Published in final edited form as:

J Pediatr. 2016 November ; 178: 101–107.e2. doi:10.1016/j.jpeds.2016.07.052.

Predictive Validity of the Modified Checklist for Autism in Toddlers (M-CHAT) Born Very Preterm

So Hyun Kim, PhD^a, Robert M. Joseph, PhD^b, Jean A. Frazier, MD^c, Thomas M. O'Shea, MD, MPH^d, Katarzyna Chawarska, PhD^e, Elizabeth N Allred, MS^{f,g}, Alan Leviton, MD^{f,g}, and Karl K. Kuban, MD, SMEpi^h on behalf of the Extremely Low Gestational Age Newborn (ELGAN) Study Investigators*

^aDepartment of Psychiatry, Weill Cornell Medicine, New York, NY, USA

^bDepartment of Anatomy and Neurobiology, Boston University School of Medicine, Boston, MA, USA

^cDepartment of Psychiatry and Pediatrics, University of Massachusetts Memorial Health Care and University of Massachusetts Medical School, Boston, MA, USA

^dDepartment of Pediatrics, University of North Carolina, Chapel Hill NC, USA

^eYale Child Study Center, Yale University School of Medicine, New Haven, CT, USA

^fBoston Children's Hospital, Boston, MA, USA

^gHarvard Medical School, Boston, MA, USA

^hDepartment of Pediatrics, Boston Medical Center, Boston, MA, USA

Abstract

Objective—To examine the predictive validity of the Modified Checklist for Autism in Toddlers (M-CHAT) administered at 24 months of age for autism spectrum disorder (ASD) diagnosed at 10 years in a U.S. cohort of 827 Extremely Low Gestational Age Newborns (ELGAN) followed from birth.

Study design—We examined the sensitivity, specificity, positive predictive value and negative predictive value of the M-CHAT in predicting an ASD diagnosis at age 10 based on gold-standard diagnostic instruments. We then assessed how these predictive parameters were affected by sensorimotor and cognitive impairments, and socioeconomic status (SES), as well as emotional/behavioral dysregulation at age 2.

Results—Using standard criteria, the M-CHAT had a sensitivity of 52%, a specificity of 84%, a positive predictive value (PPV) of 20%, and the negative predictive value (NPV) of 96%. False

Corresponding Author: So Hyun Kim, Department of Psychiatry, Weill Cornell Medical College, 21 Bloomingdale Rd, White Plains, NY. sok2015@med.cornell.edu.

*List of additional ELGAN Study Investigators is available at www.jpeds.com.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

positive and false negative rates were high among children who had hearing and vision impairments. High false positive rates were also associated with lower SES, motor and cognitive impairments, and emotional/behavioral dysregulation at age 2.

Conclusions—Among extremely preterm children with ASD, almost one-half were not correctly screened by the M-CHAT at age 2. Sensorimotor and cognitive impairments, SES, and emotional/behavioral dysregulation contributed significantly to M-CHAT misclassifications. Clinicians are advised to consider these factors when screening very preterm toddlers for ASD.

Keywords

Autism; M-CHAT; Screening; Preterm Children

The Modified Checklist for Autism in Toddlers (M-CHAT)^{1,2} is a widely-used screening instrument for autism spectrum disorder (ASD) for toddlers. M-CHAT consists of two phases: a parent-administered questionnaire and an inconsistently used follow-up interview with the parent.³ Because the most recent version of the M-CHAT (M-CHAT-Revised with Follow-Up) was validated in 2014, prior studies mainly used the M-CHAT as a questionnaire alone (as we do in this study), and resulted in high sensitivity and specificity (all above 90%).^{4,5} In the absence of interview follow-up, positive predictive values (PPV) of the M-CHAT have ranged from 0.14 to 0.64 in community-based samples.^{4,5}

Although the prevalence of ASD is 1 to 2% in the general population,^{6,7} the prevalence in preterm children is several magnitudes higher (1.8 to 8%^{8–11}). Sensory, motor, and cognitive impairments,^{11–13} as well as emotional/behavioral dysregulation,¹⁴ which can affect the validity of the M-CHAT, occur more often in very preterm toddlers than term children. Therefore, misclassification rates might be higher among preterm children with such deficits. A recent study has examined the validity of M-CHAT in preterm toddlers in relation to a concurrent ASD diagnosis made at age 2–4¹³, but no studies of preterm toddlers have assessed how well the M-CHAT predicts the much more reliable, longer-term diagnosis of ASD in the preterm children at school age.

The purpose of this study was to examine the predictive validity of the M-CHAT administered at 24 months of age in relation to the diagnosis of ASD at school age in a cohort of Extremely Low Gestational Age Newborns (ELGAN) followed from birth. We evaluated overall M-CHAT predictive validity as well as the validity of each specific item with regard to ASD diagnosis. We also examined the extent to which developmental, demographic, behavioral and cognitive characteristics of extremely preterm children affected M-CHAT predictive validity.

METHODS

The ELGAN study is a multicenter prospective, observational study of the risk of structural and functional neurologic disorders in extremely preterm infants.¹⁵ A total of 1506 infants born before the 28th week of gestation were enrolled during the years 2002–2004 and 1200 survived to 2 years. Analyses at age 24 months resulted in a report of overall rates of M-CHAT positivity and the association of M-CHAT positivity with concurrent motor,

cognitive, visual and hearing impairments.¹² Of the 1200 surviving children, 889 children were enrolled for the 10-year follow-up (Table I and Figure; Figure available at www.jpeds.com), when they were carefully evaluated for ASD. This enabled us to assess the predictive validity of the M-CHAT for ASD.

At approximately 24-months corrected age, children received a developmental assessment, which included a neurological examination, the Bayley Scales of Infant Development, second edition (BSID-II)¹⁶, and several parent reported assessments, including the M-CHAT and Child Behavior Checklist for Ages 1½ – 5 (CBCL)¹⁷ (Figure). The parent completed questionnaires regarding the child's sensory and motor impairments. Nine hundred sixty-six families who participated in the 24-month evaluations were contacted by mail and then by phone to invite them to participate in the 10-year follow up. We searched for families who were lost to follow up using state vaccination registries, and other openly available websites. Facebook was also used where approved by the local institution's Institutional Review Board. The enrollment and consent processes were approved by the Institutional Review Boards at each site.

M-CHAT

Primary caregivers completed the M-CHAT screener.^{12,13} The M-CHAT consists of 23 items for which the primary caregiver rates whether the child has or does not have the behavior specified.⁴ A child was considered to screen positive if 2 of 6 “critical” items (Table II) or three of any of the 23 total items were endorsed. A follow-up caregiver interview was not completed as part of the present investigation.

Gross motor function classification system (GMFCS)

Children's motor function was assessed with the BSID-II Psychomotor Developmental Index (PDI) and the GMFCS at age 2 and 10.¹⁸ At age 2, a child was classified as GMFCS level 2 or higher if s/he could not sit, stand, or walk independently. A child who needed assistance to walk was classified as level 1, and a child who could walk was classified as level <1. At age 10, a child was classified as GMFCS level 5 if he or she had no self-mobility. Because ASD cannot be validly diagnosed in children with severe motor impairments, children with no self-mobility at age 10 were excluded from diagnostic consideration of ASD.

Sensory impairments

Parents were asked to provide information about their child's vision and hearing at age 2 and 10. A child was considered to have visual impairment if the parent reported that the child was legally blind in at least one eye or if the child was receiving treatment or had surgery for lazy eye, strabismus, squint, or crossed eyes. A child was considered to have hearing impairments if the parent reported that the child used hearing aids, had a cochlear implant, or was receiving special services for the hearing impaired.¹² As with children who had severe motor impairment, children with uncorrectable functional blindness in both eyes at age 10 were excluded from diagnostic assessment of ASD. No child had a hearing impairment of a severity that precluded a valid ASD assessment.

Cognitive function

BSID-II Mental Development Index (MDI) was used to estimate the cognitive function at age 2.

Emotional/Behavioral dysregulation problems

The child's primary caregiver chose one of three responses to each of the 99 characteristics listed in the CBCL/1½-5 at age 2: "not true," "somewhat/sometimes true," and "very true/often true."¹⁶ Children were classified as having a significant dysregulation profile if the sum of the T scores for attention problems, aggressive behavior, and anxious/depressed subscales was ≥ 180 .¹⁴

Autism assessment at age 10

All children were screened by parent report for risk of ASD with the Social Communication Questionnaire (SCQ).¹⁹ The SCQ includes 39 ratings for children with simple sentence speech and 33 ratings for those without simple sentence speech. To increase screener sensitivity, a score ≥ 11 , recommended by the authors for individuals at higher-than-normal risk for ASD was used instead of the standard criterion of ≥ 15 . Children determined at risk on the SCQ, were assessed with the Autism Diagnostic Interview-Revised (ADI-R), an in-depth parent interview.²⁰ Children meeting ADI-R modified criteria for ASD as suggested by the authors^{20,21} were administered the Autism Diagnostic Observation Schedule-2 (ADOS-2).²² The only exceptions to this ASD assessment procedure were made for 9 children who did not meet ADI-R criteria for ASD, but who were evaluated with the ADOS-2 because the child had a prior clinical diagnosis of ASD or the child was thought likely to meet ASD criteria based on the site psychologist's clinical observation during cognitive testing of the child. For two additional children who met ADOS-2 diagnostic criteria for ASD, the ADI-R was not completed²³.

Data analyses

We examined the sensitivity, specificity, PPV and NPV of the M-CHAT at the item and total score criteria level. The standard criteria for screening positive are "either 3 out of 23 total items OR 2 out of 6 critical items." Due to a low sensitivity obtained from the standard criteria, we relaxed the cutoff scores to determine if a better balance between sensitivity and specificity could be achieved with more lenient criteria: (1) either 3 of 23 total items OR 1 of 6 critical items; (2) either 2 of 23 total items OR 2 of 6 critical items; and (3) either 2 of 23 total items OR 1 of 6 critical items.

We examined 24 month correlates by comparing the rates of motor, sensory, and cognitive impairments, emotional/behavioral dysregulation problems, and socioeconomic status among the correctly classified and misclassified cases in relation to the standard M-CHAT criteria.

RESULTS

Of 889 children in the sample, 26 children were excluded from an assessment of ASD at age 10, 17 because of severe motor impairment and severe ID, 7 for functional blindness, and 2

for severe motor impairment, blindness, and ID combined. Of these 26 children, 19 did not achieve basal IQ scores. One child who met SCQ criteria and 5 children who met both SCQ and ADI-R criteria for ASD did not return to complete the ASD assessment, and were not included in the final sample. Of these 6 children, 4 did not achieve basal IQ scores, 1 scored in the mild ID range, and 1 family refused IQ testing. Of the 857 children who were evaluated for ASD at age 10, 827 had a completed M-CHAT of whom 58 met criteria for ASD (Figure).

Twenty percent 20% ($n = 166$) of the sample was born at 23–24 weeks, 45% ($n = 370$) at 25–26 weeks of gestation, and 35% ($n = 291$) at 27 weeks of gestation. Thirty-six percent of the sample ($n = 301$) had a birth weight at or below 750 grams, 44% ($n = 361$) had a birth weight between 751 and 1000 grams, and 20% ($n = 165$) a birth weight more than 1000 grams.

Children of mothers with black, Hispanic or other backgrounds were more likely to screen positive on the M-CHAT than children of white mothers (Table I). Children of single mothers and of mothers receiving public insurance were more likely to screen positive compared with children of married mothers and of mothers with HMO or private insurance. Male children were more likely to receive a diagnosis of ASD than female children. Lower birth weight was also associated with higher rates of screening positive on the M-CHAT and of ASD diagnosis.

Predictive validity of M-CHAT items

Sensitivities for the 6 critical items ranged from 10 to 43% (Table II). Sensitivities varied more for non-critical items, ranging from 0 to 43%. Specificities were notably higher for all items, ranging from 77 to 99%. PPVs ranged from 0 to 43%, but NPVs were higher, in the range of 93 to 96%.

Predictive validity of M-CHAT classification for ASD

When the standard criteria of the M-CHAT were used, 52% (sensitivity) of children who were later diagnosed with ASD were correctly identified at age 2 years, and 84% (specificity) of children without ASD were correctly excluded (Table III). Of the 153 children who screened positive, only 20% (PPV) were subsequently diagnosed with ASD. Almost all children who screened negative (NPV of 96%) did not receive a diagnosis of ASD at age 10. Lower cutoffs on both total and critical item totals scores yielded more balanced sensitivities and specificities but lower PPVs.

We found moderate to strong associations between SES (ie, maternal education and public insurance status) and misclassification rates, specifically for false positives (Table IV). For instance, the false positive rate was highest for those whose parents received a 12th-grade or less education (21%), lower for those whose parents received 13–15th-grade education (15%), and the lowest for those whose parents received a 16th-grade or higher education (8%). Similarly, the false positive rate was higher for those who were eligible for public insurance (24%) than those who were not eligible (10%).

The more severe a child's motor impairments as assessed by the GMFCS and BSID-II Motor Scale (PDI), the more likely the child without ASD was to incorrectly screen positive (Table IV). For instance, the false positive rate was lowest in those who could walk (GMFCS < 1, 14%), intermediate in those needing assistance to walk (GMFCS = 1, 29%), and highest in those who could not sit or walk even with assistance (GMFCS ≥ 2, 48%). Moreover, the lower a child's BSID-II PDI (another indicator of motor ability), the more likely the child without ASD was misclassified as having ASD (PDI < 55, 27%; PDI 56 to 69, 23%; PDI ≥ 70, 11%). Similar to children without ASD, children with ASD were also more likely to screen positive as their motor impairments became more severe.

Vision and hearing impairments were associated with higher misclassification rates, both for false positives and false negatives (Table IV). For instance, the rate of false positives was higher in those with vision (38%) or hearing (41%) impairments compared with those without vision (15%) or hearing (14%) impairments, respectively. Similarly, the rate of false negatives was higher in those with vision (19%) or hearing (12%) impairments than in those without vision (3%) or hearing (3%) impairments, respectively.

The false positive rate was highest among children whose BSID-II MDI was below 55 (32%), intermediate in those whose MDI was between 55 and 70 (28%), and lowest in those with an MDI ≥ 70 or higher (10%) (Table IV).

The rate of false positives was higher in those with (38%) than without (12%) the emotional/behavioral dysregulation profile (Table IV).

DISCUSSION

This study evaluated the predictive validity of the M-CHAT at 2 years for the diagnosis of ASD at 10 years among children born extremely preterm. Of 58 children with ASD, about half screened positive on the M-CHAT (sensitivity = 52%). Of 153 children who screened positive, only 20% (PPV) were subsequently diagnosed with ASD. When predictive validity was examined at the item level, the prevalence of many behavioral features commonly considered early red flags for ASD varied widely among children later diagnosed with ASD, with sensitivities of individual items ranging from 0 to 43%. In contrast, 84% (specificity) of children without ASD did not screen positive on the M-CHAT. The item-level analyses also indicated that many of the behavioral features captured by the M-CHAT were highly specific to children with ASD.

Past studies using the M-CHAT have reported adequate sensitivities of the M-CHAT in the absence of follow-up interviews, ranging from 87 – 91%,^{2,3,5} although a recent study found lower sensitivity (ranging from 21 to 34% depending on criteria used) based on a general population sample.²⁴ The results from our study suggest that various factors associated with extreme prematurity (such as sensory impairments) significantly affect the performance of the M-CHAT. In fact, in our sample, children with ASD were more likely to be missed by the M-CHAT when they had moderate vision or hearing impairments. PPV was also lower than expected in this sample; of 153 children who screened positive, only 20% were subsequently diagnosed with ASD, although it was comparable with the rate reported by a

past validation study of M-CHAT in the absence of follow-up interviews.⁵ In our study, false positive rates were also associated with sensory, motor, and cognitive impairments, SES, and emotional/behavioral dysregulation.

These results suggest that early detection of ASD in preterm infants may be influenced by various developmental and demographic factors. For instance, some sensory impairments observed in preterm infants may mask early symptoms of ASD, leading to false negatives, as reported here for a very small number of cases (n=2 for vision impairment only, n=3 hearing impairments only, n=1 for both vision and hearing impairments). Parents of children with sensory impairments and ASD may have overlooked the symptoms of ASD while attending to more disabling conditions that had persisted since infancy. It is also possible that because the sensory impairments identified for these 6 children at age 2 resolved by age 10, their sensory impairments as well as ASD symptoms might have been too mild to affect the skills rated with the M-CHAT. This finding underscores the importance of fostering recognition among parents and healthcare professionals that child characteristics, such as co-occurring vision and hearing impairments, may lead to underreporting of autism symptoms in children born extremely preterm. Conversely, some sensory and motor impairments may mimic early symptoms of ASD (e.g., difficulty with responding to name due to hearing impairments, difficulty with bringing objects to show parents due to limited mobility) resulting in false positives. False positive rates also were higher among families from lower socioeconomic backgrounds, consistent with past studies²⁵. This finding might reflect the variability in parent's expectation of what the child's behavior should be, which may be affected by socioeconomic factors. Furthermore, factors such as sensorimotor or cognitive impairments that were found to affect the validity of the M-CHAT may be more prominent among children with lower socioeconomic backgrounds.²⁷ In fact, we found higher severity or prevalence of sensory, motor and cognitive impairments as well as dysregulation profiles among children with lower socioeconomic background in our sample (Table V; available at www.jpeds.com).

Another possible explanation for the lower sensitivity of the M-CHAT is that some children may not show fully developed symptoms of ASD until 3 years of age. The M-CHAT can be administered validly to children as young as 18 months.^{4,5} However, up to 40% of children with ASD may not meet the full criteria to warrant a diagnosis of ASD at 18 month of age.²⁸ Similarly, in a recent general population study, only a third of toddlers who later developed ASD were correctly identified by the M-CHAT at 18 months of age.²⁴ Many of these children, however, met the full criteria for ASD by age 3. It may be that a subset of ELGANs followed this later-onset trajectory, were missed by the M-CHAT at 24 months, and subsequently declined in their social communication abilities. The wide variability in sensitivities, ranging from 0 to 43% at the item level, may reflect this possibility given that almost half of preterm infants later diagnosed with ASD did not show early signs at 24 months (e.g., lack of social smile, limited eye contact, diminished interest in social-interactive play). These results point to the need for routine screening and continued developmental monitoring in order to enhance the early detection of ASD in preterm infants and to increase their access to early intervention.

The predictive validity of the M-CHAT was evaluated in our sample based on ASD diagnoses made at age 10. Given that most past studies using the M-CHAT^{4,5} have not examined the longer-term predictive validity of the M-CHAT, our findings suggest that, for very pre-term cohorts, refinement of the screening items or use of more lenient criteria (i.e., lower cutoff scores) could improve the sensitivity of the measure for longer-term diagnostic outcomes. For instance, when we relaxed the M-CHAT standard criteria, we obtained more balanced sensitivity and specificity. However, more relaxed criteria may potentially lead to even lower PPV rates, although follow-up interviews have been recommended by the authors to decrease false positives and increase PPVs. Therefore, as screening measures are designed to maximize sensitivity while maintaining an adequate level of specificity, clinicians using the M-CHAT with very preterm children should consider further adjustments of the criteria accompanied by follow-up interviews. In addition, assessments for sensory, motor, and cognitive deficits as well as emotional/behavioral dysregulation, could improve the sensitivity of the M-CHAT for populations at heightened risk for ASD, including children born extremely preterm.

One of the strengths of our study is the long-term follow-up of extremely preterm infants, who were assessed for ASD at age 10 years, whereas past studies examining the predictive validity of the M-CHAT have considered concurrent or shorter term diagnostic outcomes. In addition, our results are based on a large sample of extremely preterm infants, selected on the basis of gestational age rather than birth weight. Our sample size allowed us to follow a substantial number of children with ASD prospectively and to examine characteristics of the family and child affecting the validity of the M-CHAT. A limitation of our study is that it did not include M-CHAT follow-up interviews, which may have decreased the PPV in the present study. However, follow-up interviews are recommended to further minimize false positives.

In a large study of children born extremely preterm, the specificity and negative predictive value of the M-CHAT were high but sensitivity and positive predictive value were lower than expected. This might, in part, reflect that demographic factors as well as cognitive, sensorimotor, and emotional/behavioral dysregulation problems appear to contribute to the misclassification rates of the M-CHAT. Clinicians using the M-CHAT for very preterm populations should consider using the standard criteria with caution, accompanied by follow-up interviews. Given the potential impact of these factors on misclassification rates, screening very preterm toddlers for ASD using the M-CHAT may need to be supplemented with other screening measures.

Acknowledgments

Supported by the National Institute of Neurological Disorders and Stroke (5U01NS040069-05 and 2R01NS040069-06A2) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (5P30HD018655-28). J.F. received research support from Alcobra, Janssen Research and Development, SyneuRX, and Neuren; and has served on a data safety monitoring board for a Forest Pharmaceuticals clinical trial (ClinicalTrials.gov: <NCT number>). No funds from these entities supported this project, and none of these entities reviewed or commented on this study. The other authors declare no conflicts of interest.

We thank the children and their families who participated in this study.

Abbreviations

M-CHAT	Modified Checklist for Autism in Toddlers
ASD	Autism Spectrum Disorder
ELGAN	Extremely Low Gestational Age Newborn
SES	Socioeconomic Status
PPV	positive predictive value
NPV	negative predictive value
GMFCS	Gross Motor Functional Classification System
CBCL	Child Behavior Checklist
ADOS	Autism Diagnostic Observation Schedule
ADI	-R, Autism Diagnostic Interview-Revise
SQC	Social Communication Questionnaire
BSID-II	Bayley Scales of Infant Development-Second Edition
PDI	Psychomotor Index
MDI	Mental Developmental Index

References

1. Robins DL, Fein D, Barton ML. Modified checklist for autism in toddlers (M-CHAT) Follow-Up Interview. Self-Publ. 1999
2. Chlebowski C, Robins DL, Barton ML, Fein D. Large-scale use of the modified checklist for autism in low-risk toddlers. *Pediatrics*. 2013; 131:1121–1127.
3. Harrington JW, Bai R, Perkins AM. Screening children for autism in an urban clinic using an electronic M-CHAT. *Clin Pediatr*. 2013; 52:35–41.
4. Robins DL, Fein D, Barton ML, Green JA. The Modified Checklist for Autism in Toddlers: an initial study investigating the early detection of autism and pervasive developmental disorders. *J Autism Dev Disord*. 2001; 31:131–144. [PubMed: 11450812]
5. Robins DL, Casagrande K, Barton M, Chen CM, Dumont-Mathieu T, Fein D. Validation of the modified checklist for autism in toddlers, revised with follow-up (M-CHAT-R/F). *Pediatrics*. 2014; 133:37–45. [PubMed: 24366990]
6. Zablotsky B, Black LI, Maenner MJ, Schieve LA, Blumberg SJ. Estimated prevalence of autism and other developmental disabilities following questionnaire changes in the 2014 national health interview survey. *National Health Statistical Reports*. 2015; 87:1–20.
7. Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators, Centers for Disease Control and Prevention (CDC). Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2010. *Morb Mortal Wkly Rep Surveill Summ Wash DC* 2002. 2014; 63:1–21.
8. Hack M, Taylor HG, Schluchter M, Andreias L, Drotar D, Klein N. Behavioral outcomes of extremely low birth weight children at age 8 years. *J Dev Behav Pediatr JDBP*. 2009; 30:122. [PubMed: 19322106]

9. Pinto-Martin JA, Levy SE, Feldman JF, Lorenz JM, Paneth N, Whitaker AH. Prevalence of autism spectrum disorder in adolescents born weighing < 2000 grams. *Pediatrics*. 2011; 128:883–891. [PubMed: 22007018]
10. Johnson S, Hollis C, Kochhar P, Hennessy E, Wolke D, Marlow N. Autism spectrum disorders in extremely preterm children. *J Pediatr*. 2010; 156:525–531. [PubMed: 20056232]
11. Pritchard MA, de Dassel T, Beller E, Bogossian F, Johnston L, Paynter J, Russo S, Scott J. Autism in Toddlers Born Very Preterm. *Pediatrics*. 2016
12. Kuban KCK, O'Shea TM, Allred EN, Tager-Flusberg H, Goldstein DJ, Leviton A. Positive Screening on the Modified Checklist for Autism in Toddlers (M-CHAT) in Extremely Low Gestational Age Newborns. *J Pediatr*. 2009; 154:535–540. [PubMed: 19185317]
13. Luyster RJ, Kuban KCK, O'Shea TM, Paneth N, Allred EN, Leviton A. The Modified Checklist for Autism in Toddlers in extremely low gestational age newborns: individual items associated with motor, cognitive, vision and hearing limitations. *Paediatr Perinat Epidemiol*. 2011; 25:366–376. [PubMed: 21649679]
14. Frazier JA, Wood ME, Ware J, Joseph RM, Kuban KC, O'Shea M, et al. Antecedents of the Child Behavior Checklist–Dysregulation Profile in Children Born Extremely Preterm. *J Am Acad Child Adolesc Psychiatry*. 2015; 54:816–823. [PubMed: 26407491]
15. O'Shea TM, Allred EN, Dammann O, Hirtz D, Kuban KC, Paneth N, et al. The ELGAN study of the brain and related disorders in extremely low gestational age newborns. *Early Hum Dev*. 2009; 85:719–25. [PubMed: 19765918]
16. Bayley, N. Bayley Scales of Infant Development Manual. 2. San Antonio, TX: The Psychological Corporation; 1993.
17. Achenbach, TM.; Rescorla, L. ASEBA Preschool Forms and Profiles: an Integrated System of Multi-informant Assessment. Burlington, VT: University of Vermont, Research Center for Children, Youth and Families; 2000.
18. Palisano RJ, Rosenbaum P, Bartlett D, Livingston MH. Content validity of the expanded and revised Gross Motor Function Classification System. *Dev Med Child Neurol*. 2008; 50:744–50. [PubMed: 18834387]
19. Rutter, M.; Bailey, A.; Lord, C. The Social Communication Questionnaire–Manual. Los Angeles, CA: Western Psychological Services; 2003.
20. Rutter, M.; Le Couteur, A.; Lord, C. Autism Diagnostic Interview–Revised. Los Angeles, CA: Western Psychological Services; 2003.
21. Risi S, Lord C, Gotham K, Corsello C, Chrysler C, Szatmari P, et al. Combining information from multiple sources in the diagnosis of autism spectrum disorders. *J Am Acad Child Adolesc Psychiatry*. 2006; 30(45):1094–1103.
22. Lord, C.; Rutter, M.; DiLavore; Risi, S.; Gotham, K.; Bishop, S. Autism Diagnostic Observation Schedule–2nd edition. Los Angeles, CA: Western Psychological Corporation; 2012. (ADOS-2)
23. Joseph RM, O'Shea TM, Allred EN, Heeren T, Hirtz D, Paneth N. Prevalence and associated features of autism spectrum disorder in extremely low gestational age newborns at age 10 years. *Autism Research*. 2016
24. Stenberg N, Bresnahan M, Gunnes N, Hirtz D, Hornig M, Lie KK, et al. Identifying children with autism spectrum disorder at 18 months in a general population sample. *Paediatr Perinat Epidemiol*. 2014; 28:255–62. [PubMed: 24547686]
25. Scarpa A, Reyes NM, Patriquin MA, Lorenzi J, Hassenfeldt TA, Desai VJ, et al. The modified checklist for autism in toddlers: Reliability in a diverse rural American sample. *Journal of autism and developmental disorders*. 2013 Oct 1.43:2269–79. [PubMed: 23386118]
26. Khowaja MK, Hazzard AP, Robins DL. Sociodemographic barriers to early detection of autism: screening and evaluation using the M-CHAT, M-CHAT-R, and follow-up. *Journal of autism and developmental disorders*. 2015 Jun 1.45:1797–808. [PubMed: 25488122]
27. Spencer NJ, Blackburn CM, Read JM. Disabling chronic conditions in childhood and socioeconomic disadvantage: a systematic review and meta-analyses of observational studies. *BMJ open*. 2015; 5:e007062.

28. Ozonoff S, Young GS, Landa RJ, Brian J, Bryson S, Charman T, et al. Diagnostic stability in young children at risk for autism spectrum disorder: a baby siblings research consortium study. *Journal of Child Psychology and Psychiatry*. 2015; 56:988–998. [PubMed: 25921776]

Appendix

Additional investigators of the ELGAN Study include:

Boston Children's Hospital, Boston MA: Janice Ware, Taryn Coster, Brandi Henson, Rachel Wilson, Kirsten McGhee, Patricia Lee, Aimee Asgarian, Anjali Sadhwani; Tufts Medical Center, Boston MA: Ellen Perrin, Emily Neger, Kathryn Mattern, Jenifer Walkowiak, Susan Barron; University of Massachusetts Medical School, Worcester MA: Lauren Venuti, Beth Powers, Ann Foley, Brian Dessureau, Molly Wood, Jill Damon-Minow; Yale University School of Medicine, New Haven, CT: Richard Ehrenkranz, Jennifer Benjamin, Elaine Romano, Kathy Tsatsanis, Susan Dieterich, Karen Bearrs; Wake Forest University Baptist Medical Center, Winston-Salem NC: Nancy Peters, Patricia Brown, Emily Ansusinha, Ellen Waldrep, Jackie Friedman, Gail Hounshell, Debbie Allred; University Health Systems of Eastern Carolina, Greenville, NC: Stephen C. Engelke, Nancy Darden-Saad, Gary Stainback; North Carolina Children's Hospital, Chapel Hill, NC: Diane Warner, Janice Wereszczak, Janice Bernhardt, Joni McKeeman, Echo Meyer; Helen DeVos Children's Hospital, Grand Rapids, MI: Steve Pastyrnak, Wendy Burdo-Hartman, Julie Rathbun, Sarah Nota, Teri Crumb; Sparrow Hospital, Lansing, MI: Madeleine Lenski, Deborah Weiland, Megan Lloyd; University of Chicago Medical Center, Chicago, IL: Scott Hunter, Michael Msall, Rugile Ramoskaite, Suzanne Wiggins, Krissy Washington, Ryan Martin, Barbara Prendergast, Megan Scott; William Beaumont Hospital, Royal Oak, MI: Judith Klarr, Beth Kring, Jennifer DeRidder, Kelly Vogt.

Figure; online only.

Sample derivation. The sample (n=827) consists of the children who were evaluated for ASD at 10 years and with the M-CHAT at 2 years.

Table 1

Characteristics of M-CHAT and children positive for ASD.

		M-CHAT Positive	ASD Positive	Row N
Maternal Characteristics				
Race	White	15 [†]	7	532
	Black	24	8	202
	Other	29	4	91
Hispanic	Yes	28 [†]	5	76
	No	18	7	749
Maternal age	< 21	19	5	102
	21–35	20	7	553
	> 35	14	8	172
Years of education	12	26 [†]	8	342
	13–15	17	4	185
	16	11	7	300
Single	Yes	24 [†]	7	319
	No	15	7	508
Public insurance	Yes	28 [†]	7	284
	No	13	7	543
Perinatal characteristics				
Any antenatal corticosteroids	Yes	17 [†]	7	731
	No	26	7	95
Delivery complication	PE/FI [*]	23	9	140
	Spontaneous ^{**}	18	7	687
Newborn Characteristics				
Sex	Male	21	9 [†]	421
	Female	16	5	406
Gestational age, weeks	23–24	25	15 [†]	166
	25–26	17	6	370
	27	16	3	291
Birth weight, grams	750	23 [†]	11 [†]	301
	751–1000	17	4	361
	> 1000	14	5	165
Maximum column N		153	58	827

Data are shown as row percentages except where noted (Row N and Maximum Column N).

^{*} Preeclampsia/Fetal indication^{**} Preterm labor, preterm premature rupture of membranes, abruption, cervical insufficiency

[†]Indicates a significant association ($p < 0.05$) between the characteristic listed in the first column and M-CHAT positivity or ASD positivity, respectively.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

The sensitivity, specificity, positive predictive value and negative predictive value (and 95% confidence intervals) for each M-CHAT item's ability to predict ASD at age 10 years.

M-CHAT items	Sens	Spec	PPV	NPV	Row N
1. Does not enjoy being swung	3 (0.4, 12)	98 (96, 99)	10 (1, 32)	93 (91, 95)	20
2. Does not show interest in others	16 (7, 27)	97 (96, 98)	27 (13, 46)	94 (92, 95)	33
3. Does not like climbing	12 (5, 23)	97 (96, 98)	25 (11, 43)	94 (92, 95)	28
4. Does not enjoy peek a boo	3 (0.4, 12)	98 (97, 99)	13 (2, 4)	93 (91, 95)	15
5. Does not pretend	32 (20, 45)	97 (96, 98)	46 (30, 63)	95 (93, 96)	39
6. Does not point to ask	43 (30, 57)	93 (91, 95)	32 (22, 44)	96 (94, 97)	77
7. Does not point to indicate interest	43 (30, 57)	93 (91, 95)	32 (22, 43)	96 (94, 97)	79
8. Does not play with small toys	22 (13, 35)	95 (94, 97)	27 (15, 42)	94 (92, 95)	48
9. Does not bring objects to show you	28 (17, 41)	97 (96, 98)	43 (27, 61)	95 (93, 96)	37
10. Does not look you in the eye	7 (2, 17)	98 (96, 99)	19 (5, 42)	93 (91, 95)	21
11. Is oversensitive to noise	22 (13, 35)	77 (74, 80)	7 (4, 12)	93 (91, 95)	188
12. Does not smile in response to smile	0	99 (99, 100)	0	93 (91, 95)	5
13. Does not imitate you	36 (24, 50)	94 (92, 95)	30 (20, 43)	95 (93, 97)	69
14. Does not respond to name	10 (4, 21)	99 (98, 99)	38 (15, 65)	94 (92, 95)	16
15. Does not look at toy when you point	29 (18, 43)	96 (94, 97)	35 (22, 50)	95 (93, 96)	49
16. Does not walk	19 (10, 31)	95 (94, 97)	24 (13, 39)	94 (92, 96)	46
17. Does not look at things you look at	17 (9, 29)	96 (95, 98)	26 (13, 43)	94 (92, 95)	38
18. Makes unusual finger movements	16 (7, 27)	88 (86, 90)	9 (4, 16)	93 (91, 95)	101
19. Does not try to attract your interest	19 (10, 31)	93 (91, 95)	16 (8, 27)	94 (92, 95)	67
20. Have you wondered if child is deaf	21 (11, 33)	95 (93, 96)	24 (13, 38)	94 (92, 96)	50
21. Does not understand what people say	14 (6, 26)	98 (96, 98)	30 (14, 5)	94 (92, 95)	27
22. Stares at nothing, wanders	26 (15, 39)	86 (84, 89)	12 (7, 19)	94 (92, 95)	122
23. Does not look at your face for reaction	22 (13, 35)	91 (89, 93)	16 (9, 26)	94 (92, 96)	81

Bold items indicate 6 M-CHAT critical items.

Table 3

The sensitivity, specificity, positive predictive value and negative predictive value (and 95% confidence intervals) for several M-CHAT summary scores' ability to predict ASD at age 10 years

Criteria	Sens	Spec	PPV	NPV	Row N
Either 3 out of 23 total items OR 2 out of 6 critical items*	52 (38, 65)	84 (81, 87)	20 (14, 27)	96 (94, 97)	153
Either 3 out of 23 total items OR 1 out of 6 critical items	59 (45, 71)	79 (76, 82)	18 (13, 24)	96 (94, 98)	192
Either 2 out of 23 total items OR 2 out of 6 critical items	62 (48, 74)	71 (68, 74)	14 (10, 19)	96 (94, 98)	257
Either 2 out of 23 total items OR 1 out of 6 critical items	66 (52, 78)	69 (66, 72)	14 (10, 18)	96 (94, 98)	276

* Standard criteria

Sens Sensitivity, Spec Specificity, PPVPredictive Positive Value, NPVNegative Predictive Value.

Table 4

Correlates of M-CHAT true positive, false positive, true negative, and false negative (Standard Criteria).

			True Positive	False Positive	True Negative	False Negative	Row N
SES at birth							
Maternal education	12		5	21	71	3	331
	13–15		2	15	81	2	177
	16		3	8	85	4	294
Public insurance	Yes		4	24	69	3	277
	No		3	10	83	4	536
Motor at 2 years							
GMFCS	2		26	48	26	0	23
	1		21	29	50	0	24
	< 1		2	14	80	4	760
BSID-II PDI	< 55		21	27	47	4	95
	55–69		6	23	68	3	125
	70		0.2	11	86	3	568
Sensory at 2 years							
Vision	Yes		19	38	25	19	16
	No		3	15	79	3	805
Hearing	Yes		24	41	24	12	17
	No		3	14	79	3	804
Cognitive at 2 years							
BSID-II MDI	< 55		22	32	41	5	96
	55–69		6	28	62	5	87
	70		0.3	10	86	3	605
Emotional/behavioral Dysregulation at 2 years							
CBCL Dysregulation Profile (anxdis+atms+agrts) * 180	Yes		6	38	54	2	50
	No		4	12	81	3	581
Maximum column N			34	123	646	28	827

GMFCS Gross Motor Function Classification System, *BSID-II* Bayley Scales of Infant Development-Second edition, *MDI* Mental Development Index, *PDI* Psychomotor Development index, *CBCZ* Child Behavior Checklist for Ages 1½ – 5.

Data are shown as row percentages except for row Ns on the right and column Ns at the bottom. All classifications are significantly different ($p < 0.01$) based on chi-square analyses.

* anxdst=anxiety/depression T score; atnts=attention T score; agrts=aggression T score.

Table 5
Characteristics of ELGANs at 2-years classified by maternal education and source of health insurance.

		Maternal education			Public insurance		Row N
		12	13–15	16	Yes	No	
Motor at 2 years							
GMFCS	2	52	26	22	39	61	23
	1	57	22	22	48	52	23
	<1	40	22	37	34	66	747
BSID-II PDI	<55	53	19	28	46	54	94
	55–69	44	17	39	30	70	122
	70	39	23	38	33	67	558
Sensory at 2 years							
Vision	Yes	40	20	40	20	80	15
	No	41	22	36	34	66	792
Hearing	Yes	60	20	20	31	69	16
	No	41	22	37	34	66	791
Cognitive at 2 years							
BSID-II MDI	<55	57	24	19	48	52	94
	55–69	55	18	27	46	54	87
	70	37	22	41	30	70	593
Emotional/behavioral Dysregulation at 2 years							
CBCL Dysregulation Profile (anxdis+atmis+agrts) *	Yes	80	17	3	67	33	30
	No	40	23	37	35	65	588
Maximum column N							

Data are shown as row percentages.

* anxlds=anxiety/depression T score; atnts=attention T score; agrts=aggression T score.