediate imitation to be the best predictors of language ability at age 3 to 4 years, whereas deferred imitation and toy play were found to be the best predictors of rate of communication development from age 4 to 6.5 years. These findings highlight the importance of studying predictors at a range of ages. To improve the accuracy of prediction of language outcomes some studies are combining behaviour descriptions with neurological findings (Lombardo et al., 2015). Given the complex interplay between genetics, neurobiology and behaviour in ASD such an approach will be critical for future research (Cuthbert & Insel, 2013).
## Key points

Language and social communication ability appear closely linked but the exact way they interact during development is not well understood.

A large number of studies have investigated language outcomes but it is difficult to interpret findings due to varied methods.

Mean trajectories for children with ASD provide information at a group level about language development but individual trajectories take into account individual variation.

Trajectories of language development in children without ASD are variable in the early years but appear to become increasingly stable and predictable as children age.

Many putative predictors of language outcomes have been examined during childhood including intrinsic (e.g., autism symptoms) and extrinsic (e.g., parent interaction style).

To date no predictor alone has been able to fully explain different language outcomes in children with and without ASD. It is likely predictors of language outcome vary with age and a combination of predictors influence outcomes.

The most consistent and important predictors for later language outcomes in ASD are language ability and IQ. There is mixed evidence for the importance of ASD symptoms on influencing language outcomes.
Chapter 4  This thesis

Rationale for the thesis

Challenges in understanding communication outcomes in ASD

Despite an increase in the number of studies that have investigated communication outcomes (see Chapter 5), clinicians are still unable to provide accurate prognostic information to parents based on their child’s characteristics. This is because studies have been so varied in methodology, quality, age groups included and assessment tools used. Clinicians remain limited to very general information on outcomes. For example, children who have an IQ of less than 50 and no speech by school age are likely to have the least favourable prognosis (Howlin et al., 2014; Lord & Schopler, 1989; Venter et al., 1992). Parents need timely and accurate information about the likely communication outcomes for their child with ASD. Clinicians need evidence to inform the responses they give parents to such questions and to inform intervention and management planning. In addition, policy makers and service providers require information about communication outcomes to inform decisions regarding the best possible allocation of resources and services through childhood.

A review of the current evidence on language outcomes is required

A systematic review using emerging best methods for prognosis studies will make optimum use of the current evidence on language outcomes and provide an important summary for parents and clinicians that is easily accessible and immediately relevant. It is hoped the methods developed as part of this review will assist the development of
future methods, and inform future prognosis studies, as well as prognostic systematic review methods development.

**Existing data from a community-based sample provide new opportunities**

The Early Language in Victoria Study, described earlier in this thesis (see ‘Setting’), is a longitudinal, community-based study that contains valuable data on language development. Studies 2 and 3 utilised data from the ELVS and have the potential to provide the following benefits.

**An opportunity to examine trajectories in context and in depth**

M. S. Thomas et al. (2009) describes trajectory approaches as “a motivation to place development at the heart of explanations of developmental deficits” (pp339). Indeed, Thomas explains, the phenotypes associated with neurodevelopmental disorders (including ASD) are not set in stone when a child is born but they develop gradually over time. It is unclear from the literature whether the pathways to outcome reflect separate developmental pathways or whether they may be interrelated throughout childhood. Trajectories provide a powerful description of these pathways both between and within individuals.

At a broader level it is unknown whether the divergences in trajectories are related to extrinsic factors (e.g., parent interaction, interventions) or intrinsic factors in the child (e.g., social communication skills). It seems likely both protective and risk factors are involved in outcomes and that these influence the later emergence of ASD symptoms. Gaining a deeper understanding of trajectories of development and predictors of outcome in ASD will assist in maximizing the efficacy of intervention as well as
providing some clues as to what might be done to prevent the divergence in development in children with ASD. The ELVS is the ideal platform for studying the trajectories of language development and related behaviours in children with ASD.

One of the challenges in studying development in ASD is the extreme heterogeneity of the condition. Many published studies have used group means and general measures of communication to demonstrate differences in development between ASD and other conditions (e.g., Anderson et al., 2007; Sigman & McGovern, 2005; Thurm et al., 2007). However, this approach only permits a global picture of pathways of development. For example, we may know that a group of children moved from A to B but we don’t know the different pathways by which they got there.

The limitation of such group studies is that they mask individual difference and do not account for the rich variability in ASD. An exploration of individual trajectories using detailed assessments of language, as is being used in this thesis, enables interesting individual differences to be visible; it also allows for investigation of phenomena that may be more specific to ASD such as regression in development. In other words, the variability is accepted as important information rather than being disregarded as inconvenient noise (Dereu et al., 2012). A nuanced description of language profiles also has the potential to identify meaningful subgroups, which may help explain the underlying mechanisms at play in ASD. Further, studying the natural history of the multiple systems and dimensions that may play an important role in communication outcomes and their course through childhood is critical to a better understanding of prognosis.
It is hoped a community-based study will provide generalisable findings

With the exception of studies by Barbaro and Dissanayake (2012), Veness et al. (2012) and Bolton, Golding, Emond, and Steer (2012), which are population or community samples, most studies that have examined early communication development in ASD have used high-risk infant siblings, home videos or retrospective parent report. There are methodological limitations with these three methods, as has been discussed. The focus of the majority of these infant studies has been on early predictors of diagnostic outcome rather than language outcome (see Jones et al., 2014 for a review). With the exception of one study (Bolton et al., 2012) no studies have reported on children that have been followed from infancy to 7 years of age. Further, this study will enable both the comparison of children with ASD to children in a large community sample as well as to other groups of children (such as language impaired, typical development). This will enable a greater understanding of the way in which communication difficulties manifest and whether there are similarities between groups or features that are more common in children with ASD. Very few published longitudinal studies have used such comparison groups. The importance of cross-population comparisons for studies of language development has been highlighted by several authors (Beeghly, 2006; Rice et al., 2005; M. S. Thomas et al., 2009).

Measuring predictors of communication in a large cohort has the potential to provide novel insights

The majority of studies that have examined predictors of language outcomes in children with ASD have reported on associations using cross-sectional designs (e.g., Charman et al., 2000; Charman, Baron-Cohen, et al., 2003; Dawson et al., 2004; Ellis Weismer et al., 2010; Luyster et al., 2008; Mitchell et al., 2006). This study will investigate
predictors of later language outcome in a way that will allow the importance of social communication and ASD to be examined along with other key known predictors of outcome such as language ability and IQ.

Summary

This thesis will synthesise current evidence on language outcomes in ASD. It will also be the first of its kind to study communication trajectories at multiple time points in the same cohort of children with ASD from infancy until 7 years using a community sample. This study has several advantages over other studies. The community sample has the potential to minimize ascertainment bias, which should enable a more representative picture of ASD. Using multiple time points enables the mapping of trajectories of development. It also allows the assessment of predictors at a key time point in development facilitating an understanding of their relative importance in language outcome. By studying individual communication trajectories this study hopes to provide a nuanced and detailed report of the development of a range of communication skills. Further, this study will compare children who have been diagnosed with ASD to children with language impairment and typical development within the same community sample thus placing ASD within a developmental context.
Thesis aims

The overall aim of this thesis is to examine language trajectories and outcomes in children with ASD.

Three primary studies were conducted to address the overall aim.

- The first study consisted of a systematic review and meta-analysis of studies that have reported on language outcomes in individuals with ASD.
- The second and third studies used data from the ELVS, a longitudinal community-based study investigating language development in children.

The studies, chapters and corresponding aims of the thesis are detailed below in Table 4.
Table 4. Structure, aims and hypotheses of the thesis

<table>
<thead>
<tr>
<th>Study - Chapter</th>
<th>Title</th>
<th>Aims and hypotheses</th>
</tr>
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</table>
| Study 1 (Chapter 5) | A systematic review of language outcomes in individuals with autism spectrum disorder | 1. To systematically and comprehensively search the extant literature on language outcomes in individuals with ASD  
2. To collect clinically-relevant descriptive information on included studies  
3. To conduct quality assessments (risk of bias) of included studies  
4. To present findings from studies that reported data on language outcomes in graphical format  
5. To conduct meta-analyses where five or more studies have presented data on the same language domain  

**Hypothesis:** We hypothesised children with ASD would have delayed language relative to children without ASD and slower rate of language development, with the gap between children with and without ASD growing larger over time.  \
Study 2 (Chapter 7)

<table>
<thead>
<tr>
<th>Study - Chapter</th>
<th>Title</th>
<th>Aims and hypotheses</th>
</tr>
</thead>
</table>
| Parent reported | patterns of loss and gain in communication in 1 to 2 year old children are not unique to ASD | 1. To examine trajectories of communication development from 1 to 2 years in children with ASD and compare these trajectories to those of children with LI and TD  
2. To examine trajectories of expressive vocabulary development from 1 to 2 years in children with ASD and compare these trajectories to those of children with LI and TD  
3. To compare the proportion of children in each group (ASD, LI, TD) who lost communication skills from 1 to 2 years  
4. To compare the types of communication skills that were lost for each group (ASD, LI, TD)  
5. To compare the spread of loss of skills across different communication domains between the 3 groups (ASD, LI, TD)  
Hypotheses: We hypothesised there would be substantial variability in early communication trajectories. We expected children with ASD to demonstrate a higher proportion of children who lost skills relative to the other groups, skills would be lost across a wide range of communicative domains for children with ASD and very few children without ASD would lose skills from 1 to 2 years. |
<table>
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<tr>
<th>Study - Chapter</th>
<th>Title</th>
<th>Aims and hypotheses</th>
</tr>
</thead>
</table>
| Study 3 (Chapter 8) | Language trajectories and predictors of language outcome from 4 to 7 years in children with and without autism spectrum disorder | 1. To examine trajectories of receptive and expressive language development in children with ASD from 4 to 7 years and to compare these trajectories to those of children with LI and TD  
2. To compare the proportions of children with ASD who had declining, stable and accelerating trajectories to children with LI and TD  
3. To investigate whether children with ASD were more likely to have a greater gap between expressive and receptive language abilities from 4 to 7 years compared with children without ASD  
4. To investigate predictors of expressive and receptive language outcomes in the whole cohort from 4 to 7 years |

**Hypotheses:** We hypothesised children with ASD would have lower language ability than the typically developing children and slower language growth, with the gap between the two groups growing over time. We expected social communication, a diagnosis of ASD, early language and IQ to be important predictors of language outcome. Given the mixed evidence about relative weakness in receptive language we were uncertain if children with ASD would be more likely than the other children to have a receptive-expressive language discrepancy.
Chapter 5  Study 1. A systematic review and meta-analysis of language outcomes in autism spectrum disorder

In this study we systematically reviewed the existing literature on language outcomes in individuals with ASD. This paper is being prepared for submission to Autism Research.
Abstract

Background
Language difficulties are common in Autism Spectrum Disorder (ASD). Parents and clinicians need evidence about language trajectories in ASD to inform decision-making, evaluate interventions and understand prognosis.

Objective
To systematically review studies reporting language outcomes in individuals diagnosed with ASD.

Method
A comprehensive search strategy with a well-established sensitive prognosis filter for Medline, adapted for 5 other database searches, was used. Included studies observed individuals diagnosed with ASD for ≥ 12 months and had ≥ 30 participants. Risk of bias assessments were conducted on all included studies. Data were extracted and changes in scores mapped over time. If 5 or more studies presented data on the same language domain random effects meta-analysis was conducted.

Results
Fifty-four studies (N=5064) met inclusion criteria. Language outcomes were standardised assessments (n=35), notation of presence/absence of verbal language (n=11) or both (n=8). Age at baseline ranged from 17 months to 26 years, duration of follow-up from 1 to 38 years. Most publications (92%) were rated medium to high risk of bias. In all but one study children with ASD had substantially lower than average scores at baseline and follow-up. However, in most (n=24/25; 96%) studies reporting
standard scores, children with ASD (aged ≤11 years at follow-up) progressed at a comparable rate to age-expected norms across a range of language domains. Meta-analyses conducted on three language domains (expressive and receptive syntax, adaptive language) found mean standard scores increased over time. Between 5-32% developed the ability to use words over the course of the study. The proportion gaining phrases from single words ranged from 23-37%.

Conclusion
Although most studies had not met criteria for best methods for prognosis studies there was remarkable consistency of findings despite variations in inclusion criteria, age groups, tools used and language constructs measured. Most individuals with ASD gained language over time. Despite having below average language scores, most children under 11 years at follow up progressed at a comparable rate (in parallel) to age-expected norms.
Introduction

To meet criteria for a diagnosis of ASD, the current Diagnostic Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013) requires the presence of social communication difficulties and repetitive and restricted interests and behaviours. While other (non-social) language difficulties are not requisite for an ASD diagnosis, they are a common comorbidity and DSM-5 now requires specification about whether such a language impairment is present.

Language development is often the first issue raised by parents of children later diagnosed with autism (De Giacomo & Fombonne, 1998; Herlihy et al., 2015). Once a diagnosis is made, around 63% of children with ASD present with language disorders (Levy et al., 2010). There is substantial heterogeneity in the extent of language difficulties that co-occur with ASD (Ellis Weismer & Kover, 2015; Tager-Flusberg et al., 2005; Tek, Mesite, Fein, & Naigles, 2014). Some children have well preserved (or even superior) language abilities on formal testing, with sophisticated vocabulary and sentence structure (Boucher, 2012; Tager-Flusberg & Caronna, 2007), yet cross-sectional studies have found between 14 to 50% of children with ASD never develop the ability to use words as their primary means of communicating (Chakrabarti & Fombonne, 2001; King & Bearman, 2009; Kjelgaard & Tager-Flusberg, 2001; Lord, Risi, & Pickles, 2004; Rice et al., 2005). Further to the variability noted in language skills in this group, there is also variation in the types of difficulties seen. Stereotypical verbal behaviours are commonly described including repetitive language, idiosyncratic phrases, difficulties with pronouns and echolalia (American Psychiatric Association, 2013; Tager-Flusberg & Caronna, 2007).
There is consensus in the literature that verbal skills play a critical role in predicting long-term outcomes for children with ASD in areas such as adaptive functioning, psycho-social adjustment and wellbeing (Gillespie-Lynch et al., 2012; Hofvander et al., 2009; Howlin, 2003; Howlin & Moss, 2012; Mawhood & Howlin, 2000; Szatmari et al., 2003). Language skills are also critical to school placements and academic performance, as well as the ability to participate in successful social interactions (Thurm et al., 2007). Despite recognition of the importance of this domain to children with ASD, language outcomes remain poorly understood.

Parents of children with ASD commonly ask health professionals whether their child will talk, and if so, to what extent and how their language development will progress compared with their peers. High quality evidence is required about the likely language outcomes for children so clinicians can provide well-informed answers. Understanding the language development in children with ASD is also important so the effectiveness of communication interventions can be evaluated within a developmental context. A substantial number of studies have investigated language outcomes in children with ASD. Due to significant variation in methodologies across studies however (e.g., different length of follow-up, ages and developmental profiles of the children, interventions, tools used to measure language), it is difficult to interpret study findings in a clinically meaningful way. The aim of this review is to synthesise current evidence for verbal language outcomes in individuals with ASD with a view to inform parents, clinicians, service providers and policy makers.
Methods

Inclusion/exclusion criteria

Children and adults of all ages with a diagnosis of autism spectrum disorder, autism, autistic disorder, childhood autism, pervasive developmental disorder (PDD), PDD-not otherwise specified (PDD-NOS), atypical autism, PDD-unspecified, or Asperger’s disorder/syndrome were included in the review.

Studies were included only if the diagnosis was made at the beginning of the study using a standardised diagnostic instrument including the Autism Diagnostic Interview-Revised (ADI-R; Le Couteur, Lord, & Rutter, 2003), Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000), Diagnostic Interview for Social and Communication Disorders (DISCO; Wing, Leekam, Libby, Gould, & Larcombe, 2002), Childhood Autism Rating Scale (CARS; Schopler, Reichler, DeVellis, & Daly, 1980), Gillian Autism Rating Scale (GARS; Gilliam, 1995)and/or by using established diagnostic criteria of an accepted classification system at the time, such as DSM III-IV-IV TR, 5 (American Psychiatric Association, 1980, 2000, 2013) or ICD 9-10 (World Health Organisation, 2010). A dual diagnosis (e.g., Asperger disorder and attention deficit hyperactivity disorder, or autism and Fragile X) did not prevent inclusion.

Types of studies

Intervention and observation studies were eligible for inclusion if initially defined participants (diagnosed with ASD) were followed up for a period of 12 months or more. Retrospective and prospective cohorts were included. Studies had at least 30 participants to differentiate case series from a cohort study. Randomised control trials
presenting data separately for the comparison/control and intervention groups were only included if the comparison/control arm had more than 30 participants. Studies published in languages other than English were also included.

Types of outcome measures

Studies were included if language outcomes were measured by standardised assessments or where the study reported on the presence/absence of verbal language (e.g., no words, use of single words, phrases). Studies were also required to have a baseline and follow-up measure of language. Standardised parent report and direct assessment of language tools were included, along with broader tools such as the Vineland Adaptive Behavior Scales (Sparrow, Cicchetti, & Balla, 2005), if expressive and/or receptive communication subdomains were assessed. The general term ‘language outcomes’ is used to refer to the outcomes used by all included tools. Studies of nonverbal language (e.g., augmentative/alternative communication such as use of signs or symbols to communicate) were excluded.

Search strategy for identification of studies

Databases were searched using the search filter “prognosis sensitive” devised for the Medline database by Wilczynski and Haynes (2004). The filter was adapted for other databases that did not systematically offer this same filter. PsycINFO, Embase, CINAHL, Cochrane Database of Systematic Reviews (CDSR) and the Database of Reviews of Effectiveness (DARE) were used. Appendix B lists database specific search terms. Conference proceedings and thesis dissertation abstracts were searched. The
reference lists of included articles were reviewed and experts in the field were contacted.

**Review of studies**

Titles and abstracts of all references identified were screened by at least two authors (AB, FK, VS, SW, KW, KL) assessing every title and abstract. Studies failing to meet inclusion criteria were excluded. The full text of potentially relevant articles was obtained and again assessed by at least two authors. Disagreement between the two authors was resolved by consensus or referred to a third author for arbitration. Articles not fulfilling inclusion criteria were excluded.

**Quality Assessment**

Risk of bias was assessed using a modified Quality in Prognosis Studies (QUIPS) tool (Hayden, van der Windt, Cartwright, Côté, & Bombardier, 2013). The modification was required because the current study did not analyse confounders or prognostic factors and therefore these assessment categories did not apply. Three authors (Amanda Brignell and either Angela Morgan or Tamara May) assessed risk of bias in all included studies and any differences in ratings were resolved through consensus. Studies were assessed using the domains: study participation, study attrition and outcome measurement. If information required for assessment was not available in studies published after 2000, authors were emailed for further information. This was because it would have been difficult to track down authors of studies published more than 16 years ago. Appendix C lists subcategories of each domain and specific criteria used to rate each item as unclear, low, medium or high.
Data management

Data extraction was independently completed via a standardised template, by a minimum of two authors (AB and either FK or TM). Important clinical information likely to influence applicability and interpretation of findings (and necessary to allow assessment of homogeneity of studies) was extracted (Table 10).

Table 5  Clinical information collected from included studies.

<table>
<thead>
<tr>
<th>Clinical information collected from included studies</th>
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</thead>
<tbody>
<tr>
<td>Type of sample (population-based or clinical)</td>
</tr>
<tr>
<td>Type of recruitment (prospective or retrospective)</td>
</tr>
<tr>
<td>Type of diagnosis (e.g., autistic disorder, Asperger’s Syndrome)</td>
</tr>
<tr>
<td>Type of study (intervention or observational)</td>
</tr>
<tr>
<td>Proportion lost to follow-up</td>
</tr>
</tbody>
</table>

Tools used for measuring outcomes were categorised by five language domains: receptive and expressive vocabulary, receptive and expressive syntax, parent-rated adaptive language, parent-rated vocabulary and proportion verbal/nonverbal or using phrases. For the purposes of this review, if individuals used ‘no or few words consistently on a daily basis’ or were described as ‘minimally verbal,’ we grouped them as ‘nonverbal’. We acknowledge, as have other authors (Kasari et al., 2013; Norrelgen et al., 2014; Rose, Trembath, Keen, & Paynter, 2016; Tager-Flusberg & Kasari, 2013; Tager-Flusberg et al., 2016) there is a difference between an individual being completely nonverbal compared with using some words, however, such level of detail
was not often provided by studies and it was beyond the scope of this review to subdivide groups further.

Studies were also grouped based on developmental or cognitive level measured by either a standardised intelligence (IQ) or developmental quotient (DQ). These were identified by whether the mean IQ or DQ for the cohort was (1) less than or equal to 70 or more than 70, or (2) if more than 70%, or less than 30%, of the sample achieved an IQ/DQ of less than or equal to 70. Where a mental age was given we converted this to a DQ by dividing mental age by chronological age. If only nonverbal subtests (e.g., visual perception) of cognitive assessments were reported we used those to estimate DQ or IQ. For tools such as the Mullen Scale of Early Learning (Mullen, 1995) a standard T score (e.g., for the nonverbal subtests) of 30 which is 2 standard deviations below the mean score of 50, was considered the ‘cut point’ or equivalent to <70 on an IQ test.

If a median/mean was not provided for duration of follow-up, baseline and/or follow-up age, a mean duration or age was imputed by taking the average of the lower and upper end points of the range given. Where available, we collected information on any intervention. Where participants had been described as receiving a range of interventions in the community, they were grouped as ‘treatment in the community’ (TIC), otherwise the treatment is described as a specific intervention. Descriptive information was also collected on whether the study analysed predictors of language outcomes although this information was not analysed because this study did not aim to review predictors of outcome. In cases where the same participants were included in more than one publication (also with use of the same outcome measures) data was taken from the publication with the largest sample size and/or where data on language
outcomes could most easily be extracted. Publications using the same participants were provided with an overall study identifier label (Table 6).

**Statistical analysis**

Outcomes were presented for relevant studies in graphical format where possible. Studies were graphed when data describing mean/median standard scores or age equivalent scores could be extracted, or when the proportion of children who were verbal or used phrases at two time points was reported. This allowed comparison of trajectories from baseline to follow-up. Standard scores allow comparison to a ‘typically developing’ reference score. For most tools this is a score of 100. If development progresses at a rate expected for an individual’s age, standard scores should remain the same over time (e.g., 100 at Time 1 and 100 at Time 2).

Age equivalent scores allow comparison of an individual’s language age (age-equivalent) to their chronological age. In typical development one would expect chronological age to roughly match language age at any time point. If available, or able to be calculated, confidence intervals were added to scores. A number of studies reported raw scores. It was not possible to track change relative to age-expected levels for raw scores, instead they were interpreted with reference to direction of change (gain, plateau or loss of language skills) over time. Studies that did not report scores on the same tool at two time points are described in the text.

Due to variability in study findings we were not able to present summary statistics for all language measures. However if five or more studies reported on the same language outcome at two time points a meta-analysis was conducted followed by meta-regression
co-varying for age at baseline, language level at baseline, length of follow-up and IQ. A fixed effects meta-analysis was conducted in the first instance but if there was substantial heterogeneity observed between studies, a random effects meta-analysis was conducted using the DerSimonian and Laird method. This method takes the heterogeneity into account in the final calculation of the effect size and the confidence interval around that effect size.

**Results**

**Search results**

The literature search was completed at five time points (2006, 2007, 2010, 2013, 2016). The final search was completed at the end of Week 2 in January 2016. Figure 4 shows a flow diagram of the literature search, the number of studies that were excluded or met inclusion criteria.
The combined search yielded 19,410 studies. Review of 319 full text articles, identified 92 publications that met inclusion criteria and measured language as an outcome (see Appendix D for the full list of publications and their characteristics). Sixteen studies had two or more publications and overlapping participants. A total of 54 studies (n=5064) met inclusion criteria once duplicate publications were removed. Duplicate studies (Table 6) were grouped as one study and labelled with a study identifier.
Table 6  Studies with two or more publications and overlapping participants.

<table>
<thead>
<tr>
<th>Study identifier</th>
<th>Publications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baghdadli-Darrou cohort</td>
<td>Baghdadli 2012*, Darrou 2010&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ben Itzchak cohort</td>
<td>Ben Itzchak 2009, Ben Itzchak 2011&lt;sup&gt;c&lt;/sup&gt;, Ben Itzchak 2014*</td>
</tr>
<tr>
<td>Bennett-Starr</td>
<td>Bennett 2008, Bennett 2013, Starr 2003*</td>
</tr>
<tr>
<td>Berry-Kleinman cohort&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Berry 2009*, Kleinman 2008*</td>
</tr>
<tr>
<td>Bopp cohort&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Bopp 2006*, Bopp 2009, Bopp 2011*</td>
</tr>
<tr>
<td>Chawarska-Klintwall cohort</td>
<td>Chawarska 2009, Klintwall 2015</td>
</tr>
<tr>
<td>Freeman cohort</td>
<td>Freeman 1985*, Freeman 1999</td>
</tr>
<tr>
<td>Howlin cohort&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Howlin 2013, Howlin 2014*</td>
</tr>
<tr>
<td>Magiati-Moss&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Magiati 2011*, Moss 2008*</td>
</tr>
<tr>
<td>Mazurek-Wodka</td>
<td>Wodka 2013*, Mazurek 2012</td>
</tr>
<tr>
<td>Munson-Toth&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Munson 2008*, Toth 2006*</td>
</tr>
<tr>
<td>Study identifier</td>
<td>Publications</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Pelicano cohort</td>
<td>Pelicano 2010, Pelicano 2012*</td>
</tr>
<tr>
<td>Stockholm cohort</td>
<td>Eriksson 2013, Fernell 2010, Hedvall 2015, Norrelgen 2014*</td>
</tr>
<tr>
<td>Woynarski-Yoder</td>
<td>Woynarski 2015, Yoder 2015*</td>
</tr>
</tbody>
</table>

* Data were extracted from this publication.

a. Anderson-Lord, Berry-Kleinman, Bopp, Munson-Toth and Magiati-Moss and Ben Itzchak cohorts reported on the same participants but used different measures so data were included from both studies.

b. Twenty nine participants from Howlin 2004 were also included in Howlin 2014.

Note. Flanagan 2010 was an intervention trial and participants receiving the intervention overlapped with participants in the Ontario cohort, however, data were only extracted from participants in the control group. Blacklock 2014 recruited participants from the Ontario cohort but of a different age group to Freeman 2010 so data were extracted from both studies.
Risk of bias assessment

Risk of bias ratings are included in Table 7. We (AB, AM, TM) assessed all included publications (n=92) of the included studies (n=54) for risk of bias because factors linked to risk of bias varied for publications based on the same participants. For example, loss to follow-up at one time point could be much higher than another time point. Only one publication was at low risk of bias for study participation, study attrition and outcome measure risk of bias categories. A further eight were at low risk of bias for two of these three categories (Table 7). Thirty-three (36%) were at a high risk of bias for two or more categories. Sixty-seven publications (73%) collected information prospectively and the remainder were retrospective. Only nine publications derived their sample from a population source and the rest were derived from clinical samples. In all publications, individuals were diagnosed using DSM or ICD criteria or accepted standardised diagnostic instruments. Nine publications reported blinding the outcome assessor to the child’s baseline status. Percent followed up ranged from 24% to 100% with 46 of the 67 prospective publications (70%) reporting less than 20% of participants lost to follow-up.
### Table 7  Risk of bias rating on included publications

<table>
<thead>
<tr>
<th>Author</th>
<th>Study participation</th>
<th>Study attrition</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howlin et al. (2004)</td>
<td>L</td>
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<td>L</td>
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<tr>
<td>Bennett et al. (2014), Davidson and Ellis Weismer (2014), Knorring and Hägglöf (1993)</td>
<td>L</td>
<td>L</td>
<td>M</td>
</tr>
<tr>
<td>Anderson et al. (2009), Landa and Kalb (2012)</td>
<td>L</td>
<td>M</td>
<td>L</td>
</tr>
<tr>
<td>Berry (2010), B. J. Freeman, Ritvo, Needleman, and Yokota (1985)</td>
<td>L</td>
<td>H</td>
<td>L</td>
</tr>
<tr>
<td>Bennett et al. (2013), Eriksson et al. (2013)</td>
<td>L</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Flanagan et al. (2015), Hedvall et al. (2015), Szatmari et al. (2015)</td>
<td>L</td>
<td>H</td>
<td>M</td>
</tr>
<tr>
<td>Siller, Hutman, and Sigman (2013)</td>
<td>M</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Anderson et al. (2007), Ray-Subramanian and Ellis Weismer (2012)</td>
<td>M</td>
<td>M</td>
<td>L</td>
</tr>
<tr>
<td>Author</td>
<td>Study participation</td>
<td>Study attrition</td>
<td>Outcome measures</td>
</tr>
<tr>
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<td>------------------</td>
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<tr>
<td>Meyer (2002)</td>
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<tr>
<td>Bennett et al. (2013)</td>
<td>H</td>
<td>M</td>
<td>L</td>
</tr>
<tr>
<td>Starr, Szatmari, Bryson, and Zwaigenbaum (2003)</td>
<td>H</td>
<td>L</td>
<td>M</td>
</tr>
<tr>
<td>Bennett et al. (2008), Bopp (2006); Bopp, Mirenda, and Zumbo (2009), Bopp and Mirenda (2011), Eaves and Ho (2004), Haebig, McDuffie, and Ellis Weismer (2013a); Haebig et al. (2013b)</td>
<td>H</td>
<td>H</td>
<td>L</td>
</tr>
<tr>
<td>Author</td>
<td>Study participation</td>
<td>Study attrition</td>
<td>Outcome measures</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
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</tbody>
</table>
Language outcome measures

Of the 54 included studies, standardised parent-completed tools were reported in 29 studies, standardised clinician-completed tools in 30 and the presence/absence of verbal language in 19 studies (Figure 5). Twenty-one studies reported language outcomes using two or more measures at each time point. Language tools were grouped into 5 broad domains (Table 8).

Figure 5 Number of studies that used each type of language measure.
<table>
<thead>
<tr>
<th>Language outcome</th>
<th>Domain</th>
<th>Description</th>
<th>Tools</th>
</tr>
</thead>
</table>
| Standardized clinician-completed              | Receptive and expressive syntax     | Measures receptive or expressive language more broadly (i.e. range of language domains assessed) | Clinical Evaluation of Language Fundamentals (CELF)  
Mullen Scales of Early Learning (MSEL)  
Preschool Language Scales (PLS)  
Reynell Developmental Language Scales (RDLS)  
Sequenced Inventory of Communication Development (SIDC)  
Test of Auditory Comprehension of Language (TACL)  
Test of Oral Language Development (TOLD) |
|                                              | Receptive and expressive vocabulary | Measures receptive or expressive vocabulary only                              | Expressive One Word Vocabulary Test (EOWVT)  
Expressive Vocabulary Test (EVT)  
Peabody Picture Vocabulary Test (PPVT)  
British Picture Vocabulary Scales (BPVS) |
| Standardized parent-completed                 | Adaptive language                   | Measures adaptive communication skills                                       | Vineland Adaptive Behaviour Scales (VABS) |
|                                              | Expressive and receptive vocabulary | Measures number of words understood or expressed                            | MacArthur Bates Communicative Inventories (CDI) |
| Presence/absence of verbal language          | Verbal or phrase language           | Measures whether individual had verbal language/were nonverbal or using phrases | ADI-R questions  
ADOS module  
Categorical descriptions/rating scales developed by the study e.g., <10 words used functionally on a daily basis or the use of phrases. |
**Characteristics of studies**

The number of participants ranged from 32 to 1433 with 74% (n=40) having more than 50 participants. Study duration ranged from 1 to 38 years. Age at baseline ranged from 17 months to 26 years and at follow-up 35 months to 59 years. Eleven studies included children classified with autistic disorder or autism only, two did not specify the type of diagnosis and the remaining 40 (74%) included children from the autism spectrum. In 25 studies (46%) the majority of children had a cognitive impairment (as defined by 70% or more children having an IQ or DQ <70 or mean IQ or DQ of 70 or less). Fifteen studies (28%) included children with mean IQ/DQ over 70 or >70% of the sample had an IQ>70 and 14 studies did not present data on IQ or it was not possible to extract the required information. Ten studies (19%) involved administration of a specific intervention where outcomes had been followed up over time. The remaining studies (81%) were observational and included children who had received a broad range of interventions in the community (Appendix D).

**Language outcome measures in each study**

The 54 studies used 14 different tools to assess language (Table 9). The measures used by the most studies were the VABS (n=25), MSEL (n=14), notation of presence/absence of verbal language (n=19) and the PPVT (n=6). The most commonly used standardised assessment of expressive and receptive language was the PLS (n=6). For a variety of reasons (e.g., study did not use same measure at each time point or could not be grouped with others) some studies could not be represented graphically and are presented in the text.
Table 9  Language outcome measures used by each study.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Verbal or phrase speech</th>
<th>Parent completed tool</th>
<th>Syntax</th>
<th>Vocabulary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson-Lord cohort</td>
<td>x</td>
<td>VABS +/-or CDI</td>
<td>MSEL &amp; SICD</td>
<td></td>
</tr>
<tr>
<td>Baghdadli-Darrou cohort, Stockholm cohort</td>
<td>x</td>
<td>VABS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bennett-Starr cohort</td>
<td>x</td>
<td>VABS</td>
<td>TOLD</td>
<td></td>
</tr>
<tr>
<td>Bopp cohort</td>
<td>CDI</td>
<td>PLS</td>
<td>PPVT &amp; EOWVT</td>
<td></td>
</tr>
<tr>
<td>Eaves 2004, Wisconsin cohort</td>
<td>VABS</td>
<td>PLS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Freeman cohort</td>
<td>x</td>
<td>VABS</td>
<td>TOLD &amp; TACL</td>
<td>PPVT</td>
</tr>
<tr>
<td>Author, year</td>
<td>Verbal or phrase speech</td>
<td>Parent completed tool</td>
<td>Syntax PLS +/- CELF +/- RDLS +/- MSEL +/- TOLD +/- SICD</td>
<td>Vocabulary PPVT +/- BPVS +/- EOVWT +/- EVT</td>
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<tr>
<td>Green 2014, Hellendoorn 2015, Siller 2013, Vivanti 2013</td>
<td></td>
<td></td>
<td>MSEL</td>
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<tr>
<td>Howlin 2004</td>
<td></td>
<td></td>
<td>PPVT &amp; BPVS</td>
<td></td>
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<tr>
<td>Howlin cohort</td>
<td></td>
<td></td>
<td></td>
<td>BPVS &amp; EOVVT</td>
</tr>
<tr>
<td>Magiati-Moss cohort</td>
<td>X</td>
<td>VABS</td>
<td>BPVS &amp; EOVVT</td>
<td></td>
</tr>
<tr>
<td>Miniscalco 2014, Oosterling 2010</td>
<td></td>
<td></td>
<td>CDI</td>
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<tr>
<td>Pathways cohort, Smith, I 2015</td>
<td></td>
<td>VABS</td>
<td>CELF &amp; PLS</td>
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<tr>
<td>Pelicano cohort, Thomas 2010</td>
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<td>PPVT</td>
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<tr>
<td>Sigman 2005</td>
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<td></td>
<td>CELF &amp; RDLS</td>
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<tr>
<td>Steele 2003</td>
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<td>PPVT &amp; EVT</td>
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<tr>
<td>Stone 2003</td>
<td></td>
<td></td>
<td>SICD</td>
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<tr>
<td>Author, year</td>
<td>Verbal or phrase speech</td>
<td>Parent completed tool</td>
<td>Syntax</td>
<td>Vocabulary</td>
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<tr>
<td></td>
<td></td>
<td>VABS +/- or CDI</td>
<td>PLS +/- or CELF +/- or MSEL +/- or TOLD +/- SICD</td>
<td>PPVT +/- or BPVS +/- or EOVWT +/- EVT</td>
</tr>
<tr>
<td>Thurm 2015</td>
<td>x</td>
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<td>MSEL</td>
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<tr>
<td>Yoder-Woynaroski 2015</td>
<td></td>
<td>CDI</td>
<td>MSEL</td>
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<tr>
<td>Ziehurt 2002</td>
<td></td>
<td></td>
<td>RDLS</td>
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Clinician-administered tools

Receptive and expressive syntax

Change in standard scores

Seven studies measured receptive (Ben Itzchak cohort, Berry-Kleinman cohort, Wisconsin cohort, Lombardo 2015, Paul 2008, Smith T 2015, Vivanti 2015) and expressive syntax respectively (Ben Itzchak cohort, Berry-Kleinman cohort, Wisconsin cohort 2014, Lombardo 2015, Paul 2008, Smith T 2015, Vivanti 2015). In all aforementioned studies, mean language scores for children with ASD were below age-expected levels.

All 7 studies that measured receptive syntax reported an increase in mean standard scores for children with ASD (i.e. more gain than expected relative to age-matched peers) (Figure 6a). Fifty-seven percent (n=4/7) of these studies showed a statistically significant (p<0.05) increase in scores over time (Paul 2008, Berry-Kleinman cohort, Wisconsin cohort, Vivanti 2015) indicating some language ‘catch up’ to reference norms. All 7 expressive syntax studies reported an increase in mean standard scores with 43% (n=3/7) reporting a statistically significant (p<0.05) increase (Paul 2008, Wisconsin cohort, Vivanti 2015) (Figure 6b). Participants in Ben Itzchak cohort and Smith I (2015) received intensive behavioural interventions. Participants in the remaining studies received a variety of interventions in the community.
Figure 6  Standard scores in receptive (a) and expressive syntax (b) at baseline and follow-up with 95% confidence intervals for studies using the MSEL and PLS
Combining the results of seven studies in a random effects meta-analysis, there was an estimated overall increase of 9.4 units (95% CI: 4.9-13.8; I² 86.6%, df 0.6, p<0.001) on receptive syntax scales observed in a study over time, Figure 7. Substantial heterogeneity was found between studies. In the meta-analysis a score of 0 indicates children are progressing at rate expected for their age (i.e. norm references). A score over 0 indicates some ‘catch up’ or acceleration.

Figure 7  Random effects meta-analysis on seven studies using PLS or MSEL as a scoring system for receptive syntax outcomes.
For expressive syntax, combining the results of seven studies in a random effects meta-analysis, there was an estimated overall increase of 5.1 units (95% CI: 3.3-7.0; I² 39.0%, df 0.6, p=0.132) on expressive syntax scales observed in a study over time, Figure 8.

**Change in age equivalent scores**

Four studies provided age equivalent scores on combined expressive and receptive syntax (Bopp cohort, Chawarska-Klintwall cohort, Stone 2003, Ziehurt 2012) and one study provided separate scores for expressive/receptive syntax in children aged under 5 years at baseline. There was divergence away from the expected trajectory for chronological age and the participant’s language age over time in 2 of the 4 studies in studies reporting on combined receptive/expressive syntax (Figure 9a).
Figure 9  Combined receptive/expressive syntax language and receptive vocabulary language age relative to chronological age
Note. The grey line represents a chronological age equivalent to language age, the line of 'average' development. Stone (2003) only reported expressive syntax age-equivalents. Smith I (2015) reported receptive language (RL) and expressive language (EL) age equivalent scores separately. PPVT: Freeman cohort, Bopp cohort, Steele (2003); RDLS: Ziehurt (2002); MSEL: Smith I (2015), Klintwall (2015); SICD: Stone (2003); PLS: Bopp cohort.
In the studies of children who were under 5 years at baseline the mean language age was substantially below chronological age at baseline, ranging from 11 months behind at 4.1 years to 2.8 years delay at 4.2 years of age. At follow-up, mean language age ranged from 1.8 years behind at 5.2 years to 3.3 years behind at 6.2 years. A study of older children from 12 (middle childhood) to 19 years (adolescence) showed a much lower mean language age based on the RDLS/CELF tool than chronological age at baseline with a substantially increasing gap between the two metrics over time. This was reflected in quite flat language trajectories with a 1.4 month language gain over 6 years for children with an IQ<70 and a 2.5 year gain in language over a 6-7 year period for children with an IQ>70 (Sigman 2003). One study (Howlin 2004) provided only age-equivalents at study end. Participants had an average language age of 8.26 (SD 6.21) at a mean chronological age of 29.33 years. One study provided only log adjusted scores which showed an increase in language age for participants over time (Siller 2013).

**Change in raw scores**

Three studies provided raw scores on clinician-administered tools (Bopp cohort, Hellendoorn 2015, Ray Subramanian 2012), detailed in Appendix E. In receptive syntax, mean scores increased from 13.39 to 29.19 over 2 years (Bopp cohort), 16.04 to 37.22 over 1.5 years (Hellendoorn 2015) and 20.35 to 28.44 over 1 year (Ray Subramanian 2012). In expressive syntax mean scores increased from 14.38 to 26.05 over 2 years (Bopp cohort), 17.02 to 36.49 over 1.5 years (Hellendoorn 2015) and 24.96 to 32.25 over 1 year (Ray Subramanian 2012). This indicates improvement in language ability over time in all studies however assessment of progress relative to what is expected is not possible with raw scores.
Expressive and receptive vocabulary

Change in standard scores

Three studies reported data on receptive vocabulary (Pelicano cohort, Magiati-Moss cohort, Thomas 2009) and one on expressive vocabulary (Magiati-Moss cohort). In all but one study (Pelicano cohort), that only included children with verbal IQ > 80, baseline scores were substantially lower than age-expected levels.

Two of three studies (Thomas 2009, Magiati-Moss cohort) reported an increase in standard scores over time, from 48.6 (95% confidence interval (CI) 43.1-54.1) to 55.6 (CI 48.4-62.6) over 6.9 years in one study (Magiati-Moss cohort) and from 70.9 (CI 64.4-77.3) to 77.5 (CI 71.3-83.7) over 5 years in another (Thomas 2009). The third study demonstrated a decrease in standard scores over 2.7 years (Pelicano cohort). In this study scores decreased from 97.1 (CI 93.7-100.5) to 93.9 (CI 88.7 to 99.1). In the study reporting data on expressive vocabulary standard scores, the mean standard score decreased from 69.3 (CI: 65.1-73.4) to 65.49 (CI: 59.7-71.3) (Magiati-Moss cohort).

No studies that reported on receptive and expressive vocabulary demonstrated significant catch up or loss relative to age-matched peers. Despite having lower scores at baseline and follow-up, on average, the children with ASD progressed at a comparable rate to reference norms. In all studies there was greater variability in standard scores over time, evidenced by wider confidence intervals at follow-up compared with baseline, indicating substantial heterogeneity in language trajectories.

One study could not be presented graphically because it only reported standard scores on the PLS at follow-up (Eaves 2004). In this study, children with autistic disorder (n=36) achieved mean scores of 52.9 (SD 16.2) in expressive and 54.9 (SD 17.3) in
receptive language at follow-up and those with PDD-NOS achieved mean scores of 63.0 (SD 27.8) in expressive and 64.3 (SD 26.7) receptive language. It was not possible to comment on change over time in this study because age-equivalents were used at baseline and language measures varied across time points.

**Change in age equivalent scores**

All studies that provided data on age-equivalents reported gains in mean receptive vocabulary language age over time (Bopp cohort, Freeman cohort, Steele 2003). Of these three studies, one demonstrated some “catch up” to chronological age with a gap between chronological and language age of 2.2 years at baseline and 1.8 years at follow-up (Steele 2003). The other two studies reported a widening gap between language and chronological age from a gap of 3.31 years at baseline to 3.8 years at follow-up in one study (Bopp cohort) and 2.6 years at baseline to 3.7 years at follow-up (Freeman cohort), Figure 9 (b). Participants in all studies received a variety of interventions in the community rather than the study being an intervention trial.

**Change in raw scores**

Two studies provided raw scores on expressive and receptive vocabulary (Bopp cohort, Steele 2003), detailed in Appendix E. In both studies mean raw scores increased. This indicates improvement in language ability over time however assessment of progress relative to what is expected is not possible with raw scores.
Parent-report tools

*Adaptive language*

Change in standard scores

Thirteen studies had data on standard scores that could be extracted on the VABS and displayed graphically (Figure 10).

Figure 10  Standard scores on the VABS at baseline and follow-up.

![Figure 10](image.png)

Note. Smith I-A and Smith I-B are two cohorts from the same study grouped into IQ< 70 and IQ> 70 (Smith I 2015). Participants in the Flanagan (2012) study had substantially lower IQs (Time 2 IQ 39.50 (SD 18.93) than the participants in other studies. One study presented data by poor and good language groups, here we provide a combined mean (Lombardo 2015).
A higher score on the VABS communication domain is an indication of better functioning and the mean standard score on the VABS is 100. All of these studies reported mean baseline standard scores below the average range. Eighty-five percent of studies (n=11/13) reported higher standard scores at follow-up than baseline and 31% (n=4/13) of these studies reported a statistically significant (p<0.05) improvement in scores from baseline to follow-up (Sullivan 2010, Landa 2012, Smith I-B 2015, Blacklock 2013).

Two studies (Eaves 2004, Magiati-Moss cohort) reported a decline in scores from baseline to follow-up and one of these reported a statistically significant (p<0.05) decline (Magiati-Moss cohort). There were no substantial differences between Magiati-Moss cohort and the other studies in participant characteristics (e.g., IQ levels) or methodology to explain the different trajectories, however the Magiati-Moss study did have a longer follow-up period and individuals were older at follow-up compared with the other studies. In addition, the Magiati-Moss cohort recruited children to the study in the late 1990s, which was substantially earlier than some of the other studies. The other three studies where participants showed the least amount of language gain recruited participants at the three next earliest time points (i.e. in the 1990s/early 2000s) relative to the other studies (Berry-Kleinman cohort, Eaves 2004, Meyer 2002). It was not possible to investigate whether type, dose or frequency of intervention may have explained differences in study findings because descriptions of interventions were not detailed within all papers.

In all but two studies (Meyer 2002, Smith I-B 2015) there was greater variability in standard scores between participants at follow-up than at baseline, evidenced by wider confidence intervals around the mean at outcome. Participants in Freeman 2010, Ben

One study of children with IQ>70 (mean: 107.03) was unable to be presented graphically. This study reported a mean standard score of 86.44 (SD 16.53) at 8.3 years. At 12.9 years 12% of children improved in their standard scores, 68% remained unchanged, 20% decreased (Pugliese 2016).

Combining the results of the fourteen studies in a random effects meta-analysis, there was an estimated overall increase of 4.0 units on the VABS scale observed in a study over time (95% CI 0.8, 7.4; I² 82.1%; df 13; p=0.016), Figure 11. There was substantial heterogeneity between studies. Length of follow up was the only covariate which explained some of the observed between-study variance with each year of follow up resulting in an estimated decrease of 3.4 (95% CI -6.1, -0.7; I² 64%; df 12; p=0.001) in the observed VABS score when the Magiati-Moss study was included in the analysis. When the Magiati-Moss study was removed from the meta-regression, none of the study-level covariates VABS score at baseline, average age at baseline, average length of follow up and reported average IQ (<70 or >=70) provided any insight into the observed heterogeneity.
Change in age equivalent scores

One study presented age-equivalents on the VABS for the communication scale. Children were followed from 3.6 years of age for 2 years and gained 0.73 age-equivalence points per month (Munson-Toth). Two studies provided age-equivalents on the VABS split into receptive and expressive communication. In one study, children were aged 1.8 years at baseline and gained 1.85 years in expressive communication and 1.92 years in receptive communication over 2.5 years (Paul 2008). In the other study that contained some children without ASD, children gained 6.9 years in receptive communication and 6.7 years in expressive communication over 17 years (Pickles 2014).
There were five studies where data could not be extracted because they did not provide communication subscale scores from the VABS (Mosconi 2009, Green 2014, Stockholm cohort, Pathways cohort). In cases where data appeared to have been collected but not presented we contacted authors but were not successful in receiving such data.

**Expressive vocabulary**

**Change in raw scores**

Three studies reported raw data on parent-reported expressive vocabulary using the CDI (Oosterling 2010, Bopp cohort, Woynaroski-Yoder cohort). The number of words gained from baseline to follow-up ranged from 35 to 76 over 1.25 years in one study (Oosterling 2010). In one study an average of 58 words was gained over 4.41 years (Bopp cohort) and in study another (Yoder-Woynaroski cohort) 73 words were gained over 1.3 years (Appendix E). Authors of one study were contacted but were not able to provide results from both time points although this information had been collected (Miniscalco 2014).

**Presence or absence of verbal language and phrase language**

**Verbal language**

(n=12) that report both baseline and follow-up data. Seven studies included children aged 5 years and under at baseline and 5 studies children over 5 years at baseline (Figure 12 a,b). The proportion of children who were verbal at baseline ranged from 40% to 70% and at follow-up 66% to 91%. For children over 5 years, the proportion of children verbal at baseline ranged from 23% to 80% and at follow-up 55% to 88%. Nineteen % to 30% of children aged 5 years and under gained verbal language. For children aged over 5 years 5% to 32% gained verbal language over the course of study.
Figure 12 Proportion of individuals with ASD were verbal aged ≤5 years (preschool) (a) and > 5 years (b)
Figure 13  Proportion of individuals with ASD who used phrases (and longer) at baseline and follow-up.
The Howlin cohort followed individuals with an IQ of ≥70 from 6.75 years (SD 2.8) to 44.2 years (SD 9.3). In this study 75% (45/60) of children were verbal and by adulthood 95% (57/60) were verbal. Five studies provided only follow-up data that could be extracted on the proportion of individuals who were verbal (Ballaban-Gil 1996 (93/99; 94%), Howlin 2004 (61/67; 91%), Knorring 1993 (25/34; 74%), Freeman cohort (44/53; 83%). One study grouped by those who were nonverbal (25/165; 15%) and minimally-verbal (17/165; 10%) at outcome (Stockholm cohort). In addition, Anderson-Lord cohort reported 58% (N=74) of children who were nonverbal at 2 years were verbal at 9 years.

**Phrase and/or functional language**

Eleven studies reported on participants who gained the ability to use phrases (Anderson-Lord cohort, Jonsdottir 2007, Kobayashi 1992, Magiati-Moss cohort, Pry 2011, Wolf 1986, Howlin cohort, Sigman 2005, Baghdadli-Darrou cohort, Stockholm cohort, Thurm 2015) and those studies with both baseline and follow-up are presented in Figure 13. The percentage of participants at the end of the study who were able to use phrases ranged between 17% (mean age 7.8 years at follow-up) to 85% (mean age 9 years at follow-up and for children with PDD only (i.e. excluded autistic disorder)). For those children aged over 8 years at baseline, 20% of non-phrase speaking children in one study gained the ability to use phrases over a period of 10 years (Wolf 1986).

Four studies provided only follow-up data that could be extracted on the proportion of individuals using phrases (Howlin cohort 33/68 (49%), Sigman 2005 25/48 (52%), Stockholm cohort 123/165 (75%), Anderson-Lord cohort (Autistic Disorder 48% and PDD-NOS 85%)). One study reported on children who used functional language at baseline (20%) and at follow-up (47%) (Baghdadli-Darrou cohort).
Combining the findings from all studies, the proportion of participants at the end of the study duration who were verbal ranged between 55% (median age 20 years at follow-up) to 95% (mean age 44.2 years at follow-up). The proportion of participants using phrases ranged from 33% (mean age at follow-up 17 years) to 85% (mean age at follow-up 9 years).

**Predictors of language outcomes**

Twenty-three studies (43%) investigated one or more predictors of language outcomes including child factors (baseline language levels, adaptive behaviour, IQ, autism symptomology, theory of mind, acting out behaviours, inattentive behaviour, rate of change in language, age, play, joint attention, motor imitation and fine and gross motor ability), parent factors (parent language styles and maternal responsiveness) and external factors (intervention). Appendix D provides more information on the predictors assessed in each study but as this review was not designed to assess predictors of outcome no further information is presented.

**Discussion**

Language development in individuals with ASD is complex and heterogeneous. Not all children with ASD experience language difficulties, but the majority do (Levy et al., 2010). A substantial number of studies (n=54) collectively including a large number of children (N=5064) has been published that have provided valuable longitudinal information on language outcomes in ASD. To date however, it has been challenging for clinicians and parents to interpret these findings. This is because there is inconsistency and variability in study methods and participant characteristics.
Moreover, the quality of the studies varies, which may contribute to difficulty weighing the significance of the findings from each study.

**Summary of findings from studies**

We synthesised available information on verbal language outcomes and assessed the quality of included studies. Substantial variability was seen in mean language scores and slopes of the language trajectories across studies. Yet, studies reported generally similar overall findings in that mean baseline and outcome scores on standardised language tests were consistently lower for children with ASD than reference norms, with one exception that included only children with IQ>80 (Pellicano cohort).

Moreover, in all included studies the majority of children with ASD continued to make positive language gains, including children aged over 5 years at baseline. Language gains occurred across multiple domains, including syntax (receptive and expressive), vocabulary (receptive and expressive), adaptive language and the acquisition of verbal language. Children under 9 years progressed at a rate comparable to reference norms based on receptive and expressive syntax and receptive vocabulary standard scores, with some studies showing a significantly faster rate of progress or ‘catch up’ compared with reference norms in receptive (n=4; 57%) and expressive syntax (n=3; 43%). Findings from studies that reported age-equivalent scores for syntax and receptive vocabulary were less consistent, with evidence of some divergence from an age expected rate of progress in some studies but not others. The vast majority of studies (n=12/13; 92%) reporting data on adaptive language in children aged under 11 years demonstrated a rate of progress comparable to age expected norms with 31% of studies reporting some ‘catch up’ to age expected norms, based on standard scores. Gains in these studies (n=12) were observed both in children with and without intellectual disability, across
different ASD subgroups and across studies where participants accessed intensive behavioural interventions or intervention in the community.

The findings from studies of individuals followed from middle childhood to adulthood are less consistent than for younger children but suggest the same rate of progress experienced during childhood may not be maintained beyond 9 years of age. Language trajectories reported in the few studies conducted during adolescence were flatter for children from middle childhood to adolescence with a growing gap between language ability in children with ASD and reference norms (Pickles et al., 2014; Sigman & McGovern, 2005). Similar findings were reported in studies of adults (Howlin et al., 2004). There are a number of potential explanations for slowing of language trajectories into adulthood. There is some evidence of a ‘second wave of deficit’ or ‘second hit’ that emerges in the second decade of life that may impact trajectories of development (Minshew & Williams, 2007; Picci & Scherf, 2015). It may also be that individuals with ASD have difficulty managing the increasing complexity of language required during adolescence and adulthood.

Alternatively, it is possible more recently published studies including younger cohorts have included individuals diagnosed using broader criteria than previous studies. As such, more recent studies may include individuals with less severe phenotypes and a smaller proportion of children with intellectual disabilities (Keyes et al., 2012). This was evidenced by the studies demonstrating faster rates of development being those more recently published. Finally, interventions, particularly intensive interventions, are more readily available in more recent years and this may have an impact on outcomes on children under 8 years. Many funding programs are also focused on early rather than life course interventions, and it is possible that as interventions are reduced progress
also decreases. Further research on language trajectories into and throughout adulthood is vital if we are to understand the communication support needs of adults with ASD in the future (Magiati et al., 2014).

**Considerations for interpreting data in this review**

In the current review we have reported findings at a group level (group means) as this is how included studies reported their findings, yet substantial variability was seen within cohorts for individual baseline and outcome scores, evidenced by large standard deviations. Some children with ASD may make dramatic progress, while others may make limited progress. Future studies should examine individual variation and present data for important subgroups so we can refine predictions of prognosis. Furthermore, a review specifically designed to analyse predictors of language outcome will aid our understanding of important factors that may impact language trajectory.

Although we have used standard scores cross-sectionally to report trajectories here to increase clinical utility the shape of trajectories between time points is not known. The potential for regression to the mean when plotting trajectories has been underscored by some authors (Tomblin et al., 2003) and consideration should be given to the heterogeneity between studies when interpreting the meta-analysis findings. Furthermore, we used reference norms for comparison and did not require studies to include typically developing children. It is known that some variability in scores over time is not unique to ASD (Conti-Ramsden et al., 2012; McKean et al., 2015; Ukoumunne et al., 2012) so ideally studies would include other groups of children so language development in ASD can be placed within a developmental context.
There is some evidence from this review that studies that used age-equivalent scores reported slower rates of development than those studies reporting standard scores and there may be some bias in the way data is presented by studies. Studies of children who are more severely affected may be more likely to report age-equivalents as children may not reach the basal levels required for reporting standard scores and there may be floor effects. A related consideration is that it can be challenging (and inappropriate) to assess some children (e.g., minimally verbal children) using standardised tools as the children may not have the ability to complete the tasks and/or may not reach the basal level for scoring (Kasari et al., 2013). In addition, there may be a proportion of children with ASD who are not represented here because of severe language impairment and their lack of inclusion in studies may have resulted in an over-estimate of language gain in summary scores. Finally, the VABS is an important parent-reported measure of adaptive communication but it is susceptible to reporting bias and is not a measure of structural language ability so caution should be taken when interpreting the findings from this tool regarding a child’s structural language abilities.

Research implications

Improvements are needed in both the methodology and reporting of language outcome studies for ASD cohorts. Recommendations and guidelines have been developed for designing high-quality prognosis studies and for assessing the quality of studies (Hayden et al., 2013). These best practice guidelines were used here to assess risk of bias in included studies. The majority of included studies were rated medium to high risk of bias, with less than 5% at low risk of bias. While the high risk of bias in some studies may be because they were not intentionally planned prognosis studies, best practice methodological approaches for prognosis are crucial for interpreting and
weighting the findings of individual studies. It is important that information be collected prospectively on a sample of children diagnosed according to best practice at study commencement. Inclusion criteria for this review stated all children required a diagnostic assessment using established diagnostic criteria at baseline (e.g., DSM, ICD), however a substantial number (33%) of studies were retrospective and did not report on the children who were not available at follow-up. This may have the potential to bias toward a positive outcome.

Ideally, studies should recruit from a population-based sample or from clinical services that provide services for the broad population of children with ASD, so the individuals are representative of individuals in the general population with ASD. Only five studies derived their samples from a population source, with the rest being selected clinical samples. Clinical samples have been reported to be skewed toward more severely affected individuals and as such the findings may be less transferrable to the full range of individuals with ASD. Data from such studies can still be useful, but application is limited to children or adults with the same types of strengths and difficulties.

Studies should attempt to ensure high retention of participants over time and it is important to report on differences between participants that were lost to follow-up and those who were not. Of the studies in this review that were prospective, 53% retained more than 80% of participants at follow-up. Few studies provided detailed descriptions of the individuals who were lost to follow-up. Finally, clinicians completing the assessments should be blind to individual’s baseline characteristics and diagnosis to avoid bias. In this review only 10% of studies provided information about blinding of clinicians. Individuals in studies reporting age-equivalent scores had slower trajectories than in studies reporting standard scores. This may reflect bias as it is possible studies
may choose to report age-equivalents when they contain participants who are lower functioning or less able to complete standardised tools or obtain standard scores.

Clinical implications

Despite methodological variations there was a general pattern in overall findings, which although not fine-tuned for individuals, will be useful for clinicians and those caring for people with ASD. Key messages are highlighted below. Table 10.
### Key messages for clinicians

<table>
<thead>
<tr>
<th>Key messages for clinicians</th>
</tr>
</thead>
<tbody>
<tr>
<td>55-95% of individuals who were minimally verbal became verbal at follow up</td>
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<tr>
<td>In all but one study children with ASD had mean scores below average at baseline and follow up</td>
</tr>
<tr>
<td>96% of studies showed that children aged under 11 with ASD tracked at comparable rate of language development to age-expected rates, based on standard scores. This occurred in children with and without intellectual disability and in children who received intensive behavioural interventions and those who received intervention in the community.</td>
</tr>
<tr>
<td>In 40% of studies reporting standard scores children under 11 years demonstrated some ‘catch up’ to peers (i.e. faster rate of progress than age-expected norms)</td>
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<tr>
<td>There was some evidence language development began to slow down in later years.</td>
</tr>
<tr>
<td>There is a high need for research on adolescent and adult language outcomes.</td>
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</tbody>
</table>

### Future directions

It is clear much needs to be done to refine the accuracy of predictions of language outcomes. Understanding how language trajectories may change across the lifespan and the developmental periods where individuals may be more ‘vulnerable’ to slower progress (e.g., before 2 years and after 10 years) is highly relevant for policy makers and service providers so they can accurately plan future funding, support and service needs for individuals with ASD across the lifespan. Moreover, families and clinicians
need clear and accurate information on the likely communication outcomes for their children ASD based on their child’s characteristics so they can better anticipate ongoing needs. A more fine-tuned understanding of language trajectories should also enable more tailored interventions.

Very few studies reported individual trajectories or clinical subgroups of ASD. Few studies assessed individuals beyond the age of 11 years using language specific tools. We need information to apply the findings from the studies to individuals of different ages and with a broad range of clinical characteristics. This study has also highlighted an important subgroup with ASD who fail to develop the ability to speak by 24 years of age (5-45%). The implications of being unable to speak are substantial in terms of the impact on participation and function and the likely support needs of these individuals. Evidence-based interventions are sorely lacking for this population but are crucial if we are to prevent the adverse sequelae that are likely to accompany poor language outcomes (Kasari et al., 2014; Paul et al., 2013; Tager-Flusberg et al., 2016).
Chapter 6  Methodology for Studies 2 and 3

The methods for each study in this thesis will be described in the relevant chapter: Study 2 in Chapter 7 and Study 3 in Chapter 8. This Chapter provides further detail about overarching methods used in Study 2 and 3 that have not been described in the subsequent chapters.

Study design

The participants in Study 2 and 3 were drawn from the Early Language in Victoria Study (ELVS). This is a prospective, longitudinal community-based study of language development in children living in Victoria. The overarching aim of the ELVS was to study the epidemiology and natural history of language development in children from infancy to 7 years (for more detail see Reilly et al., 2006; Reilly et al., 2007)

Population representation

At study inception (2003-2004) 1910 participants were recruited to the ELVS. In 2011 when participants were 7 years of age there were 1189 participants, which represented 62% of the original sample. The participants in the ELVS have been followed up until 13 years but in Study 2 and 3 we used data up until Wave 8, when participants were 7 years old.

Measures

Participants were initially enrolled in the ELVS at 7.5-10 months of age and were assessed almost yearly using direct assessments and/or parent-completed questionnaires
focused on language development. Direct assessments occurred at 4, 5 and 7 years.

Information was also collected on areas related to language and communication (child, family and environmental factors) such as general development, health, parent-child interaction, literacy, temperament, child behaviour and demographic factors.

The specific measures used by Study 2 and 3 are described below in Tables 11-13.

**Demographic information**

Demographic data was collected by questionnaire when participants were 8-12 months for the following: gender, date of birth, number of children in the home, English as main language spoken at home, Indigenous status, married/de facto, Socio-Economic Index for Areas (SEIFA) score, maternal age at birth and primary caregiver completed high school.
### Language measures

#### Table 11 Language and communication measures

<table>
<thead>
<tr>
<th>Study</th>
<th>Purpose of measure</th>
<th>Measure</th>
<th>Brief description</th>
<th>Age administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 2</td>
<td>Trajectories</td>
<td>MacArthur Bates Communicative Development Inventories -Words and Gestures form and Words and Sentences form (CDI; Fenson, 1993). Only expressive vocabulary raw scores were used.</td>
<td>Parent-completed questionnaire of early communication. The CDI has been validated in the general population and in children with developmental difficulties and has frequently been applied in ASD studies (e.g., Bopp &amp; Mirenda, 2011; Charman, Drew, et al., 2003; Luyster et al., 2007; Mitchell et al., 2006).</td>
<td>1 year (CDI: Words and Gestures) 2 years (CDI: Words and Sentences)</td>
</tr>
<tr>
<td>Study 2</td>
<td>Trajectories</td>
<td>Communication Symbolic Behaviours Scales-Infant Toddler Checklist (CSBS-ITC; Wetherby &amp; Prizant, 2002). Raw scores used.</td>
<td>Parent-completed questionnaire on early communication, social and symbolic development. Validated as a broadband screener for ASD (Wetherby, Brosnan-Maddox, Peace, &amp; Newton, 2008). There are seven clusters: emotion and eye gaze (0-8 possible points), communication (0-8), gestures (0-10), sounds (0-8), words (0-6), understanding (0-6) and object use (0-11). The cluster scores are collapsed into 3 composite scores: social (emotion, eye gaze, communication, gesture) (0-26), speech (words and sounds) (0-14),</td>
<td>1 &amp; 2 years</td>
</tr>
<tr>
<td>Study</td>
<td>Purpose of measure</td>
<td>Measure</td>
<td>Brief description</td>
<td>Age administered</td>
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</table>
| Study 2 & 3 | Determining comparison groups Trajectories and predictor analysis (Study 3) | The Clinical Evaluation of Language Fundamentals (Fourth Edition and Preschool 2 version)(CELF-4, CELF-P2; Semel, Wiig, & Secord, 2003; Wiig, Secord, & Semel, 2006) | This is a comprehensive standardised tool that measures receptive and expressive language. Language domains including morphology (grammar), syntax (sentence structure), semantics (word meanings) and vocabulary are assessed. The CELF P2 is for children aged 3 to 6 years and the CELF 4 is for individuals aged 5 to 21 years. Test-retest reliability on the CELF-4 is high ($r=0.71$ to $0.86$ for subtests and $r=0.88$ to $0.92$ for composite scores). Internal consistency range from $0.87$ to $0.95$ for subtests and $0.97$ to $0.95$ for composite scores. The CELF-4 has sensitivity of 1 and specificity of 0.82 at -1 standard deviation (Semel et al., 2003). | CELF-P2 at 4 years  
CELF-4 at 5 and 7 years |
Table 12  Nonverbal IQ measures

<table>
<thead>
<tr>
<th>Study</th>
<th>Purpose of measure</th>
<th>Measure</th>
<th>Brief description</th>
<th>Age administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 3</td>
<td>Predictor measure</td>
<td>The Kaufman Brief Intelligence Test-2 (K BIT 2; Kaufman &amp; Kaufman, 2004).</td>
<td>A direct assessment measure of nonverbal intelligence. The matrix reasoning subtest was used. Nonverbal interval consistency correlations were 0.78 to 0.93. Test retest yielded correlations from 0.76 to 0.93. Correlations with the WASI, WISC-IV were in the moderate to high range (Kaufman &amp; Kaufman, 2004)</td>
<td>4 years</td>
</tr>
<tr>
<td>Study 2 &amp; 3</td>
<td>Determining comparison groups</td>
<td>Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999)</td>
<td>A direct assessment of nonverbal intelligence. The block design and matrix reasoning subtests were used. Internal reliability for the subtests varies by age but ranges between upper 80s to upper 90s. Test re-test reliability ranged from 0.76 to 0.93 for the subtests. It has high correlations with the WISC-IV IQ tests ranging from 0.75 to 0.83 depending on the subtest. (Wechsler, 1999).</td>
<td>7 years</td>
</tr>
</tbody>
</table>
## Social communication measures

### Table 13  Social communication measures

<table>
<thead>
<tr>
<th>Study</th>
<th>Purpose of measure</th>
<th>Measure</th>
<th>Brief description</th>
<th>Age administered</th>
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<tbody>
<tr>
<td>Study 2 &amp; 3</td>
<td>Determining comparison groups</td>
<td>Social Communication Questionnaire (SCQ; Rutter, Bailey, &amp; Lord, 2003)</td>
<td>The SCQ is a 40 item parent-report questionnaire based on the ADI-R. In a study comparing the SCQ with other screening tools this tool performed the most highly with sensitivity at 0.86 and specificity at 0.78 (Charman et al., 2007).</td>
<td>7 years</td>
</tr>
<tr>
<td>Study 3</td>
<td>Predictor measure</td>
<td>The Pediatric Quality of Life Inventory 4.0: parent report form (Peds QL; Varni, Seid, &amp; Kurtin, 2001)</td>
<td>A parent-completed questionnaire that assesses a child’s quality of life. The social functioning subscale was used from the Peds QL. Examples of social items include: ‘I have trouble getting along with other children’; ‘other kids do not want to be my friend’. A critical review reported the Peds QL was the most frequently used tool and the only tool in which reliability and validity had been established for ASD (Ikeda, Hinckson, &amp; Krageloh, 2014). Significant correlations were found between the Peds QL and measures of ASD symptoms and functional impairments.</td>
<td>4 years</td>
</tr>
<tr>
<td>Study</td>
<td>Purpose of measure</td>
<td>Measure</td>
<td>Brief description</td>
<td>Age administered</td>
</tr>
<tr>
<td>----------</td>
<td>--------------------</td>
<td>----------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Study 3</td>
<td>Predictor measure</td>
<td>Strengths and Difficulties Questionnaire</td>
<td>A parent-completed questionnaire. The peer relationship problems and pro-social behaviour subscales were used. Examples of social items include: ‘rather solitary, tends to play alone’; ‘shares readily with other children’. The SDQ has been evaluated with children with ASD in a number of studies (Iizuka et al., 2010). One study examined the SDQ as a predictor of parent-reported diagnosis of ASD and found sensitivity was 79% and specificity 93% (Russell, Rodgers, &amp; Ford, 2013).</td>
<td>4 years</td>
</tr>
</tbody>
</table>
Change in language tool versions over different study waves

A different version of the CELF was used at 4 years (CELF-P2; n=1560) compared with 5 and 7 years (CELF-4; n=982 at 5 years and n=1204 at 7 years). To check consistency between the measures we compared means and ranges for the sample on each wave (Table 14). The scores were comparable across versions.

Table 14  Mean scores for the CELF-P and CELF-4 at each year the tool was administered.

<table>
<thead>
<tr>
<th>Tool (age administered)</th>
<th>Mean (SD; range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CELF-P2 (4 years)</td>
<td>99.62 (15.1; 50-140)</td>
</tr>
<tr>
<td>CELF-4 (5 years)</td>
<td>100.6 (13.9; 55-144)</td>
</tr>
<tr>
<td>CELF-4 (7 years)</td>
<td>98.8 (13.6; 45-136)</td>
</tr>
</tbody>
</table>

Participants

Selection criteria

Inclusion and exclusion criteria varied for each study and are detailed in the flow chart below (Figure 14).
Loss to follow up

In Study 2 only 7% (3/44) of the children with ASD were lost to follow up. In Study 3 a larger number of children with ASD (36%, n=16/44) were lost to follow up or excluded from the study based on selection criteria. To ensure our study did not have systematic bias due to loss to follow up we tested whether there were important differences between characteristics of children with ASD who remained in the study and those who did not. Children lost to follow up or excluded from the study had lower mean nonverbal IQ and expressive vocabulary scores however the differences between the groups were not significant (p>0.05). There were also no significant differences in any of the demographic characteristics collected (Table 15).
### Table 15. Characteristics of those children with ASD included and not included in Study 3.

<table>
<thead>
<tr>
<th></th>
<th>Not included</th>
<th>Included</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>16</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>75</td>
<td>85.7</td>
<td>0.375</td>
</tr>
<tr>
<td>No. children at home M(SD)</td>
<td>1.56 (0.62)</td>
<td>1.75 (0.7)</td>
<td>0.381</td>
</tr>
<tr>
<td>English as main language spoken at home (%)</td>
<td>93.8</td>
<td>100</td>
<td>0.181</td>
</tr>
<tr>
<td>Married/defacto (%)</td>
<td>100</td>
<td>96.4</td>
<td>0.444</td>
</tr>
<tr>
<td>Socio-economic index (SEIFA) M (SD)</td>
<td>1043 (61.74)</td>
<td>1021 (63.99)</td>
<td>0.284</td>
</tr>
<tr>
<td>Maternal age at birth M (SD)</td>
<td>32.9 (6.40)</td>
<td>33.07 (4.96)</td>
<td>0.910</td>
</tr>
<tr>
<td>Primary caregiver has completed high school (%)</td>
<td>80</td>
<td>75</td>
<td>0.712</td>
</tr>
<tr>
<td>CDI score at 2 years M (SD)</td>
<td>104.67 (140.97)</td>
<td>178.48 (161.21)</td>
<td>0.146</td>
</tr>
<tr>
<td>Nonverbal IQ M (SD)</td>
<td>82.71 (21.06)</td>
<td>99.71 (14.35)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

### Ethical considerations

Ethical approval was obtained from the Human Research Ethics Committee at the Royal Children’s Hospital (no. 23018) and La Trobe Health Sciences Human Ethics Committee (no. 03-32).

### Statistical Analysis

All statistical analyses were conducted using Stata version 13.1 and version 14.0. Details regarding the statistical analysis relative to identified aims for the three main studies is provided in the relevant chapter.
Summary of overarching methods

Studies 2 and 3 in this thesis use data from a large longitudinal community-based study. The findings from these studies are combined with a systematic review to examine trajectories of language development in children with and without ASD. The systematic review (Study 1) predominantly included studies that used clinical samples and Studies 2 and 3 (utilising the ELVS data) extend the current literature to investigate language trajectories using a community sample.
Chapter 7  Study 2. Parent reported patterns of loss and gain in communication in 1 to 2 year old children are not unique to autism spectrum disorder

The following paper examined trajectories of communication from 1 to 2 years in children with ASD compared with children with LI and TD. It also compared the proportion of children who lost skills, the types of skills lost and the extent of skill loss across different communication domains between the three groups (ASD, LI, TD). This paper was published in Autism in May 2016.
Parent-reported patterns of loss and gain in communication in 1- to 2-year-old children are not unique to autism spectrum disorder

Amanda Brignell1,2, Katrina Williams1,2,3, Margot Prior1, Susan Donath1,2, Sheena Reilly2,4, Edith L Bavin5, Patricia Eadie1 and Angela T Morgan1,2

Abstract
We compared loss and gain in communication from 1 to 2 years in children later diagnosed with autism spectrum disorder (n = 41), language impairment (n = 110) and in children with typical language development at 7 years (n = 831). Participants were selected from a prospective population cohort study of child language (the Early Language in Victoria Study). Parent-completed communication tools were used. As a group, children with autism spectrum disorder demonstrated slower median skill gain, with an increasing gap between trajectories compared to children with typical development and language impairment. A proportion from all groups lost skills in at least one domain (autism spectrum disorder (41%), language impairment (30%), typical development (26%)), with more children with autism spectrum disorder losing skills in more than one domain (autism spectrum disorder (47%), language impairment (15%, p = 0.0003), typical development (16%, p < 0.001)). Loss was most common for all groups in the domain of ‘emotion and eye gaze’ but with a higher proportion for children with autism spectrum disorder (27%; language impairment (12%, p = 0.03), typical development (14%, p=0.03)). A higher proportion of children with autism spectrum disorder also lost skills in gesture (p = 0.01), sounds (p = 0.009) and understanding (p = 0.004) compared to children with typical development but not with language impairment. These findings add to our understanding of early communication development and highlight that loss is not unique to autism spectrum disorder.

Keywords
autism spectrum disorder, communication, language, regression, skill loss, trajectory

Introduction
Autism spectrum disorder (ASD) is one of the most common neurodevelopmental disorders and is known to be heterogeneous. In addition to phenotypic heterogeneity, children with ASD demonstrate heterogeneous patterns of onset and trajectories of development (Kim et al., 2015; Landa et al., 2013; Ozonoff et al., 2010; Shumway et al., 2011). There has been a substantial focus on early social communication development in ASD because a deeper understanding of the loss and gain in skills in the first few years of life has the potential to build knowledge of how ASD unfolds. It may also assist identification, help delineate potential subgroups of children with ASD and shed light on the neurobiological mechanisms that underpin the disorder. However, one of the challenges in studying early social communication development in ASD is that children are not typically diagnosed before 3 years of age (Bent et al., 2015).

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Retrospective studies have traditionally described two distinct patterns of onset in ASD: early onset ASD and regressive ASD. Early onset ASD is the gradual unfolding of symptoms over the course of the first few years of life. Regressive onset is a pattern of normal or near normal development followed by an abrupt or gradual loss of skills (Stefanatos, 2008), primarily involving the loss of words and/or social communication skills (Lord et al., 2004). Approaches to defining and measuring regression are varied in the literature. The vast majority of retrospective studies have used the Autism Diagnostic Interview–Revised (ADI-R; Lord et al., 1994) to measure regression. This tool defines loss of skill as being ‘communicative use of at least five different words (other than “mama” and “dada”) on a daily basis for at least 3 months’ and requires that there has been a loss of the skill for at least 3 months (quoted from a test booklet of an assessment tool; Lord et al., 1994). A small number of retrospective studies have used the Regression Validation Interview (Luyster et al., 2005; Thurm et al., 2014). This is a detailed semi-structured parent interview that obtains more comprehensive information on skill attainment and loss. Prospective studies have generally taken a repeated measures approach by examining change in social communication skills and language across frequent time intervals (Brian et al., 2014; Landa et al., 2013; Ozonoff et al., 2010).

A systematic review of 85 studies (n=29,035) of which 98% were retrospective, and the remainder high-risk sibling studies, included data on regression in ASD (Barger et al., 2013). The prevalence of regression in ASD was reported to be approximately 32% (95% confidence interval (CI) 30–35). The average age at which regression occurred was 20 months (95% CI 1.7–1.9; Barger et al., 2013). In children with typical development (TD), language impairment (LI) or developmental delay, regression has been reported as less common, ranging from 0% to 24% (Baird et al., 2008; Landa et al., 2013; Lord et al., 2004; Pickles et al., 2009; Thurm et al., 2014).

Retrospective studies of children with ASD carry a number of methodological limitations that substantially increase risk of bias and limit detailed assessment of development (Ozonoff et al., 2008, 2011). By contrast, high-risk sibling studies have been developed to prospectively monitor development on the pathway to ASD, recruiting siblings of children with ASD during pregnancy or soon after birth (Chawarska et al., 2014; Messinger et al., 2013; Ozonoff et al., 2010; see Jones et al., 2014 for a review). The findings from high-risk studies have challenged the way early social communication development in ASD has traditionally been understood, suggesting that dichotomous categories of regression do not adequately capture the many ways ASD can emerge (Kalb et al., 2010; Landa et al., 2013; Landa and Garrett-Mayer, 2006; Ozonoff et al., 2010; Shumway et al., 2011; Siperstein and Volkmar, 2004). Some studies, for example, have proposed a range of onset patterns including early onset (early delays, no loss), delay and regression (some early delays before loss), plateau (no early delays, no loss) and regression (no delays before a clear loss of skills; Kalb et al., 2010; Ozonoff et al., 2008; Shumway et al., 2011). Whereas two high-risk sibling studies grouped children by different developmental trajectory types or classes such as accelerated development, normative development, delay in some areas of development (e.g. fine/gross motor and language) and widespread delay with declining trajectories (Brian et al., 2014; Landa et al., 2012). These studies have highlighted the importance of placing loss of different types of skills within the context of trajectories of development.

Different elements of development have been reported to be lost by different studies. Specifically, loss of eye contact and gaze to faces has been reported to be the most common social communication skill lost by a number of retrospective studies (e.g. Ozonoff et al., 2005; Thurm et al., 2014). Eye gaze, shared positive affect, social interest, smiling and initiating interactive games have been reported to show declining trajectories in prospective high-risk sibling studies (Landa et al., 2007, 2013; Ozonoff et al., 2010) with word loss less common (Landa et al., 2013).

There has been debate about whether children in high-risk sibling studies are representative of children without a family history of ASD. For example, high-risk siblings may have different phenotypes to children without a family history of ASD (Mitchell et al., 2006; Pandey et al., 2008; Sebat et al., 2007) and may be more at risk of other developmental difficulties, including LI and learning difficulties (Landa et al., 2013; Szatmari et al., 2000).

To our knowledge no longitudinal population-based studies have been published that have investigated loss and gain in communication skills prior to the child’s ASD diagnosis. Nor have any studies used large samples of children without ASD as comparison groups. This study uses data from a prospective population-based study investigating language development collected at 1 and 2 years to describe early communication trajectories.

The aim of this study was to describe loss and gain of communication skills from 1 to 2 years in children later diagnosed with ASD, LI and in children with typical language development. Specifically, we wanted to investigate the proportion of children in each group who lost skills, the type of skills that were lost and the spread of loss across communication domains.

Methods

Study design

Participants were drawn from the Early Language in Victoria Study (ELVS), a prospective, longitudinal, population-based study in Victoria, Australia (Reilly et al., 2006, 2007). Children (n=1910) were recruited from 6 of 31 geographical areas in Melbourne, 8–10 months of age and followed up almost annually. The Socio-Economic
Index for Areas (SEIFA) from the 2001 census data was used (based on income, educational attainment and unemployment from the Census of Population and Housing) to stratify 31 local government areas (LGAs) into three levels (high, medium and low). Two LGAs from each level were then approached for recruiting participants. Participants were recruited via Maternal Child Health nurses, at universal hearing screening appointments, and through public notices. Exclusion criteria included cerebral palsy, known developmental delays or other significant intellectual or physical disability. Participants were also excluded if parents did not speak or read English to a satisfactory level to complete the questionnaires. Demographic information was collected from the primary caregiver when the child was 8 months of age. Parent questionnaires were completed annually, providing information about communication and behaviour development, family factors and the child’s environment. Direct assessments (Clinical Evaluation of Language Fundamentals (CELF)–fourth edition (Semel et al., 2003), and/or Preschool–second edition (Wiig et al., 2006) and the Wechsler Abbreviated Scale of Intelligence (WASI; block design and matrix reasoning subtests; Wechsler, 1999)) were completed by trained psychology graduates or speech pathologists in the child’s home or school, depending on the wave of the study and caregiver preference. The CELF was administered at 4, 5 and 7 years and the WASI at 7 years. Further details on the ELVS study design and sampling methods can be found in Reilly et al. (2006, 2007).

**Ethical considerations**

Ethical approval was obtained from the Human Research Ethics Committee at the Royal Children’s Hospital, Melbourne (#23018) and La Trobe University, Human Ethics Committee (#03–32).

**Outcome measures**

Two parent-completed questionnaires, the Communication Symbolic Behaviours Scales–Infant Toddler Checklist (CSBS-ITC; Wetherby and Prizant, 2002) and the MacArthur-Bates Communicative Development Inventories (CDI; Fenson, 1993) were used to assess early communication at 1 and 2 years. The CDI (Words and Gestures form and Words and Sentences form) is a widely used parent-completed measure of early communication. Only the expressive vocabulary data were used here. The CDI has been validated in the general population and in children with developmental difficulties and has frequently been applied in ASD studies (e.g. Bopp and Mirenda, 2011; Charman et al., 2003; Luyster et al., 2007; Mitchell et al., 2006). The CSBS-ITC is a parent-completed questionnaire on early communication, social and symbolic development. It has been validated as a broadband screener for ASD (Wetherby et al., 2008). There are seven clusters: emotion and eye gaze (0–8 possible points), communication (0–8), gestures (0–10), sounds (0–8), words (0–6), understanding (0–6) and object use (0–11). The cluster scores are collapsed into three composite scores: social (emotion, eye gaze, communication, gesture; 0–26), speech (words and sounds; 0–14) and symbolic (understanding and use of objects; 0–17). A total score (0–57) can also be calculated. We used raw scores from the CSBS-ITC and CDI in this study because we were specifically interested in examining loss of skills.

**Group allocation**

**ASD.** From 4 years of age, all participating parents (n = 1623 at 4 years) were asked via the annual questionnaire whether their child had ever received a diagnosis of ASD. If yes, parents were telephoned by a clinical psychologist or speech pathologist (M.P., P.E.) experienced in the diagnosis of ASD during which information was obtained about how the diagnosis was made, the name and professions of the individuals making the diagnosis, child age at diagnosis and type of diagnosis (e.g. Asperger’s syndrome, autistic disorder) as allocated using classification systems of the time, like the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.; DSM-IV-TR; American Psychiatric Association (APA), 2000). Information about the child’s behaviour and co-morbidities was also obtained. The majority (93%) of children were given a clinical diagnosis by a multidisciplinary team that involved at least two professionals (typically a paediatrician and psychologist and/or speech pathologist). The other children were given a diagnosis by a paediatrician only. When the children were aged 7 years parents were asked to complete the Social Communication Questionnaire (SCQ), a widely used screening questionnaire derived from the ADI-R (Rutter et al., 2003). Mean scores on the SCQ were 14.53 (standard deviation (SD): 4.66; range 5–26; Veness et al., 2014). By 7 years, 44 children had been diagnosed with ASD with a mean age of reported diagnosis of 4 years 8 months (range 2–7 years). Further details on the children with ASD in this sample can be found in Veness et al. (2012, 2014).

**LI and typical language development.** Children were allocated to these categories following review of their performance on the CELF (Preschool–second edition and/or fourth edition) and the WASI. None of the children in the LI and TD groups were reported to have ASD. Figure 1 shows the tools used for this study, the ages they were administered and their role in group allocation and measuring outcomes of interest. Allocation to groups was completed when children were 7 years.

**Exclusion criteria**

A total of 743 children were excluded because (1) there were incomplete or missing data at both time points (1 and
(2) they were not assessed or did not complete the CELF at 7 years and at one other time point and (3) they did not complete a non-verbal IQ measure at 7 years. They were also excluded if they did not fit into the pre-specified groups (ASD, LI and TD), for example, if the child was delayed on both the CELF-4 and the WASI and was not diagnosed as ASD. The total sample in this study consisted of 982 children (ASD: n = 41; LI: n = 110; and TD: n = 831).

**Statistical procedures/data analysis**

All analyses were conducted using Stata version 13.1. The ELVS sample is skewed towards families who are more advantaged and thus SEIFA quintiles, based on the Australian Bureau of Statistics reference, were used for adjusted data analysis where appropriate.

**Trajectories**

On inspection prior to analysis, it was clear that the data distribution was asymmetric for the children with ASD for the CSBS-ITC and CDI scores at each wave. Hence, non-parametric analyses were conducted and medians (interquartile ranges) were reported instead of means (SDs). Raw scores on the CSBS-ITC (social, speech and symbolic composites and total score) were plotted for each individual with ASD at 1 and 2 years. Classification into trajectory types was done as follows: acceleration: higher gradient than the mean gradient for TD children, improving: higher score at 2 than 1 year but no acceleration, plateau: same score at 1 and 2 years and loss: lower score at 2 than 1 year. Median CDI scores (number of words produced) for each group were plotted at 1 and 2 years.

Comparison was made between median scores on CSBS-ITC and CDI for children with ASD, TD and LI at 1 and 2 years using the Wilcoxon rank sum test, corrected for multiple comparisons using Bonferroni correction with p < 0.002 required to reach statistical significance. Box plots were graphed to show the differences in medians (interquartile ranges) and the rate and direction of change on the CSBS-ITC composites and total scores from 1 to 2 years. Questionnaires at both 1 and 2 years were all completed within 2 months either side of the child’s birthday.

**Definition of loss of skills**

The period between 1 and 2 years is typically a period of great growth in communication skills (Fenson and Dale, 1994; Goldfield and Reznick, 1990) and it would be considered unusual for a child to lose skills previously obtained over this 1-year period, either by not using a previously acquired skill or by changing from being able to use a skill ‘always’ to only using the skill ‘sometimes’. Hence, children were classified as having lost skills if they achieved a
lower raw score at 2 than 1 year on the CSBS-ITC and/or if they had fewer words on the CDI at 2 years compared to 1 year. The definition of ‘loss of skills’ for the CDI was developed because to our knowledge there is no published, standardised definition of how ‘loss of skills’ should be defined. Our definition is conservative because between 1 and 2 years of age children often have rapid word acquisition, and gain of only a single word or no word gain could also be considered atypical. In the absence of agreement, we decided a conservative approach was ideal.

CSBS-ITC. Differences in scores were calculated for cluster, composite, and total scores. Average magnitude of loss (and range) was calculated for each group. The number of children per group who lost skills in one or more clusters was calculated and graphed. Odds ratios (with CIs and p values) were used to compare loss of skills in the cluster, composite and total scores across the different groups (ASD vs LI; ASD vs TD). Odds ratios were adjusted for gender and socio-economic status.

CDI. The difference between scores at 1 and 2 years was calculated using the total expressive vocabulary score on the Words and Gestures and Words and Sentences forms. We used the full vocabulary from the latter form to provide a more conservative estimate. This ensured that substitution of early words with more complex words was not counted as a loss.

Table 1. Sample characteristics for children with ASD, language impairment and typical development.

<table>
<thead>
<tr>
<th>Sample Characteristics</th>
<th>ASD (n=41)</th>
<th>LI (n=110)</th>
<th>TD (n=831)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>83</td>
<td>55</td>
<td>45</td>
<td>ASD &gt; TD (&lt;0.001) ASD &gt; LI (=0.002)</td>
</tr>
<tr>
<td>Number of children at home (mean (SD; range))</td>
<td>1.7 (0.7; 1−3)</td>
<td>1.9 (0.9; 1−5)</td>
<td>1.7 (0.8; 1−5)</td>
<td>LI &gt; TD (=0.0007)</td>
</tr>
<tr>
<td>English as main language spoken at home (%)</td>
<td>97.6</td>
<td>94.6</td>
<td>97.5</td>
<td>–</td>
</tr>
<tr>
<td>Indigenous (%)</td>
<td>0</td>
<td>0</td>
<td>0.12</td>
<td>–</td>
</tr>
<tr>
<td>Married or de facto (%)</td>
<td>97.6</td>
<td>91.8</td>
<td>96.9</td>
<td>–</td>
</tr>
<tr>
<td>SEIFA score (mean (SD; range))</td>
<td>1029.8 (65.5; 855.5−1104.1)</td>
<td>1012.4 (68.1; 834.4−1107.6)</td>
<td>1046.7 (51.8; 834.4−1147.0)</td>
<td>TD &gt; LI (=0.008)</td>
</tr>
<tr>
<td>Maternal age at birth (mean (SD; range))</td>
<td>32.9 (5.4; 21−46)</td>
<td>32.2 (4.8; 19−43)</td>
<td>32.4 (4.2; 19−44)</td>
<td>–</td>
</tr>
<tr>
<td>Primary caregiver has completed high school (grade 12; %)</td>
<td>77.5</td>
<td>63.3</td>
<td>82.2</td>
<td>TD &gt; LI (=0.001)</td>
</tr>
</tbody>
</table>

ASD: autism spectrum disorder; LI: language impairment; TD: typical development; SD: standard deviation; SEIFA: Socio-Economic Index for Areas. Socio-economic status was measured using the SEIFA Disadvantage Index. SEIFA has a mean of 1000 and a SD of 100 with higher scores indicating greater advantage. Only the p values that reached significance (p < 0.01) for the group comparisons are reported.

Results

There was a higher proportion of males in the ASD group compared to the TD and LI groups (p < 0.01), see Table 1 for descriptive characteristics. No significant difference was found in the ASD group compared to the TD and LI groups on any other feature.

Trajectories

Individual trajectories of raw scores from the CSBS-ITC were plotted for children with ASD (Figure 2). Substantial variation between children with ASD is shown, with four main trajectory types seen on both the CSBS-ITC and the CDI: worsening, plateau, improving and accelerating (Figure 3). The majority of children fell into the ‘improved’ trajectory type for both tools. The median composite and total scores at 1 year for the children in all three groups who lost skills were within the average range (see Figure 2, for example).

Median raw scores for all three groups increased over time for both the CDI and CSBS-ITC (Figures 4 and 5 and Table 2). At 1 year, no significant difference was seen in scores on the CDI between the children with TD, LI and ASD groups. However, there was a widening gap between the TD and ASD/LI groups over the next 12 months, which reached significance (p < 0.0001) at 2 years for the difference between the ASD and the TD group but not between the children with ASD and LI.

On the CSBS-ITC, there was a statistically significant difference between the median scores for children with ASD and children with TD at 1 year in the social composite (p < 0.002) and the total score (p < 0.002). At 2 years, a statistically significant difference between medians was found for all the composites and total score for the ASD group compared to the LI and TD groups (p < 0.002), except in the speech composite where there was not a statistically significant difference between the LI and ASD children.

Differences in proportions of children who lost communication skills across groups

Only two children in the study sample had a smaller vocabulary at 2 than 1 year on the CDI. One child diagnosed with ASD used five words at 1 year (grandma, baa,
A proportion of children in all three groups had lower scores on the CSBS-ITC at 2 than 1 year. Percentages are reported for CSBS-ITC cluster scores within each composite on the CSBS-ITC. The ASD group had a higher percentage of children who lost skills compared to the LI and TD groups in all clusters except ‘use of objects’ (Table 3). In total, 41% of children with ASD lost skills in at least one cluster compared to LI (30%) and TD (26%). The cluster with the greatest loss for all groups was ‘emotion and use of eye gaze’, with the ASD group having around double the percentage of children who lost skills compared to the other two groups (27% ASD, 12% LI and 14% TD). Few females in the ASD group demonstrated loss of skills, while the number who lost skills in the LI and TD groups were more evenly split by gender (Table 3).

Odds ratios were calculated to investigate whether children with ASD had greater odds of losing skills than the other two groups (Table 4). In the cluster of ‘emotion and use of eye gaze’, the odds of losing skills for the children with ASD were 2.3 to 3 times higher than those for children with TD (p < 0.05) and LI (p < 0.05) respectively. Loss of skills was also significantly higher for

Figure 2. Individual trajectories of communication development (social, speech, symbolic composites and total raw scores, CSBS-ITC) from 1 to 2 years for children with ASD (n = 41).

Figure 3. Trajectory types for children with ASD (loss, plateau, improve and accelerate) for the CSBS-ITC and the CDI. Bars for each composite or CDI score are in order of appearance in the legend.
Figure 4. Trajectory of median number of words produced for children with ASD, LI and TD at 1 and 2 years.

Figure 5. Median and interquartile range for raw scores on the CSBS-ITC (total score and composite scores) from 1 to 2 years for children with ASD, LI and TD. Groups are presented left to right as TD, LI and ASD at each age.
Autism children with ASD than TD in the clusters of gesture (p < 0.05), sounds (p < 0.01) and understanding (p < 0.01). The proportion of children who lost skills was significantly higher in children with ASD compared to TD in the speech (p < 0.001) and symbolic (p < 0.05) composites as well as the total score (p < 0.01). Odds ratios were not statistically different for other comparisons that were possible between ASD and LI, and odds ratios could not be calculated for the total score in children with LI compared to ASD as no child in the LI group demonstrated a loss of skills.

Table 2. CDI median scores for each group (ASD, LI and TD) at 1 and 2 years.

<table>
<thead>
<tr>
<th></th>
<th>Median (interquartile range)</th>
<th>Aged 1 year</th>
<th>Aged 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD</td>
<td>2 (0−6)</td>
<td>99.5 (34−206)*</td>
<td></td>
</tr>
<tr>
<td>LI</td>
<td>1 (0−4)</td>
<td>114 (41−227)</td>
<td></td>
</tr>
<tr>
<td>TD</td>
<td>4 (0−8)</td>
<td>282 (175−404)*</td>
<td></td>
</tr>
</tbody>
</table>

CDI: Communicative Development Inventories; ASD: autism spectrum disorder; LI: language impairment; TD: typical development.

*Significant difference between these two medians (p < 0.0001).

Table 3. Proportion of children with ASD, LI and TD with lower scores at 2 years compared to 1 year on the CSBS-ITC.

<table>
<thead>
<tr>
<th></th>
<th>ASD</th>
<th>LI</th>
<th>TD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=41</td>
<td>n=110</td>
<td>n=831</td>
</tr>
<tr>
<td>Males</td>
<td>Males</td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td>Emotion eye gaze</td>
<td>29</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Communication</td>
<td>12</td>
<td>29</td>
<td>6</td>
</tr>
<tr>
<td>Gesture</td>
<td>18</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Social composite</td>
<td>15</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Sounds</td>
<td>18</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Words</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Speech composite</td>
<td>9</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Understanding</td>
<td>6</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Object use</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Symbolic composite</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Total score</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>


Table 4. Adjusted odds ratios for loss of skills in children with ASD compared to LI and TD.

<table>
<thead>
<tr>
<th></th>
<th>ASD versus LI</th>
<th>ASD versus TD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Emotion eye gaze</td>
<td>3 (1.1−7.9)*</td>
<td>0.03</td>
</tr>
<tr>
<td>Communication</td>
<td>2.5 (0.7−8.5)</td>
<td>0.14</td>
</tr>
<tr>
<td>Gesture</td>
<td>3.1 (0.8−11.6)</td>
<td>0.09</td>
</tr>
<tr>
<td>Social composite</td>
<td>1.9 (0.5−6.9)</td>
<td>0.35</td>
</tr>
<tr>
<td>Sounds</td>
<td>1.4 (0.3−6.7)</td>
<td>0.67</td>
</tr>
<tr>
<td>Words</td>
<td>2.4 (0.1−43.7)</td>
<td>0.56</td>
</tr>
<tr>
<td>Speech composite</td>
<td>1.4 (0.3−6.7)</td>
<td>0.66</td>
</tr>
<tr>
<td>Understanding</td>
<td>1.4 (0.2−9.5)</td>
<td>0.71</td>
</tr>
<tr>
<td>Object use</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Symbolic composite</td>
<td>1.4 (0.2−9.5)</td>
<td>0.90</td>
</tr>
<tr>
<td>Total score</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

ASD: autism spectrum disorder; LI: language impairment; TD: typical development; CI: confidence interval.

Odds ratios were adjusted for gender and neighbourhood disadvantage (using Socio-Economic Index for Areas (SEIFA) quintiles as previously described). Only adjusted figures are presented in the table. There was little difference between adjusted and unadjusted figures in all odds ratios except for the cluster of gesture for the ASD versus LI comparison, which no longer met significance once adjusted.

*p < 0.05; **p < 0.01.
The children in the ASD group were comparable to the other groups for magnitude of loss (mean and range) on the CSBS-ITC, with amount of loss ranging from −6 to −1 in the ASD group, −6 to −1 in the LI group and −7 to −1 in the TD group.

**Number of children who lost communication skills in one or more cluster**

A proportion of children from all groups lost skills in at least one domain (Figure 6). A higher proportion of children with ASD lost skills in more than one area compared to the other two groups (ASD > TD: \( p < 0.001; \) ASD > LI: \( p < 0.001 \)). For those children who lost skills in more than one cluster, they were more likely to lose in the ‘eye contact and emotion’ and ‘communication’ domains.

**Discussion**

**Trajectories**

Children in all three groups demonstrated an overall median gain in all areas of communication from 1 to 2 years. However, individual trajectories were variable and there were differences between the groups in the rate of gain of skills. Our findings are consistent with those of other prospective studies reporting slower developmental trajectories from 1 to 2 years for children with ASD relative to their peers on language (Landa et al., 2007, 2012; Mitchell et al., 2006; Ozonoff et al., 2010) and social communication (Bryson et al., 2007; Landa et al., 2007, 2012; Ozonoff et al., 2010; Rozga et al., 2011; Veness et al., 2014; Young et al., 2009; Zwaigenbaum et al., 2005). The finding that there was no significant difference between children with ASD and LI at 1 and 2 years on both the CDI and the speech cluster on the CSBS-ITC has implications for differential diagnosis for these two groups at this young age. The CSBS-ITC speech composite includes questions about both speech (e.g. number of sounds used) and language (e.g. number of words produced or word combinations used). Prospective studies have found mixed evidence on whether there are differences in early language and speech between high-risk siblings who develop ASD and those who do not (see Jones et al., 2014 for a review). Very few of these prospective studies have compared speech and language development in children with ASD to a defined group of children later diagnosed with LI. Two studies with a comparison group of children with LI have produced similar findings to this study (Landa and Garrett-Mayer, 2006; Paul et al., 2008). One prospective community-based study did not find a significant difference between the language-impaired/developmentally delayed children (\( n = 20 \)) and those with ASD (\( n = 42 \)) on an expressive language measure at 24 months (Barbaro and Dissanayake, 2012). However, there was a significant difference between the children with LI and the children with autistic disorder. A study focused on speech found children with ASD had a higher proportion of atypical vocalisations (e.g. squeal, growl), compared to age and language matched peers but there were no significant differences in the proportion of correct consonants produced (Schoen et al., 2011). It seems likely that if there are differences between the groups in speech sound development they are unlikely to be detected by a parent-rated tool such as the CSBS-ITC. Given the similarities in trajectories for language-impaired and ASD groups, it would seem using speech and language ability for differential diagnosis may not be useful but, instead, contributes to an understanding of their ability to communicate and participate, that may impact other behaviours.

**Loss of skills**

**Loss of social communication skills.** A minority of children lost skills, either completely or with a decrease in their frequency of use, in all three groups but with a greater risk of skill loss and more pervasive skill loss in children with ASD. Of those children with ASD who lost skills, the majority lost skills in the ‘use of emotion and eye gaze’ cluster. This is in keeping with findings from past retrospective (Ozonoff et al., 2005; Thurm et al., 2014) and prospective studies (Landa et al., 2007, 2013; Ozonoff et al., 2011) investigating skill loss in ASD. Children in our study did not regress significantly more than other groups in the ‘communication’ cluster. This finding was unexpected given communication is considered a key diagnostic feature of ASD. One possible explanation for this finding is that a child’s ‘vulnerability’ to losing skills may occur at different stages of development for different skills. In support of this hypothesis, one study found some skills typically problematic in ASD (e.g. response to joint attention, amount of requesting and use of gesture) had improving trajectories between 1 and 2 years whereas other skills (e.g. eye contact and overall quality of rapport) had declining trajectories (Lord, 2014).

![Figure 6. Proportion of children who lost skills in one or more clusters for each group (ASD, LI and TD). Bars for each group are in order of appearance in the legend.](aut.sagepub.com)
In general, the children in this study lost more in social communication skills than in other skills such as use of words. However, loss of skills was not as common as has been reported in other prospective studies (e.g. Ozonoff et al., 2010). There are several possible explanations for this. Our study assessed children at only two time points so may not have captured some of the subtle losses and variability that may have occurred in communication. Because several questions have been combined into clusters and composites, children may experience a loss in some areas and gain in others and this may counterbalance their overall score and underestimate loss of skills. It may also be argued that social communication skills are more challenging for parents to assess compared to direct clinical observations of behaviour such as has been used in some prospective studies (Landa et al., 2007; Ozonoff et al., 2010).

**Loss of words.** Very few children in this study lost words on the CDI. This was perhaps unsurprising given children may have few words to lose at 1 year of age. Two children (one each from the ASD and LI group) lost words. Both had a small number of words at 1 year of age (3 and 5 words). The ages children were assessed in this study were limited to the waves data collected in the broader study and consequently may have underestimated loss as children may lose and regain words within the 1- to 2-year period.

**Loss across multiple skill domains**

A majority of children lost skills in one cluster; yet, many also made gains in other clusters over the same time period. This suggests loss of skills, when it does occur, is not typically pervasive across all areas of communication (Meilleur and Fombonne, 2009; Thurm et al., 2014). Of those children who lost skills in more than one area, the majority had ASD. Only one child (of n=41) in this study represented the more ‘classic’ description of regression with substantial loss of skills across multiple clusters. Consistent with this finding there has been increasing consensus in the literature that dramatic, catastrophic loss of skills in ASD is quite rare (Lord, 2014; Ozonoff et al., 2010; Siperstein and Volkmar, 2004; Thurm et al., 2014).

**Loss of skills in children without ASD**

Unexpectedly, a proportion of non-ASD children in this study were reported by parents to have a loss of communication skills from 1 to 2 years. One prospective study also found skill loss in children without ASD (Brian et al., 2014). In this study, 7.5% of the total sample (n=29/389) plateaued or had a lower raw score on a subsequent developmental assessment. Here, 2.8% of low-risk infants, 5.2% of high-risk infants without ASD and 21% of high-risk infants with ASD demonstrated a reduction in raw scores, thus, suggesting loss of skills is not unique to ASD. To date, all studies investigating loss in non-ASD children have been retrospective (Baird et al., 2008; Lord et al., 2004; Pickles et al., 2009; but see Landa et al., 2013 and Brian et al., 2014 for exception). Few high-risk studies have compared developmental trajectories of the non-ASD children in detail and to our knowledge no prospective study has included a sample of TD and LI children as large as this study (Landa et al., 2007, 2013; Mitchell et al., 2006; Ozonoff et al., 2010). It is possible the smaller samples of non-ASD children in high-risk samples may not have captured the broad range of developmental trajectories that may occur in TD children. No prospective studies have compared ASD to a defined group of language-impaired children. In addition, they have not included children with ASD who were being diagnosed as late as middle childhood. As a result, our study may include a higher proportion of children with milder phenotypes and later diagnoses.

Another important difference between this study and others is the tools used to determine loss of skills. The questions in the CSBS-ITC and CDI are quite specific and based on skills being used at the current time in multiple natural contexts. In contrast, the majority of retrospective studies (such as Baird et al., 2008; Pickles et al., 2009) have relied on general questions about regression from tools that were not specifically designed to study regression. One prospective study of regression that investigated development of specific social communication behaviours reported a mean decrease in some communicative behaviours over discrete time periods in children with TD. This included gaze to faces between 6 to 18 months and directed vocalisation from 24 to 36 months (Ozonoff et al., 2010). It is likely that a proportion of TD and LI children experience some natural wax and wane in the development of specific communication skills, and loss of skills may be a natural part of development for some children. This suggestion is supported by other studies of communication development in children, which have reported a lack of stability in language skills measured over time (Lord et al., 2012; Ukoumunne et al., 2012). Our knowledge of loss of skills in children who have LI or TD remains limited, as there are very few studies that have specifically investigated loss of communication skills at an individual level.

Study limitations include that the ASD diagnostic assessments were not completed within the study but in the community and therefore were not uniform. The study may be prone to selection bias since we only included those children that had completed specific waves of the study. However, a high proportion of children were retained in the ASD group (93%). Our classification and cut-off points for loss of skills, plateau, improving and accelerating were quite narrowly defined. We are not aware of any published, consistently used guidelines or definitions of loss and trajectory classifications that have been used in longitudinal studies. Given there is

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substantial instability in these early years and our cut-offs required just one point difference, it is possible some chil-
dren were misclassified. We have made our definitions as clear as possible in the article, so the reader can interpret
the findings along with their limitations. Measurement
error and classification bias can occur in parent-reported
tools such as the CDI and CSBS-ITC. This may have influ-
enced the number of children who had a reduction in
scores and may have impacted the study findings. The use
of other groups (TD and LI) for comparison in this study,
however, may mitigate the effect of classification bias to
some extent. One would not expect between group differ-
ences for data collected prior to problems being identified,
unless there are characteristics of parents of children with
ASD that are in some way different to parents of non-ASD
children that influence the way they score.

Clinical implications

This study demonstrated that children have variable path-
ways to ASD, TD or LI and these pathways may or may not
include some loss of skills. The variability and overlap in
trajectories between the groups highlights the challenge in
making differential diagnoses at this young age (Lord et al.,
2012; Veness et al., 2014). Consistent with the findings of
other prospective studies, children in this study demon-
strated more loss in social communication domains than in
words. Change in social communication may be subtle, and
it may be that tools have not yet been adequately developed
to capture these changes over time. Children who experi-
dence dramatic loss of skills were rare in our sample, but
these children warrant special investigation and attention.
A deeper understanding of the rate of change, patterns of
derailment and individual variation in trajectories will help
inform the development of targeted, developmentally sen-
titive intervention, the most effective and efficient resource
allocation as well as inform prognosis. This is highly rele-
vant for families, clinicians and policymakers.

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References

Statistical Manual of Mental Disorders (DSM-IV-TR). 4th
ed. Text revision, Washington, DC: APA.
opmental trajectory and associated problems in disorders in
the autism spectrum: the SNAP study. Journal of Autism
and Developmental Disorders 38: 1827–1836.
Barbaro J and Dissanayake C (2012) Developmental profiles of
infants and toddlers with autism spectrum disorders identi-
ﬁed prospectively in a community-based setting. Journal of Autism
Barger BD, Campbell JM and McDonough JD (2013) Prevalence
and onset of regression within autism spectrum disorders: a
meta-analytic review. Journal of Autism and Developmental
Bent CA, Dissanayake C and Barbara J (2015) Mapping the diag-
osis of autism spectrum disorders in children aged under 7
years in Australia, 2010–2012. Medical Journal of Australia
Bopp KD and Miranda P (2011) Prelinguistic predictors of lan-
guage development in children with autism spectrum dis-
orders over four-five years. Journal of Child Language 38:
485–503.
proﬁles in high-risk infants with and without autism spec-
trum disorder. Research in Autism Spectrum Disorders 8:
1557–1566.
Bryson SE, Zwaigenbaum L, Brian J, et al. (2007) A pro-
spective case series of high-risk infants who developed
autism. Journal of Autism and Developmental Disorders
37: 12–24.
language development in preschool children with autism
spectrum disorder using the MacArthur Communicative
Development Inventory (Infant Form). Journal of Child
Language 30: 213–236.
Chawarska K, Shic F, Macari S, et al. (2014) 18-month predic-
tors of later outcomes in younger siblings of children with
autism spectrum disorder: a baby siblings research consorti-
unm study. Journal of the American Academy of Child and
Fenson L (1993) MacArthur Communicative Development
Fenson L and Dale PS (1994) Variability in early communicative
development. Monographs of the Society for Research in
Goldfield BA and Reznick JS (1990) Early lexical acquisition:
rate, content, and the vocabulary spurt. Journal of Child
Language 17: 171–183.
Jones EJ, Gliga T, Bedford R, et al. (2014) Developmental path-
ways to autism: a review of prospective studies of infants at
risk. Neuroscience and Biobehavioural Reviews 39: 1–33.
36 months in autism spectrum disorders. Journal of Autism
and Developmental Disorders 40: 1389–1402.
Kim SH, Macari S, Koller J, et al. (2015) Examining the pheno-
typic heterogeneity of early autism spectrum disorder: sub-
types and short-term outcomes. Journal of Child Psychology
and Psychiatry and Allied Disciplines. Epub ahead of print
12 August. DOI: 10.1111/jcpp.12448.
autism spectrum disorders: a prospective study. Journal of
Child Psychology and Psychiatry and Allied Disciplines
47: 629–638.
Landa RJ, Gross AL, Stuart EA, et al. (2012) Latent class anal-
ysis of early developmental trajectory in baby siblings of


Veness C, Prior M, Eadie P, et al. (2014) Predicting autism diagnosis by 7 years of age using parent report of infant social


Chapter 8  Study 3. Language trajectories and predictors of language outcome from 4 to 7 years in children with and without autism spectrum disorder

In this chapter we examined trajectories of language development in children with ASD from 4 to 7 years compared with children with LI and TD. We explored whether children with ASD had a greater gap between expressive and receptive language compared with children without ASD. Nine predictors of language outcomes for all children (n=1004) were examined. We hypothesised that ASD and social communication would be important predictors of later language outcome. This paper is being prepared for submission to the Journal of Pediatrics.
Abstract

Objective
To describe trajectories and predictors of language development from 4 to 7 years in children with autism spectrum disorder (ASD) compared with children with typical language (TD) and language impairment (LI).

Study design
In a prospective, community-based study (the Early Language in Victoria Study, n=1910) children completed standardised language assessments at 4, 5 and 7 years. Individual trajectories for the children with ASD were plotted. Mean trajectories and proportions of children who had declining, increasing and stable trajectories for ASD (n=26-27), TD (n=858-861) and LI (n=119) groups, were compared. We analysed the following predictors of receptive and expressive language outcome: gender, IQ, baseline receptive and expressive language ability, social ability, diagnosis of ASD and socioeconomic disadvantage.

Results
Similar proportions of children with ASD had decreasing, accelerating and stable trajectory types as seen in the TD and LI groups. Mean trajectories for children with ASD showed stable development, again comparable to LI and TD groups. Language level and IQ at four years predicted language outcomes at 7 years but not social abilities or diagnosis of ASD.
Conclusion

Children with ASD and LI had similar language scores at baseline that were lower on average than those who had TD. Language progressed at a similar rate for all groups, with progress influenced by IQ and language ability at four years rather than a diagnosis of ASD.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that affects more than one in 70 individuals (Centers for Disease Control and Prevention, 2014). Social communication difficulties and restricted, repetitive behaviours are defining features of ASD (American Psychiatric Association, 2013).

Structural language skills (including vocabulary, use of grammar, syntax and phonology) in children with ASD vary widely. Some children with ASD never develop the ability to speak while others demonstrate superior language ability (Tager-Flusberg et al., 2011). In addition, children with ASD may show atypical language presentation such as stronger expressive compared with receptive language ability (Ellis Weismer & Kover, 2015; Pickles et al., 2014), regression in communication skills in the first few years of life (see Barger et al., 2013 for a review) and persistent or unusual repetitive, stereotyped language (Tager-Flusberg et al., 2011). Verbal skills in childhood play an important role in predicting long-term outcome in children with ASD in wellbeing, adaptive functioning and mental health (Billstedt, Gillberg, & Gillberg, 2011; Gillespie-Lynch et al., 2012; Howlin & Moss, 2012; Howlin et al., 2013).
Children with ASD have differing trajectories of language development, which include loss of skills, plateau, improvement and acceleration (Anderson et al., 2007; Ellis Weismer & Kover, 2015). Children with ASD and higher verbal skills have been reported to have trajectories comparable to those with typically developing language on most measures while children with low verbal skills have made slower progress (Tek et al., 2014). Substantial variability in communication trajectories has also been reported in the first few years of life in ASD (Brignell et al., 2016; Landa et al., 2013), with more stable and predictable patterns of development reported from 6 to 19 years (Pickles et al., 2014).

Variability in trajectories seen in ASD may not be unique to the condition. Studies of language trajectories in children with specific language impairment, have also reported greater variability in trajectories before 6 years and relative consistency from 6 years of age onwards (Conti-Ramsden et al., 2012). Variability has also been found in population studies of children under 8 years (McKean et al., 2015; C. Taylor et al., 2013) and in children under 9 years with non-spectrum developmental disabilities (Anderson et al., 2007; Ellis Weismer & Kover, 2015). However, clearly-defined comparison groups of the same age within the same study cohort are needed to test whether this pattern of language trajectory is indeed unique to ASD.

Language trajectories may differ according to the severity of the child’s language problems and the time period being studied (Tek et al., 2014; Toth et al., 2006). Studies of children with ASD have examined a range of factors that may impact on later language outcome, focusing both on environmental (e.g., parent interaction style, socio-economic status and intervention (Ellis Weismer & Kover, 2015; McDuffie & Yoder, 2010; Siller et al., 2013) and child factors (e.g., play, gesture, joint attention, imitation,
Nonverbal IQ is the most consistently reported significant predictor of later language outcome (Thurm et al., 2015; Wodka et al., 2013). Earlier language ability has also been found to be important (Ellis Weismer & Kover, 2015; Turner, Stone, Pozdol, & Coonrod, 2006). To our knowledge, no studies have specifically investigated gender as a potential predictor of language outcomes. There have been inconsistent findings around the importance of ASD symptoms in predicting language outcomes. Severity of ASD symptoms are reported as significant by some (Baghdadli et al., 2012; Ellis Weismer & Kover, 2015; Magiati et al., 2011), whereas others have noted they are less important after factors such as nonverbal IQ are taken into account (Sigman & McGovern, 2005; Thurm et al., 2015).

Despite an increase in the number of studies that have investigated language trajectories and predictors of language outcome in ASD, clinicians are still unable to provide timely, accurate prognostic information about language outcomes to parents based on their child’s individual skill profile. Policy makers and service providers also require information about communication outcomes to inform decisions regarding allocation of resources and services. The aim of this study was to (a) examine trajectories of receptive and expressive language development in children with ASD from 4 to 7 years and to compare the trajectories of children with ASD over time to children with language impairment (LI) and typical development (TD); b) compare the proportions of children with ASD who had declining, stable and accelerating trajectories and development over time to children with TD and LI; (c) investigate whether children with ASD have relative weakness in receptive compared with expressive language (d)
investigate predictors of language outcomes from 4 to 7 years, in a representative community sample.

**Methods**

**Participants**

Participants were drawn from the Early Language in Victoria Study (ELVS), a longitudinal, community-based study of language development in children (n=1910). Participants were recruited from 6 of 31 local government areas around metropolitan Melbourne to represent a range of social economic advantage and disadvantage. Infants were enrolled in the ELVS at 7.5-10 months of age and were assessed almost yearly using direct assessments of language and/or parent-completed questionnaires and related areas. Exclusion criteria included a diagnosis of developmental delay, cerebral palsy and if parents had inadequate English to complete questionnaires (see Reilly et al., 2006; Reilly et al., 2007 for further details). Several groups were selected from the ELVS for comparison.

**Measures**

Demographic details were collected when participants were aged 8-12 months. The Clinical Evaluation of Language Fundamentals-Preschool Edition (CELF-P2; Wiig et al., 2006) was administered to participants at 4 years and the CELF-Fourth Edition (CELF-4; Semel et al., 2003) at 5 and 7 years. This comprehensive standardised tool measures receptive and expressive language. Language domains including morphology (grammar), syntax (sentence structure), semantics (word meanings) and vocabulary are assessed. The Kaufman Brief Intelligence Test-2 (KBIT-2; Kaufman & Kaufman, 2004)
and Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) were administered at 4 and 7 years, respectively. The Pediatric Quality of Life Inventory 4.0: parent report form (Peds-QL; Varni et al., 2001) and the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) were completed by parents when participants were aged 4 years.

**Procedures**

Trained psychology graduates and speech pathologists administered direct language assessments in the child’s school or home. All children were seen within two months either side of their birthday at each time point.

**Identification of subgroups**

*Identification of participants with autism spectrum disorder.* From 4 years of age all parents were asked if their child had received a diagnosis of ASD. Following parent report a psychologist (MP), experienced in the diagnosis of ASD, conducted a telephone interview to verify the diagnosis, collect information on age of diagnosis and comorbidities, and determine who made the diagnosis. The majority of children (n=41/44; 93%) received a diagnosis of ASD from a multidisciplinary team that involved at least two professionals (typically a paediatrician, psychologist, speech pathologist). The remaining children (n=3) were diagnosed by a paediatrician. Forty-four children in the sample were diagnosed with ASD but in the present study only those children who had completed the CELF at 4 or 5 and 7 years (n=26-27) were included in the analysis.

Families of children with ASD also completed the Social Communication Questionnaire
(SCQ; Rutter et al., 2003) at 7 years of age. Mean scores on the SCQ for the children in this study were 13.3 (standard deviation 4.08; range 5-20).

Identification of language impaired and typical language development. Children were allocated to the language impaired (LI) and typical language (TD) groups based on their performance on the CELF and the WASI. Group allocation was conducted at 7 years. Children in the LI group had a WASI score greater or equal to 70 and a CELF score at two time points (at 7 years and at 4 or 5 years) more than or equal to 1.25 standard deviations below the mean. For the TD group children were required to have a WASI score of greater or equal to 85 and a CELF score at 7 years and 4 or 5 years of greater than 1.25 standard deviations below the mean. Children were excluded from these groups if they were reported to have ASD. Children were only included in the current study if their language skills were measured on the CELF at 4 or 5 and 7 years. This produced 119 children in the LI group and 861 children in the TD group.

Sixteen children were excluded from the predictor and trajectory analysis because they were missing data from either the nine predictor measures or the two CELF time points. Reasons for missing data included: withdrew from the ELVS (n=4), verbal ability too limited to complete CELF (n=2), unable to schedule (n=3), child non-compliant to testing (n=4) and parents too busy with other interventions to find time to schedule assessment (n=3). We tested whether there were differences between the characteristics of children with ASD who were lost to follow up and those who were included in the study. For children with ASD there were no significant differences (p>0.05) between those children who remained in the study (n=27) and those with ASD that were lost to follow up or were missing data (n=16) in any of the 8 demographic factors (Chapter 6, Table 15). While scores on language and IQ measures were lower for the children with
ASD who were not included in the analysis, there were also no significant differences (p>0.05) between the two groups in language and communication ability at 2 years of age as measured by the MacArthur Bates Communicative Development Inventories (CDI: Fenson, 1993) and the Communication Symbolic Behaviour Scales-Infant Toddler Checklist (CSBS-ITC: Wetherby & Prizant, 2002). See Chapter 6, Table 15. Information was not consistently collected on the receptive and expressive language skills of the children who were not able to complete the CELF due to their limited verbal ability. We have noted the language ability of these children in the text but were not able to include these children in the trajectory analysis, as we could not provide valid comparison scores.

**Outcome measures**

Language was measured with the CELF-4 at 7 years. Receptive and expressive indexes from the CELF-4 were reported.

**Predictor measures**

Nine predictors were used in this study. Social communication skills were measured using the social subscales from the Peds-QL and the SDQ. The social functioning subscale was used from the Peds-QL. The peer relationship problems and prosocial behaviour subscales were used from the SDQ. Autism was assigned as described above. Nonverbal IQ was measured using the KBIT-2 matrices subtest. Baseline receptive and expressive language ability was based on a child’s standard score at 4 or 5 years on the CELF-P or the CELF-4. The ELVS sample at 7 years is skewed toward families who are more socio-economically advantaged (McKean et al., 2015), thus Socio-Economic
Indexes for Areas (SEIFA) quintiles were used based on the Australian Bureau of Statistics reference.

Ethical approval was obtained from the Royal Children’s Hospital (#23018) and La Trobe University, Human Ethics Committee (#03–32). All parents provided written, informed consent.

**Statistical Analysis**

All analyses were conducted using Stata version 13.1. Individual trajectories from 4 to 7 years were plotted for the children with ASD. Proportions of children with ASD who had declining, increasing and stable trajectories were compared with children with LI and TD using the Chi square statistic. We defined declining and increasing trajectories as more than one standard deviation change (+/- 15 points) in standard scores between 4 and 7 years on the CELF. Data were also analysed using the Generalised Estimating Equations (GEE) method for fitting the marginal models. An exchangeable correlation structure was used and “robust” standard errors from the sandwich estimator, which takes the dependence of the responses into account. GEE was used to plot mean trajectories from 4 to 7 years for each group. To assess whether a diagnosis of ASD predicted a greater gap between receptive and expressive language at 4 and 7 years of age we used linear regression with autism diagnosis the explanatory variable and CELF scores at 4 and 7 years the outcome variables.

We also used linear regression to analyse predictors of language outcome. Predictors were included in the model if they were found to be significant univariate predictors of language outcome. Multicollinearity between the social communication measures (i.e.}
subscales of the SDQ, Peds-QL) was assessed to prioritise the measures. A variance inflation factor of 1.2 indicated low correlation so all three social communication measures were kept in the model.

**Results**

There was no significant difference between any of the three groups in number of indigenous children, families where English was the main language spoken at home and maternal age at birth. A higher proportion of children with ASD were male compared with the other groups (p=0.004). Children with LI were more likely to have a greater number of children living in the home and parents who had not completed high school and who were not married/defacto compared with the TD group (p=0.001). The LI group was more socially disadvantaged than both the TD and ASD groups (p<0.012). Mean IQ was 99.71 (SD 14.35) for children included in the trajectory and predictor analysis with no child having an IQ<70. Appendix F and Table 15 (Chapter 6) of this thesis provides further detail on the demographic, IQ and language scores of children with ASD in the ELVS whose data was not included in the analysis.

**Individual trajectories**

Individual trajectories are shown in Figure 15. Three main trajectory types: declining, accelerating and stable were found for receptive and expressive language in children with ASD from 4 to 7 years. The majority of children with ASD had stable trajectories with scores remaining within 1 standard deviation of their previous standard score from 4 to 7 years. Three children with ASD could not be tested on the CELF at all three time points due to limited language abilities. One child was minimally verbal (≤ 10 words) at
4 years and continued to have limited receptive and expressive language at 7 years. Another child was verbal but did not have adequate language to complete testing at 4 and 7 years. The third child could only use a limited number of phrases and communicated primarily using sign at 4 and 5 years. This child was verbal by 7 years and able to complete the CELF-4.
Figure 15   Individual language trajectories from 4 to 7 years of children with ASD. Standard scores on the CELF are presented.

Receptive language

Expressive language

Note. One child in Figure 15 demonstrated a steep decline in his receptive language ability with very low scores on 2 of 3 subtests in the receptive language index at 7 years. His score on the third receptive language subtest was age appropriate. We completed sensitivity analyses by removing this child’s scores from the analyses and the overall summary findings remained the same.
Trajectory types

Trajectories were described using standard scores for children who were able to complete the CELF (n=27). Three children who did not complete the CELF are described separately and are not included in the sample of 27. Declining trajectory was defined a decrease of more than one standard deviation (15 points) in standard score on the CELF from 4 to 7 years. A stable trajectory was defined as a standard score that remained within one standard deviation (within 15 points in either direction) from 4 to 7 years. An accelerating trajectory was one that improved by more than one standard deviation (15 points) on the CELF from 4 to 7 years. Overall there were no significant differences between the three groups (ASD, LI, TD) in the proportions of children who demonstrated declining, stable and accelerating trajectories in receptive language (chi square statistic 4.0932; p= 0.394) and expressive language (chi square statistic 5.9358; p= 0.204) (Table 16). Eighty-one and eighty-five percent of children with ASD had relatively stable standard scores in receptive and expressive language respectively from 4 to 7 years. Eight and eleven percent of children had increasing and 7 and 8 % declining trajectories, in receptive and expressive language respectively.
Table 16    Trajectory types (decline, maintain and accelerate) for children with ASD, LI and TD.

<table>
<thead>
<tr>
<th></th>
<th>ASD</th>
<th>Language impaired</th>
<th>Typical development</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Receptive language</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean (SD), range</td>
<td>87.9 (16.5)</td>
<td>81.3 (10.3)</td>
<td>102.9 (11.6)</td>
</tr>
<tr>
<td></td>
<td>54-115</td>
<td>50-105</td>
<td>64-132</td>
</tr>
<tr>
<td>Follow up mean (SD), range</td>
<td>87.5 (17.1)</td>
<td>73.2 (10.9)</td>
<td>99.4 (9.4)</td>
</tr>
<tr>
<td></td>
<td>53-111</td>
<td>45-100</td>
<td>82-125</td>
</tr>
<tr>
<td>Decline (n, %)</td>
<td>2 (7)</td>
<td>24 (20)</td>
<td>147 (17)</td>
</tr>
<tr>
<td>Maintain (n, %)</td>
<td>22 (81)</td>
<td>90 (76)</td>
<td>665 (77)</td>
</tr>
<tr>
<td>Accelerate (n, %)</td>
<td>3 (11)</td>
<td>5 (4)</td>
<td>49 (6)</td>
</tr>
<tr>
<td><strong>Expressive language</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean (SD), range</td>
<td>89.3 (17.9)</td>
<td>81.3 (10.3)</td>
<td>105.6 (11.7)</td>
</tr>
<tr>
<td></td>
<td>50-122</td>
<td>50-105</td>
<td>72-140</td>
</tr>
<tr>
<td>Follow up mean (SD), range</td>
<td>89.7 (20.4)</td>
<td>78.3 (11.7)</td>
<td>103.3 (10.0)</td>
</tr>
<tr>
<td></td>
<td>45-126</td>
<td>45-110</td>
<td>82-136</td>
</tr>
<tr>
<td>Decline (n, %)</td>
<td>2 (8)</td>
<td>17 (14)</td>
<td>84 (10)</td>
</tr>
<tr>
<td>Maintain (n, %)</td>
<td>22 (85)</td>
<td>94 (79)</td>
<td>742 (86)</td>
</tr>
<tr>
<td>Accelerate (n, %)</td>
<td>2 (8)</td>
<td>8 (7)</td>
<td>32 (4)</td>
</tr>
</tbody>
</table>

Note. A declining or improving trajectory type was defined using criteria of +/-1 standard deviation difference between standard scores at 4 and 7 years (i.e. change of +/-15 standard score points).
Mean trajectories

Receptive language

The estimated mean standard scores for the LI group were 24.6 units lower than the TD group across the three waves of data collection (p<0.001; 95% CI -26.1, -23.1). The estimated mean standard scores for the ASD group were 18.0 units lower than the TD group across the three waves of data collection (p<0.001; 95% CI -23.2, -12.7). There was a small effect of gender in the whole cohort (ASD, LI and TD) with girls having a mean standard score 1.6 units higher than boys (p=0.005; 95% CI 0.5, 2.8). There was no evidence of an interaction between gender and grouping (i.e. ASD, LI, TD).

Expressive language

Estimated mean standard scores were 24.4 units lower for the LI than the TD group across the three waves of data collection (p<0.001; 95% CI -26.1, -22.6). Estimated mean standard scores were 18.1 units lower for the ASD than the TD group across the three waves of data collection (p<0.001; 95% CI -24.0, -12.2). There was no evidence of an effect of gender on the mean standard scores for the whole cohort nor was there any evidence of an interaction between gender and grouping.

Mean trajectories from four to seven years for children with ASD, LI and TD are presented in Figure 16 (a,b). While language ability varied between the three groups, the slopes of the trajectories in each group were generally flat, indicating the development of language was generally at a comparable rate. Exceptions to this were girls with ASD who demonstrated variable trajectories and the LI group who demonstrated a decrease of approximately 7 standard score points from 5 to 7 years in expressive language. Of
note, girls with ASD achieved lowest scores of all three groups in receptive language. Upon inspection of the graphs mean standard scores for expressive language were higher than receptive language for all three groups.
Figure 16  Mean language trajectories (CELF standard scores) for male and female subgroups of children with ASD, TD, LI.
Note. Figure (a) represents receptive language and Figure (b) expressive language. Solid line is the smoothed mean from 4 to 7 years and dashed lines show actual mean scores at 4, 5 and 7 years. LI and TD groups were pre-defined by the authors based on inclusion/exclusion criteria (see Participants above). For standard scores, a declining trajectory indicates progress at a slower rate but this does not necessarily indicate a loss of skills.
Receptive-expressive language profiles

There was a wide range of receptive/expressive difference scores observed in children with and without ASD at 4 years (-30 to 36), 5 years (-43 to 43) and 7 years (-35 to 51). (Figure 17). There was no evidence that having a diagnosis of ASD resulted in any difference in receptive/expressive difference scores at 4 years, 5 years or 7 years of age (ASD n=30, whole cohort n=1560 at 4 years; ASD n=23, whole cohort n=982 at 5 years; ASD n=30, whole cohort n=1204 at 7 years). Children with ASD aged 4 years had on average a 0.45 unit lower difference between expressive and receptive language than children without ASD (95% CI -4.0, 3.1, p=0.81). At 5 years children with ASD had on average a mean difference 2.0 units higher than children without ASD (95% CI -2.9, 6.8; p=0.43) and at 7 years children with ASD had on average a mean difference 1.7 units lower than children without ASD (95% CI -5.8, 2.3, p=0.40).
Figure 17  Distribution of the receptive-expressive difference scores for non-ASD and ASD children at 4 (a) and 7 years (b).
Predictors of receptive and expressive language outcomes at 7 years

Five of nine predictors examined using multivariate analysis made a statistically significant independent contribution to variance in receptive language outcome. These included receptive and expressive baseline scores, gender, socio-economic disadvantage and IQ. For expressive language only receptive and expressive baseline scores and IQ were significant. A diagnosis of autism and social ability at 4 years were not significant predictors of either receptive or expressive language ability at 7 years once gender, baseline receptive language skills, baseline expressive language skills and IQ at 4 years of age were taken into account. The model explained 44% of the variance in receptive language outcome (p<0.001) and 58% of the variance in expressive language outcome (p<0.001). See Table 17.
Table 17  Predictors of language outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Receptive language outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline receptive</td>
<td>0.38</td>
<td>0.32 to 0.44</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Baseline expressive</td>
<td>0.23</td>
<td>0.17 to 0.29</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Peds-QL social</td>
<td>0.01</td>
<td>-0.05 to 0.06</td>
<td>0.794</td>
</tr>
<tr>
<td>SDQ pro-social(^a)</td>
<td>-0.12</td>
<td>-0.47 to 0.22</td>
<td>0.497</td>
</tr>
<tr>
<td>SDQ peer problems</td>
<td>-0.22</td>
<td>-0.68 to 0.23</td>
<td>0.334</td>
</tr>
<tr>
<td>Autism</td>
<td>3.66</td>
<td>-0.67 to 8.0</td>
<td>0.098</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.63</td>
<td>0.38 to 2.88</td>
<td>0.01</td>
</tr>
<tr>
<td>Nonverbal IQ</td>
<td>0.17</td>
<td>0.12 to 0.22</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>SEIFA disadvantage</td>
<td>0.63</td>
<td>0.09 to 1.18</td>
<td>0.022</td>
</tr>
<tr>
<td><strong>Expressive language outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline receptive</td>
<td>0.19</td>
<td>0.14 to 0.24</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Baseline expressive</td>
<td>0.56</td>
<td>0.50 to 0.61</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Peds-QL social</td>
<td>-0.03</td>
<td>-0.08 to 0.02</td>
<td>0.240</td>
</tr>
<tr>
<td>SDQ pro-social(^a)</td>
<td>0.04</td>
<td>-0.25 to 0.34</td>
<td>0.773</td>
</tr>
<tr>
<td>SDQ peer problems</td>
<td>-0.01</td>
<td>-0.40 to 0.38</td>
<td>0.953</td>
</tr>
<tr>
<td>Autism</td>
<td>-0.75</td>
<td>-4.41 to 2.92</td>
<td>0.689</td>
</tr>
<tr>
<td>Female gender</td>
<td>-0.80</td>
<td>-1.85 to 0.26</td>
<td>0.139</td>
</tr>
<tr>
<td>Nonverbal IQ</td>
<td>0.07</td>
<td>0.03 to 0.11</td>
<td>0.002</td>
</tr>
<tr>
<td>SEIFA disadvantage</td>
<td>0.31</td>
<td>-0.16 to 0.77</td>
<td>0.194</td>
</tr>
</tbody>
</table>

\(^a\) lower score in this subscale indicates more difficulties in this domain

Note. Baseline receptive and expressive language at 4 or 5 years was measured using the CELF-P or CELF-4. Outcome expressive and receptive language was measured at 7 years using the CELF-4. Social communication was measured at 4 years using the prosocial and peer problems subscales from the SDQ and the social subscale from the Peds-QL. Nonverbal IQ was measured at 4 years using the KBIT-2. Socio-Economic Indexes for Areas (SEIFA) quintiles were used based on the Australian Bureau of Statistics reference.
Discussion

To our knowledge this study is the first to report on children with ASD using clinician administered, comprehensive, standardised language assessments in a longitudinal community sample that includes and has used the same measures for children with LI and TD. The community sample minimizes ascertainment bias, maximises external validity and enables a broader picture of ASD as well as important comparisons.

Children with ASD demonstrated some heterogeneity in trajectory types but most demonstrated rates of language development comparable to those with LI and TD with parallel trajectories. In other words, progress over time for the ASD group was similar to LI groups, and the TD group, albeit with the ASD and LI groups starting from a lower baseline. This finding is consistent with the ‘tracking’ hypothesis proposed by other researchers. This hypothesis suggests that despite children with LI having lower mean scores than TD children, on average they track in parallel to TD children with stable growth in expressive and receptive language ability over time (Law et al., 2008). Some evidence of acceleration in receptive language ability from 7 to 8 years of age has also been reported (Conti-Ramsden et al., 2012).

The three groups were also comparable in the proportions of children with declining, maintaining and accelerating trajectory types. Criteria used to assess trajectory variation (i.e. decline, maintain, accelerate) has differed from study to study and the threshold used in the current study (more than one standard deviation difference between time points) may be wider and less likely to find a difference compared with other studies. Our finding that trajectories were relatively stable for many children with ASD is, however, consistent with a previous study (Pickles et al., 2014).
Children with minimal verbal ability did make progress in their communication skills, however it was not possible to assess their rate of development and they may not maintain the same pace of development as other children. To date evidence points to children with ASD who had relatively lower expressive language ability at baseline experiencing a slower rate of language growth compared with children with typical language development (Ellis Weismer & Kover, 2015; Tek et al., 2014).

A strength of this study is that we were able to report on receptive and expressive language separately. This study did not find a significant mean difference between the two language domains for children with ASD at any of the time points measured. Our finding regarding children with ASD is consistent with a meta-analytic review of studies investigating the receptive-expressive discrepancy in ASD (Kwok et al., 2015).

Receptive and expressive language ability and nonverbal IQ at 4 years were found to be important predictors of later language at 7 years, convergent with previous research using clinical samples of children with ASD (Ellis Weismer & Kover, 2015; Luyster et al., 2007). Of interest, a diagnosis of ASD and social communication ability were not significant predictors of later language outcome when other factors were controlled for. Methods used here differ from previous studies examining predictors of language outcomes in ASD. A categorical diagnosis of ASD rather than ASD symptom severity was used and comparison between children with and without ASD (n=1086) was possible.

Socio-economic disadvantage (specifically being in the most disadvantaged quintile), and gender were predictors of receptive but not expressive language in the current study. This finding is consistent with a study of children with ASD which found
maternal education discriminated higher versus low verbal outcomes (Ellis Weismer & Kover, 2015). Low maternal education and low family income were also found to be a risk factor of receptive vocabulary at 7 years in another large cohort longitudinal population-based study, although expressive vocabulary was not measured (C. Taylor et al., 2013). Low maternal education and socioeconomic status also predicted adverse receptive and expressive language outcomes at 4 years in another study that used data from the same cohort as the current study (Reilly et al., 2010). At this time it remains unclear why socioeconomic disadvantage/advantage predicted receptive but not expressive language at 7 years in this study.

Diagnosis of ASD and parent-reported social ability at 4-5 years of age were not predictors of expressive or receptive language at 7 years once factors such as IQ and baseline language ability were taken into account. The methodology used in this study was unique in being able to test diagnosis of ASD as a predictor of language outcomes in a large cohort of children with and without ASD. However, direct comparison to the findings of previous studies is therefore not possible. Our sample of children with ASD was small and we were not able to classify children into different levels of severity of ASD symptoms so results should be viewed with caution and await replication.

Despite the lack of receptive-expressive gap our study did find some differences in the types of predictors relevant to each language domain. Other studies have found ASD symptom severity to be an important predictor of growth in expressive and receptive language while cognition predicted growth in expressive language (Ellis Weismer & Kover, 2015).
Limitations

The analysis in this study was limited to children who could complete the CELF, with qualitative information provided about three children with ASD who were not able to complete the CELF at two time points due to limited language and/or cognitive ability and floor effects on tools (i.e. children were not able to achieve basal scores). Therefore, findings are only relevant to those children who had verbal language and children with IQ>70. The exclusion of children who were minimally verbal is likely to skew our findings and have implications for generalising to the general population of children with ASD. Our sample size of children with ASD (n=27) is quite small which reduces statistical power. The substantial difference in sample size between the children with ASD relative to those without ASD also needs to be considered when interpreting our findings. Given this was a community-based study, the children in the study were not diagnosed with ASD uniformly using the same methods and we relied on parent report of ASD, with verification through interview. Different versions of the CELF were used at 4 years compared with 5 and 7 years, however mean scores, standard deviations and ranges for the whole sample were very similar each version of the CELF (4 years: mean 99.62 (SD 15.1; 50-140); 5 years: mean 100.6 (SD 13.9; 55-144); 7 years: mean 98.8 (SD 13.6; 45-136)).

Clinical implications

Our findings contribute new knowledge to our current understanding of language development in children with ASD. While limited by a small sample size and inconsistent diagnostic methods, the findings provide preliminary information that for verbal children with ASD aged 4 to 7 years who do not have an intellectual disability, a diagnosis of ASD in itself does not necessarily mean a child will fall further behind
their peers in language development, and that other factors may be more relevant to later language ability such as nonverbal IQ and earlier language level than a diagnosis of ASD. This is important information for clinicians to consider when parents ask them about their child’s likely language outcome.

The age at which this study investigated predictors (4 years) of later outcomes is consistent with the mean age children are typically diagnosed with ASD in Australia before 7 years of age (Bent et al., 2015) and the factors found to be predictive of language outcomes should be readily available to clinicians who diagnose children with ASD, as part of recommended best practice assessment.

This study was not able to provide clinicians with useful prognostic information on language development in children with ASD who have intellectual disability and/or those children who do not have adequate language ability to complete formal testing. Such information would be highly valuable for parents and for clinicians who are working with this subgroup of children and needs to be a research priority. Further research is also needed to bring together the multiple factors that interact and impact language outcomes more personalised prognostic information can be provided to families about the likely outcomes for their particular child.
Chapter 9  Discussion

This thesis has investigated trajectories of language development in children with ASD in three studies. First, a systematic review and meta-analysis (Study 1) synthesised existing literature on language outcomes in individuals with ASD and assessed the quality of included studies. An important priority of the systematic review was to present findings in a clinically meaningful way so they were relevant and useful to clinicians and families. The review identified a large number of studies had measured language outcomes, however, most were of medium and high risk of bias and there was substantial heterogeneity in study methodology. Gaps in our knowledge were identified in existing literature and with reference to best practice methods for prognosis studies. Key suggestions were made for future research.

Second, Study 2 and 3 utilised data from a prospective, longitudinal, community-based study. Study 2 described individual and group trajectories of communication development from 1 to 2 years in children with ASD and investigated loss of communication skills over the same period. Study 3 described individual and group trajectories of language development in children with ASD from 4 to 7 years and examined predictors of language outcomes in the whole cohort. This study also investigated whether children with ASD were more likely to have weakness in receptive relative to expressive language than children without ASD at several time points. In Study 2 and 3 language trajectories in children with ASD were compared with large cohorts of children with LI and TD, thus placing language trajectories of children with ASD within a broad developmental context.
Summary of principle findings

Language ability was found to be highly heterogeneous for children with ASD in all three studies, with some children achieving scores on standardised testing that were well above average and others demonstrating severe delays. Mean scores on standardised language tools for children with ASD in communication, expressive vocabulary and receptive/expressive language domains were lower than typically developing children at two years of age and from four to seven years of age (Study 2 and 3) and in all but one study included in the systematic review compared with reference norms (Study 1).

Communication trajectories from 1 to 2 years of age

From 1 to 2 years of age individual communication trajectories for children with ASD were highly variable (Study 2). Some children demonstrated accelerated development, some improved, some plateaued and others lost skills over the one-year period. These trajectory types were not consistent across each type of skill in each child. Some children gained skills in some communication domains and lost skills in others. The rate of communication development from 1 to 2 years was slower for children with ASD relative to children with LI and TD in all areas of communication except between children with ASD and LI in expressive vocabulary and use of sounds. As such, the gap between the children with and without ASD grew over the one-year period. This is convergent with the findings from other studies that have investigated language development through repeated behaviour observations in younger, high-risk siblings of children with ASD (Landa et al., 2013; Ozonoff et al., 2010) with authors from one study describing a ‘derailment’ of skills for some children during the first few years (Landa et al., 2013). We found in most areas of language and social communication
there were no significant differences between children with ASD and those with LI or TD at 12 months of age. These findings gain cautious support from studies of high-risk siblings that have found a lack of reliable behavioural markers for ASD prior to 12 months of age (Jones et al., 2014), as well as theories of abnormal neurodevelopment in ASD that have proposed differences in early brain development and subsequent unfolding of the expression of ASD symptoms that centre around social communication (Courchesne et al., 2011; Lombardo et al., 2015).

Contrary to findings in previous studies, the majority of which have been retrospective (Baird et al., 2008; Ozonoff et al., 2005; Pickles et al., 2009; Thurm et al., 2014), a proportion of children in all three groups (ASD, LI and TD) in our study demonstrated loss of some communication skills. Specific types of communication skills were more likely to be lost by children with ASD relative to the other two groups. Compared with both the LI and TD groups, children with ASD had higher odds of losing skills in the area of ‘use emotion and eye contact’.

Use of eye contact has also been identified as an important domain regarding loss of skills in 2 high-risk sibling studies (Landa & Garrett-Mayer, 2006; Ozonoff et al., 2010) and one retrospective study (Thurm et al., 2014). Children with ASD had higher odds of losing skills in the areas of gesture, sounds, speech and understanding relative to children with TD but not LI. This has important implications for differential diagnosis and for our understanding of common features that cut across neurodevelopmental disorders such as ASD and LI. To some extent these findings are not surprising given the neurodevelopmental and genetic overlap between such conditions (Zhu et al., 2014).
A further aim in this study was to assess spread of loss of skills across different communication domains. Here a higher proportion of children with ASD lost skills across two or more communication domains relative to children without ASD. Only one child (2.4% of the sample of children with ASD) demonstrated a dramatic, widespread loss of communication ability. This child went on to have a poor language outcome and did not have adequate language to complete the CELF-4 at 4 or 7 years.

One explanation for the contrast in findings between this study and past studies regarding loss of skills in non-ASD populations is differing methodology. This study was the first of its kind to compare large groups of clearly defined children without ASD across a wide spectrum of ability and demographic characteristics. Moreover, our study used parent report collected prospectively at the time the child was exhibiting their behaviour.

Our findings regarding loss of skills occurring in all three groups in our study could indicate synaptic pruning during early brain development. It has been reported babies have been found to be able to identify sounds from multiple languages between 6-8 months of age but enter a critical period from 10-12 months where they tune in to the sounds of their own language and become less sensitive to the sounds in non-native languages (Kuhl, 2004). There may be a degree of ‘normal’ pruning and wax and wane in development for children without ASD, which may in part explain loss of skills in children without ASD (Karmiloff-Smith, 2016; M. S. Thomas et al., 2016). It has been hypothesised that children with ASD may experience over-aggressive pruning in the first few years of life and this may go some way to explain the heterogeneity and timing of the onset in ASD (M. S. Thomas et al., 2016; M. S. Thomas et al., 2011). This hypothesis is convergent with findings from high-risk sibling studies that have reported
few behavioural markers for ASD in the first 12 months (Jones et al., 2014; Zwaigenbaum et al., 2013). If this is the case, it could be proposed there is a continuum of synaptic pruning (atypical mechanism) with the more extreme forms, perhaps both extreme over and under pruning resulting in loss of skills seen in ASD, less extreme forms resulting in developmental variation that results in ‘good enough’ developmental outcome or milder neurodisability and ‘normal’ levels resulting in optimal developmental progress. Much is still to be learned regarding synaptic pruning and early brain development. Considering this, monitoring the specific skills children with ASD are vulnerable to losing may provide important information for diagnosis of ASD. Furthermore, information about loss of skills may help delineate subgroups of children with ASD. Our study provided unique insight into how ASD may differ from other conditions. While some high-risk sibling studies include small groups of non-ASD children they have not included clearly defined cohorts of children with LI or TD who have retained their language profile/classification at several time points over time.

Language trajectories from 4 to 9 years of age

Receptive and expressive syntax and vocabulary

The individual trajectories of receptive and expressive language development for children with ASD from 4 to 7 years (Study 3) were variable, but there appeared to be more consistency and stability or consistency in the trajectories than between 1-2 years of age (Study 2). The proportions of children who demonstrated declining, improving and plateauing trajectories were not significantly different for children with ASD compared with children with LI and TD. The majority of children with ASD, TD and LI maintained the same rate of progress (within 1 standard deviation) over time in receptive (ASD 81%, LI 76%, TD 77%) and expressive (ASD 85%, LI 79%, TD 86%)
language. This is consistent with other studies investigating language trajectories in children with ASD (Ellis Weismer & Kover, 2015; Pickles et al., 2014), LI (Conti-Ramsden et al., 2012; Law et al., 2008) and TD (Ukoumunne et al., 2012) that have reported increasingly stable trajectories with age. This finding is also supported by the mean receptive and expressive trajectories that were mapped from 4 to 7 years for children with ASD, LI and TD (Study 3). Here children with ASD and LI had lower mean scores on a comprehensive, standardised language assessment compared with the TD group but the majority of children with ASD who had verbal language developed language at a comparable rate to the children with TD and the gap between the groups did not grow over time.

In the systematic review across all four language domains trajectories were parallel (or in some studies accelerated) to reference norms. This occurred in studies where children had received specific intensive intervention or more general intervention in the community, and in studies that included children with and without intellectual disability. Our community-based sample (Study 3) mapped mean trajectories over time using a comprehensive measure of receptive and expressive language. Findings from this study were consistent with the majority of findings from studies that had used selected clinical samples and that had reported on receptive and expressive syntax and vocabulary in the systematic review (Study 1). However, children in Study 3 did not demonstrate the ‘catch up’ to reference norms demonstrated in 43-57% of studies in the systematic review.

There are several possible explanations for this difference. First, the community sample may have less study bias in regard to sample selection. All but one study (Vivanti et al., 2013) that demonstrated ‘catch up’ in the systematic review used clinical samples.
These children may have different characteristics to population-based samples, for example they may have more significant ASD symptoms and lower language ability (Constantino & Todd, 2003; Posserud, Lundervold, & Gillberg, 2006). This may produce a greater likelihood of regression to the mean or acceleration in language skills (Tomblin et al., 2003).

Second, it has been reported that social communication ability (i.e. ASD symptoms) may have a greater association with language ability in the early period (around time of diagnosis) relative to a year after diagnosis (Bennett et al., 2015). It is possible children in the clinical sample have more significant ASD symptoms at baseline and that over time there is an ‘unyoking’ or ‘decoupling’ of the two domains that allows language to develop in a more typical way or to ‘catch up’. In other words, social communication difficulties have less influence on language development as children grow older.

Finally, it is also possible the children from clinical samples were accessing more intensive interventions than children access in the general population. Study 3 did not collect detailed information on amount of intervention received by children with ASD so the impact of intervention could not be assessed.

Females with ASD had lower mean receptive and expressive language ability than males in the study with less stable language trajectories. The small sample of females (n=4) in our study, however, limits the conclusions that can be drawn about language trajectories for females with ASD.

**Adaptive language**

Of the studies in the systematic review reporting on adaptive language standard scores in children with ASD under 11 years, the vast majority demonstrated progress at an age-
expected rate, with one study demonstrating a significant decline in standard scores and 30% reporting some ‘catch up’ to reference norms. Overall there was a 4 unit increase in adaptive language standard scores based on the meta-analysis. Adaptive language in this study refers to parent report measures of communication. Adaptive language measures do not provide the same level of detail on language ability as formal standardised tests, however they provide an important indication of an individual’s communicative functioning related to activity and participation. Measuring an individual’s ability to communicate ‘enough’ to participate, even if language is imperfect, is highly relevant and important and consistent with the International Classification of Functioning model (de Schipper et al., 2015; World Health Organisation, 2001). Other fields of neurodisability including lifelong conditions such as cerebral palsy have begun re-orienting their thinking about disability toward a strengths-based approach, emphasising the importance of factors such as function, family, fitness, fun, friends and future, relative to the child’s ability to ‘perform’ on a standardised test (Rosenbaum, 2015; Rosenbaum & Gorter, 2012). This will also be an important way forward in ASD research.

**Language trajectories beyond 9 years of age**

Study 3 only followed children until 7 years, and the systematic review identified few studies that investigated language development beyond 9 years of age. Studies that follow children beyond 9 years are needed to build our knowledge of language development across the lifespan, so we can fully understand the natural history of language development in ASD and better predict future support needs of individuals with ASD. This is especially important given the biggest proportion of one’s life is spent in adulthood.
Our knowledge of language trajectories in children with ASD beyond nine years of age remains limited due to the small number of studies focused on this age group. Of the few studies (n=3) included in the review that reported findings using standardised direct or parent-report measures at two time points after nine years, all have reported slower rates of development relative to studies reporting on children’s development prior to nine years, with more shallow trajectories and a widening gap between language age relative to chronological age (Magiati et al., 2011; Pickles et al., 2014; Sigman & McGovern, 2005).

In interpreting the findings of these studies several considerations are needed. All three of these studies recruited participants in the late 1990s and earlier. A number of factors have changed over time that may have influenced the characteristics of children with ASD diagnosed today such as changes to the diagnostic criteria, improved access to early intervention and better identification of milder cases. Whether this pattern of slowed rate of development will occur in more recently recruited cohorts of children is not yet known.

A number of possible explanations for the slowing of development through middle childhood to adolescence have been proposed. One hypothesis based on evidence from observing adaptive behaviour changes over time in children with ASD, describes a ‘two-hit’ model of ASD (Picci & Scherf, 2015). This theory describes early perturbations in neural development in the very early years (i.e. prior to age 3) are the first hit and suggests following this earlier disruption to neural development the system is built to fail when children reach puberty and the ‘second hit’ occurs. Around 30% of individuals with ASD demonstrated a marked decline in adaptive behaviour in this study (Picci & Scherf, 2015). It is relevant to note two of the three above-mentioned
included studies conducted during adolescence measured adaptive communication rather than direct assessments of receptive/expressive language. This may converge with the findings of other studies investigating more general adaptive behaviour trajectories (Picci & Scherf, 2015).

Slowed rates of development after 9 years of age could be also explained by several other factors. Alternative explanations include: a reduction in the amount of support services at this age, the complexity of language and social demands may increase during puberty and children with ASD may struggle to cope with these additional demands, major hormonal and brain changes that occur during puberty have the potential to impact affective brain function and mental health (Whittle et al., 2015), there is increased risk for depression and other mental disorders and antisocial behaviours and a discrepancy between biological and social maturation (Patton & Viner, 2007) and these may impact children with ASD more than children without ASD and lastly, an increase in the onset of epilepsy has been reported during adolescence in some studies and epilepsy is associated with brain changes (Viscidi et al., 2013).

**Predictors of language outcomes**

The systematic review presented in Study 1 was not designed to study predictors of language outcomes with analysis of predictors requiring a different systematic review and methodological approach. A substantial number of studies included in the systematic review reported one or more predictors of language outcomes (43% of studies), however, for a number of reasons it is difficult to integrate and interpret the findings from these studies. A broad variety of predictors were analysed including child characteristics, parent factors and external factors. These predictors were measured at
different ages, using a variety of language outcomes and analysis conducted in different ways between studies.

Despite these differences, the most consistent finding across studies is that IQ and early language are important predictors of later language outcome in ASD (Ellis Weismer & Kover, 2015; Thurm et al., 2015; Toth et al., 2006). There is mixed evidence for whether the severity of ASD symptoms is an important predictor of language outcomes (Ellis Weismer & Kover, 2015; Thurm et al., 2007).

Rather than investigating predictors of language outcomes in children with ASD, as described above, Study 3 in this thesis adopted a unique approach. Utilising the whole community sample, Study 3 was able to assess the impact of a diagnosis of ASD and social communication difficulties on receptive and expressive language outcomes for children in a whole community cohort with and without ASD. While the samples and methods differ between Study 3 and the aforementioned studies, the findings were generally consistent. In Study 3 nonverbal IQ and language ability at baseline were important predictors of language outcome. While social communication ability and diagnosis of ASD were both univariate predictors of later language outcome, when nonverbal IQ and language ability were included in the regression model, they were no longer significant.

All children in Study 3 were verbal with IQ>70. This is an important consideration for interpreting findings. Some authors have suggested different predictors may be differentially important at specific ages and language ability levels (Toth et al., 2006). It would be reasonable to hypothesise that social communication abilities (e.g., joint attention) at age 4 may be more relevant as a predictor for future language for children
who have intellectual disability, limited language ability or more significant social communication difficulties. This is supported by another study, which found weaker associations between language and social communication in children with ASD with age (Bennett et al., 2015).

Prediction studies don’t always assist in assessing risk for individuals unless large sample sizes are used and there is a clear understanding of expected progress with and without risk factors. A future systematic review with a focus on already identified predictors of language outcome will now be possible. A better understanding of how predictors of outcomes may influence outcome and interact will inform the type and timing of intervention as well as refine prognostic predictions.

**Expressive and receptive language discrepancy**

In Study 3 we investigated whether a diagnosis of ASD predicted a larger receptive-expressive gap relative to children without ASD. There was substantial variability in the difference between receptive-expressive language scores in both directions for children with and without ASD but children with ASD were no more likely than other children to have a gap between these language domains. A diagnosis of ASD did not predict a larger gap between receptive and expressive language for verbal children.

There has been mixed evidence about whether having weaker receptive relative to expressive language may be hallmark of ASD with some authors finding a discrepancy (Ellis Weismer & Kover, 2015; Hudry et al., 2010; Pickles et al., 2014) and others not finding a discrepancy, once other factors such as IQ are taken into account, although slower progression in receptive relative to expressive vocabulary over time was noted.
A systematic review did not find children with ASD were more likely to demonstrate a discrepancy between receptive and expressive language (Kwok et al., 2015).

A limitation of previous studies in this area is a lack of large, well characterised samples of children without ASD for comparison. Furthermore, most studies have used parent report tools (Hudry et al., 2010) or subscales of more general developmental assessment tools (Barbaro & Dissanayake, 2012). To our knowledge only one study prior to ours used a standardised comprehensive language assessment of children with ASD over multiple time points (Ellis Weismer & Kover, 2015).

**Children with ASD who are minimally verbal**

The systematic review (Study 1) included studies that reported on the proportion of children who were nonverbal or verbal at baseline and outcome. There was substantial variability in outcomes but all studies reported the proportion of children who were verbal increased over time. Approximately 19-30% of those who were under 6 years and nonverbal gained verbal language and 5-32% of those who were over 6 years and nonverbal gained verbal language. Adult studies reported between 91-95% were verbal at outcome, although most of these studies included individuals with IQ>70.

In study 3 we found (n=3) 10% of children with ASD at 4 years and 6% (n=2) at 7 years of age did not have adequate language ability to complete direct assessments of language on the CELF. One of the children who was minimally verbal at 7 years had intellectual disability (nonverbal (NV) IQ 55) and one did not (NVIQ 77). Language ability and IQ can be closely linked and nonverbal IQ can assist with understanding a
child’s developmental profile but the limited description of language ability in these children prevents us from drawing conclusions about their language development.

Ideally, these children would be tested using an assessment tool that is more appropriate for their language ability so a clear picture of change in language over time could be described (Kasari et al., 2013; Tager-Flusberg et al., 2016)

It has been hypothesised that rate of language development may be slower in children with poorer language ability than those with better verbal ability (Ellis Weismer & Kover, 2015; Tek et al., 2014). Our study did not contain adequate sample sizes or appropriate measures to test this hypothesis and add further clarity. Children with ASD who are minimally verbal have long been a group of children neglected in the literature and are often excluded from studies (Tager-Flusberg & Kasari, 2013). Language measures for these children have traditionally been very broad (e.g., whether an individual can use words) and this prevents us from gaining a nuanced account of how language changes over time in these children. Crucially, children with severe language impairments are the most likely to have the poorest outcomes in a range of areas (Billstedt et al., 2007; Howlin, 2011)

A focus on children who are minimally verbal has been pursued in the past five years with the development of the National Institutes of Health special workshop for school-aged children with ASD who are minimally verbal (National Institute of Health, 2010). Evidence-based recommendations regarding assessment and conducting research for this group of children have now been published (Kasari et al., 2014; Plesa Skwerer, Jordan, Brukilacchio, & Tager-Flusberg, 2016; Tager-Flusberg et al., 2016). Further detail on these children will allow more accurate prognostication and may guide the development of novel and alternative approaches for intervention.
Strengths and Limitations

Methodology

The methodology used in Study 2 and 3 of this thesis is distinct and adds to the current literature in several ways. First, it used very early measures of communication development collected prospectively in a representative community sample prior to a diagnosis of ASD. The vast majority of studies that have investigated early language development in ASD include high-risk younger siblings of children with ASD or are retrospective in design. In comparison to high-risk sibling studies, the current study included children with and without a family history of ASD. As such the study is not prone to the same sampling bias as high-risk sibling studies.

The limitations of the high-risk sibling study design have been highlighted by several authors (Barbaro & Dissanayake, 2012; Zwaigenbaum et al., 2007) for example, it has been argued the phenotypes of children with and without a family history of ASD may differ (L. J. Taylor et al., 2015). Second, previous studies (with one exception, Thurm et al., 2014) have typically described regression or loss of skills categorically (e.g., regression/no regression, late onset/early onset/plateau; (Baird et al., 2008; Landa et al., 2013; Ozonoff et al., 2011; Shumway et al., 2011).

Our study was able to investigate loss and gain of skills at an individual skill level. As such, it compared types of communication skills lost relative to others over the one-year period. Third, large samples of clearly defined children with LI and TD allowed us to examine whether loss of skills was unique to children with ASD and to place language development in ASD within a developmental context. Finally, the vast majority of
studies of children with ASD have used selected clinical samples. These studies typically provide detailed descriptions of children with ASD, however there is evidence that they tend to recruit children at the more severe end of the spectrum. Our community-based study recruited children with ASD across a range of ability as evidenced by the individual trajectory plots in Study 2 and 3.

The current study had large well-defined samples of children without ASD within the same cohort for comparison. This enabled a better understanding of what was unique to language development in ASD and what was common across two other populations (LI and TD). To our knowledge, no other study of language development in ASD has compared children with ASD to such large samples of children without ASD. The large cohort of children in the ELVS with the same language measures allowed us to examine whether a diagnosis of ASD itself predicts language ability and whether children with ASD are more likely to have a receptive-expressive language discrepancy.

A major strength of Study 1 is that we conducted risk of bias assessments of studies so study quality could be assessed along with findings. We also combined findings from language domains that contained five or more studies into meta-analyses and presented data to show change over time. This allows for an overall summary of findings and is clinically meaningful and interpretable to clinicians and families. Information on IQ was described. This will assist clinicians and parents tailor prognostic information for individuals based on these broad characteristics and their age.

Limitations of the systematic review (Study 1) include the potential for reporting bias as we were not able to extract data from all included studies. To aid clinical interpretation of the highly variable methodology used in studies we compared the children’s
development to that expected based on standard scores from the normed population (reference norms) or age-equivalents. Ideally studies would include non-ASD populations in same cohort followed over time for comparison, as done in Study 2 and 3.

The definition of ‘nonverbal’ or ‘minimally verbal’ in the systematic review was quite blunt due to the wide variety of ways in which studies reported verbal abilities in children. The difference between a child who is completely nonverbal and one who uses 10 words may be clinically significant both in terms of the child’s functioning and prognosis and may dictate an alternate intervention approach. The complexity in finding consensus for the terminology used to describe minimally verbal individuals has been emphasized by several authors (Norrelgen et al., 2014; Rose et al., 2016; Tager-Flusberg & Kasari, 2013).

The systematic review was only able to report mean scores for a whole cohort and mean scores do not provide the full picture of individual variation in language trajectories. Due to the way data were provided by studies (cohort rather than individual participant data) we could only report mean scores and confidence intervals (when able to be calculated). Data were presented as mean scores in graphical form as trajectories to aid clinical translation. These were not actual trajectories provided by studies but cross sectional time points at baseline and follow up. As a result, we do not know the actual shape of trajectories between these two time points. Furthermore, we have used meta-analysis when more than 5 or more studies reported data. There was substantial heterogeneity in studies, which limits the robustness and validity of the meta-analysis findings.
There is potential for reporting bias in the systematic review around the ways studies presented data. Studies of children who have more severe disabilities may be more likely to report age-equivalents or raw scores because it can be challenging to obtain valid standard scores for these children due to floor effects of tools. It was difficult to compare the results from studies presenting data in these alternate forms to what is expected for age, as we cannot establish with certainty whether children demonstrated significant change or a variation that was within the normal range. It is possible that by focusing more heavily on standard scores we are including a higher proportion of studies where children had more positive outcomes.

**Sample**

Studies 2 and 3 drew participants from a broad community base, systematically designed to include a range of socioeconomic advantage/disadvantage. The prevalence of ASD in the ELVS sample (2.3%) and proportion of males to females (82%) is consistent with prevalence estimates from another population-based study in Victoria (prevalence: 1.5-2.5% and males: 81.2-83.6%) (Randall et al., 2015) and does appear to representative of the broader population of children with ASD aged under 7 years of age in Victoria. A future aim would be to update our findings for children diagnosed with ASD by 11 years, the next planned wave of the ELVS.

This community-based approach brings methodological strengths, such as being more easily generalizable and providing insight into the history of ASD across a broad spectrum of severity. There are however, limitations to the approach that need to be acknowledged.
One of the exclusion criteria for entry to the ELVS was a known developmental disorder or medical condition. Although the likely number of such children identifiable during infancy would be small, ELVS data may not be representative of all children with ASD, particularly those with intellectual disability or genetic conditions known to be associated with ASD.

Furthermore, the language trajectories described in Study 3 did not include any children with intellectual disability. All children had an IQ>70. There were a small number of children in our sample who did not have the required level of language to complete the CELF assessment so we cannot comment definitively on how language changed over time for these children. The small sample of children with ASD in the trajectory analysis from 4 to 7 years (n=26-27 for all analyses) limits statistical power to detect differences and our ability to create meaningful subgroups based on trajectory type or language phenotype. The limitations of our sample need be acknowledged when generalising to minimally verbal children, as well as to those children with comorbidities such as intellectual disability (specifically, nonverbal IQ that is 2 standard deviations below the mean) and known genetic disorders.

Lastly, Study 3 followed children until 7 years of age. Although we expect the number of children to be diagnosed after the age of 7 to be small, some individuals identified as TD or LI may later receive an ASD diagnosis.

**Measures**

The measures used in Study 2 and 3 and information collected on the phenotypes of children with ASD may be less detailed and standardised than a study specifically
designed to follow children diagnosed with ASD. For example, although 93% of the children in our study were diagnosed with ASD by a multidisciplinary team (i.e. including two or more relevant health professionals), children in the study did not have uniform diagnostic assessments.

Two of our measures to assess early communication skills in Study 2 were parent report. Although parent-report can have advantages such as being able to capture the children’s communication ability across natural environments by those who know the child best, this method may add misclassification bias if parents are not accurate reporters.

Our definition of ‘loss of skills’ as lower raw scores at 24 than 12 months and one standard deviation on standard scores for declining, improving or stable trajectories from 4 to 7 years was informed by the current literature but was necessarily arbitrary. To date there is no well-recognised gold standard ways of measuring loss or gain in skills or what a ‘clinically significant’ increase or decrease in standard score might be. We hope clear definitions used for loss of skills will be useful for future studies and allow replication and/or comparison.

Another consequence of using a community-based study is that measures were limited to predetermined study waves rather than time periods that may be more relevant to ASD. More frequent assessments in early toddlerhood using the CDI and CSBS-ITC measures (e.g., at 18 months) would have provided valuable information regarding the loss and gain in language during this sensitive period when loss of skills is most likely to occur.
A strength of Study 3 was that we had direct assessments of language using a detailed, comprehensive, standardised language tool. The vast majority of studies that have assessed language ability over time in children with ASD have used parent-completed checklists about communication more generally (e.g., the Vineland Adaptive Behaviour Scales) or subscales within more general assessment tools (e.g., language subscales within the Mullen Scale of Early Learning). By using the CELF we were also able to investigate receptive and expressive language separately over time. This is especially important given the debate about relative weakness in receptive language for children with ASD in the literature. A potential limitation was that the trajectories from 4 to 7 years were mapped using different versions of the CELF (CELF P2 and CELF 4). It is possible that each version taps into different aspects of language ability and this may affect our interpretation of change over time. However, to test this theory we compared mean scores for the sample at 4, 5, 7 years (see Chapter 6). Mean scores and standard deviations were commensurate across versions of the tool for the whole cohort.

Loss to follow up

We assessed whether children with more severe forms of ASD or intellectual disability were more likely to be lost to follow up. This could occur if assessments are challenging or unsuitable for them. Similarly, there may be demographic characteristics of children who do not complete all assessments that are different to children who do complete them. We compared the children included in the mapped trajectories (n=28) to those who remained in the study but whose trajectories were not mapped (n=12). There were no significant differences in any of the demographic factors measured or expressive vocabulary when children were 2 years old (see Chapter 6). The included children achieved a higher mean nonverbal IQ score at 7 years (M 99.71; SD 14.35; CI 94.39-
than the children who did not have their trajectories mapped (M 82.71; SD 21.06; CI 67.11-98.31) but the difference in scores did not reach statistical significance (p=0.08). We provided a detailed description of demographics, cognitive and language levels for each group to allow comparison to the findings of future studies.

**Clinical implications**

Understanding how language develops throughout childhood in ASD is important for several reasons. First, parents understandably want to know what their child’s likely future will look like and what to expect over the coming years. This will help them plan and prioritise interventions and the services needed to assist them. Service providers and policy makers require information on language prognosis so they can allocate intervention and support resources in the most efficient way. Second, a better understanding of the factors that contribute to better or worse language outcomes will help tailor and focus interventions. Knowledge about natural development in ASD could also provide clues as to the impact of interventions. Lastly, it is well established that language ability in childhood is one of the most important predictors of later outcomes in a range of areas such as employment, relationships, mental health and quality of life (Howlin et al., 2004; Mawhood & Howlin, 2000) Importantly, restricted language skills impact one’s ability to function and participate fully in the community.

The findings from this thesis have immediate clinical utility and will better inform the answers clinicians provide parents when they ask about their child’s likely language future. We can inform parents and clinicians that based on the findings from the systematic review, while there is substantial variability in language trajectories, on average children with ASD have delayed language relative to typically developing
children. On average, most children with ASD improve in their language abilities and track at a similar pace to children without ASD between 2 to 9 years with a proportion of those children (around 30-50%) demonstrating accelerated language development. This has been reported to occur across a range of language domains such as receptive and expressive syntax and vocabulary and adaptive language. Based on the findings of this thesis and previous literature, language ability and IQ at age 4 are more important in predicting a child’s language outcome than factors such as social communication ability and a diagnosis of ASD. This has important implications for the timing and type of intervention for children at 4 years, which is the average age of ASD diagnosis in Australia for those children under 7 diagnosed (Bent et al., 2015).

For families of children who are minimally verbal, we can provide parents with specific information regarding the proportion of children who do develop verbal language over time. For example, in children who are minimally verbal and under 6 years, 19-30% will gain verbal language and for those aged over 6 years 5-32% will gain verbal language if over 6 years. Around 91-95% of adults are reported to be verbal. This is highly relevant and meaningful information for parents.

Communication trajectories from one to two years were highly variable for children with and without ASD. This is important information to consider if making a diagnosis of ASD at an early age. The slowing of development from 1 to 2 years of age and loss of skills will not always indicate a child has ASD since a proportion of children without ASD also experienced loss of skills. Providing inaccurate diagnoses of ASD for children who are demonstrating an atypical developmental pathways can have important social and economic costs and these costs need to be considered when making a diagnosis at a very young age. However, atypical development does indicate the need
for close monitoring of development. Children with ASD who present with catastrophic loss of skills across a range of communication areas, although rare in our study, are likely to warrant an alternate care pathway and medical investigations. These children may be a subgroup of ASD or a distinct neurodevelopmental group.

Our study highlighted convergence and difference in communicative development in children with and without ASD. This has implications for the differential diagnosis. For example, it was found that expressive language and speech sound development were comparable for children with LI and ASD but different to children with TD. We also found children with ASD were no more likely to have weakness in receptive language relative to expressive language. The findings from our study and others (e.g., Kwok et al., 2015) were not consistent with previous reports (Ellis Weismer & Kover, 2015; Hudry et al., 2010) and suggest receptive-expressive language discrepancy may not be a reliable or important behavioural marker for differential diagnosis of ASD, as has previously been suggested. Understanding differences between clinical groups and typically developing children informs our knowledge about how language develops and may contribute to a greater understanding of some of the neurobiological mechanisms and pathways at play that may influence development.
Future directions

Improved methods for prognosis studies

Most studies on language outcomes identified by the systematic review were of medium to high risk of bias. Well-designed prognosis studies that use consistent methods and tools and are based on best practice methods for prognosis studies guidelines are needed (Hayden et al., 2013).

Gaps in the literature

Study 1 identified four gaps in the literature. First, there was a dearth of studies identified by the review that followed children from nine years of age into adulthood. As a result, our knowledge of how language develops over this period is limited. The studies focused on this age group included children who were diagnosed up to 20 years ago and these children may not be representative of the children diagnosed with ASD today. Studies that monitor change in language after 9 years of age are needed. Comprehensive standardised tools also need to be developed that allow language change to be monitored over broad periods of time and that are appropriate for a wide range of ability and ages so trajectories of all children across the spectrum of language ability can be well described.

Second, most studies in the systematic review provide only categorical descriptions of children with ASD who are minimally verbal (i.e. they change from being nonverbal to verbal or remain nonverbal). Little detail has been provided about the communication ability of these children, including their functional communication and use of augmentative or alternative communication. We do not yet fully understand how
communication develops in these children or why they seem to be less responsive to mainstream ASD interventions than verbal children (Kasari et al., 2014; Paul et al., 2013).

Several authors have underlined the challenge of accurately assessing and characterising communication development in children who are minimally verbal (Norrelgen et al., 2014; Rose et al., 2016; Tager-Flusberg & Kasari, 2013), however, encouragingly guidelines are now being developed for the assessment of minimally verbal children with ASD (Kasari et al., 2013; Plesa Skwerer et al., 2016). High quality assessments tailored to the child’s language ability are crucial if we are to develop accurate, personalised prognostic information about these children. Subgrouping children by language profile is similarly important given preliminary evidence children with poorer verbal ability may have different trajectories to those with relatively stronger language ability (Ellis Weismer & Kover, 2015; Tek et al., 2014).

Third, although almost half of the studies included in the systematic review analysed predictors of language there was methodological variability including; age groups studied, types of children included, types of predictors and outcome measures. A systematic review of studies investigating predictors of language outcome would complement the trajectory findings in this thesis and provide valuable information about intervention targets. Such information will also help move us toward the ultimate goal which is more accurate, personalised prognostication based on an individual’s specific characteristics.

Fourth, our study identified a lack of studies that used groups of children without ASD from the same cohort for comparison. In order for us to place language development in
ASD within the context of language development more generally and to identify what is unique to ASD and what is common across conditions such groups are vital.

**New frontiers**

Given the pivotal interactions between genes, the brain, and behaviour throughout early development it is not surprising neurodevelopmental disabilities such as ASD are so heterogeneous. A complete explanatory framework of ASD, especially its onset, subsequent trajectories of development and co-occurring conditions such as language impairment will need to cross disciplines as well as cut across populations (e.g., conditions with similar features and children with typical development). Ongoing work that monitors and tests current theories about early development in ASD, including loss of skills language development in ASD are needed but we must also be prepared to approach ASD in novel ways. This will require pushing away from diagnostic constraints toward a dimensional approach of the types of difficulties and behaviours seen in ASD (Cuthbert & Insel, 2013).

**Concluding remarks**

This thesis provides a unique contribution to our understanding of how language develops in ASD. It is the first work, to our knowledge, to use large samples of children with LI and TD for comparison and the first to use a community sample to study language development using comprehensive standardised tools. In this study, divergence in trajectory was noted between children with ASD and other children in most areas of communication between 1 to 2 years. From 2 years even though the children with ASD had lower scores than expected for their age they appear to develop
at a similar pace to reference norms. From 9 years of age there are some preliminary indications that children experience another divergence in trajectory and rate of development slows. Characterising relative strengths and weaknesses in language development will help delineate the neurocognitive phenotype in ASD. It will also assist with subgrouping. Ultimately it will contribute towards our knowledge of how genes, the brain and other factors interact to influence development and behaviour in early and later life.
Bibliography


Ketelaars, M. P., Cuperus, J., Jansonius, K., & Verhoeven, L. (2010). Pragmatic language impairment and associated behavioural problems. *International
Journal of Language and Communication Disorders, 45(2), 204-214. doi: 10.3109/13682820902863090


Meyer, E. (2002). Variability in the development of social behavior among children with autism. (Doctor of Philosophy), Univeristy of Massachusetts, Univeristy of Massachusetts, Boston, Massachusetts, US.


Cognitive And Behavioral Neurology, 22(1), 1-21. doi: 10.1097/WNN.0b013e318190d185


Russell, G., Rodgers, L. R., & Ford, T. (2013). The strengths and difficulties questionnaire as a predictor of parent-reported diagnosis of autism spectrum disorder and attention deficit hyperactivity disorder. PloS One, 8(12), e80247. doi: 10.1371/journal.pone.0080247


Zierhut, C. (2002). *Facilitative factors in the home environments of children with autism* (Doctor of Philosophy), Univeristy of California, Los Angeles, Univeristy of California, Los Angeles, California, US.


Appendices
Appendix A. Published article on regression in autism spectrum disorders
Regression in autism spectrum disorders

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Abstract: Since the Journal of Paediatrics and Child Health was first published, there has been substantial change in the field of autism spectrum disorders (ASDs) with an exponential increase in the amount of funded and published research. In this paper, we focus on regression in children with ASD, a phenomenon that remains poorly understood. We discuss the implications of what we know about regression in ASD for the way we think about ASD more broadly and for paediatric practice.

Key words: behavioural; developmental; general paediatrics; neurology.

Background

The clinical features of children who were described as ‘autistic’ were published by Kanner1 in English 21 years before the Journal of Paediatrics and Child Health was launched. The recent surge of activity and interest in autism spectrum disorders (ASDs) is reflected in the number of articles with autism in the title in PubMed, with 90% published in 1994 or more recently (Fig. 1). Many reviews about ASD are now available including three published in this journal.2–4 Major changes that have occurred are reflected in the number of articles with autism in the title in PubMed, with 90% published in 1994 or more recently (Fig. 1).

Kanner’s original description (1943) did not report regression, rather that autism was congenital or occurred shortly after birth.1 However, reports emerged in the 1960s that noted behavioural regression in children with autism.5,6 and in the mid-1980s, studies were published that focused specifically on the loss of early speech in autism.7 Since that time, substantial research has accumulated about a subgroup of children with ASD who experience some form of developmental change, plateau or regression in the first few years of life,8,9 with a recent review of the prevalence of regression in ASD identifying 85 relevant publications.10

In an attempt to disentangle the types and possible causes of ASD, a dimensional approach is being recommended and subtypes within the autism spectrum are being explored. It is thought that children displaying regression could form one important subtype. There are a number of reasons why regression in ASD has sparked interest: it could (i) provide clues as to cause and underlying neurobiological mechanisms; (ii) assist in the delineation of potential subtypes in what is currently a heterogeneous condition; and (iii) inform prognosis. However, questions remain about whether the reports of loss of skills in ASD is regression as we think of it for other progressive neurodevelopmental disorders. For the remainder of this article, we will focus on what is known about this phenomenon and what this means for paediatric practice.

What Is Regression in ASD?

Regression is described by parents of children with ASD as apparently normal development for the first 1 to 2 years of life, followed by an abrupt or gradual loss of previously acquired skills. The developmental skills that are typically reported to regress in ASD are language and/or social communication. A frequently used tool to assist in characterising regression is the Autism Diagnostic Interview-Revised (ADI-R) because it includes specific questions and guidance about regression.11 The characteristics required by the ADI-R for a diagnosis of language regression are that prior to the reported loss, ‘communicative use of at least five different words (other than “mama” and “dada”) on a daily basis for at least 3 months’ is established and that there has been a loss of the skill for at least 3 months (quoted from a test booklet of an assessment tool).11 Some
Regression in autism

How Common Is Regression in ASD and Other Developmental Problems?

A recent meta-analytic review, which included 85 studies \((n = 29,035)\), reported the overall prevalence of regression in ASD to be 32.1\% (confidence interval (CI): 29.5–34.8) and the mean age of onset of regression as 1.78 years (CI: 1.69–1.89).\(^9\)

Prevalence rates of regression vary according to how regression is defined.\(^10,13\) No significant difference in the risk of regression between males and females has been reported.\(^8,10,14\) and regression is not more common among any particular socio-economic group.\(^13,13\) One hypothesis is that the age of regression depends on the stage of brain maturation and developmental level of the child rather than their chronological age.\(^8\)

Regression is rare in other neurodevelopmental disabilities, apart from a select few, including seizure disorders (e.g. Landau–Kleffner syndrome, acquired epileptic aphasia), genetic disorders (e.g. Rett syndrome) and known disorders of metabolism (e.g. glycogen storage disorders). In these, there is continued deterioration unless the underlying cause can be treated or there are treatments to decrease the secondary consequences of the underlying cause. Childhood disintegrative disorder (CDD) is one other rare condition in which regression occurs with no known underlying cause. Under the Diagnostic Statistical Manual of Mental Disorders, Fourth Edition,\(^16\) CDD was defined separately as apparently normal development in the first 2 years after birth followed by loss of skills before the age of 10, with skill loss that could extend beyond social communication and language. With the release of the Diagnostic Statistical Manual of Mental Disorders, Fifth Edition,\(^17\) CDD is now included under the diagnosis of ASD and is no longer a separate disorder.

The occurrence of reported regression is higher in ASD than other idiopathic developmental conditions. For example, only 1\% of children with specific language impairment regressed compared with 15\% with ASD in one study.\(^18\) and 3\% of children with developmental delay were reported to regress compared with 38\% in ASD in another.\(^15\) In both of these studies, the non-ASD children who regressed had significant medical or neurodevelopmental problems such as encephalitis, Down syndrome with leukaemia, a stroke and epilepsy.

Cause and Underlying Neurobiological Mechanism

To date, studies that have investigated the processes that may be involved in regression have been based on cross-sectional associations. Studies have examined a potential association between the measles mumps and rubella vaccination,\(^20\) gastrointestinal problems\(^15,17\) and mitochondrial diseases.\(^21\) None of these have found differences in risk factors that are substantial enough to differentiate subgroups of children with regressive and non-regressive ASD, nor have they been fruitful in identifying a potential cause. Studies investigating traditional risk factors such as pre- or post-natal complications and viral infections have also failed to yield a cause.\(^13,15\)

There has been substantial exploration of epilepsy as a cause of regression but to date, the findings have been inconsistent. In one study, a high proportion of children, most (90\%) with an IQ less than 70, who had experienced regression with ASD had co-morbid epilepsy.\(^22\) In another, increased seizure activity was associated with regression.\(^23\) However, in this study, there was no significant difference between the risks of epilepsy in children with ASD who had regressed when compared with those

Box 1 Changes in the past 20 years

1. Acceptance of the spectrum concept of autism
2. Emergence of many theories purporting to explain the neuropsychological underpinning of autism spectrum disorder (ASD), like theory of mind, but with none yet achieving this
3. Acceptance that ASD is biologically (rather than psychologically) based, albeit with slow progress towards detailing the biological underpinnings
4. Emergence of a plethora of biological theories of causation, many of which have been disproven; the remainder are not yet proven despite extensive research investment
5. Widespread communication about and uptake of interventions based on unproven theories of causation that have been harmful
6. Development of systematic, expert and sophisticated methods for assessment and diagnosis of ASD, but variations in diagnostic practice remain widespread and inconsistency in diagnosis persists
7. Major growth in our understanding of the cognitive strengths and weaknesses, and preferred learning styles of children with ASD, which can be applied to interventions and educational settings
8. Greater understanding of co-morbid features such as anxiety and hyperactivity, which contribute to the behavioural problems and which need particular treatment and management, with Diagnostic Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) allowing co-diagnoses...
who had not.24 Many other studies have found no association between epilepsy and regression.13,14,19

A number of theories have been proposed to help explain the neurobiolopy of regression. It has been suggested that regression in ASD may occur in a particular genetic subgroup. While this may seem logical, research has so far failed to identify any genetic differences between children who regress compared with those who do not.23 One study found the risk of regression for children with ASD in multiplex families was similar to the rate of regression in singleton families.23 In the same study, later born children who were diagnosed with ASD were not found to be at increased risk of regressive ASD if they had an older sibling who has regressive ASD. Another study found similar rates of the broader autism phenotype in parents of children who had both regressive and non-regressive forms of ASD.26 To date, none of the suggested neurobiological theories, many based on neuroimaging findings, have consistently explained regressive ASD.27,28 New computer-modelled theories are emerging but are also unproven.29

**Is There a Clear Regression Subtype?**

In the last 7 years, studies have looked at the onset of ASD prospectively, including population sample studies10,31 and studies of high-risk siblings.12 In one study, around 50% of children who were later diagnosed with ASD showed typical development (apart from exhibiting fewer gaze shifts) prior to 14 months but then experienced a period of developmental change that involved arrest, slowing and/or regression.33 A continuum of impairment, where children reach a threshold for diagnosis of ASD at different points in time in the first 3 years of life, was described.13 Another study reported that the symptoms of ASD emerged over a period of time beginning around the second year of life. Repeated observations of children in this study found a decline in social communication skills in 86% of children.9 It remains to be established whether these prospective studies have captured the full range of patterns of onset of developmental problems that are later diagnosed as ASD and all the ways regression may occur. To date, few have reported the more dramatic, rapid loss of skills, which may represent an important subtype of regression. The methodological limitations of prospective studies to date (e.g. primarily high-risk siblings and small sample sizes) prevent us from forming firm conclusions.

**Prognosis**

There have been mixed findings in the literature about whether children with ASD who experience regression have better or worse long-term outcomes than children who do not experience regression. Some studies have reported no difference in outcome for children who regressed versus those who did not (e.g. Shumway et al.34) and others have found that those who regressed were more impaired in areas such as language, co-morbid psychopathology, adaptive function, challenging behaviours and social skills than their counterparts.7,19,35,36 In one study, the loss of non-specific vocalisations was associated with lower IQ and higher ASD symptomatology (as measured on the Autism Diagnostic Observation Schedule).8 However, for those children who developed words and phrases by 5 years of age, those with word loss had similar outcomes to the children without word loss.

**No Changes yet for Clinical Care**

For the paediatrician, the approach to a child who presents with regression and problems of the type seen in ASD is unchanged. A thorough history to tease out the developmental trajectory will assist with assessing if regression has occurred and what developmental dimensions are involved. When regression has occurred, investigation and referrals should take into account important potential underlying pathophysiology, like seizure disorders and metabolic and genetic causes. When ordering genetic tests, like microarray, a history of suspected regression should be provided along with the diagnosis of ASD. If this is done consistently, it may assist in identifying genetic underpinnings for some children and families that are unlikely to be found in research studies, because of sample size limitations. If the presence of regression is uncertain, then review to monitor progress against baseline abilities and difficulties is needed.

**Still No Answers but Maybe Now We Are Asking the Right Questions**

Research about regression in ASD, including prospective studies of early development, has not yet provided clear answers about whether there is a distinct subtype of children with autistic regression. A lack of clarity about the subtype is likely to explain why findings are still mixed about the possible causes and prognosis of children who are reported to regress. However, evidence from ASD research focusing on regression has contributed to an emerging interest in the dimensions of developmental difficulties for children with ASD, including timing of onset and subsequent trajectory. This approach, rather than a categoric approach to the diagnosis of ASD, provides hope as an important new framework from which to ask the right questions about causes of and interventions for ASD, and how it is associated with other developmental difficulties and disorders. If this dimensional thinking can underpin research using new technology for both genetic and epigenetic research and neuroimaging and computer models of brain function, there could be more rapid progress towards providing the sorts of answers we need to assist children and families in ways that are tailored to their needs. However, we do not see biological advances as all that are needed to create a better life for children with ASD and their families. In fact, biological advances will need to be embedded in strong human rights and ethical frameworks to ensure they do not create more problems than they solve.

**References**

Regression in autism


Appendix B. Databases and search terms used for the systematic review
<table>
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<tbody>
<tr>
<td>Autism terms</td>
<td>1. exp child development disorders, pervasive/ or exp asperger syndrome/ or exp autistic disorder/ or exp schizophrenia, childhood/ 2. autis$.tw. 3. kanner$.tw. 4. (childhood adj3 schizophrenia).tw. 5. pervasive development$ disorder$.tw. 6. asperger$.tw. 7. (infantile adj3 psychosis).tw. 8. (childhood adj3 psychosis).tw. 9. or/1-8</td>
<td>1. autis$.tw. 2. kanner$.tw. 3. (childhood adj3 schizophrenia).tw. 4. pervasive development$ disorder$.tw. 5. asperger$.tw. 6. (infantile adj3 psychosis).tw. 7. (childhood adj3 psychosis).tw. 8. exp EARLY INFANTILE AUTISM/ or exp AUTISM/ 9. exp Childhood Schizophrenia/ 10. exp Pervasive Developmental Disorders/ or exp Autistic Children/ 11. exp Childhood Psychosis/ 12. or/1-11</td>
<td>1. autis$.tw. 2. kanner$.tw. 3. (childhood adj3 schizophrenia).tw. 4. pervasive development$ disorder$.tw. 5. asperger$.tw. 6. (infantile adj3 psychosis).tw. 7. (childhood adj3 psychosis).tw. 8. exp Childhood Schizophrenia/ 9. exp AUTISM/ 10. exp Asperger Syndrome/ or exp pervasive developmental disorder/ 11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10</td>
<td>1. (MH “Child Development Disorders, Pervasive+”) 2. AB pervasive development* disorder* 3. AB autis* 4. AB Asperger* 5. AB Kanner* 6. AB (childhood N4 psychos*) 7. AB (childhood N4 schizophren*) 8. 1 or 2 or 3 or 4 or 5 or 6 or 7</td>
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<tr>
<td>and Dying&quot;/</td>
<td>infant death/</td>
<td>infant death/</td>
<td>10. (MH &quot;Mortality+&quot;)</td>
<td>10. (MH &quot;Mortality+&quot;)</td>
</tr>
<tr>
<td>15. sudden infant death/</td>
<td>13. mortality/</td>
<td>14. prognos$.tw.</td>
<td>11. (MH &quot;Incidence&quot;)</td>
<td>12. AB prognos*</td>
</tr>
<tr>
<td>16. mortality rate/</td>
<td>15. predict$.tw.</td>
<td>16. course.tw.</td>
<td>13. AB predict*</td>
<td>14. AB course</td>
</tr>
<tr>
<td>17. followup studies/</td>
<td>17. or/13-20</td>
<td></td>
<td>15. mortalit*</td>
<td>16. 9 or 10 or 11 or 12 or 13 or 14 or 15</td>
</tr>
<tr>
<td>18. prognos$.tw.</td>
<td>19. predict$.tw.</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>19. predict$.tw.</td>
<td>20. course.tw.</td>
<td></td>
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<td>20. course.tw.</td>
<td>21. or/13-20</td>
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<tr>
<td>21. or/13-20</td>
<td></td>
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<tr>
<td>Combinations</td>
<td>10. limit 9 to &quot;prognosis (sensitivity)&quot;</td>
<td>22. 12 and 21</td>
<td>18. 11 and 17</td>
<td>14. 8 and 16</td>
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</tbody>
</table>

* when the supplier moved from OVID to EBSCO in 2009 for CINAHL the search was adapted. Search terms for EBSCO are reported here. Details on the search terms used under OVID are available upon request.
Appendix C. Risk of bias criteria (adapted from Hayden et al., 2013)
<table>
<thead>
<tr>
<th>Criteria</th>
<th>Unclear</th>
<th>High</th>
<th>Medium</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Study participation</td>
<td>The study sample adequately represents population of interest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source population (described)</td>
<td>Clinical (not community based)</td>
<td>Clinical but drawn from broad community base</td>
<td>Population-based</td>
<td></td>
</tr>
<tr>
<td>Description of sampling frame</td>
<td>Not described</td>
<td>Some description but not adequate/complete</td>
<td>Well described</td>
<td></td>
</tr>
<tr>
<td>Description of baseline study sample</td>
<td>Not described</td>
<td>Some description but not adequate/complete</td>
<td>Well described</td>
<td></td>
</tr>
<tr>
<td>Description of inclusion/exclusion criteria</td>
<td>Not described</td>
<td>Some description but not adequate/complete</td>
<td>Well described</td>
<td></td>
</tr>
<tr>
<td>Adequacy of participation in study by all eligible</td>
<td>No</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>2. Study attrition</td>
<td>The study data available (those not lost to follow-up) adequately represents the study sample</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recruitment</td>
<td>Retrospective</td>
<td>Retrospective with whole cohort considered</td>
<td>Prospective</td>
<td></td>
</tr>
<tr>
<td>Loss to follow-up (LFU) (%)</td>
<td>&lt;80% remain</td>
<td>≥80% remain</td>
<td>≥ 85% remain</td>
<td></td>
</tr>
<tr>
<td>Description of attempts to collect information on those LFU</td>
<td>No</td>
<td>Some information provided but not adequate</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Reasons for LFU provided?</td>
<td>No</td>
<td>Some information provided but not adequate</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Reasons for LFU linked to outcome?</td>
<td>No</td>
<td>Some information provided but not adequate</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Criteria</td>
<td>Unclear</td>
<td>High</td>
<td>Medium</td>
<td>Low</td>
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<td>----------------------------------------</td>
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<tr>
<td>Adequate description of LFU participants?</td>
<td>No</td>
<td>Some information provided but not adequate</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Analysis: important differences between LFU and non-LFU in study?</td>
<td>Important differences</td>
<td></td>
<td>No important differences</td>
<td></td>
</tr>
<tr>
<td>3. Outcome measurement</td>
<td>The outcomes of interest are measured in a similar way for all participants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding</td>
<td>Not blinded</td>
<td>Blinding inadequate</td>
<td>Blinding adequate</td>
<td></td>
</tr>
<tr>
<td>Clear definition of outcome provided?</td>
<td>No</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Same outcome tool for all?</td>
<td>Not same tool for all</td>
<td></td>
<td>Same for all</td>
<td></td>
</tr>
<tr>
<td>Valid and reliable tool?</td>
<td>Not valid, reliable tool used</td>
<td></td>
<td>Valid/reliable tool but parent rating</td>
<td>Standardised, reliable, valid tool used</td>
</tr>
<tr>
<td>Method and setting of outcome measurement same for all participants?</td>
<td>No</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Completeness of outcome measure</td>
<td>Not all tools completed (&gt;90% missing)</td>
<td></td>
<td>Not all tools completed but not &gt;90% missing</td>
<td>All tools completed</td>
</tr>
</tbody>
</table>
Appendix D. Characteristics of studies included in the systematic review.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Setting (clinical, intervention trial, population)</th>
<th>Number participants at BL (and sex)</th>
<th>Classification/ study population</th>
<th>IQ (tool used, levels) Mean (M) (SD; range) Median (Med) (IQR range)</th>
<th>IQ&lt;70 or IQ&gt;70</th>
<th>Age at baseline (yrs)</th>
<th>Age at follow up (yrs) Mean (M) (SD; range) Median (Med) (IQR range)</th>
<th>Follow up duration (yrs)</th>
<th>Language tools used</th>
<th>Proportion followed up</th>
<th>Predictors of language outcome measured?</th>
<th>Type of intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson, 2007</td>
<td>Prospective, clinical</td>
<td>166 (221 children in total but 50 were non-ASD) (sex not stated for ASD group)</td>
<td>autism n=101 PDD-NOS n=60</td>
<td>DSM IV; ADOS; ADI-R with paediatrician</td>
<td>Completed assessment with WISC; MSEL, DAS but unable to extract scores from paper</td>
<td>ND</td>
<td>M 2.42 (0.43) (includes all children not just those with ASD)</td>
<td>Varied by site and referral status. Some seen at 2, 3, 5, 9 yrs, others at 3 out of 4 time periods, some not seen at age 5.</td>
<td>Follow up varied by site and referral group. As a minimum seen 4 times until 9 yrs. Inclusion in analysis required child be seen twice.</td>
<td>MSEL, nonverbal category based on ADI-R and ADOS module</td>
<td>93% (206/221) families eligible (reasons for loss follow up given)</td>
<td>Y. Investigated age of diagnosis, demographic factors, nonverbal IQ, ASD diagnosis as predictors. Nonverbal IQ and joint attention were strongest predictors of verbal outcome.</td>
</tr>
<tr>
<td>Anderson, 2009</td>
<td>Prospective, clinical</td>
<td>144 (sex not stated for ASD group)</td>
<td>Autism n= 93; PDD-NOS n=51</td>
<td>DSM IV; ADOS; ADI-R with paediatrician</td>
<td>MSEL or Merrill-Palmer (n=1) NVIQ Autism: M 62.4 (17.36) PDD-NOS M 72.5 (20.53)</td>
<td>&lt;70</td>
<td>Autism M 2.5 (0.38) PDD-NOS M 2.45 (0.47)</td>
<td>Autism M 3.5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 (calculated)</td>
<td>1, 3, 7, 11</td>
<td>SCD-R</td>
<td>69% (148/214 at 13 yrs) Note: total sample includes non-ASD. Do not provide stats for only ASD.</td>
<td>N. A specific intervention (MPST therapy) predicted improved verbal abilities</td>
</tr>
<tr>
<td>Anderson, 2014</td>
<td>Prospective, clinical</td>
<td>142 (sex not stated)</td>
<td>ASD</td>
<td>DSM IV; ADI-R; ADOS</td>
<td>MSEL, WASI, VIQ=70 n=53; VIQ ≥ 70 n=32</td>
<td>&gt;70 (VIQ)</td>
<td>M 2.44 (0.42)</td>
<td>M 19.1 (1.08)</td>
<td>16.6 (calculated)</td>
<td>MSEL, VABS</td>
<td>53% (85/159)</td>
<td>Y. Verbal IQ at 19 yr outcome. Predictors at 2-3 years included verbal IQ at 3 yrs, RRB at 2 years, RRB change 2-3 years. Verbal IQ at 3 years was predictor for IQ&lt;70 group and RRB change 2-3 yrs a predictor for the IQ≥70 group.</td>
</tr>
<tr>
<td>Baghdadi 2012</td>
<td>Prospective, clinical</td>
<td>280 (229 male)</td>
<td>CA n=238; AA n=42</td>
<td>ICD-10; CARS, ADI-R on 1/3 sample</td>
<td>ECSP cognition related to object assessment measure M 22.4 months (11.9)</td>
<td>&lt;70</td>
<td>M 4.75 (1.15)</td>
<td>T2: M 8.08 (1.25) T3: M 15 (1.5)</td>
<td>3 &amp; 10</td>
<td>VABS; mute, words, functional language</td>
<td>T1-T2=78% (219/280) &amp; T1- T3=50% (152/280)</td>
<td>Y. Higher CARS score, amount intervention and language at T1 predicted communication trajectory on VABS</td>
</tr>
<tr>
<td>Author, year</td>
<td>Setting (clinical, intervention trials, population)</td>
<td>Number participants at BL (and sex)</td>
<td>Classification/ study population</td>
<td>Criteria, tool</td>
<td>IQ (tool used, levels) Mean (M) (SD; range)</td>
<td>IQ&lt;70 or IQ&gt;70 Age at baseline (yrs)</td>
<td>Age at follow up (yrs) Mean (M) (SD; range)</td>
<td>Follow up duration (yrs)</td>
<td>Language tools used</td>
<td>Proportion followed up</td>
<td>Predictors of language outcome measured?</td>
<td>Type of intervention</td>
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<tr>
<td>Bagley 1989</td>
<td>Retrospective clinical</td>
<td>53 (37 male)</td>
<td>CA DSM III</td>
<td>ND</td>
<td>M 8 (4.5). M 12.8 (0.31-0.45)</td>
<td>18.5</td>
<td>Mute or full sentences.</td>
<td>ND Missing data on many children.</td>
<td>N</td>
<td>TIC</td>
<td></td>
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<tr>
<td>Bal, 2015</td>
<td>Prospective, clinical</td>
<td>152 (sex not stated)</td>
<td>ASD ADI-R, ADOS</td>
<td>&lt;70</td>
<td>M 2.44 (0.42). M 2.44 (calculated)</td>
<td>21</td>
<td>18.5</td>
<td>MSEL</td>
<td>VABS</td>
<td>24% (36/152)</td>
<td>N</td>
<td>TIC</td>
</tr>
<tr>
<td>Ballaban-Gil 1996</td>
<td>Prospective, clinical</td>
<td>102 (93 male) (45 adults; 54 adolescents)</td>
<td>Autism (but appears to be range of PDD as per DSM IV) Diagnosis made by criteria published by Rapin (1988), consistent with DSM IV</td>
<td>ND</td>
<td>M 6.8 (0.79-20.3). M 18.1 (12-29.5)</td>
<td>M 11.3 (3.2 - 22.7)</td>
<td>Proportion verbal. Based on interview. Data per cognitive group.</td>
<td>61% (102/163)</td>
<td>N</td>
<td>TIC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bedford 2015</td>
<td>Prospective, clinical</td>
<td>Whole gp (incl DD) n=209 (170 male) ASD only gp n=151 (139 male)</td>
<td>ASD or PDD-ADOS ADI-R</td>
<td>&gt;70</td>
<td>M 2.41 (0.03) M 9.37 (0.1)</td>
<td>7</td>
<td>VABS, MSEL</td>
<td>95% (209/221)</td>
<td>Y. Early gross motor score was significant predictor of both expressive and receptive language development</td>
<td>TCP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ben Itzchak 2009</td>
<td>Retrospective clinical, intervention</td>
<td>68 (62 male)</td>
<td>Autism (6 with ASD were excluded at baseline) Clinical Dx by paediatrician DSM IV, ADOS, ADI-R</td>
<td>ND</td>
<td>M 2.12 (0.33; 1.5-2.9) M 3.12 (calculated)</td>
<td>1</td>
<td>VABS, MSEL</td>
<td>ND 100% (66/68)</td>
<td>Y. Change in diagnostic classification predicted post-intervention achievement in language outcomes</td>
<td>Centre based IBI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ben Itzchak 2010</td>
<td>Retrospective clinical, intervention</td>
<td>78 (71 male)</td>
<td>ASD</td>
<td>Clinical Dx by paediatrician DSM IV, ADOS, ADI-R</td>
<td>&gt;70</td>
<td>1.25-2.9. Unclear if this is at BL or duration of study 2.25-3.92 (calculated)</td>
<td>1</td>
<td>MSEL</td>
<td>100% (78/78) (some missing data)</td>
<td>N</td>
<td>Centre based IBI</td>
<td>TCP</td>
</tr>
<tr>
<td>Ben Itzchak 2014</td>
<td>Retrospective clinical, intervention</td>
<td>46 (39 male)</td>
<td>ASD</td>
<td>Clinical Dx by paediatrician DSM IV, ADOS, ADI-R</td>
<td>&gt;70</td>
<td>M 2.13 (0.33; 1.4-7.25) M 3.13 (T2) 4.13 (T3) (calculated)</td>
<td>1 &amp; 2</td>
<td>VABS, MSEL</td>
<td>100% (46/46) (some data missing VABS n=36)</td>
<td>N</td>
<td>TCP</td>
<td>Intervention based on ABA, provide detail</td>
</tr>
</tbody>
</table>

**Notes:**
- **IQ** refers to Intelligence Quotient.
- **TIC** refers to Treatment Implementation Checklist.
- **ND** indicates not documented.
- **MSEL** refers to Mullen Scales of Early Learning.
- **WASI** refers to Wechsler Abbreviated Scale of Intelligence.
- **DAS** refers to Differential Ability Scales.
- **ADI-R** refers to Autism Diagnostic Interview-Revised.
- **ADOS** refers to Autism Diagnostic Observation Schedule.
- **VABS** refers to Vineland Adaptive Behavior Scales.
- **TIC** refers to Treatment Implementation Checklist.
- **IBI** refers to Intensive Behavioral Intervention.
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<th>Author, year</th>
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<th>Predictors of language outcome measured?</th>
<th>Type of intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennett 2008</td>
<td>Prospective, clinical</td>
<td>64 (45 HFA (42 male) and 19 AS (15 male))</td>
<td>HFA and AS, IQ&gt;68</td>
<td>ADI</td>
<td>HFA: M 87.24 (18.94) AS: M 99.98 (16.38) Stanford Binet &gt;70, Leiter IQ &gt;68</td>
<td>&gt;70</td>
<td>HFA: M 5.41 (1) AS: M 5.77 (4.36)</td>
<td>HFA: M 7.41 AS: M 7.77 (calculated) *have presented data separately for SLI or no SLI groups and AD/HFA groups</td>
<td>2 (approximately)</td>
<td>TOLD, VABS</td>
<td>97% (62/64)</td>
<td>Y. SLI at T1 and T2, clinical diagnosis predicted variation in communication subscales of VABS</td>
<td>TIC</td>
</tr>
<tr>
<td>Bennett 2013</td>
<td>Prospective, clinical</td>
<td>39 (31 male)</td>
<td>HFA (needed IQ&gt;68 for inclusion)</td>
<td>DSM III-R, ADI-R</td>
<td>Leiter NV IQ T1 M 66.48 (17.34; 36-127)</td>
<td>&gt;70</td>
<td>M 7.45 (0.13; 6.08-9.33)</td>
<td>T2: M 15.19 (1.19; 13.17-17.58) T3: M 17.38 (1.48; 14.58-21.17)</td>
<td>2 yrs for TOLD and 8 yrs for VABS</td>
<td>VABS, TOLD</td>
<td>92% (36/39)</td>
<td>Y. Theory of mind and language on adaptive communication outcomes (VABS). Language at T1 predicted communication domain on VABS and was mediated by ToM.</td>
<td>TIC</td>
</tr>
<tr>
<td>Bennett 2014</td>
<td>Prospective, clinical</td>
<td>330 (276 male)</td>
<td>ASD with and without language impairment and with ID</td>
<td>DSM IV, ADI-R, ADOS</td>
<td>Merrill-Palmer developmental index standard score M 58.92 (24.82)</td>
<td>&lt;70</td>
<td>M 3.2 (0.7)</td>
<td>M 4.2 (calculated)</td>
<td>1</td>
<td>PLS-4, CELF 4, VABS</td>
<td>87% (288/330)</td>
<td>N</td>
<td>TIC</td>
</tr>
<tr>
<td>Bennett 2015</td>
<td>Prospective, clinical</td>
<td>365 (sex not stated)</td>
<td>ASD</td>
<td>DSM IV, ADI-R, ADOS</td>
<td>Merrill-Palmer developmental index standard score M 57.29 (24.65) 10-150</td>
<td>&lt;70</td>
<td>M 3.2 (0.7)</td>
<td>M 4.2 (calculated)</td>
<td>1</td>
<td>PLS-4, CELF 4, VABS</td>
<td>90% (330/365)</td>
<td>N</td>
<td>TIC</td>
</tr>
<tr>
<td>Berry, 2010</td>
<td>Retrospective clinical, intervention</td>
<td>114 (98 male)</td>
<td>Autism n=73; PDD-NOS n=41</td>
<td>DSM IV-TR, CARP, ADI-R, ADOS</td>
<td>Scores presented separately for ASD_AS and ASD-NON children. BL ASD IQ M 57.31 (9.74) *also have FU IQ scores. T1: Bayley’s, MSEL; T2 MSEL, DAS</td>
<td>&lt;70</td>
<td>ASD-ASD M 4.44 (0.94) ASD-NON M 4.46 (0.62)</td>
<td>ASD-ASD M 2.23 (calculated) ASD-NON M 2.21 (calculated)</td>
<td>VABS, MSEL</td>
<td>100% (114/114)</td>
<td>(only included those that had been measured twice)</td>
<td>N</td>
<td>TIC</td>
</tr>
</tbody>
</table>

* TIC: Theory of mind and language on adaptive communication outcomes (VABS). Language at T1 predicted communication domain on VABS and was mediated by ToM.
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</tr>
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<tr>
<td>Blacklock 2014</td>
<td>Retrospective clinical</td>
<td>68 (56 male)</td>
<td>Autism/AD n=37, PDD or ASD n=26, PDD-NOS n= 5</td>
<td>Diagnosis completed by local diagnosticia ns who referred to IBI program CARS, DSM IV (see Perry 2008)</td>
<td>Range of IQ measures. MSEL, WISC, Stanford Binet, WPPSI</td>
<td>&lt;70</td>
<td>M 7.40 (range 5.8-13.58)</td>
<td>M 9.02 (calculated)</td>
<td>1.62 (0.83-5.8)</td>
<td>VABS</td>
<td>78% (53/68) (unclear if LFU or incomplete tools).</td>
<td>N</td>
<td>Intensive IBI (publicly funded)</td>
</tr>
<tr>
<td>Bopp 2006</td>
<td>Retrospective clinical</td>
<td>70 (58 male)</td>
<td>AD SS, PDD- NOS 15</td>
<td>Diagnoses done by diagnosticia ns in the community not involved in the study</td>
<td>ND</td>
<td>ND</td>
<td>M 4.2 (range 1.6-6)</td>
<td>M 5.2 (at 1 yr) M 6.2 (at 2yr) (calculated)</td>
<td>0.5, 1 &amp; 2</td>
<td>PLS-3, EOVT, PPVT III, CDI</td>
<td>90% (63/70).</td>
<td>Y. Higher scores in acting out behaviour, inattentive behaviour and reduced stereotypic behaviour predicted greater increase in rate of change in language.</td>
<td>TIC</td>
</tr>
<tr>
<td>Bopp 2009</td>
<td>Retrospective clinical</td>
<td>69 (58 male)</td>
<td>AD n=55 PDD- NOS n=14</td>
<td>Diagnosed in community, confirmed with CARS by blinded assessor</td>
<td>Estimated NVIQ using MSEL fine motor and visual subtests for 60 children (do not provide scores in table)</td>
<td>ND</td>
<td>M 4.2 (1.75-6)</td>
<td>At 1 yr M 5.2 and 2 yr M 6.2</td>
<td>0.5, 1 &amp; 2</td>
<td>PLS-3, PPVT III, EOVT</td>
<td>100 % (69/69)</td>
<td>Y. Exploratory—child behaviour predictors (e.g., inattentiveness, acting out, social unresponsivenes s, insistence on sameness, repetitive behaviours) on language outcomes. Social unresponsiveness and inattentive behaviours predictive of language outcomes</td>
<td>TIC</td>
</tr>
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<tr>
<td>Bopp 2011</td>
<td>Retrospective clinical</td>
<td>44 (37 male)</td>
<td>AD n=36, PDD-NOS n=8</td>
<td>Diagnosed in community, confirmed with CARS by blinded assessor</td>
<td>MSEL at T1, NVIQ estimated for 39 children - combined visual reception and fine motor subscales from the MSEL; scores not available for other 5 children</td>
<td>ND</td>
<td>M 3.9 (1.75-5.9)</td>
<td>T6 M 9.3 (6.2-10.3)</td>
<td>4-5 yrs. Data collected at baseline (T1), and (on average) 6, 12, 24, 33 and 53 months later (T2–T6).</td>
<td>PPVT III, EDWVT, PLS-3, CDI</td>
<td>100% (44/44)</td>
<td>Y. Pre-language skills investigated as predictors: initiate joint attention, conventional gestures, games-and-routines, actions with objects, pretend to be a parent, imitations of other adult actions. When all factors put in model ability to participate in games routines was the only significant predictor.</td>
<td>TIC</td>
</tr>
<tr>
<td>Carbonnel Chabas 2009</td>
<td>Prospective, clinical</td>
<td>32 (29 male)</td>
<td>IA n=18, AA n=2, AS n=1, another PDD n=3 PDD-NOS n=8</td>
<td>ICD-10 and CFTMEA-R criteria</td>
<td>Very few tested-results ND</td>
<td>ND</td>
<td>3-7 yrs (at entry to program)</td>
<td>12-25 yrs (in 2006)</td>
<td>Unable to determine (assume between 9 and 18 yrs)</td>
<td>Questionnaire about language level (phrase, no language, only a few words, echolalic speech, generally uses correct sentences)</td>
<td>54% (32/59)</td>
<td>N</td>
<td>TIC</td>
</tr>
<tr>
<td>Cederlund 2008</td>
<td>Prospective, clinical</td>
<td>140 (140 male)</td>
<td>Autism (n=70; n=62 with autism, n=22 with atypical autism including 2 with disintegrative disorder) or AS (n=70)</td>
<td>DSM-III or III-R for Autism, Gillberg &amp; Gilberg criteria for AS. Confirmed with DISCO</td>
<td>Autism: &lt; 70: n=70 ≥70: n=14: VIQ 107.2 (18.6) PIQ 94.6 (18.7) NB: based on original sample.</td>
<td>Autism &lt;70 and AS&gt;70</td>
<td>Autism: &lt;10 years AS: 11.3 (3.8)</td>
<td>Autism: 24.5 (5.4; 16.1–36.1) AS: 21.5 (4.4; 16.0–33.0)</td>
<td>Autism: 14.5 (calculated) AS</td>
<td>VABS</td>
<td>76% (140/184)</td>
<td>N</td>
<td>TIC</td>
</tr>
<tr>
<td>Author, year</td>
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<tr>
<td>Chawarska 2009</td>
<td>Prospective, clinical</td>
<td>89 (sex not stated for whole group only diagnostic change subgroups ranges 75-90% male)</td>
<td>Confirmatory diagnosis autism n=36; PDD-NOS n=28 Autism (provisional T1) to PDD-NOS (confirmatory T2) n=11, autism to autism n=32; PDD-NOS to PDD-NOS n=15.</td>
<td>DSM IV; MDT,ADOS, provisional diagnosis. 91% met diagnosis on ADOS</td>
<td>MSEL: NVDO autism: M 75 (21) 56 % NVDO&gt;70, PDD-NOS M 99 (16) 99% NVDO &gt;70, VIQ autism: M 68 (29) 42% VDO &gt;70 PDD-NOS: M 99 (15) 96% VDO &gt;70.</td>
<td>&gt;70</td>
<td>M 1.79 (0.41; 1.1-2.25)</td>
<td>M 3.91 (0.64; 2.5-5.08 mo.)</td>
<td>M 2.12 (calculated)</td>
<td>MSEL</td>
<td>ND, 100% (89/89) (assumed)</td>
<td>N</td>
<td>TIC</td>
</tr>
<tr>
<td>Darrou 2010</td>
<td>Prospective, clinical</td>
<td>208 (166 male)</td>
<td>A n=175; AA n=28, other n=5</td>
<td>ICID-10; psychiatrist, CARS</td>
<td>VABS DQ (unclear): DQ T1: &gt;70 n=9 (IQR 4.3), 50-69 n=48 (IQR=23.1), &lt;49 n=151 (IQR=72.6)</td>
<td>&lt;70</td>
<td>Med 5</td>
<td>Med 8</td>
<td>3</td>
<td>VABS; words, sentences, no speech</td>
<td>74% (154/208)</td>
<td>N. Looked at combined outcome of high or low level based on degree of autism, speech level, developmental age, not language on its own as an outcome.</td>
<td>TIC</td>
</tr>
<tr>
<td>Davidson 2014</td>
<td>Prospective, clinical</td>
<td>127 (sex not stated)</td>
<td>ASD</td>
<td>ADI-R, ADOS, ADOS-T</td>
<td>MSEL (nonverbal ratio IQ scores) T1 M 75.98 (14.66; 38-115) T2 M 78.04 (17.9; 35-108)</td>
<td>&gt;70</td>
<td>M 2.57 (0.83; 1.91-3.25)</td>
<td>M 5.54 (0.41; 4.75-8.6)</td>
<td>M 2.97 (calculated)</td>
<td>PLS-4, VABS</td>
<td>80% (101/127)</td>
<td>N</td>
<td>TIC</td>
</tr>
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<td>IQ (tool used, levels) Mean (M) (SD; range) Median (Med) (IQR range)</td>
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<td>Age at baseline (yrs) Mean (M) (SD; range) Median (Med) (IQR range)</td>
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<tr>
<td>Eaves 1996</td>
<td>Retrospective clinical</td>
<td>76 (57 male)</td>
<td>ASD (classify at time 2 into AD and PDD)</td>
<td>DSM III or IIIIR and CARS and clinic consensus. If seen before DSM III diagnosis based on notes and authors opinion. Some had diagnosis retrospectively applied to notes as criteria not available when patients seen.</td>
<td>IQ at T1: VIQ M 58 (6-135) and PIQ M 63 (6-126) WISC –R, Stanford Binet, Leiter, Bayley’s. The n, % of sample, and mean IQ score on each measure is also provided</td>
<td>&lt;70</td>
<td>M 7.1 (3.1 to 12.7)</td>
<td>M 11.6 (8-17)</td>
<td>M 4 (calculated)</td>
<td>Proportion verbal/ nonverbal</td>
<td>100% (76/76)</td>
<td>N</td>
<td>TIC</td>
</tr>
<tr>
<td>Eaves 2004</td>
<td>Prospective, clinical</td>
<td>49 (sex not stated)</td>
<td>AD and PDD-NOS</td>
<td>CARS, DSM IV, MDT.</td>
<td>Bayley, WPPSI-R, Leiter, Stanford Binet</td>
<td>&lt;70</td>
<td>M 2.75 (0.38)</td>
<td>M 4.9 (0.62)</td>
<td>2.25</td>
<td>VABS/PLS</td>
<td>93% (40/43)</td>
<td>N</td>
<td>TIC</td>
</tr>
<tr>
<td>Ellis Weismer 2015</td>
<td>Prospective, clinical</td>
<td>129 (112 male)</td>
<td>ASD</td>
<td>ADI-R, ADOS, ADOS-T</td>
<td>Bayley cognitive scale T1: M 84.8 (12.1)</td>
<td>&gt;70</td>
<td>M T1 2.6 (0.34)</td>
<td>M T4 5.55 (0.4)</td>
<td>2.95 (calculated)</td>
<td>PLS-4, VABS, PPVT-4 (T4 only)</td>
<td>80% (103/129)</td>
<td>Y. Better receptive and expressive language at 2.5 years predicted more language growth in preschool than those with limited early language. Two variables played largest role were cognition and ASD severity.</td>
<td>TIC</td>
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<tr>
<td>Eriksson 2013</td>
<td>Population based, prospective</td>
<td>208 (176 male)</td>
<td>AD/CA n=105; AA n=58, AS n=13</td>
<td>Tool not stated for baseline data but IQ&lt;70 n=95 &amp; borderline IQ/low normal n=50 &amp; average or above average IQ n=51</td>
<td>&gt;70</td>
<td>n=64 referred before 36 months; n=83 referred between 37-48 months, n=61 referred between 49-54 months.</td>
<td>N=64 &gt;60 mo.; n=83 between 61-72 mo.; n=61 between 73-78 months (calculated-note some LFU but do not describe age of ones LFU)</td>
<td>2 yrs</td>
<td>VABS</td>
<td>95% (198/208)</td>
<td>N</td>
<td>N=208 received intervention based on ABA. N=93 received intensive targeted intervention and n=105 non-intensive. See Fernell 2011 for detail.</td>
<td></td>
</tr>
<tr>
<td>Fernell 2011</td>
<td>Population based, prospective</td>
<td>208 (176 male)</td>
<td>AD/CA n=105; AA n=58, AS n=13</td>
<td>Range of tools used. See Eriksson 2013 for detail.</td>
<td>&gt;70</td>
<td>1.6-4.5 yrs months</td>
<td>3.6-6.5 yrs (calculated)</td>
<td>1.74 (0.27)</td>
<td>VABS</td>
<td>95% (198/208)</td>
<td>N</td>
<td>TIC. High intensity n=65; other targeted interventions with ABA technique n=41; Fewer targeted interventions n=64. Detail provided.</td>
<td></td>
</tr>
<tr>
<td>Flanagan 2012</td>
<td>Retrospective clinical, intervention</td>
<td>122 (61 Tx (53 male), 61 WL (51 male)</td>
<td>PDD-NOS n=61; autism n=61. All children met diagnostic criteria for ASD towards severe end.</td>
<td>CARS MSEL, WPPSI-III, MA/CA. TX gp: M 55.71; WL gp: M 36.46. Note measured at time 2 not baseline Tx: 18% IQ in average range (&gt;85) WL: 3.3% IQ&lt;85</td>
<td>&lt;70</td>
<td>Tx gp: M 3.58 (0.96), WL gp: M 3.57 (0.88)</td>
<td>Tx gp: M 5.44; WL gp: M 4.98 (calculated)</td>
<td>Tx gp: M = 2.32 (0.68) WL gp: M 1.42 (0.23)</td>
<td>VABS</td>
<td>100% (122/122)</td>
<td>N</td>
<td>Intensive IBI intervention program (publicly funded)</td>
<td></td>
</tr>
<tr>
<td>Flanagan 2015</td>
<td>Prospective, clinical</td>
<td>369 (309 male)</td>
<td>ASD</td>
<td>Merrill-Palmer developmental index standard score. No delay (n=23), mild-moderate (n=47) and severe (n=45) at 2 years (and also 3,4,6 years).</td>
<td>&lt;70</td>
<td>T1 M 3.43 (0.75)</td>
<td>T2 M 4.54 (0.75) T3 M 6.59 (0.32)</td>
<td>T1-T2 M 1.11 T1-T3 M 3.16 (calculated)</td>
<td>VABS, PLS, CELF</td>
<td>ND</td>
<td>N</td>
<td>TIC. Provides some description of interventions received in community.</td>
<td></td>
</tr>
<tr>
<td>Author, year</td>
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<td>Criteria, tool</td>
<td>IQ (tool used, levels) Mean (M) (SD; range) Median (Med) (IQR range)</td>
<td>IQ&lt;70 or IQ&gt;70</td>
<td>Age at baseline (yrs)</td>
<td>Age at follow up (yrs) Mean (M) (SD; range) Median (Med) (IQR; range)</td>
<td>Follow up duration (yrs)</td>
<td>Language tools used</td>
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<tr>
<td>Freeman 1985</td>
<td>Prospective, clinical</td>
<td>62 (54 male)</td>
<td>&quot;Syndrome of autism&quot;</td>
<td>DSM III</td>
<td>High (VCI and PRI scores &gt;70) =23%; medium (VCI&lt;70, PRI&gt;70)=29%; low (VCI and PRI &lt;70)=48%</td>
<td>&lt;70</td>
<td>M 3.10 (2-6)</td>
<td>M 8.10 (calculated)</td>
<td>Annually for 5 yrs.</td>
<td>PPVT, TOLD, TACL</td>
<td>ND. Missing data: for cognitive and language testing.</td>
<td>N</td>
<td>TIC</td>
</tr>
<tr>
<td>Freeman 1991</td>
<td>Prospective, clinical</td>
<td>62 (54 male)</td>
<td>&quot;Autism syndrome&quot;</td>
<td>DSM III</td>
<td>77% had verbal IQ's &lt;70. High (VCI and PRI scores &gt;70)=23%; medium (VCI&lt;70, PRI&gt;70)=29%; low (VCI and PRI &lt;70)=48%</td>
<td>&lt;70</td>
<td>M 3.8 (2.6-5.9)</td>
<td>M 14.6 (9-20)</td>
<td>12 (10-17)</td>
<td>VABS; proportion nonverbal</td>
<td>85% (53/62)</td>
<td>N</td>
<td>TIC</td>
</tr>
<tr>
<td>Freeman 2010</td>
<td>Retrospective, clinical</td>
<td>89 (73 male)</td>
<td>AD n=55; PDD-NOS n=26; PDD or ASD n=7</td>
<td>DSM IV; CARS</td>
<td>Tools not described. MA M 18.03 mo. (9.06-8.55)=31 FSIQ M 36.65 (14.83-15.77)=31</td>
<td>&lt;70</td>
<td>M 4.47 (1.09; 1.67-6.92)</td>
<td>M 6.09 (calculated)</td>
<td>1.62 (0.81; 0.42-3.92)</td>
<td>VABS</td>
<td>100% (89/89)</td>
<td>All received IBI intervention, publicly funded program.</td>
<td>N</td>
</tr>
<tr>
<td>Georgiades 2014</td>
<td>Prospective, clinical</td>
<td>280 (241 male)</td>
<td>ASD</td>
<td>ADOS, ADI-R, DSM IV</td>
<td>MSEL</td>
<td>ND</td>
<td>M 3.4 (0.76; 2.0-4.9)</td>
<td>M 6.6 (0.3; 6.0-6.9)</td>
<td>3.2 (calculated)</td>
<td>VABS</td>
<td>100% (280/280)</td>
<td>Only included participants with data at both time points.</td>
<td>N</td>
</tr>
<tr>
<td>Green 2014</td>
<td>Prospective. Selected from larger longitudinal study. Unsure if clinical or population-based</td>
<td>161 (128 male)</td>
<td>Autism, PDD-NOS</td>
<td>ADOS, ADI-R</td>
<td>MSEL IQ&lt;70 Composite score: M 66.69 (16.73). Nonverbal IQ &gt;70: M 77.15 (17.69)</td>
<td>&lt;70</td>
<td>M 2.4 (0.35)</td>
<td>T3 M 4.42 (0.37)</td>
<td>2 (calculated)</td>
<td>VABS, MSEL</td>
<td>T2 92% (161/175) and T3 57% (91/175)</td>
<td>N</td>
<td>ND. TIC.</td>
</tr>
<tr>
<td>Haebig 2013a</td>
<td>Prospective, clinical</td>
<td>34 (28 male)</td>
<td>autism n=14; ASD n=20</td>
<td>ADI-R, ADOS</td>
<td>MSEL: NVMA M 24.32 (4.01)</td>
<td>&lt;70</td>
<td>M 2.61 (0.37)</td>
<td>M 5.58 (0.48)</td>
<td>M 2.96</td>
<td>PLS IV</td>
<td>100% (34/34) (assumed), Some missing data.</td>
<td>Y. Responsive verbal behaviours examined as predictors. Parent directives that followed into the child’s focus of attention predicted</td>
<td>TIC</td>
</tr>
<tr>
<td>Author, year</td>
<td>Setting (clinical, intervention trial, population)</td>
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<td>Criteria, tool</td>
<td>IQ (tool used, levels) Mean (M) (SD; range) Median (Med) (IQR range)</td>
<td>IQ&lt;70 or IQ&gt;70</td>
<td>Age at baseline (yrs) Mean (M) (SD; range) Median (Med) (IQR range)</td>
<td>Age at follow up (yrs) Mean (M) (SD; range) Median (Med) (IQR; range)</td>
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<tr>
<td>Haebig 2013b</td>
<td>Prospective, clinical</td>
<td>40 (33 male)</td>
<td>autism n=17; ASD n=23</td>
<td>ADOS, ADI-R</td>
<td>MSEL: NVMA M 24.24 (4.64; 17-34). Only 34 participants had valid NYMA data</td>
<td>&lt;70</td>
<td>M 2.6 (0.36; 2-3.25)</td>
<td>‘on average’ 1 yr later i.e. 3.63 (3-4.25) (calculated)</td>
<td>1</td>
<td>PLS IV</td>
<td>100% (40/40) (assumed); Some missing data.</td>
<td>receptive language gains at 3 yr flup. Parent comments had differential effects depending on initial language level. Minimally verbal chn at 2.5 yrs benefited from parent comments, but verbally fluent children did not.</td>
<td>TIC</td>
</tr>
<tr>
<td>Hedvall 2015</td>
<td>Prospective, population-based</td>
<td>208 (176 male)</td>
<td>AD n=128; PDD-NOS n=54; Aspergers n=9; autistic features n=17</td>
<td>In depth clinical assessment with ref to DSM IV</td>
<td>Griffith, PEP, Merrill Palmer, WPPSI</td>
<td>&lt;70 (based on Fernell 2011)</td>
<td>T0 M 3.25 (SD 0.7) 1.7-4.42 T1 3.75 (SD 0.7) 2.5 T2 M 5.5 (SD 0.7) 3.7-6.75</td>
<td>2 (as reported by study)</td>
<td>CDI at T1, VABS at T1 and T2</td>
<td>95% (198/208)</td>
<td>N</td>
<td>ND. TIC</td>
<td></td>
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<tr>
<td>Helendoorn, 2015</td>
<td>Prospective, population based</td>
<td>63 (49 male)</td>
<td>ASD</td>
<td>ADOS, ADI-R</td>
<td>MSEL- only raw scores reported</td>
<td>ND</td>
<td>M 2.26 (0.73)</td>
<td>M 3.82 (0.6)</td>
<td>1.56 (calculated)</td>
<td>MSEL</td>
<td>73% (46/63)</td>
<td>Y. Fine motor functioning was predictive of later receptive and expressive language</td>
<td>ND. TIC</td>
</tr>
<tr>
<td>Howlin 2004</td>
<td>Prospective, clinical</td>
<td>68 (61 male)</td>
<td>CA</td>
<td>Rutter (1966, 1972, 1978) criteria used for early cases, and then DSM-IV-TR (or ICD-10?)</td>
<td>NVIQ &gt;50 Initial PIQ M 80.21 (19.28; 51-137), Initial VIQ (n=22) M 51.49 (21.26; 21-106). Used: WAIS-R, Raven, Merrill Palmer and Leiter</td>
<td>&gt;70 (based on NVIQ only)</td>
<td>M 7.24 (3.1; 3.1-15.66)</td>
<td>M 29.33 (7.97; 21.16-48.58)</td>
<td>M 22.09 (calculated)</td>
<td>BPVS, PPVT, used VIQ as preferred measure for final language score. ADI-R ratings of good, moderate, severe.</td>
<td>86% (68/79) (note: reports the 10 individuals who refused or were not contacted did not differ from study sample –unclear what happened to the extra 1 person)</td>
<td>N</td>
<td>TIC</td>
</tr>
<tr>
<td>Howlin 2013</td>
<td>Prospective, clinical</td>
<td>60 (49 male)</td>
<td>Autism NVIQ&gt;70</td>
<td>Diagnosed autism, confirmed with ADI/ADI-R</td>
<td>WISC, WPPSI, WAIS, Merrill Palmer, Letter:</td>
<td>&gt;70</td>
<td>6.9 (2.9; 2.9–13)</td>
<td>44.2 (9.4; 29–64)</td>
<td>37.6 (9.2; 23-59)</td>
<td>ADI_R rating of language (item 30). See Howlin 2014</td>
<td>67% (60/90)</td>
<td>N. “Total outcome”, not specifically language outcomes.</td>
<td>ND. TIC</td>
</tr>
<tr>
<td>Howlin 2014</td>
<td>Prospective, clinical</td>
<td>60 (49 male)</td>
<td>Autism</td>
<td>ICD-9 or 10, confirmed with ADI/ADI-R</td>
<td>WISC, WPPSI, WAIS, Merrill Palmer, Letter: M 86.3</td>
<td>&gt;70</td>
<td>6.9 (2.9; 2.9–13)</td>
<td>44.2 (9.4; 29–64)</td>
<td>37.6 (9.2) 23-59</td>
<td>EOWPVT, BPVS, overall level of language on ADI-R (i.e. functional use of spontaneous phrases; no phrase speech and &gt;5 word vocab; no speech)</td>
<td>66% (60/91)</td>
<td>N</td>
<td>ND. TIC</td>
</tr>
<tr>
<td>Jonsdottir 2007</td>
<td>Prospective, clinical</td>
<td>41 (sex not stated)</td>
<td>PDD (CA and all other ICD 10 categories of PDD)</td>
<td>ICD-10</td>
<td>ND</td>
<td>ND</td>
<td>M 3.45 (0.76; 1.83-4.92)</td>
<td>M 5.8 (0.35, 5.1-6.6)</td>
<td>M 2.3 (0.78; 1-4.1), (minimum time between assessments was 1 yr)</td>
<td>ADI-R (proportion verbal/nonverbal) and VABS at follow up</td>
<td>ND. Provide information on who was excluded but no loss to follow up.</td>
<td>N</td>
<td>TIC</td>
</tr>
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<td>Age at baseline (yrs)</td>
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<tr>
<td>Kleinman 2008</td>
<td>Prospective, clinical from population screening</td>
<td>46 (sex not stated)</td>
<td>DSM IV, AD-R, CARBS, ADOS</td>
<td>FSIQ MSEL (n=35) or DAS (n=42); T1: autistic mean IQ M 53.24 (7.34) PDD-NOS: M 62.33 (16.19)</td>
<td>&lt;70</td>
<td>AD: M 2.26 (0.54) PDD-NOS: M 2.4 (0.24)</td>
<td>AD: M 4.4 (0.67; 3.4-6.8). Note: this is data for full 77 (not only the 46 ASD)</td>
<td>AD: M 4.26 (0.57) PDD-NOS: M 4.44 (0.46)</td>
<td></td>
<td>VABS, MSEL</td>
<td>75% (46/71)</td>
<td>N</td>
<td>TIC</td>
</tr>
<tr>
<td>Klintwall 2015</td>
<td>Prospective, clinical</td>
<td>70 (62 male)</td>
<td>ASD</td>
<td>ADOS-T AODS, clinical best estimate diagnosis</td>
<td>MSEL T1 nonverbal DQ: T1=46.7 (SD 26.7)</td>
<td>&lt;70</td>
<td>M 1.82 (SD 0.25)</td>
<td>M 3.18 (SD 0.37)</td>
<td>1.36 (calculated)</td>
<td>MSEL, VABS</td>
<td>100% (70/70)</td>
<td>Y. Level of interest during ADOS at 2 years predicted rate of verbal skill acquisition. Interest level predicted subsequent acquisition rate of verbal mental age.</td>
<td>TIC</td>
</tr>
<tr>
<td>Knorring 1993</td>
<td>Prospective, population-based</td>
<td>38 (23 male)</td>
<td>PDD n=1; IA n=37</td>
<td>At baseline – Flutter and DSM III and at follow up DSM III R</td>
<td>ND</td>
<td>ND</td>
<td>Age of first symptoms M 13.7 (8.4; 2-26) Whole sample range 3-26.</td>
<td>M 18.9 (4.8; 10-29)</td>
<td>8-9</td>
<td>Medical Research Council Schedule of Handicaps, Behaviours and Skills. Categories: no speech, no nonverbal communication, some abnormality.</td>
<td>89% (34/38). Note: 39 children in original study. 1 did not meet DSM III R criteria as not symptomatic until 36 mo.</td>
<td>N</td>
<td>TIC</td>
</tr>
<tr>
<td>Kobayashi 1992</td>
<td>Retrospective clinical</td>
<td>201 adults (170 male)</td>
<td>Autism</td>
<td>DSM III-R applied to case notes</td>
<td>IQ (unclear when measured) mild or more delayed 76.4%; borderline or above (i.e., normal) 23.6%.</td>
<td>&lt;70</td>
<td>M 6.4 (2.8)</td>
<td>M 21.5 (3.6; 18-33)</td>
<td>M 15.4 (4.5; 5-28)</td>
<td>Categorise into very good, good, fair, poor, very poor.</td>
<td>88% (197/201) Some missing data.</td>
<td>N</td>
<td>TIC</td>
</tr>
<tr>
<td>Landa 2012</td>
<td>Prospective, clinical intervention</td>
<td>48 (39 male)</td>
<td>ASD or autism</td>
<td>ADOS or expert clinician</td>
<td>MSEL: 81% IQ&lt;70 and 58% VABS scores &lt;70</td>
<td>&lt;70</td>
<td>M 2.27 (0.23)</td>
<td>T4: M 6.05 (1.46)</td>
<td>M 3.8</td>
<td>VABS</td>
<td>88% (42/48)</td>
<td>N</td>
<td>6 month comprehensive intervention based on ABA/routines-based teaching and visual</td>
</tr>
</tbody>
</table>

250
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Setting (clinical, intervention trial, population)</th>
<th>Number participants at BL (and sex)</th>
<th>Classification/ study population</th>
<th>Criteria, tool</th>
<th>IQ (tool used, levels) Mean (M) (SD; range)</th>
<th>IQ&lt;70 or IQ&gt;70 Age at baseline (yrs)</th>
<th>Age at follow up (yrs) Mean (M) (SD; range)</th>
<th>Age at follow up (yrs) Median (Med) (IQR range)</th>
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<tbody>
<tr>
<td><strong>Lombardo 2015</strong></td>
<td>Prospective, clinical</td>
<td>60 (47 male)</td>
<td>ASD poor language: &lt;1 SD below norm on MSEL n=24 (19 male) and better language: &gt;1 SD below norm n=36 (28 male) at outcome</td>
<td>ADOS, DSM IV MSEL IQ Poor language IQ&lt;70 but good language IQ &gt;70. Poor language: ELC: 52.95 (37.06) Good language: ELC: 89.11 (17.81). Mean of means=74.6</td>
<td>&gt;70</td>
<td>Poor: M 1.98 (SD 0.55). Good: M 1.78 (0.63)</td>
<td>Poor: M 3.14 (0.48). Good: M 2.8 (0.61)</td>
<td>Poor: 1.16. Good: 1.02 (calculated)</td>
<td>MSEL</td>
<td>100% (60/60)</td>
<td>Y. FMRI findings (or combination of behavioural and speech-related FMRI findings) predictive of poor or good language groups. Multimodal classifier (ADOS, Vineland, Mullen and fMRI) predicted language group best.</td>
<td>TIC</td>
<td></td>
</tr>
<tr>
<td><strong>Magiati 2011</strong></td>
<td>Prospective, clinical</td>
<td>44 (sex not stated)</td>
<td>ASD 9; autism 27</td>
<td>ADI-R and independent diagnosis of ASD</td>
<td>Bayley or WPSIII=T1 MA; M 26.3 mo. (13.6) 5-11 IQ; M 64.4 (30; 16-137.5) (also have T2 and T3 IQ) 26.3/40.8=64.5</td>
<td>&lt;70</td>
<td>T2: M 5.5 (0.6) T3: M 10.3 (0.8)</td>
<td>T2: 2 yrs post; T3: 4-5yrs post; i.e., 6-7yrs f/up period</td>
<td>BPVS, EOWVT</td>
<td>T2: 100% (44/44) T3: 82% (36/44)</td>
<td>N. Combined outcome ranks at T3 (combination of adaptive behaviour/IQ/language). Not specifically looking at language outcomes.</td>
<td>TIC. All in 'relatively intensive' specialist preschool programs. Detail provided.</td>
<td></td>
</tr>
<tr>
<td><strong>Mazurek 2012</strong></td>
<td>Retrospective, Simons Complex database</td>
<td>1433 (1240 male)</td>
<td>ASD</td>
<td>ADOS, ADI-R FSIQ scores M 83.3. Med 86.0; (27.4; 7- 167)</td>
<td>&gt;70</td>
<td>5 years (retrospective)</td>
<td>M 10.2 ( 3.1; 6-17)</td>
<td>5.2 (calculated)</td>
<td>ADI-R question; 'communicative or not communicate speech’</td>
<td>100% (1433/1433)</td>
<td>Y. For those that were nonverbal at age 5 (n=402), initial severity, age, race, gender, nonverbal IQ, and treatment history predictive of presence/absence of communicative</td>
<td>TIC</td>
<td></td>
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<td>IQ (tool used, levels) Mean (M)</td>
<td>SD; range</td>
<td>Median (Med)</td>
<td>IQ&lt;70 or IQ&gt;70</td>
<td>Age at baseline (yrs)</td>
<td>Age at follow up (yrs)</td>
<td>Mean (M)</td>
<td>SD; range</td>
<td>Median (Med)</td>
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<tr>
<td>Meyer 2002</td>
<td>Prospective, clinical</td>
<td>54 (45 male)</td>
<td>Autism (AD and PDD)</td>
<td>ADI-R, ADOS-G, DSM IV</td>
<td>DAS: FSIQ: M 78.17 (20.96; 25-141), VIQ: M 78.26, (18.58; 51-118), PIQ: M 86.65 (20.31; 49-153)</td>
<td>&gt;70</td>
<td>M 6.7 (1.25; 4-10.3)</td>
<td>9.7 (calculated)</td>
<td>3</td>
<td>PPVT (yr 1), VABS (yr1,3)</td>
<td>92% (46/50)</td>
<td>N</td>
<td>TIC but mainly TEACCH</td>
</tr>
<tr>
<td>Miniscalco 2014</td>
<td>Prospective, clinical</td>
<td>34 (29 male)</td>
<td>AD n=21, PDD-NOS n=12, Asperger n=1</td>
<td>ADOS-G, DSM IV, multidisciplinary team</td>
<td>WPPSI-R or Griffiths IQ/DQ scores M 79.5 (18.3; 46-114)</td>
<td>&gt;70</td>
<td>M 3.42 (0.69; 27-55)</td>
<td>M 4.52 (calculated)</td>
<td>M 1.1 (0.34; 0.5-1.6)</td>
<td>CDI at T1 and T2</td>
<td>100% (34/34)</td>
<td>Note: selected from larger sample</td>
<td>51% (27/53)</td>
</tr>
<tr>
<td>Mosconi 2005</td>
<td>Prospective, clinical</td>
<td>53 (sex not stated)</td>
<td>AD</td>
<td>DSM IV, ADOS, ADI-R</td>
<td>MSEL AE (mo.) T1 M 15.1 (5.1) T2 M 27.7 (15.2) MA/CA=15.1/31.2=49</td>
<td>&lt;70</td>
<td>M 2.6 (0.34)</td>
<td>M 4.8 (0.46)</td>
<td>2</td>
<td>MSEL, VABS</td>
<td>51% (27/53)</td>
<td>N</td>
<td>TIC</td>
</tr>
<tr>
<td>Moss 2008</td>
<td>Prospective, clinical</td>
<td>35 (32 male)</td>
<td>AD or ASD</td>
<td>Needed to meet ADI-R criteria to be included</td>
<td>Mean IQ T1 M 68.9 (33; 16-137.5), IQ measured using: WISC, WPPSI, Bayley, Merrill-Palmer depending on CA, dev level and language ability.</td>
<td>&lt;70</td>
<td>M 3.5 (0.6; 2.3-4.5)</td>
<td>M 10.5 (0.8; 9.1-12.1)</td>
<td>6-8</td>
<td>VABS, BPVS, EOWVT, presence of verbal language</td>
<td>47% (36/75) of original sample (75 seen at BL, 56 agreed to study and only 35 met inclusion criteria).</td>
<td>N</td>
<td>TIC. Do not provide detail but see Moss above as same cohort.</td>
</tr>
<tr>
<td>Munson 2008</td>
<td>Prospective, clinical</td>
<td>70 (58 male)</td>
<td>ASD</td>
<td>DSM IV, ADOS, ADI-R, clinician judgement</td>
<td>MSEL NVDQ Visual Reception, M 27.90 (11.92; 20–61); Fine Motor, M 24.77 (9.03; 20–59)</td>
<td>&lt;70</td>
<td>M 3.63 (0.35; 2.83-4.33)</td>
<td>Varies per group (36-78 months)</td>
<td>Average of 6.6 follow up assessments from 6.63 to 10.5 (calculated)</td>
<td>VABS</td>
<td>ND</td>
<td>Y. Nonverbal problem-solving ability and the ability to learn reward associations predicted growth in communication on VABS</td>
<td>TIC</td>
</tr>
<tr>
<td>Author, year</td>
<td>Setting (clinical, intervention trial, population)</td>
<td>Number participants at BL (and sex)</td>
<td>Classification/ study population</td>
<td>Criteria, tool</td>
<td>IQ (tool used, levels) Mean (M)</td>
<td>SD; range</td>
<td>Median (Med)</td>
<td>IQ&lt;70 or IQ&gt;70 Age at baseline (yrs)</td>
<td>Age at follow up (yrs) Mean (M)</td>
<td>SD; range</td>
<td>Median (Med)</td>
<td>IQR; range</td>
<td>Follow up duration (yrs)</td>
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<tr>
<td>Norrelgen 2014</td>
<td>Prospective population-based</td>
<td>165 (141 male)</td>
<td>ASD autistic syndrome n=97, PDD-NOS n=56 AS n=12.</td>
<td>DISCO and DSM IV by MDT</td>
<td>WPPSI_III, Griffiths. IQ ≥70 n=81, IQ 50-69 n=27, IQ&lt;50 n=52, IQ,70 n=5</td>
<td>&gt;70</td>
<td>Range: 4-6.5 yrs 4 yrs n=42, 5 yrs n=74 and 6 yrs n=49.</td>
<td>6-8.5 yrs (calculated)</td>
<td>2 yrs</td>
<td>VABS expressive domain to classify speech as nonverbal (&lt;3 words or expressive AE&lt;15 months), minimally verbal (using at least 3 words but never or only sometimes/partly 2 word phrases and (expressive AE &lt;24 months), Phrase speech: two word phrases or AE &gt;24 months level.</td>
<td>63% (165/208)</td>
<td>N</td>
<td>TIC. All children were receiving interventions through the Autism Centre for Young Children. Intervention was based on ABA at different levels of intensity (Fernell 2011).</td>
</tr>
<tr>
<td>Oosterling 2010</td>
<td>Prospective, clinical intervention</td>
<td>75 (60 male; Tx gp 30/40 male; Co gp 30/35 male)</td>
<td>AD n=65 PDD-NOS n=10</td>
<td>ADI-R;ADOS</td>
<td>DQ MSEL or PEP-R=Tx gp M 58.4 (16.8), Co: DQ; M 58 (16.9)</td>
<td>&lt;70</td>
<td>Tx gp: M 2.93 (0.46), Co gp: M 2.78 (0.53)</td>
<td>T gp: M 4.18; Co gp: M 4.03 (calculated)</td>
<td>M 1.25 (0.19)</td>
<td>CDI</td>
<td>83% (62/75)</td>
<td>Y</td>
<td>The intervention was not a predictor of language outcomes. Focus Parent Training for toddlers intervention (Drew et al 2002)</td>
</tr>
<tr>
<td>Paul 2008</td>
<td>Prospective, clinical</td>
<td>37 (sex not stated)</td>
<td>T1 autism n=27; PDD-NOS n=10; T2 autism n=19; PDD-NOS n=18</td>
<td>ADOS</td>
<td>Visual reception on MSEL (T1 M 41.5 (11.3). Fine Motor T1 M 35.8 (11.1)</td>
<td>&gt;70</td>
<td>M 1.82 (0.24; 1.25-2.1)</td>
<td>M 3.91 (0.5; 3-4.83)</td>
<td>M 2.5</td>
<td>VABS, MSEL</td>
<td>100% (37/37) (assumed “all children had diagnosis at fup”).</td>
<td>Y</td>
<td>Investigated NVIQ, VABS (receptive/expressive language), symbolic play, play and gestures, response to joint attention, stereotypic behaviours. Receptive language and presence of stereotypic and repetitive behaviours at the T1 predicted</td>
</tr>
</tbody>
</table>

253
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Setting (clinical, intervention trial, population)</th>
<th>Number participants at BL (and sex)</th>
<th>Classification/ study population</th>
<th>Criteria, tool</th>
<th>IQ (tool used, levels) Mean (M) (SD; range) Median (Med) (IQR range)</th>
<th>IQ&lt;70 or IQ&gt;70</th>
<th>Age at baseline (yrs)</th>
<th>Age at follow up (yrs) Mean (M) (SD; range) Median (Med) (IQR; range)</th>
<th>Follow up duration (yrs)</th>
<th>Language tools used</th>
<th>Proportion followed up</th>
<th>Predictors of language outcome measured?</th>
<th>Type of intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelicano 2010</td>
<td>Prospective, clinical</td>
<td>45 (40 male)</td>
<td>AD n=31 PDD-NOS n=12 AS n=2</td>
<td>DSM IV; ADI-R; NVIQ M 113.27 (13.93; 83-141) VIQ 97.08 (11.52; 80-122)</td>
<td>&gt;70</td>
<td>M 5.67 (0.83; 4.1-7.33)</td>
<td>M 8.41 (0.92)</td>
<td>3</td>
<td>PPVT-III</td>
<td>82% (37/45).</td>
<td>N</td>
<td>T2 expressive language outcome.</td>
<td></td>
</tr>
<tr>
<td>Pelicano 2012</td>
<td>Prospective, clinical</td>
<td>45 (40 male)</td>
<td>AD n=30 (67%); PDD-NOS n=12 AS n=3 (6%)</td>
<td>DSM IV; ADI-R (ADOS at follow up only)</td>
<td>&gt;70</td>
<td>M 5.63 (0.86)</td>
<td>M 8.34 (0.95; 6.6-9.9)</td>
<td>M 2.74</td>
<td>PPVT-III</td>
<td>82% (37/45)</td>
<td>N</td>
<td>TIC. Provides some detail.</td>
<td></td>
</tr>
<tr>
<td>Perry 2008</td>
<td>Retrospective clinical, intervention</td>
<td>332 (276 male)</td>
<td>AD n=194, PDD-NOS n=46 ASD/PDD n=92</td>
<td>Diagnosis completed by local diagnositicians who referred to IBI program CARS, DSM IV</td>
<td>&lt;70</td>
<td>M 4.46 (1.05; 20-86)</td>
<td>M 5.96 (calculated)</td>
<td>M 1.5 (0.7; 4-47)</td>
<td>VABS</td>
<td>100% (322/322) (assumed)</td>
<td>N</td>
<td>IBI intervention program, publicly funded</td>
<td></td>
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<tr>
<td>Perry 2011</td>
<td>Retrospective clinical, intervention</td>
<td>332 (276 male)</td>
<td>AD, PDD-NOS, ASD</td>
<td>Diagnosis completed by local diagnositicians who referred to IBI program CARS, DSM IV</td>
<td>&lt;70</td>
<td>M 4.46 (1.05; 20-86)</td>
<td>M 5.96 (calculated)</td>
<td>M 1.5 (0.7; 4-47)</td>
<td>VABS</td>
<td>100% (322/322) (assumed)</td>
<td>N</td>
<td>IBI intervention program, publicly funded</td>
<td></td>
</tr>
<tr>
<td>Perry 2013</td>
<td>Retrospective clinical, intervention</td>
<td>207 (168 male)</td>
<td>AD, PDD-NOS, ASD</td>
<td>Diagnosis completed by local diagnositicians who referred to IBI program CARS</td>
<td>&lt;70</td>
<td>M 5.33 (2.01; 2.08-14.5)</td>
<td>M 7.01 (calculated)</td>
<td>M 1.68 (0.72; 10-55)</td>
<td>VABS</td>
<td>100% (207/207)</td>
<td>N</td>
<td>IBI intervention program, publicly funded</td>
<td></td>
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<tr>
<td>Author, year</td>
<td>Setting (clinical, intervention trial, population)</td>
<td>Number participants at BL (and sex)</td>
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<td>Criteria, tool</td>
<td>IQ (tool used, levels) Mean (M); (SD; range) Median (Med) (IQR range)</td>
<td>IQ&lt;70 or IQ&gt;70</td>
<td>Age at baseline (yrs)</td>
<td>Age at follow up (yrs) Mean (M); (SD; range) Median (Med) (IQR range)</td>
<td>Follow up duration (yrs)</td>
<td>Language tools used</td>
<td>Proportion followed up</td>
<td>Predictors of language outcome measured?</td>
<td>Type of intervention</td>
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<tr>
<td>Pickles 2015</td>
<td>Prospective, clinical</td>
<td>192 (162 male)</td>
<td>Includes non-ASD children</td>
<td>ADI-R, ADOS</td>
<td>MSEL: NVIQ 2 years M 66.9 (21.8); 19 years M 57.5 (40.9)</td>
<td>&lt;70</td>
<td>2</td>
<td>19</td>
<td>17 (calculated)</td>
<td>VABS</td>
<td>55% (106/192)</td>
<td>N</td>
<td>TIC. Provide detail on of hours in a range of interventions.</td>
</tr>
<tr>
<td>Pry 2011</td>
<td>Retrospective population-based</td>
<td>60 (48 male)</td>
<td>ICD-10</td>
<td>ICD-10; ADOS, CARS</td>
<td>Brunet: T1=Med (25-75%iles=33-59 ; range=17-95; T2 Med= 40 (25-75%iles=26-53; range 12-89)</td>
<td>&lt;70</td>
<td>Med 5 (IQR 4-6)</td>
<td>Med 8 (IQR 7-9)</td>
<td>3</td>
<td>ADI-R (good, intermediate, poor)</td>
<td>100% (60/60) (retrospective, randomly selected from epi data base)</td>
<td>Y. Symptom intensity (CARS) and daily living skills predicted morpheme production. Number of phonemes also predictive of lexical development. No. utterances not predictive.</td>
<td>TIC</td>
</tr>
<tr>
<td>Pugliese 2016</td>
<td>Prospective, clinical</td>
<td>64 (51 male)</td>
<td>ASD without ID</td>
<td>ADI-R (n=54); ADOS (n=56), DSM-IV</td>
<td>WISC, WASI, WPPSI M 107.03 (19.83; T2-154) (n=64)</td>
<td>&gt;70</td>
<td>M 8.34 (2.29; 3-14)</td>
<td>12.88 (3.46; 7-23)</td>
<td>4.54 (calculated)</td>
<td>VABS</td>
<td>100% (64/64). Data collected retrospectively.</td>
<td>N</td>
<td>ND. TIC.</td>
</tr>
<tr>
<td>Ray- Subramanian 2012</td>
<td>Prospective, clinical</td>
<td>115 (97 male)</td>
<td>AD n=106 PDD-NOS n=9</td>
<td>DSM IV; ADI-R ADOS or ADOS-T</td>
<td>MSEL: T1 (n=101) M 26.29 (5.04; 11-36; T2 (n=112) M 34.54 (8.22; 15-50). Not able to assess all children.</td>
<td>&lt;70</td>
<td>M 2.58 (0.34)</td>
<td>M 3.67 (0.34)</td>
<td>M 1.12 (0.11)</td>
<td>PLS 4</td>
<td>90% (based on larger study)</td>
<td>100% based on excluded if not both time points for RRB data</td>
<td>N</td>
</tr>
<tr>
<td>Sigman 2005</td>
<td>Prospective, clinical</td>
<td>48 (42 male)</td>
<td>Autism</td>
<td>Not specified</td>
<td>39/43 IQ M 52.2 (13.3).</td>
<td>&lt;70</td>
<td>M 3.9 (1)</td>
<td>T2 12.67 (3.75) T3 19 (3.83)</td>
<td>Preschool to middle years (approx. 8 yrs). Middle yrs to adolescence (approx. 6-7 yrs)</td>
<td>RDLS and CELF</td>
<td>73% (51/70) T2 and 48/70 participated in T3. Note: 3 families participated in adolescent f/up who were not</td>
<td>Y. Investigated IQ and early language skills as predictors of later language. Those with IQ&lt;70 gained significantly more language</td>
<td>TIC</td>
</tr>
<tr>
<td>Author, year</td>
<td>Setting (clinical, intervention trial, population)</td>
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<td>Criteria, tool</td>
<td>IQ (tool used, levels) Mean (M) (SD; range) Median (Med) (IQR range)</td>
<td>IQ&lt;70 or IQ&gt;70</td>
<td>Age at baseline (yrs)</td>
<td>Age at follow up (yrs) Mean (M) (SD; range) Median (Med) (IQR range)</td>
<td>Follow up duration (yrs)</td>
<td>Language tools used</td>
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<td>Predictors of language outcome measured?</td>
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<tr>
<td>Siller 2013</td>
<td>Prospective, clinical, intervention</td>
<td>70 (64 male)</td>
<td>All AD on ADI-R, AD n=64 on ADOS (5 met criteria for ASD on ADOS and 1 not administered ADOS)</td>
<td>ADOS; ADI-R</td>
<td>MSEL: visual reception Tx M 26.6 (9.4) Cx: M 24.6 (11.2)</td>
<td>ND</td>
<td>Tx gp: M 4.86 (1.06), Co gp: M 4.4 (0.99)</td>
<td>Tx gp: M 6.02 Co gp: M 5.82 (calculated)</td>
<td>M 1.16 (0.39; 0.75-2.67)</td>
<td>MSEL-expressive language</td>
<td>89% (62/70)</td>
<td>Y. Conditional effect of focused playtime intervention (FPI) on expressive language outcomes at f/up. Children with baseline language ability &lt; 12 months most likely to benefit from FPI</td>
<td>FPI intervention</td>
</tr>
<tr>
<td>Smith I 2015</td>
<td>Retrospective clinical, intervention</td>
<td>118 (101 male)</td>
<td>ASD</td>
<td>Merrill-Palmer IQ&gt;=70: n=36 M 87.44 (11.52); IQ 40-69 n=40 M 55.69 (8.94); IQ&lt;40 n=42 M 19.43 (10.50) Total sample: M 54.55 (29.31)</td>
<td>&lt;70</td>
<td>4.1 (0.6) (40% 3 yrs; 39% 4 yrs; 8% 2 yrs, 14% 5 yrs)</td>
<td>8 months and 1.1 yrs (SD 0.12)</td>
<td>4.54 (calculated)</td>
<td>VABS</td>
<td>100% (118/118)</td>
<td>Y. IQ (but not age of enrolment in IBI program) was predictive of expressive and receptive language outcomes</td>
<td>EIBI: PRT, PECS, positive behaviour support (provide detail on amount and type of intervention)</td>
<td></td>
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<tr>
<td>Author, year</td>
<td>Setting (clinical, intervention trial, population)</td>
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<td>IQ (tool used, levels) Mean (M) (SD; range) Median (Med) (IQR range)</td>
<td>IQ&lt;70 or IQ&gt;70</td>
<td>Age at baseline (yrs)</td>
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<td>Follow up duration (yrs)</td>
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<tr>
<td>Smith T 2015</td>
<td>Prospective, clinical, intervention</td>
<td>71 (60 male)</td>
<td>ASD (aged between 20-59 months)</td>
<td>ADI-R, ADOS</td>
<td>MSEL IQ &lt;70. T1: M 58.80 (13.39; 49-20[ sic]) T2: M 64.43 (18.25; 49-114); T3: M 64.93 (18.01; 49-112)</td>
<td>&lt;70</td>
<td>T1 M 3.27 (0.65; 1.96-4.85) T2 (n=67): M 4.46 (0.67) T3: (n=64) M 5.65 (0.81)</td>
<td>T2: 1.19 (calculated) T3: 2.38</td>
<td>VABS, MSEL, ADI-R (z scores for verbal and nonverbal algorithm).</td>
<td>T2: 94% (67/71) &amp; T3 90% (64/71)</td>
<td>85% (58/68)</td>
<td>N</td>
<td>EIBI based on Lovas UCLA model (discrete trial). ABA hours per year=866.37 (SD 243.77)</td>
</tr>
<tr>
<td>Starr 2003</td>
<td>Prospective, clinical</td>
<td>68 (51 male: AD n=38 male; AS n=13 male)</td>
<td>HFA n=41; AS n=17.</td>
<td>IQ &gt; 68 or 70 depending on test. Leiter IQ M 86.05 (17.96) for HFA gp and M 97.47 (16.15) for Asperger’s gp.</td>
<td>&gt;70</td>
<td>M 5.82 (1.3) for those classified as having autism and M 6.2 (0.89) for those with AS</td>
<td>M 7.8 (calculated)</td>
<td>2</td>
<td>ADI-R question re: nonverbal</td>
<td>ND</td>
<td>N</td>
<td>TIC</td>
<td></td>
</tr>
<tr>
<td>Steele 2003</td>
<td>Prospective, clinical</td>
<td>57 (sex not stated)</td>
<td>Autism</td>
<td>DSM –IV</td>
<td>Measured at baseline (DAS). ND</td>
<td>ND</td>
<td>M 7.6 (2.3; 4.3-14.2)</td>
<td>M 8.8 (1.8; 5.1-15.4)</td>
<td>1</td>
<td>PPVT, EVT</td>
<td>ND</td>
<td>N</td>
<td>TIC</td>
</tr>
<tr>
<td>Stone 2003</td>
<td>Prospective, clinical, intervention.</td>
<td>37 (29 male)</td>
<td>AD and PDD- NOS</td>
<td>DSM III R and DSM IV depending on date seen (recruited 1993-1995)</td>
<td>MA M 17.1mth (3.7mths) Calculated DQ 54 (17.1/31.4)</td>
<td>&lt;70</td>
<td>M 2.62 (0.25)</td>
<td>M 4.88 (0.37)</td>
<td>M 2.25 (calculated)</td>
<td>SICD (n=29) or PLS-3 (n=1). Scores on SICD derived from combination of parent report and behaviour observation</td>
<td>100% (38/38) (assumed). Note: inclusion criteria stated children had been seen at both time periods</td>
<td>N</td>
<td>TIC</td>
</tr>
<tr>
<td>Sullivan 2010</td>
<td>Retrospective clinical, intervention</td>
<td>75 (62 male)</td>
<td>Autism 43; PDD-NOS 32</td>
<td>CARS used on n=70. &quot;Diagnosed with ASD&quot;</td>
<td>FSIQ on n=24 M 45.96 (15.06; 28-74)</td>
<td>&lt;70</td>
<td>M 3.94 (1.19; 1.670-5.02)</td>
<td>S 12 (calculated)</td>
<td>M 2.18 (0.81; 1-5.25)</td>
<td>VABS (n=66)</td>
<td>100% (75/75) (retrospectively chosen)</td>
<td>N</td>
<td>All in IBI intervention, publicly funded</td>
</tr>
<tr>
<td>Szatmari 2009</td>
<td>Prospective, clinical</td>
<td>55 (50 male)</td>
<td>Autism: n=36 (31 male) AS: n=21 (19 male)</td>
<td>DSM III and ADI/ADI-R</td>
<td>Autism: M 84.5 (16.11) AS: M 101.33 (18.02)</td>
<td>&gt;70</td>
<td>Autism M 5.46 (0.98) AS: M 5.6 (0.93)</td>
<td>Autism: 17.7 (1.56) AS: 17.6 (1.17) Followed up at 3 time points</td>
<td>Autism: M 12.24; AD: M 12</td>
<td>VABS</td>
<td>93% (53/57)</td>
<td>Y. Investigated age, language ability/change, IQ as predictors of later communication ability (VABS.) IQ and change in language not predictive but presence of structural language impairment predictive of ND. TIC.</td>
<td></td>
</tr>
<tr>
<td>Author, year</td>
<td>Setting (clinical, intervention trial, population)</td>
<td>Number participants at BL (and sex)</td>
<td>Classification/ study population</td>
<td>Criteria, tool</td>
<td>IQ (tool used, levels) Mean (M) (SD; range)</td>
<td>Median (Med) (IQR range)</td>
<td>IQ&lt;70 or IQ&gt;70</td>
<td>Age at baseline (yrs)</td>
<td>Age at follow up (yrs) Mean (M) (SD; range)</td>
<td>Median (Med) (IQR; range)</td>
<td>Follow up duration (yrs)</td>
<td>Language tools used</td>
<td>Proportion followed up</td>
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<tr>
<td>Szatmari 2015</td>
<td>Prospective, clinical</td>
<td>421 (355 male)</td>
<td>ASD</td>
<td>ADOS, ADI-R, DSM IV</td>
<td>Merrill-Palmer IQ M 57.23 (26.20)</td>
<td>&lt;70</td>
<td>3.32 (0.73)</td>
<td>6 years</td>
<td>M 2.68 (calculated)</td>
<td>VABS, PLS-IV</td>
<td>68% (285/421)</td>
<td>N</td>
<td>TIC. Timing and type of intervention varied by site. Offered Hanen More than Words program soon after diagnosis.</td>
</tr>
<tr>
<td>Takeda 2005</td>
<td>Retrospective clinical</td>
<td>57 adults (45 male)</td>
<td>ASD AD n=18 (12 males, 6 females); PDD-NOS n=38 (32 males, 6 females), AS n=1 (male)</td>
<td>DSM IV (used ICD 10 for atypical autism/ PDD-NOS)</td>
<td>Japanese version of Binet, WISC, K-test (Kyoto Scales of psychological development)</td>
<td>At outcome evaluation: 39 had IQ/DQ &lt; 70 (called MR); 18 had IQ/DQ &gt; 70 at outcome (called HFA)</td>
<td>&lt;70</td>
<td>M 2.61 (0.3; 1.91-2.92)</td>
<td>M 5.5 (0.56, 5-7.5)</td>
<td>M 2.97 (calculated)</td>
<td>Categorical score: more than 3 words or less than 3 words.</td>
<td>ND, 100% (57/57) assumed. Enrolment requirement was 2 assessments (aged 2 and 5 or later)</td>
<td>N</td>
</tr>
<tr>
<td>Thomas 2010</td>
<td>Retrospective clinical, intervention</td>
<td>89 (55 male)</td>
<td>ND</td>
<td>&quot;Independence medical diagnosis&quot;. CARS used, but only on n=65</td>
<td>AEPS cog domain to assess cognition. No scores.</td>
<td>ND</td>
<td>M 4.42 (3.17-5.58)</td>
<td>M 5.25 (3.67-6.42)</td>
<td>Approximately 5 yrs</td>
<td>PPVT-III</td>
<td>ND (lists missing data from but not overall LFU)</td>
<td>Y. Cognitive ability, social skills predictive of communication outcome on PPVT III</td>
<td>All attended Project DATA comprehensive treatment intervention</td>
</tr>
<tr>
<td>Thurum 2007</td>
<td>Prospective, clinical</td>
<td>59 (52 male)</td>
<td>Autism n=59; PDD-NOS n=24</td>
<td>DSM IV</td>
<td>DAS, MSEL if not able to do DAS) Provide AE ratios at 2 years (0.57 in ASD gp); 0.71 in PDD-NOS group).</td>
<td>&lt;70</td>
<td>Autism M 2.5 (0.36); PDD-NOS M 2.53 (0.39)</td>
<td>Autism M 4.75 (0.62); PDD M 4.76 (0.54)</td>
<td>Autism M 2.25; PDD-NOS M 2.2 (calculated). Authors describe it as &quot;2 years&quot;.</td>
<td>MSEL (n=66) and DAS (n=52) language subtests, depending on whether reached ceiling or not. Also used 'no language' vs 'at least some'</td>
<td>88% (97/110). Of the 131 participants, 13 children (all autism) did not receive full battery during the age 5 year testing. 118 chn with complete longitudinal data</td>
<td>Y. Investigated nonverbal ability, receptive &amp; expressive communication and socialization at age 2 &amp; 3 as predictors of receptive and expressive language age 5. Nonverbal</td>
<td>TIC. Many received some intervention from TEACCH.</td>
</tr>
<tr>
<td>Author, year</td>
<td>Setting (clinical, intervention trial, population)</td>
<td>Number participants at BL (and sex)</td>
<td>Classification/ study population</td>
<td>Criteria, tool</td>
<td>IQ (tool used, levels) Mean (M) (SD; range) Median (Med) (IQR range)</td>
<td>IQ&lt;70 or IQ&gt;70</td>
<td>Age at baseline (yrs)</td>
<td>Age at follow up (yrs) Mean (M) (SD; range) Median (Med) (IQR; range)</td>
<td>Follow up duration (yrs)</td>
<td>Language tools used</td>
<td>Proportion followed up</td>
<td>Predictors of language outcome measured?</td>
<td>Type of intervention</td>
</tr>
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</tr>
<tr>
<td>Thurm 2015</td>
<td>Retrospective clinical</td>
<td>70 (53 male)</td>
<td>AD</td>
<td>DSM-IV, ADOS, ADI_R, best clinical judgement</td>
<td>MSEL T1 (also report T2). Min verbal to min verbal group IQ&lt;70 M NVDQ=56 M 33 (12.57) MV-&gt;phrase speech grp IQ&lt;70 NVDQ M 65.17 (15.4) PS-&gt;PS grp IQ&gt;70 NVDQ: M 75.01 (13.92)</td>
<td>&gt;70 (calculated mean IQ)</td>
<td>M 3.56 (0.85; 1.76-4.98)</td>
<td>M 5.45 (0.37; 4.62-5.98)</td>
<td>M 1.9 (0.81; 0.9-3.6)</td>
<td>MSEL</td>
<td>100 % (70/70)</td>
<td>Y. VDQ and NVDQ predicted language status and VIQ on MSEL expressive language. T1 ADOS did not predict language status after controlling for NVDQ. Change in ADOS and RRB also not predictive of language status</td>
<td>ND. TIC.</td>
</tr>
</tbody>
</table>

'language' as per ADI-R.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Setting (clinical, intervention trial, population)</th>
<th>Number participants at BL (and sex)</th>
<th>Classification/ study population</th>
<th>Criteria, tool</th>
<th>IQ (tool used, levels) Mean (M) (SD; range) Median (Med) (IQR range)</th>
<th>IQ&lt;70 or IQ&gt;70 Age at baseline (yrs)</th>
<th>Age at follow up (yrs) Mean (M) (SD; range) Median (Med) (IQR; range)</th>
<th>Follow up duration (yrs)</th>
<th>Language tools used</th>
<th>Proportion followed up</th>
<th>Predictors of language outcome measured?</th>
<th>Type of intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toth 2006</td>
<td>Prospective, clinical</td>
<td>60 (51 male)</td>
<td>AD n=42 (70%), PDD-NOS n=18 (30%)</td>
<td>DSM IV; ADOS, ADI-R, clinician judgement</td>
<td>MSEL composite 58.1 (19.8; 30-101)</td>
<td>&lt;70 M 3.63 (0.36; 2.83-4.33)</td>
<td>Varies per group (seen every 6 months for VABS until 6.5 years)</td>
<td>2.87 (calculated)</td>
<td>VABS</td>
<td>ND (assume 100%)</td>
<td>Y. Investigated joint attention, imitation, toy play, language &amp; communication ability on later language ability. Initiating protodeclarative joint attention and immediate imitation most strongly associated with language ability at 3-4 yrs. Toy play and deferred imitation were best predictors of rate of communication development from 4 to 6.5 years.</td>
<td>ND. TIC.</td>
</tr>
<tr>
<td>Venker 2014</td>
<td>Prospective, clinical</td>
<td>129 (112 male)</td>
<td>ASD</td>
<td>DSM IV, ADOS</td>
<td>MSEL M 76.39 (14.46; 38-115)</td>
<td>&gt;70 M 2.6 (0.34; 23-39)</td>
<td>M 5.5 (0.42; 57-79)</td>
<td>3 years</td>
<td>PLS-4</td>
<td>78% (100/129)</td>
<td>N</td>
<td>ND. TIC.</td>
</tr>
<tr>
<td>Vivanti 2013</td>
<td>Prospective, clinical and surveillance samples</td>
<td>Clinical (S1): N=23 (22 male) Surveillance (S2) n=60 (45 male)</td>
<td>ASD</td>
<td>S1: ASD diagnosis done in community and also ADOS confirmed S2: ADI-R and ADOS</td>
<td>MSEL MA S1; MA AE: M 21.4 (12) 8-54.5 DQ=21.4/40=53 S2: MA AE: M 16.7 (3.4) 8-26 DQ=16.7/25=67</td>
<td>&lt;70 S1: M 3.33 (0.9; 1.83-5) S2: M 2.08 (0.17; 1.92-2.75) S1: M 4.33 (calculated) S2: M 4.17</td>
<td>S2: 1 yr S2: 2.17 yr (calculated)</td>
<td>S1 67% (60/89) S2 100% (23/23)</td>
<td>MSEL</td>
<td>N</td>
<td>Y. Predictors examined for phrase speech: nonverbal IQ, autism symptomology. Predictors for TIC</td>
<td></td>
</tr>
<tr>
<td>Wodka 2013</td>
<td>Retrospective clinical (Simons Complex database)</td>
<td>535 (444 male)</td>
<td>ASD</td>
<td>ADOS, ADI-R</td>
<td>IQ&lt;70 n=114 M 5.4 yr, IQ 70-85 n=94 M 5.3 y, IQ 86+ n=164 M 4.8yr (MSEL, DAS, WAIS). Reported for</td>
<td>&gt;70 4 (based on ADI-R) No phrase speech=11.5; phrase speech 11.7; only phrase speech=11; No phrase speech 7.5; phrase speech 7.7; only phrase speech 7; fluent speech 8 (calculated) ADI-R question re: nonverbal (and ADOS behaviour samples to verify)</td>
<td>100% (535/535) (strict inclusion criteria)</td>
<td>N</td>
<td>TIC</td>
<td>Y.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author, year</td>
<td>Setting (clinical, intervention trial, population)</td>
<td>Number participants at BL (and sex)</td>
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<td>IQ (tool used, levels) Mean (M) (SD; range) Median (Med) (IQR range)</td>
<td>IQ&lt;70 or IQ&gt;70</td>
<td>Age at baseline (yrs)</td>
<td>Age at follow up (yrs) Mean (M) (SD; range) Median (Med) (IQR range)</td>
<td>Follow up duration (yrs)</td>
<td>Language tools used</td>
<td>Proportion followed up</td>
<td>Predictors of language outcome measured?</td>
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</tr>
<tr>
<td>Woynarski 2015</td>
<td>Prospective, clinical</td>
<td>87 (71 male)</td>
<td>Autism n=83, PDD-NOS n=4 All had &lt;20 words on CDI. Clinical diagnosis in community and confirmed by ADOS, DSM IV.</td>
<td>subgroups only-fluent and phrase speech groups</td>
<td>fluent speech=12</td>
<td>M 2.89 (0.6; 1.7-4.0)</td>
<td>4.2 (calculated)</td>
<td>1.3 (T1=4 months T2=4 mo, T3=12 month after T2).</td>
<td>MSEL (composite) at T1 and vocab CDI at T1-T3.</td>
<td>100% (71/71)</td>
<td>N</td>
<td>fluent speech; nonverbal IQ, autism symptomology (Higher NVIQ and less social impairment and earlier age at acquisition associated with attaining phrase/fluent speech. Stereotyped behaviour/senory interests not associated.</td>
</tr>
<tr>
<td>Wolf 1986</td>
<td>Retrospective clinical</td>
<td>64 adolescents and adults (sex not stated)</td>
<td>Mentally retarded n= 71 (89%) and borderline to normal IQ n=9 (11%). Of mentally retarded: Mild n=15; Severe n=26; Profound n=3; Untestable n=2)</td>
<td>&lt;70</td>
<td>Not provided</td>
<td>M 20. &quot;covered a wide span – 31% &lt;20 yrs; 61% between 20-29yrs; 7%&gt;30 yrs&quot;</td>
<td>6 adolescents were followed up between 5 and 10 yrs but the remainder of the sample were f/u for &gt; 10 yr</td>
<td>Language development questionnaire. Categorical: normal, good, fair, very poor.</td>
<td>80% (64/80)</td>
<td>N</td>
<td>TIC</td>
<td></td>
</tr>
<tr>
<td>Yoder 2015</td>
<td>Prospective, clinical</td>
<td>87 (71 male)</td>
<td>ASD: autism n=83, PDD-NOS n=4</td>
<td>MSEL ELC M 50.9 (4.1; 49-68)</td>
<td>&lt;70</td>
<td>2.89 (0.6; 1.7-4.0)</td>
<td>4.2 Calculated. 5 time periods about 4 months apart</td>
<td>1.3 (T1=04 months T2=4 mo, T3=12 month after T2).</td>
<td>MSEL at T1 and vocab CDI at T1-T5</td>
<td>100% (71/71)</td>
<td>Y. Nine predictors of expressive language and 7 of receptive language growth. Responding to JA, intentional communication,</td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Author, year</th>
<th>Setting (clinical, intervention trial, population)</th>
<th>Number participants at BL (and sex)</th>
<th>Classification/study population</th>
<th>Criteria, tool</th>
<th>IQ (tool used, levels) Mean (M) (SD; range), Median (Med) (IQR range)</th>
<th>IQ&lt;70 or IQ&gt;70</th>
<th>Age at baseline (yrs)</th>
<th>Age at follow up (yrs) Mean (M) (SD; range), Median (Med) (IQR; range)</th>
<th>Follow up duration (yrs)</th>
<th>Language tools used</th>
<th>Proportion followed up</th>
<th>Predictors of language outcome measured?</th>
<th>Type of intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziehurt 2002</td>
<td>Prospective, clinical</td>
<td>34 (25 male)</td>
<td>Autism and PDD-NOS</td>
<td>ADI-R, ADOS G, clinical interview and observation</td>
<td>MSEL or subtests of Stanford Binet, Initial MA: M 28.5 mths (range 10-82 mths) DQ=59 (28.5/47.5)</td>
<td>&lt;70</td>
<td>M 3.96 (2.6-5.42)</td>
<td>M 4.8 (3.6-6.3) (3.6-6.3)</td>
<td>1</td>
<td>RDLS</td>
<td>81% (34/42)</td>
<td>parent linguistic responses were value added predictors of both. Consonant inventory was a value added predictor of expressive growth and early receptive vocab and ASD severity were value added predictors of receptive growth.</td>
<td>TIC</td>
</tr>
</tbody>
</table>

List of abbreviations: AA: atypical autism; AD: autistic disorder; ADI: Autism Diagnostic Interview; ADOS: Autism Diagnostic Observation Scale; AE: age equivalent; AS: Asperger’s Syndrome; CA: chronological age; CARS: Childhood Autism Rating Scale; CDI: MacArthur Bates Communicative Development Inventories; Co: control; DAS: Differential Ability Scales; DQ: developmental quotient; DSM: Diagnostic Statistical Manual of Mental Disorders; Dx: diagnosis; EIBI: early intensive behaviour intervention; FPI: focused play intervention; FSIQ: full scale IQ; HFA: high functioning autism; ICD: Internal classification of diseases; IBI intensive behaviour intervention; LFU: loss to follow up; MA: mental age; MDT: multidisciplinary team; MSEL: Mullen Scale of Early Learning; ND: not described; NVIQ: nonverbal IQ; PDD-NOS-pervasive developmental disorder; TIC: treatment in the community; Tx: treatment; VIQ: verbal IQ; WISC: Wechsler Intelligence Scale for Children WL Wait list; WPPSI: Wechsler Preschool and Primary Scale of Intelligence.
Appendix E. Studies reporting raw scores in the systematic review.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>N</th>
<th>Age at baseline, years. Mean (SD; range)</th>
<th>Max duration of follow-up, years. Mean (SD; range)</th>
<th>Raw score at baseline, Mean (SD; range)</th>
<th>Raw score at follow-up, Mean (SD; range)</th>
<th>Comments/notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bopp, 2006 (PPVT)</td>
<td>70</td>
<td>4;2, (1;7-6;0)</td>
<td>2</td>
<td>10.64 (18.71; 0-85)</td>
<td>28.80 (27.67; 0-108)</td>
<td>Data used from the 2 year follow-up (were also followed up at 6 and 12 months)</td>
</tr>
<tr>
<td>Bopp, 2006 cont. (EOWVT)</td>
<td>70</td>
<td>4;2, (1;7-6;0)</td>
<td>2</td>
<td>25.17 (23.12; 0-86)</td>
<td>34.80 (26.91; 0-96)</td>
<td></td>
</tr>
<tr>
<td>Bopp, 2011 (CDI)</td>
<td>44</td>
<td>3:11 (1:9-5/11)</td>
<td>4.41</td>
<td>WU: 12.66 (12.60; 3-60)</td>
<td>WU: 85.56 (33.32; 17-138)</td>
<td>Followed up 4 other times too: 6,12,24,33 months.</td>
</tr>
<tr>
<td>Hellendoorn, 2015 (MSEL)</td>
<td>63</td>
<td>2.26 (0.73)</td>
<td>1.56</td>
<td>RL: 16.04 (8.45)</td>
<td>RL: 37.22 (6.56)</td>
<td></td>
</tr>
<tr>
<td>Oosterling, 2010 (CDI)</td>
<td>75</td>
<td>Control group: 2.78 (0.53)</td>
<td>1.25 (0.19)</td>
<td>Control gp: WU: 181.5 (121.4) WS: 101.7 (109.7)</td>
<td>Mean difference between T1 and T2. Control gp: WU=35.2 (66.1), WS=56.1 (97.2)</td>
<td>Only control group means presented here.</td>
</tr>
<tr>
<td>Author, year</td>
<td>N</td>
<td>Age at baseline, years. Mean (SD; range)</td>
<td>Max duration of follow-up, years. Mean (SD; range)</td>
<td>Raw score at baseline. Mean (SD; range)</td>
<td>Raw score at follow-up. Mean (SD; range)</td>
<td>Comments/notes</td>
</tr>
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</tr>
<tr>
<td>Ray-Subramanian, 2012 (PLS)</td>
<td>115</td>
<td>2.58 (0.34)</td>
<td>1.1 (0.11)</td>
<td>AC: 20.35 (5.21; 10-42)</td>
<td>AC: 28.44 (11.58; 13-61)</td>
<td>Used PLS-4 subscale raw scores, controlling for chronological age</td>
</tr>
<tr>
<td>Steele, 2003 (PPVT)</td>
<td>57</td>
<td>7.6 (2.33; 4.25-14.17)</td>
<td>1</td>
<td>64.4 (32.6; 12-155)</td>
<td>81.7 (34.8; 26-177)</td>
<td></td>
</tr>
<tr>
<td>Steele, 2003 cont. (EVT)</td>
<td>57</td>
<td>7.6 (2.33; 4.25-14.17)</td>
<td>1</td>
<td>49.6 (19.2; 21-118)</td>
<td>60.7 (22.8) 28-137</td>
<td></td>
</tr>
<tr>
<td>Yoder cohort, 2015 (CDI)</td>
<td>87</td>
<td>2.89 (0.6)</td>
<td>1.3</td>
<td>WU: 75.8 (85.4; 0-385)</td>
<td>WU: 169.8 (116.4; 0-396)</td>
<td>Followed up every 4 months.</td>
</tr>
</tbody>
</table>

Appendix F. Scores for children not included in analyses for Study 3
Language and nonverbal IQ scores for children with ASD in Study 3 who did not have language and IQ scores at required time points.

<table>
<thead>
<tr>
<th>Child</th>
<th>NVIQ</th>
<th>Rec (4yr)</th>
<th>Exp (4yr)</th>
<th>Rec (5yr)</th>
<th>Exp (5yr)</th>
<th>Rec (7yr)</th>
<th>Exp (7yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>74</td>
<td>A</td>
<td>-</td>
<td>-</td>
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<td>2</td>
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<td>55 (E)</td>
<td>57 (E)</td>
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<tr>
<td>5</td>
<td>107</td>
<td>81</td>
<td>81</td>
<td>64</td>
<td>78</td>
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<td>80</td>
<td>-</td>
<td>-</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>58</td>
<td>A (RDLS)</td>
</tr>
<tr>
<td>11</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>58 (PLS)</td>
<td>53 (PLS)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Note. RDLS: Reynell Developmental Language Scales; PLS: Preschool Language Scales, E: assessment completed externally

Total number of children with ASD by 7 years: n=44. Lost to follow up/no data at any wave: n=4. Trajectory mapped: n= 28. Unable to complete but attempted: n= 3 (receptive only in one) (IQ 55, 77, 93). Not mapped: n=11 (table above)
Author/s: Brignell, Amanda

Title: Language development in autism spectrum disorder: longitudinal comparison with a community cohort of children with language impairment and typical development

Date: 2016

Persistent Link: http://hdl.handle.net/11343/127483

File Description: Language development in autism spectrum disorder: longitudinal comparison with a community cohort of children with language impairment and typical development

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