

Research Article

The Language Profile of Preschool Children With 22q11.2 Deletion Syndrome and the Relationship With Speech Intelligibility

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ABSTRACT

Purpose: Young children with 22q11.2 deletion syndrome (22q11DS) often have impaired language development and poor speech intelligibility. Here, we report a comprehensive overview of standardized language assessment in a relatively large sample of preschool-aged children with 22q11DS. We furthermore explored whether speech ability explained variability in language skills.

Method: Forty-four monolingual Dutch preschoolers (3–6 years) with a confirmed genetic 22q11DS diagnosis participated in this prospective cohort study. Standardized tests (Clinical Evaluation of Language Fundamentals Preschool-2-NL and Peabody Picture Vocabulary Test-III-NL) were administered. Speech intelligibility was rated by two expert speech and language therapists using a standardized procedure.

Results: Most children had impaired language skills across all tested domains. The composite score for expressive language was significantly lower than that for receptive language, but the two were strongly correlated. Only small differences between the mean scores on the various subtests were observed, with the lowest scores for expressive morphosyntactic skills. Language scores showed a moderate positive relation with speech intelligibility, but language abilities varied greatly among the children with intelligible speech.

Conclusions: We show that the majority of preschool children with 22q11DS have a broad range of language problems. Other than the relatively larger impairment in expressive than in receptive language skills, our results do not show a clearly delineated language profile. As many of the children with intelligible speech still had below-average language scores, we highlight that language problems require a broad assessment and care in all young children with 22q11DS. Future research using spontaneous language and detailed speech analysis is recommended, to provide more in-depth understanding of children's language profile and the relationship between speech and language in 22q11DS.

The 22q11.2 deletion syndrome (22q11DS; OMIM #192430, #188400, #611867), previously called DiGeorge or velo-cardio-facial syndrome, is the most common microdeletion syndrome with an estimated incidence of 1

per 2,148 live births (Blagojevic et al., 2021). 22q11DS is characterized by large phenotypical variation. The most common physical symptoms include congenital heart disease and palatal abnormalities (McDonald-McGinn et al., 2015). With regard to the cognitive phenotype, most children with 22q11DS have intellectual abilities in the borderline range (intelligence quotient [IQ]: 70–85) or mild intellectual disability (IQ: 55–70; De Smedt et al., 2007; Swillen et al., 2018). Additionally, 22q11DS is associated with an increased risk for neurodevelopmental disorders or

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psychiatric disorders, such as anxiety disorders, attention-deficit/hyperactivity disorder, and autism spectrum disorder in childhood and schizophrenia in adolescence and early adulthood (Fiksinski et al., 2018). Speech-language problems are reported in ~95% of children with 22q11DS (Solot et al., 2019), making this one of the most prevalent symptoms in early childhood. The negative effect of early language impairment on social interactions, socio-emotional development, and well-being has been widely acknowledged (Bleses et al., 2016; Conti-Ramsden et al., 2018; Durkin et al., 2017; Le et al., 2021; Longobardi et al., 2016; McKean et al., 2017). In this study, we therefore first comprehensively describe the language profile of young children with 22q11DS to extend the knowledge on the language abilities of these children at an early age, using standardized language assessments that are frequently used in clinical practice. Second, we explore the relationship between children's language skills and their speech intelligibility.

Language Abilities of Children With 22q11DS

School-aged children with 22q11DS (i.e., 6- to 12-year-olds) experience difficulties with semantics, syntactic accuracy and complexity, and narrative production and comprehension (Glaser et al., 2002; Moss et al., 1999; Persson et al., 2006; Rakonjac et al., 2016; Selten et al., 2021; Van Den Heuvel et al., 2018). Studies with participants in this age range typically report that children's receptive language impairment is more pronounced than the expressive language impairment, although both receptive and expressive language abilities lag behind age-adequate levels (Glaser et al., 2002; Marden, 1999; for an overview, see Van Den Heuvel et al., 2018). Language skills of children with 22q11DS are also below what is expected given their level of intellectual functioning (Persson et al., 2006; Scherer et al., 1999; Selten et al., 2021; Van Den Heuvel et al., 2018).

The delays in expressive language are often one of the first behavioral symptoms that are noted by parents of children with 22q11DS. Studies on the language abilities of toddlers and preschoolers with 22q11DS have primarily used parental report to describe children's expressive language milestones. The onset of the first words and sentences is reported to be delayed in over 90% of young children with 22q11DS (Gerdes et al., 1999; Mills et al., 2006; Solot et al., 2000). Children with 22q11DS are on average 23–26 months old when they produce their first words and start to produce two-word combinations (Roizen et al., 2007). However, 69% of children with 22q11DS have been reported to still be nonverbal at the age of 24 months (Solot et al., 2000). Three studies with relatively large sample sizes have used standardized language assessments to evaluate language skills of preschool-aged (ages 1–5.5 years) children with 22q11DS; they reported impairments on composite measures of global, receptive, and expressive

language abilities (Gerdes et al., 1999, 2001; Solot et al., 2001). Both parental report and standardized language assessment suggest a larger delay in expressive than receptive language abilities in preschool children with 22q11DS (Gerdes et al., 1999; Scherer et al., 1999; Shprintzen, 2000; Solot et al., 2001), which stands in contrast with research with school-aged children with 22q11DS for whom the opposite has been observed. These contrasting findings may stem from differences in the types of measures used but most likely also reflect differential developmental trajectories for receptive and expressive language abilities.

Additionally, in school-aged children, a profile of relatively weak receptive semantic abilities and strong expressive syntactic abilities has been described, based on the evaluation of different subtests that are part of standardized language assessments (Glaser et al., 2002; Van Den Heuvel et al., 2018). Such specific knowledge of the language profile in 22q11DS can support the development of targeted intervention, as well as spur research investigating factors that may influence impaired development in specific language domains. Currently, such a specific language profile is lacking for preschool children with 22q11DS, as none of the previous studies using standardized assessments have reported subtest outcomes.

The Relationship Between Speech and Language in 22q11DS

Speech problems, such as hypernasality, are common in 22q11DS (Baylis & Shriberg, 2019; Solot et al., 2019). Especially below the age of 5 years, the majority of children with 22q11DS have poor speech intelligibility (Antshel et al., 2009; Persson et al., 2003; Solot et al., 2000). The exact cause of poor intelligibility in 22q11DS often remains unclear, as it may be the result of a variety of neurological problems, such as dyspraxia or a speech sound disorder, and/or anatomical abnormalities, including velopharyngeal insufficiency in the absence of a cleft palate (Baylis & Shriberg, 2019; Gerdes et al., 1999; Golding-Kushner, 2005; Jackson et al., 2019; Persson et al., 2003; Solot et al., 2019).

The number of studies that address the relationship between speech and language in children with 22q11DS is limited. A study by Gerdes et al. (1999) found no difference between children with 22q11DS with and without palatal abnormalities on standardized language outcomes. This is supported by findings from Solot et al. (2001), who mention that there are no correlations between language, speech, and palatal abnormalities in their sample of school-aged children with 22q11DS. A study by Fritz (2005) compared nine 4- to 6-year-old children with 22q11DS to children with an idiopathic cleft palate and found that the latter group obtained age-adequate standardized language scores, whereas children with 22q11DS scored significantly below the norm for their age. However,

they did not report the prevalence of palatal abnormalities in their 22q11DS sample. Together, these results suggest that palatal abnormalities may not influence language outcomes in 22q11DS. However, it has been suggested that poor speech intelligibility rather than anatomical abnormalities may negatively affect language development in children with 22q11DS (Shprintzen, 2000). This is supported by the finding that, in children with an idiopathic cleft palate and lip, low intelligibility is associated with weak language ability (Særvold et al., 2019). The etiology of the association between speech intelligibility and language difficulties is unclear. It may be that the presence of language difficulties affects children's speech intelligibility, as it has been observed that impaired language development also affects articulatory processes (Mahr et al., 2020; Vuolo & Goffman, 2018). On the other hand, children with relatively poor intelligibility have been shown to be less assertive conversation partners (Frederickson et al., 2006; Hardin-Jones & Chapman, 2011), which could negatively affect parent-child interactions (Kuehn & Moller, 2000). For children with 22q11DS, it has indeed been suggested that parents may be less likely to reinforce early speech attempts if their child has poor speech intelligibility (Shprintzen, 2000). Poor speech intelligibility may thus hamper language development in young children with 22q11DS, as poor intelligibility can negatively affect interactions, thereby reducing their exposure to linguistic input, as well as limit opportunities to practice their language skills (Antshel et al., 2009).

This Study

Research describing standardized language outcomes in preschool-aged children with 22q11DS is scarce. Standardized language assessments are frequently used by speech-language pathologists (SLPs), as they are typically required for a diagnosis and access to specialized education and care. Therefore, a more detailed description of standardized language scores may be particularly relevant to SLPs working with children with 22q11DS. Moreover, a more detailed description of standardized language scores can aid the identification of strengths and weaknesses in the early language profile of children with 22q11DS, supporting targeted intervention. This study therefore aims to provide a comprehensive overview of the language profile of 3- to 6-year-old children with 22q11DS using standardized instruments, the Clinical Evaluation of Language Fundamentals (CELF Preschool-2-NL) and the Peabody Picture Vocabulary Test (PPVT-III-NL). Additionally, we asked parents about the age at which their child produced their first word and sentence. Based on previous research, we expect children with 22q11DS to have impaired language abilities as indicated by norm scores in the below-average range (Gerdes et al., 1999, 2001; Solot et al., 2001). We furthermore expect expressive abilities to be more impaired than receptive abilities

(Gerdes et al., 1999; Scherer et al., 1999; Shprintzen, 2000; Solot et al., 2001). We do not have hypotheses with regard to specific language domains, as previous studies with children in this age range have not reported outcomes of subtests measuring specific language domains.

Speech intelligibility rather than the presence of anatomical abnormalities could impact early language development, by negatively impacting parent-child interactions thereby affecting the quantity and quality of language input and practice a child gets (Antshel et al., 2009; Særvold et al., 2019; Shprintzen, 2000). To explore this relationship, we investigated whether speech intelligibility, as rated by two expert SLPs, could explain variability in language skills of preschool children with 22q11DS.

Method

Participants

Forty-four children with 22q11DS participated in a larger prospective cohort study ("3T project") investigating children's language, cognitive, and behavioral development. The children were recruited and assessed for eligibility in the span of 1 year (November 2018 to November 2019) through the national multidisciplinary outpatient clinic for children with 22q11DS (University Medical Centre Utrecht, the Netherlands), four other medical centers in the Netherlands, and the Dutch 22q11DS patient support group (Stichting Steun 22Q11; see Appendix A). Inclusion criteria were (a) a genetically confirmed diagnosis of 22q11DS, (b) monolingual Dutch, (c) aged between 3;0 and 6;5 years, and (d) absence of bilateral permanent hearing loss (> 35 dB) as reported by parents. Parents are considered reliable informants regarding hearing loss of this severity, given that multiple standardized hearing assessments are part of the routine clinical follow-up for all infants (otoacoustic emissions tests) and preschoolers (pure tone/tonal audiometry test) in the Netherlands. Demographic characteristics of our participants are described in Table 1.

Procedure

The study was conducted in accordance with the Declaration of Helsinki (World Medical Association, 2013) and was approved by the Medical Ethical review board of the University Medical Center Utrecht (CCMO registry nr. NL63223.041.17). All parents provided written informed consent.

Parents filled in online questionnaires regarding demographic information and their child's language development. Language assessment took place at the child's school or day care center and was part of two 45-min sessions conducted by a trained researcher. All researchers

Table 1. Participant characteristics of the total sample ($N = 44$).

Variable	<i>n</i>	<i>M</i>	<i>SD</i>	Range	
Female/male	19/25				
Average age in months	44	58.8	12.4	37–77	
IQ ^a	42 ^a	80.0	12.1	50–103	
Parental education ^b	44	6.4	1.8	2–9	

	Yes		No		Unclear	Missing
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	<i>n</i>
Speech-language therapy	41	93	3 ^c	7	—	—
Suspected VPI ^d	21	48	9	20	12	2
Cleft palate ^e	3	7	41	93	—	—
Congenital heart defect ^f	25 ^g	57	19	43	—	—
Tympanostomy tubes	15	34	29	66	—	—
Ear infections	26		18		—	—

Frequency (<i>n</i>)	Never	1–3 times in life	A few times	Very frequently
	18	7	6	13

Note. IQ = intelligence quotient; VPI = velopharyngeal insufficiency.

^aIntelligence quotient (IQ) scores were obtained from medical records or schools. These IQ tests were administered by a licensed psychologist in the context of formal cognitive assessments and included the Bayley Scale of Infant Development (BSID-III-NL; $n = 3$), age-appropriate Wechsler tests ($n = 19$) or Snijders–Oomen Nonverbal Intelligence Test -Revised¹ ($n = 18$). Two children with 22q11.2 Deletion Syndrome had no recent IQ scores. For one of these children, a trained researcher from this study administered the shortened version of the Wechsler Non-Verbal (Wechsler & Naglieri, 2008). No IQ data could be obtained for the other child due to restrictions regarding the COVID-19 pandemic. The IQ score of a third child could not be obtained due to a developmental age that was too low for the BSID-III-NL. In total, eight children had an intellectual disability as represented by an IQ score of < 70 . ^bParental education was indexed by the average education level of both parents, ranked on a 9-point scale reflecting the Dutch educational system (ranging from 1 = no education to 9 = university degree), see Appendix B for more detailed information. ^cOne of these children started therapy for hypernasality after the start of this project, another one of these children did have yearly checkups with a speech-language pathologist (SLP) at the local hospital. ^dSuspicion of VPI was based on the judgment of the same SLPs who performed the intelligibility ratings (see Measures section below) using the same audio recordings. No nasometry, scoping, or other procedures to measure VPI were performed. ^eBased on parent-report and medical records. All three cases are submucous clefts. ^fThe presence of any type of congenital heart defect was assessed by a pediatric cardiologist based on the review of medical records. ^gOf these, 16 (64%) were hemodynamically significant, 18 (72%) were corrected by means of surgical intervention. Thirteen cases presented in isolation, whereas 12 cases presented with more than one type of cardiac defect. The most common cardiac defect in our sample was Ventricular Septal Defect ($n = 16$).

had at least a master's degree in the field of cognitive psychology, developmental psychology, or linguistics and had extensive previous experience working with young children in a research and/or clinical context. Language tests were mixed with cognitive tasks and administered in a fixed order. Children's responses to expressive language subtests of the CELF were recorded and were also scored by a second researcher. In case of discrepancies, final scores were determined through a consensus procedure.

Measures

Language

We used the Dutch version of the CELF Preschool-2-NL (Wiiig et al., 2012). This standardized language test for children between ages 3;0 and 6;11 (years;months) comprises seven subtests that measure language abilities in various domains, both receptively (syntax and semantics)

and expressively (morphosyntax, syntax, and semantics). The CELF subtest scores for each task can be transformed into age-corrected norm scores ($M = 10$, $SD = 3$). Combining norm scores of different subtests results in three age-corrected index scores ($M = 100$, $SD = 15$). The Core Language Index (CLI) reflects overall language level and is composed of one receptive and two expressive subtests. The Receptive Language Index (RLI) and Expressive Language Index (ELI) are composed of the three receptive and the three expressive subtests, respectively. The reliability kappa's of the CELF Preschool-2-NL vary between .73 and .96 for the various subtest and index scores. Regarding validity, the CELF Preschool-2-NL shows sufficient correlation with other measures: .71 with the verbal IQ component of the WPPSI and .66 to .74 with the CELF 4 (in a group of children in the age range that overlaps between the CELF Preschool and the CELF 4). Sensitivity with clinical groups is .89, and specificity is .83.

We also administered the Dutch version of the PPVT-III-NL (Schlichting, 2005), a standardized measure for receptive vocabulary, resulting in age-corrected norm-scores ($M = 100$, $SD = 15$). The reliability of the PPVT-III-NL is good, with a Lamda-2 coefficient between

¹The Snijders-Oomen (SON-R) IQ test is a standardized non-verbal IQ test, which is often used in the Netherlands and has been objectively evaluated as valid and reliable with a high correlation with other IQ tests such as the WPPSI and WISC.

.89 and 0.97 and correlation of 0.94 for test–retest reliability. For a detailed description of the instruments (including the different subtests of the CELF), see Appendix C.

Parents reported the approximate age of onset of their child’s first word and sentence by choosing one of five age categories, which were based on the Van Wiechen-Developmental screening instrument (Laurent de Angulo et al., 2005; see Appendix D).

Speech Intelligibility

Speech intelligibility was scored based on recordings of spontaneous speech of each child. The spontaneous speech was recorded during a play break between standardized language tasks. Speech was recorded in Audacity 2.3.0 using a Samson Go Mic portable USB condenser microphone. During this 15-min play break, all children were given the same set of toys and coloring materials. Researchers were trained and used a standardized protocol. They were instructed to let the child determine the narrative of the play situation and to ask as few questions as possible and if doing so to use open-ended questions. The 3 min of audio with the most speech uttered by the child from this play-break were selected for analysis.

Two SLPs affiliated with the 22q11DS outpatient clinic, who have extensive experience working with children with 22q11DS, individually performed blind ratings of children’s speech intelligibility based on the 3-min audio recordings of spontaneous speech. The SLPs rated speech intelligibility according to the intelligibility scale from the Cleft Audit Protocol for Speech (CAPS-A; Sell et al., 2009). Prior to assessing the speech data, the SLPs did a consensus training using audio recordings of children with 22q11DS who were not taking part in this study. Recordings were scored in the same order by both SLPs. Original scores were inverted, so that the scale ranged from 1 (*impossible to understand*) to 5 (*normal speech intelligibility*). The ratings of the two SLPs never differed more than two points. For cases in which there was a 2-point difference ($n = 4$), a final rating was determined by consensus. Final ratings thus never differed more than 1 point. The average of both ratings was used for further analyses.

Data Analyses

The first aim of this study was to provide a detailed overview of the language profile of young children with 22q11DS. We report the composite index scores and subtest norm scores of the language measures. If children did not complete one or more CELF subtests, this resulted in missing index scores. Analyses always included the maximum number of available participant scores. We used χ^2 - or t tests to check for differences between the groups of children with and without CELF index scores in sex, age, IQ, speech intelligibility, and parental education. Next, we conducted a

paired samples t test to determine whether there was a difference between the CELF RLI and the ELI. In addition, we explored intraindividual variability by means of a correlation between CELF RLI and ELI. We did not statistically analyze differences between subtest scores, as the large number of comparison relative to our sample size would likely result in Type-I errors. We report the number of children with a score more than $-1 SD$ below the normed mean, as this is a clinically relevant cutoff score according to the CELF manual (Wiig et al., 2012). Additionally, we present parent report of early language milestones.

The second aim was to investigate the relationship between children’s language abilities and speech intelligibility. As speech intelligibility scores were an ordinal variable, we used Kendall’s tau correlation to determine the correlation with the CELF index scores (CLI, RLI, and ELI) and PPVT score. In case of significant correlations, we subsequently conducted regression analyses with each of these four language scores as dependent variable and intelligibility score as a predictor. We only corrected for age in these analyses if age and speech intelligibility were significantly correlated. Last, to explore the possible relationship between speech intelligibility and language abilities beyond the group level, we visually inspected the data by means of scatterplots using the CELF index scores and speech intelligibility score.

All analyses were performed in R version 4.0.2 (R Core Team, 2020) using the tidyverse (v1.3.0; Wickham et al., 2019), rstatix (v0.6.0; Kassambara, 2020), e1071 (v1.7.3; Meyer et al., 2019), pastecs (v1.3.21; Grosjean et al., 2018), expss (v0.10.6; Demin & Jeworutzki, 2020), and the effectsize (v0.4.4–1; Ben-Shachar et al., 2020) packages. Figures were made using IBM SPSS 27.0 (2020) and MS PowerPoint. Effects sizes were interpreted following Lovakov and Agadullina (2021). Parametric results are reported unless nonparametric tests were required and showed different outcomes than parametric tests.

Results

Task Completion Data

Not all participants could complete the PPVT or all CELF subtests, resulting in one or more missing CELF index scores. Experimenter observations suggest that incomplete task data was predominantly the result of limited task compliance and insufficient expressive language skills. Intelligibility scores of two children could not be determined because these children produced insufficient spontaneous speech.

Children who could not complete one or more tasks required to calculate CELF index scores were significantly younger ($n = 13$; $M_{\text{age}} = 52$ months, $SD = 12.2$) than

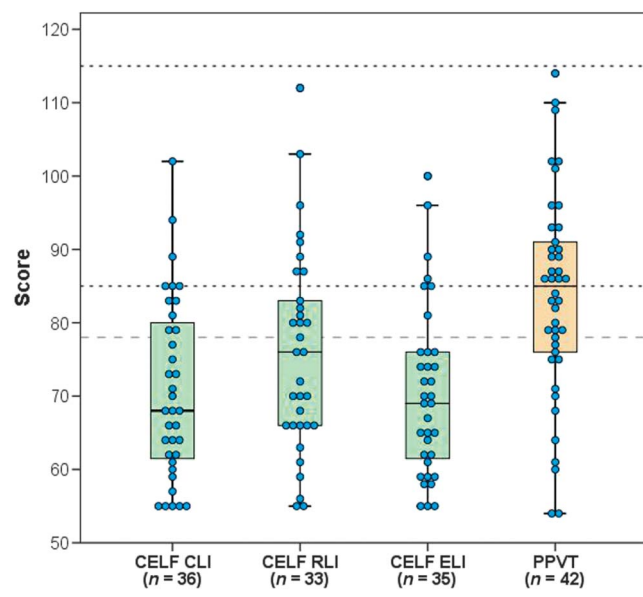
children who completed all tasks, $n = 31$; $M_{\text{age}} = 62$ months, $SD = 11.6$; $t(21.62) = -2.31$, $p = .031$, $d = 0.78$, 95% CI $[-17.43, -0.93]$ and had lower intelligibility scores ($M = 2.64$, $SD = 0.67$) than children with complete data, $M = 3.16$, $SD = 0.90$; $U = 98.5$, $p = .036$, $r = -0.42$, 95% CI $[-1.0, -6.46]$. There was no difference between these groups in sex distribution, $\chi^2(1) = 0.01$, $p = .940$, $V = 0.06$, parental education, $t(20.95) = -1.14$, $p = .269$, $d = 0.39$, 95% CI $[-1.94, 0.57]$, or IQ scores, $t(14.52) = -1.59$, $p = .134$, $d = 0.64$, 95% CI $[-19.27, 2.86]$.

Language Profile of Young Children With 22q11DS

Group mean scores for the three CELF index scores and the PPVT were all in the below-average range ($< -1 SD$). Most children obtained below-average scores on the CELF CLI (83%), RLI (76%), and ELI (83%). On the PPVT, 50% of the children scored in the below-average range (see Figure 1 and Appendix E). On average, the children obtained significantly higher scores on the CELF RLI than on the CELF ELI, $t(30) = 3.22$, $p = .003$, $g = 0.58$, 95% CI $[1.97, 8.81]$. Scores on the CELF RLI and ELI were strongly correlated, $r(31) = 0.75$, $p < .001$, 95% CI $[0.55, 0.88]$.

Similar to the CELF index scores, we found that most children scored in the below-average range on each

Figure 1. Box and whisker plot (boxplot with individual data points) for the three Clinical Evaluation of Language Fundamentals index scores (green) and the PPVT (orange). Dotted lines indicate $\pm 1 SD$ around the normed mean. The dashed line indicates $-1.5 SD$ below the normed mean. Blue dots represent individual data points. CLI = Core Language Index; RLI = Receptive Language Index; ELI = Expressive Language Index; PPVT = Peabody Picture Vocabulary Test.



of the CELF subtests norm scores (see Table 2). One child had a single subtest norm score that was more than $+1 SD$ above the normed mean; all subtest norm scores of all other children were in the average to below-average range. At group level, there were no clear differences between subtests norm scores. The lowest mean norm score was obtained for Word Structure, which measures expressive morphosyntax. The highest mean norm scores were found for the subtests Basic Concepts (subtest for 3-year-olds) and Word Categories-Receptive (subtest for 4- to 6-year-olds), which are both designed to gauge receptive semantics. Basic Concepts was only completed by 50% of children in the appropriate age range; outcomes should therefore be interpreted with caution. Last, parents reported a delayed production of the first word and sentence in 23 (52%) and 34 (78%) children, respectively (see Figure 2).

Language Abilities and Speech Intelligibility

The intelligibility scores ranged between 1.5 and 4.5, with a mean score of 3.0 ($SD = 0.9$). A total of 30 children (70%) had a score of 3 or higher, indicating minor to no speech intelligibility problems. Speech intelligibility scores were not significantly correlated with age ($\tau_b = -0.03$, $p = .798$).

Intelligibility scores were weakly to moderately correlated with language outcomes (CELF CLI: $\tau_b = 0.35$, $p = .005$; CELF RLI: $\tau_b = 0.33$, $p = .016$; CELF ELI: $\tau_b = 0.32$, $p = .012$; PPVT: $\tau_b = 0.32$, $p = .007$). Additional regression analyses showed that speech intelligibility was significantly related to all CELF index scores and the PPVT, but that intelligibility ratings shared only a moderate amount of the variance in language scores (see Table 3).

Visual inspection and exploratory descriptive analyses of CELF CLI data in relation to speech intelligibility scores provided more insight into the within-group variability (see Figure 3). Most children ($n = 20$; 56%) had CELF CLI scores in the below-average range ($< -1 SD$) with relatively high speech intelligibility ratings of 3 or more. Around a quarter of children ($n = 10$; 28%) had CELF CLI scores in the below-average range and a low (below 3) speech intelligibility score. A few children ($n = 6$; 17%) had CELF CLI scores in the average range and speech intelligibility scores of higher than 3. None of the children had CELF CLI scores in the average range combined with intelligibility scores lower than 3. Similar distributions were observed for the CELF RLI, CELF ELI, and PPVT.

Discussion

This study shows that 3- to 6-year-old children with 22q11DS have impaired language skills. Our results from standardized language assessment are in line with previous

Table 2. Norm scores of the Clinical Evaluation of Language Fundamentals (CELF) subtests for the Expressive and Receptive Language Index.

CELF subtest	Task completion ^a (n)	M ^b	SD	Range	% scores < -1 SD
Expressive Language Index					
Expressive Vocabulary ^c	39	5.2	2.3	1–10	74
Word Structure ^c	36	4.3	3.1	1–12	69
Recalling Sentences	35	4.8	2.3	1–11	83
Receptive Language Index					
Sentence Comprehension ^c	40	5.7	2.6	1–10	63
Concepts and Following Directions	36	5.5	3.2	1–15	64
3-year-olds ^d Basic Concepts	6	8.8	2.3	6–12	17
4- to 6-year-olds ^d Word Categories-Receptive	28	6.1	2.6	2–12	54

^aN = 44. ^bCELF subtest norm scores can range from minimum 1 to maximum 19 with a mean of 10 and SD of 3. ^cThese subtests comprise the Core Language Index. ^dBasic Concepts (n = 12) is administered to children between 3;0 (years;months) and 3;11, whereas Word Categories-Receptive (n = 32) is administered between 4;0 and 6;11.

research (Gerdes et al., 1999, 2001; Solot et al., 2001), and we add to the existing knowledge of language development in children with 22q11DS by providing a more detailed profile of language skills during the preschool years. Our findings indicate that impairment was apparent across all tested language domains, including morphology, syntax, and semantics, at the sentence as well as the word level. In line with previous research, we also found that most parents reported a delayed onset of their child's first word and sentence (Gerdes et al., 1999; Goorhuis-Brouwer et al., 2003; Solot et al., 2000, 2001). Despite the interindividual variation present in the language scores, we observed that only a small number of children achieved age-expected language outcomes; the majority ranged from mildly impaired to severely impaired. Thus, we add to the body of research that shows that language impairment is a core phenotypic characteristic of 22q11DS.

Both expressive and receptive language abilities were impaired in our sample of preschool children with 22q11DS. In line with previous research in this age group (Gerdes et al., 1999, 2001; Solot et al., 2001), we found that expressive language abilities were more severely impaired than receptive language abilities. Children's receptive and expressive language skills were strongly correlated; children with the most severe receptive language problems also had severe expressive language problems.

With respect to the results on the different subtests, we observed that overall expressive morphosyntactic skills seemed relatively weak (subtests Repeating Sentences and Word Structure), whereas receptive word knowledge seemed least impaired (subtest Word Categories-Receptive and the PPVT). This stands in contrast with previous research in older children with 22q11DS that showed the highest subtest scores for expressive morphosyntactic skills (Word

Figure 2. Stacked bar chart with percentages of children in a specific age category during which the first word or sentence was produced based on parental report.^a Answer categories were based on three parameters from the Van Wiechen developmental screening instrument (Laurent de Angulo et al., 2005; see Appendix D). The ages between the brackets indicate the cutoff for words before the slash and for sentences after the slash.

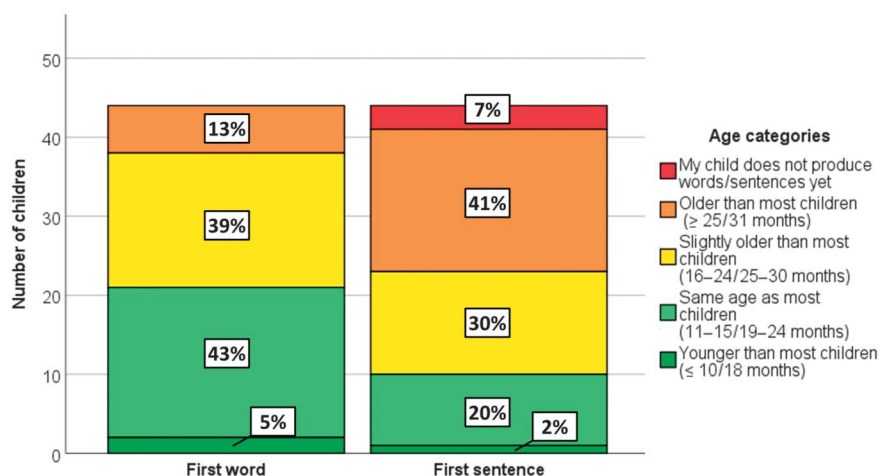


Table 3. Outcomes of the regression analyses for Clinical Evaluation of Language Fundamentals index and PPVT scores with speech intelligibility scores as a predictor.

Variable	<i>n</i>	β	95% CI	<i>F</i>	<i>df</i>	<i>p</i>	Adjusted <i>R</i> ²
Core Language Index	36	6.61	[2.31, 10.90]	9.75	1, 34	.004**	0.20
Receptive Language Index	32	6.67	[1.66, 11.67]	7.40	1, 30	.011*	0.17
Expressive Language Index	35	5.79	[1.58, 9.99]	7.84	1, 33	.008**	0.17
PPVT	41	6.83	[1.99, 11.68]	8.13	1, 39	.007**	0.15

Note. PPVT = Peabody Picture Vocabulary Test.

*significant at two-sided $p = .050$; **significant at $p = .010$.

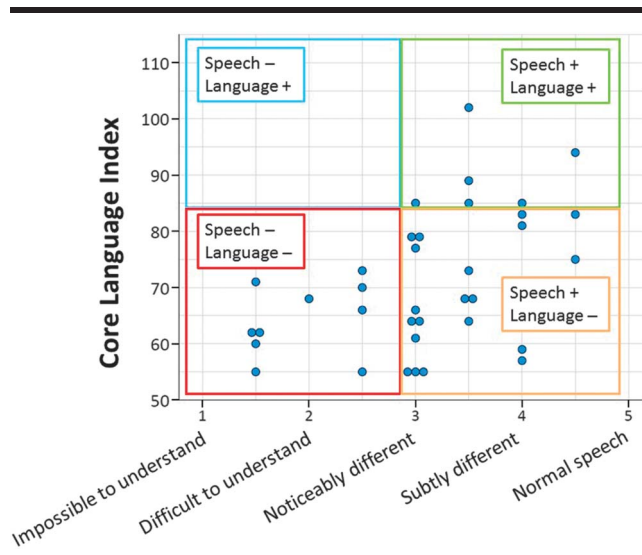
Structure and Recalling Sentences) and the lowest subtest scores for receptive semantics (Sentence Structure and Word Categories-Receptive; Glaser et al., 2002; Van Den Heuvel et al., 2018). This suggests that the level of language impairment may vary across language domains during childhood, further emphasizing the need to monitor children’s language abilities over a prolonged period of time.

While in this study, we found the lowest scores on expressive morphosyntactic skills, the observed differences between the mean scores on the various subtests were small, all indicating a below-average performance. This may indicate that the subtests of the CELF are not sensitive enough to reveal specific strengths or weaknesses. On the other hand, it may also be that the language profile of young children

with 22q11DS is not characterized by differences between specific language domains (e.g., morphology and semantics) but rather by a profile of more severe impairment in expressive than receptive abilities across all language domains.

We investigated whether variability in speech intelligibility was related to the observed variability in children’s language abilities. In line with our expectations, our results show that speech intelligibility is related to children’s language abilities. Unlike suggested by previous research (Antshel et al., 2009; Shprintzen, 2000), intelligibility problems were not only related to expressive language abilities but also to receptive languages skills. If intelligibility had only been related to expressive language abilities, this could have suggested that poor speech intelligibility hindered assessment and scoring of the language tests rather than reflecting impaired language abilities. The fact that intelligibility was also related to specifically receptive language abilities thus supports the hypothesis that intelligibility may affect quantity and quality of children’s socio-communicative interactions, thereby impacting language development. However, it should be noted that our data do not allow us to determine the direction of this relationship. Additionally, speech intelligibility and language abilities only share a moderate amount of variance, indicating that other factors are also at play. Children whose speech was judged as intelligible showed a large amount of individual variation in their language abilities (ranging from severely impaired to age adequate), whereas this variation was not observed in children with poor intelligibility, all of whom had impaired language abilities.

Figure 3. Core Language Index scores in relation to speech intelligibility scores and classification of individuals based on these scores into different categories. Dots represent individual data points. Labels used on the x-axis reflect shortened versions of the labels used in the CAPS-A. The labels as provided by the CAPS-A are (using our inverted scoring): 5 = Normal; 4 = Different from other children’s speech, but not enough to cause comment; 3 = Different enough to provoke comment, but possible to understand most speech; 2 = Only just intelligible to strangers; 1 = Impossible to understand. The colored squares indicate categories based on CLI score low (-; < 85) or high (+; ≥ 85) and speech intelligibility, low (-; < 3) or high (+; ≥ 3).



Implications

Based on our findings, we reiterate the recommendation of previous research (see recommended best practices by Solot et al., 2019) that language assessment should be included in routine clinical care for children with 22q11DS from a young age onward. Based on the small intraindividual variability that we observed in our CELF results, we conclude that a low score on the CLI of the CELF (Wiig et al., 2012), or an equivalent short language assessment, can sufficiently inform professionals about

whether a child might require more extensive assessment and care.

The majority of children in this study had impaired language abilities in the absence of poor speech intelligibility. It has been shown that specifically children with language impairment early in life have poorer academic and occupational outcomes than children with pure speech problems (Johnson et al., 2010), underscoring the need for separate assessment and monitoring of language problems in all preschool children with 22q11DS. Such assessment should be carried out regardless of their speech intelligibility problems, as these two appear to be interrelated but separate issues. This is supported by research on other neurodevelopmental or genetic conditions that are associated with speech-language difficulties, including Down syndrome, cerebral palsy, SATB2-associated syndrome, and Phelan-McDermid syndrome, which has shown that children's impaired language abilities are not or only weakly related to speech problems or low speech intelligibility (Brignell et al., 2021; Cleland et al., 2010; Nyman et al., 2021; Snijders Blok et al., 2021). Moreover, our findings highlight that it is crucial to inform professionals outside the field of speech-language pathology, such as genetic counselors and general pediatricians, about the necessity to differentiate between language problems and speech problems in children with 22q11DS, especially among those with intelligible speech. Nevertheless, we recognize that impaired language is not an isolated symptom in 22q11DS and should not be evaluated as such, given the multisystemic nature of the syndrome (McDonald-McGinn et al., 2015).

Children with 22q11DS have an increased risk for developing social-communicative problems and neurodevelopmental disorders (Fiksinski et al., 2018; McDonald-McGinn et al., 2015; Norkett et al., 2017), and this may be related to their language problems. A recent study showed that language difficulties in school-aged children with 22q11DS might be an early marker of an increased risk for the development of psychotic symptoms later in life (Solot et al., 2020), although the exact relation of childhood language difficulties to the development of psychosis warrants further research. A crucial factor in preventing psychiatric problems in children with 22q11DS may be maintaining a balance between a child's capabilities and environmental demands (Fiksinski et al., 2018). Although our results show that expressive problems are more severe in early childhood, we think that awareness of especially receptive language problems, which become more prominent in school-age years (Glaser et al., 2002; Van Den Heuvel et al., 2018), is key to ensuring that environmental demands do not exceed the child's capabilities. These receptive language problems, such as difficulties in understanding stories and instructions, are already present at this young age and may be more easily overlooked by caretakers and teachers, especially in the absence of

major speech problems (Nyman et al., 2021). Therefore, we urge professionals to monitor receptive language abilities and to raise awareness of the implications of these receptive problems in parents and other professionals working with the child.

Strengths, Limitations, and Future Directions

A strength of this study is our relatively large sample of children with 22q11DS within a narrow age range, allowing for more reliable generalization of our results. Although most participants were recruited through a specialized outpatient clinic and may therefore consist of those children with more severe phenotypic characteristics, our sample presents with similar population characteristics as reported in the literature (McDonald-McGinn et al., 2015). We did not collect data regarding race and/or ethnicity of our sample, which could limit the representativeness of our sample and the generalizability of the results. A limitation of the current results is that some children could not complete all subtests of the standardized language assessment and are missing in some of the analyses. The fact that some children could not complete certain tests is informative in and of itself, and our observations suggest that these children also had below-average language abilities. Nevertheless, the incomplete task data limit us in describing the language profile of these children.

Our findings confirm earlier suggestions that the expressive-receptive language profile of young children with 22q11DS differs from that of older children, but longitudinal research is needed to determine when this shift occurs. Moreover, although standardized tasks are useful from a clinical point of view, future research could use spontaneous language assessment to further investigate linguistic abilities of preschoolers with 22q11DS in more detail, such as grammatical complexity and error patterns. Spontaneous language analysis might aid the characterization of the language profile of children with low language levels, as this type of assessment has a higher ecological validity and can be administered to children with an even wider range of language levels. This can benefit both theory with regards to our understanding of the pathway from genes to neurological development to the development of specific linguistic abilities and clinical practice with regards to targets for intervention.

We consider the most important strength of this study that we used an instrument to evaluate the language skills of the children with 22q11DS that is commonly used, available in various languages, and can be easily integrated into clinical practice. The same holds for the speech intelligibility rating, as performed by speech and language pathologists who work with children with 22q11DS. However, the validity of the intelligibility subscale of the CAPS-A has not consistently been evaluated

as good (Chapman et al., 2016; Sell et al., 2009) and judgment of intelligibility may be subject to bias. We showed that intelligibility explained some of the variability observed in the language abilities of children with 22q11DS. Given that previous research did not detect a relationship between palatal abnormalities and language outcomes in 22q11DS (Gerdes et al., 1999; Solot et al., 2001), our findings may prompt future research to investigate how the complex and multifactorial speech and intelligibility problems in 22q11DS contribute to their impaired language abilities. It has been shown that children with 22q11DS frequently have articulation disorders (Solot et al., 2000) and have heightened incidence of apraxia of speech as compared to children with nonsyndromic cleft palate (Kummer et al., 2007). Therefore, a more detailed investigation of the underlying mechanisms of the speech errors and their relationship with intelligibility and language may be relevant to further inform our understanding of the interrelated development of speech and language abilities in the 22q11DS population. In addition, future studies are needed to investigate other factors that may affect language development, such as cognitive level or interrelations with other phenotypic characteristics of 22q11DS, such as socio-communicative difficulties (Angkustsiri et al., 2014; Campbell et al., 2011; Norkett et al., 2017; Van Den Heuvel et al., 2017).

Finally, it has been suggested that children with 22q11DS may be similar to children with developmental language disorder (DLD; Goorhuis-Brouwer et al., 2003; Kambanaros & Grohmann, 2017; Swillen et al., 2001; Vansteensel et al., 2021). As children with 22q11DS are frequently treated by SLPs who also work with children with DLD, future research could investigate to what extent the language profile of children with 22q11DS overlaps with or differs from that of children with DLD. This would be helpful in determining whether these children may benefit from the same interventions and therapies.

Conclusions

This study shows that most 3- to 6-year-old children with 22q11DS have impaired language skills in all tested language domains. Expressive abilities are relatively more impaired than receptive language abilities. We reiterate the importance of incorporating language assessment into routine clinical care, as our results contrast with findings in older children, thus suggesting the degree of impairment may vary across language domains during childhood. Speech intelligibility explains some of the variability in language outcomes, but the pathways underlying this relationship are currently unknown. Future research is warranted to further investigate the interrelatedness of speech and language impairment in these children.

Author Contributions:

Emma Everaert: Conceptualization (Equal), Data curation (Equal), Formal analysis (Equal), Investigation (Equal), Project administration (Equal), Visualization (Equal), Writing – original draft (Equal), Writing – review & editing (Equal). **Iris Selten:** Conceptualization (Equal), Data curation (Equal), Formal analysis (Equal), Investigation (Equal), Project administration (Equal), Visualization (Equal), Writing – original draft (Equal), Writing – review & editing (Equal). **Tessel Boerma:** Conceptualization (Supporting), Data curation (Equal), Investigation (Equal), Project administration (Equal), Supervision (Supporting), Writing – review & editing (Supporting). **Michiel Houben:** Resources (Lead), Supervision (Supporting), Writing – review & editing (Supporting). **Jacob Vorstman:** Conceptualization (Supporting), Supervision (Supporting), Writing – review & editing (Supporting). **Hester de Wilde:** Data curation (Supporting), Writing – review & editing (Supporting). **Desiree Derksen:** Data curation (Supporting), Writing – review & editing (Supporting). **Sarah Haverkamp:** Data curation (Supporting), Writing – review & editing (Supporting). **Frank Wijnen:** Conceptualization (Supporting), Funding acquisition (Lead), Supervision (Supporting), Writing – review & editing (Supporting). **Ellen Gerrits:** Conceptualization (Supporting), Supervision (Lead), Writing – review & editing (Supporting).

Data Availability Statement

The data sets generated and/or analyzed during this study are not publicly available due to General Data Protection Regulation compliance and legal and ethical limitations, but a limited amount of data can be shared by the corresponding author upon reasonable request.

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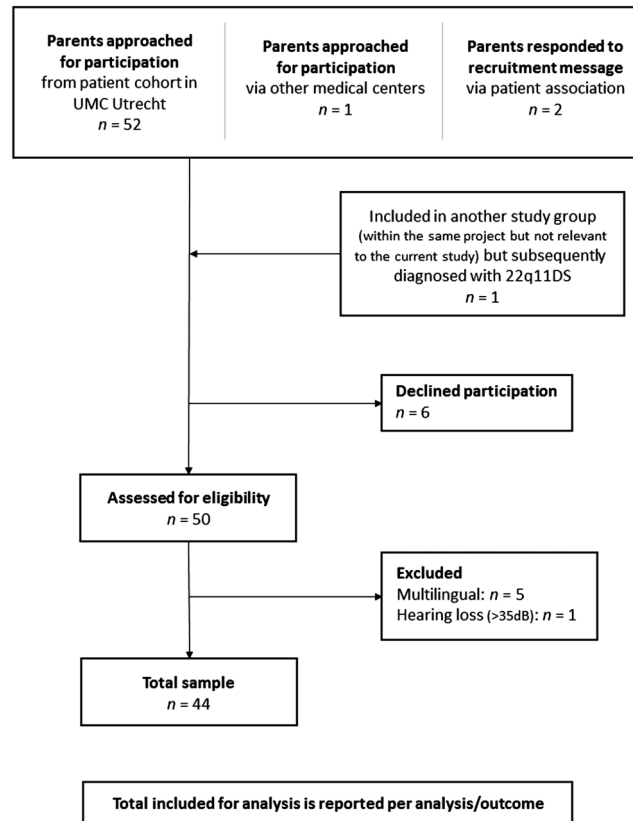
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Appendix A

Participant Recruitment

Figure A1. Flowchart of participant enrollment and inclusion. *Note.* The patient cohort is based at the national multidisciplinary outpatient clinic for children with 22q11DS at the University Medical Utrecht. The national patient association (Stichting Steun 22Q11) posted two messages on their website and one message in the yearly magazine. Four other medical centers in the Netherlands that regularly treat and refer 22q11DS patients were also approached to assist in recruitment. One center provided study information to the parents of one patient, but the other three centers indicated that there were no patients known that met the inclusion criteria and were not already known at the University Medical Center Utrecht.



Appendix B

Detailed Description of the Educational Attainment of Parents

Table B1. The highest attained educational level^a for both mother and father as compared with the average Dutch population.^b

Category	Mother		Father		Dutch population
	<i>n</i>	%	<i>n</i>	%	%
2	1	2.3	1	2.5	7
3	3	7	2	5	9.3
4	2	4.7	3	7.5	8.1
5	5	11.6	4	10	12.7
6	12	27.9	13	32.5	13.5
7	1	2.3	0	0	9.7
8	11	25.6	9	22.5	22
9	8	18.6	8	20	13.2

^aParental education was indexed a 9-point scale (ranging from 1 = *no education* to 9 = *university degree*). This scale is used by the Dutch National Bureau of Statistics (CBS). Similarly, the categories can be roughly divided into three levels: *low* (1–3), *medium* (4–6), and *high* (7–9). There were no parents in Category 1. Four children came from a single parent household, all of which were single mothers. For one other child, only the education level of father was known, as mother declined to answer this question. ^bBased on statistics by the CBS (retrieved from <https://opendata.cbs.nl/statline/#/CBS/nl/dataset/82275NED/table?fromstatweb>).

Appendix C (p. 1 of 2)

A Description of the Standardized Language Tasks Used in This Study

Peabody Picture Vocabulary Test III-NL (PPVT; Schlichting, 2005)

The PPVT is an age-normed task that measures receptive vocabulary and can be used with children from 2;3 (years;months) up into adulthood. The child is asked to point to one out of four pictures that corresponds to a word orally presented by the examiner.

Clinical Evaluation of Language Fundamentals (CELF) Preschool-2-NL (Wiig et al., 2012)

The CELF is an age-normed task for children between 3;0 and 6;11. Six subtest scores can be used to calculate composite index scores. An overview of the CELF subtests can be found in Table C1.

- > The Core Language Index (CLI) reflects global language abilities and consists of Sentence Comprehension, Word Structure, and Expressive Vocabulary.
- > The Receptive Language Index (RLI) reflects expressive language abilities, or language production, and consists of Sentence Comprehension, Concepts and Following Directions, and either Word Categories-Receptive or Basic Concepts, depending on the age of the child. Basic Concepts is normed for children from 3;0 to 3;11, whereas Word Categories-Receptive is normed for children from 4;0 to 6;11.
- > The Expressive Language Index (ELI) reflects receptive language abilities, or language comprehension, and consists of Word Structure, Expressive Vocabulary and Recalling Sentences.

Appendix C (p. 2 of 2)

A Description of the Standardized Language Tasks Used in This Study

Table C1. Description of the Clinical Evaluation of Language Fundamentals Preschool-2-NL subtests.

Receptive language index		
Task	Language domain	Description
Sentence Comprehension	Receptive syntax	The child is asked to point to one out of four pictures that corresponds to a sentence read by the examiner. This subtest has 22 items, and each correct answer is rewarded with 1 point.
Concepts and Following Directions	Receptive semantics and syntax	The child sees pictures displaying different animals of different sizes and is asked to follow instructions given orally by the examiner with regards to the order and size of the animals the child should point to. This subtest has 22 items, and each correct answer is rewarded with 1 point.
Basic Concepts (for ages 3;0–3;11)	Receptive semantics	The child is asked to point to the item in the picture that belongs to the semantic category given by the examiner (e.g., <i>which one is last / cold / long</i>). This subtest has 18 items, and each correct answer is rewarded with 1 point.
Receptive Word Categories (for ages 4;0–6;11)	Receptive semantics	The child is asked to point to the two pictures that belong together out of a set of three or four pictures. This subtest has 20 items, and each correct answer is rewarded with 1 point.
Expressive language Index		
Task	Language domain	Description
Word Structure	Expressive morphosyntax	The child is asked to finish a sentence read by the examiner accompanied by one or more pictures (e.g., <i>this is one cat, and these are two . . .</i> , where the second picture depicts two cats). This subtest includes items related to verb conjugation, adjectives, plurals, diminutives, possessives and more. It has 23 items, and each correct answer is rewarded with 1 point.
Expressive Vocabulary	Expressive semantics	The child is asked to name an object or action depicted in a picture. This subtest has 20 items, and each correct answer is rewarded with 2 points, some items having answers worth 1 point.
Recalling Sentences	Expressive syntax	The child is asked to repeat sentences increasing in length and complexity read by the examiner. There are 13 sentences and repeating the sentence without mistakes or alterations is rewarded with 3 points, one mistake/alteration is rewarded with 2 points, and two or three mistakes/alterations is rewarded with 1 point. When the child makes four or more mistakes or alterations, they receive 0 points.

Appendix D

Description of the Van Wiechen Parameters Used to Index Age of Onset of the First Word and Sentence

Answer-categories were based three parameters from the Van Wiechen developmental screening instrument (Laurent de Angulo et al., 2005):

- Parameter 37: 90% of the children will have a productive vocabulary of at least two words by the age of 15 months
- Parameter 41: 90% of the children will be able to combine two words in a short sentence by the age of 24 months
- Parameter 45: 90% of the children will be able to combine three words in a sentence by the age of 36 months

Therefore, answer categories “slightly older than most children,” “older than most children,” and “my child does not produce words/sentences yet” were grouped together as indicating a delayed onset of the first word or sentences.

Appendix E

Descriptives of the CELF Index Scores

Table E1. Task completion, mean scores, standard deviations, range of scores and percentage of children with a clinically significant score (< -1 or -1.5 *SD*) of the total sample of children with 22q11DS ($N = 44$) on each of the Clinical Evaluation of Language Fundamentals (CELF) index scores and the PPVT.^a

Outcome	Task completion (<i>n</i>)	<i>M</i>	<i>SD</i>	Range	Score < -1 <i>SD</i> (%)	Score < -1.5 <i>SD</i> ^b (%)
Core Language Index	36	70.8	12.2	55–102	83	69
Receptive Language Index	33	75.8	13.8	55–112	76	56
Expressive Language Index	35	70.4	11.6	55–100	83	80
PPVT	42	83.7	14.1	55–114	50	29

Note. PPVT = Peabody Picture Vocabulary Test.

^aCELF index and PPVT scores range from minimum 55 to maximum 145 with a mean of 100 and *SD* of 15. ^bIn some contexts or countries, -1.5 *SD* is taken as the cutoff for clinical relevance for these index scores. We therefore also report these proportions.