Improving the Early Screening Procedure for Autism Spectrum Disorder in Young Children: Experience from a Community-Based Model in Shanghai

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Most children with autism spectrum disorder (ASD) are not diagnosed until the age of 4, thus missing the opportunity for early intervention. The objective of this study was to investigate the feasibility of an early screening program for ASD applied during well-child visits in a community-based sample. The study lasted for 4 years and was divided into two stages. Stage I involved the implementation of the basic screening model in 2014. Toddlers received level 1 screening via section A of the Chinese-validated version of the Checklist for Autism in Toddlers (CHAT-23) during 18- and 24-month well-child visits in Xuhui District, Shanghai, China. Screen-positive children were referred to receive section B of the CHAT-23 for level 2 screening, and those still screen-positive were referred to undergo diagnosis and evaluation. Stage II involved the implementation of the improved screening model from 2015 to 2017 with the following modifications: (a) an added observational component in level 1 screening; (b) telephone follow-ups with the screen-positive families; and (c) dissemination of information on ASD to families. The results showed that 42 of 22,247 screened children were diagnosed with ASD. The ASD diagnosis rates were 0.1% in Stage I and 0.21% in Stage II. The screen-positive rate and the show rate of referral for level 1 screening increased by 76.92% and 58.43%, respectively, in Stage II compared to Stage I. Our results suggest that with appropriate logistic support, this two-level screening model is feasible and effective for the early screening of ASD during well-child visits. ***Autism Research*** *2018, 11: 1206–1217.* © 2018 International Society for Autism Research, Wiley Periodicals, Inc.

Lay summary: Difficulty in the timely identification of autism spectrum disorder (ASD) results in missed opportunities for many ASD children to receive early intervention. In this study, we established an early screening model for ASD among children aged 18–24 months in the community by relying on the three-level child healthcare system in China. The results showed that this model can effectively identify and diagnose ASD in children at an early age and thus enable early intervention.

Keywords: autism spectrum disorder; CHAT-23; China; community-based; early screening

Introduction

Autism spectrum disorder (ASD) encompasses a group of neurodevelopmental conditions during early development characterized by impairments in two core domains, social interaction and communication, as well as repetitive and restricted behaviors, interests, or activities [American Psychiatric Association, 2013]. The global prevalence of ASD has increased progressively in recent years [Kim et al., 2011; Wingate, Kirby, & Pettygrove, 2014], and is now estimated at 1% [Lai, Lombardo, & Baron-Cohen, 2014].

Treatments of ASD may be effective for alleviation of symptoms, improvement of functional skills, and lessening of stress in families, but no cure for ASD is yet available. Some ASD patients may not be able to live, study, or work independently in adulthood; however, others may benefit from early intervention and compensate sufficiently to function well in the proper community with minimal assistance [Amihaesei & Stefanachi, 2013; Lai et al., 2014]. Indeed, the long term outcomes including cognitive, linguistic, and adaptive behaviors may be improved with early intensive treatment [Dawson et al., 2010, 2012; Reichow, Barton, Boyd, & Hume, 2012; Church et al., 2015]. Therefore, early diagnosis is critical for life outcome. ASD can be diagnosed reliably at the age of 2 years [Wingate et al., 2014], but the average age at diagnosis is 4.5 years [Wingate et al., 2014]. This delay prevents most ASD children from receiving early

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intervention in the critical period. To address this problem, many countries in North America and Europe carry out early ASD screening among children younger than 3 years [Noland & Gabriels, 2004; Robins, 2008; Chlebowski, Robins, Barton, & Fein, 2013]. The American Academy of Pediatrics recommends universal ASD screening for all children aged 18–24 months using a standardized autism-specific screening tool [Johnson & Myers, 2007].

In China, a three-level child healthcare system is well established, with community health service centers as the first level, district maternity and child healthcare hospitals as the second level, and municipal maternity and children's healthcare/children's hospitals (tertiary hospitals) as the third level. These institutions provide basic health services and monitoring to children aged 0 to 6 years. Routine services include newborn screening, growth and development assessment, nutrition and feeding guidance, vision and hearing screens, and neuropsychological development evaluation. Primary care pediatricians and healthcare professionals in community health service centers or maternity and child healthcare hospitals are responsible for screening, monitoring, and referral, while pediatricians at tertiary hospitals are responsible for diagnosis, consultation, and treatment [Mao, 2015]. However, for ASD, there is currently a lack of effective screening tools in Chinese and a validated management model in the current child healthcare system. Thus, the majority of child healthcare institutions do not routinely perform early screening and diagnostic evaluations for ASD.

In this study, we present results from the implementation and evaluation of the first early ASD screening and monitoring model for 18–24-month-old children in Shanghai integrated with the three-level child healthcare network. We conclude that the Chinese version of the Checklist for Autism in Toddlers (CHAT-23) is an effective tool for early screening in the current Chinese healthcare system.

Methods

Ethics Approval

This study was approved by the Ethics Committee of the Children's Hospital of Fudan University (Approval number 2012–185).

Participants

Community screening group. The community screening group included all 18–24-month-old children attending routine well-child visits in Xuhui District, Shanghai, from January 2014 to December 2017. The early screen model for ASD was developed through the three-level child healthcare service network composed of a community healthcare service center (CHSC), Xuhui Maternal and Child Healthcare Hospital (XMCHH), and Children's Hospital of Fudan University (CHFU).

Voluntary visit group. The voluntary visit group included all ASD children from other districts except Xuhui District in Shanghai initially diagnosed by the autism outpatient clinic at the Department of Child Healthcare of CHFU during the same period. The area where children in voluntary visit group live does not offer early screening services for ASD.

Screening instrument

The previously validated CHAT-23 [Wong et al., 2004] was selected as the screening instrument. The CHAT-23 includes the parent-reported questions of the Modified Checklist for Autism in Toddlers (M-CHAT) as section A (CHAT-23-A) and the observational part of the CHAT as section B (CHAT-23-B). Failing any 2 of the 7 key questions (2, 5, 7, 9, 13, 15, and 23) or failing any 6 of all 23 questions meets the criteria for failure in section A. Failing any 2 of 4 items meets the criteria for failure in section B [Wong et al., 2004].

This study set the CHAT-23-A as the level 1 screening instrument and applied it to all the 18–24-month-old children attending routine well-child visits at the CHSC. The CHAT-23-B was employed as the level 2 screening instrument by XMCHH.

Screening procedures

The study lasted 4 years and was divided into two stages (Fig. 1). Stage I involved the implementation of the basic screening model from January to December 2014. When summarizing the screening data collected at this stage, the outcomes failed to meet our expectation as most of the screening indicators were lower than those of previous studies. Therefore, Stage II was carried out with three additional improvements from January 2015 to December 2017.

Screening procedure in Stage I—basic model

When children aged 18–24 months attended routine well-child visits at the CHSC, they underwent level 1 screening using the CHAT-23-A. The questionnaire was completed by the child's caregiver according to the child's daily performance. After completion, the questionnaire was collected immediately and evaluated according to the set criteria by CHSC staff. Level 1 screen-positive children were referred to XMCHH for level 2 screening. Level 2 screen could be conducted on the same day.

Child healthcare physicians at XMCHH conducted face-to-face level 2 screening of children referred by the CHSC using the CHAT-23-B.In turn, CHAT-23-B-positive cases were referred for diagnostic assessment at CHFU,

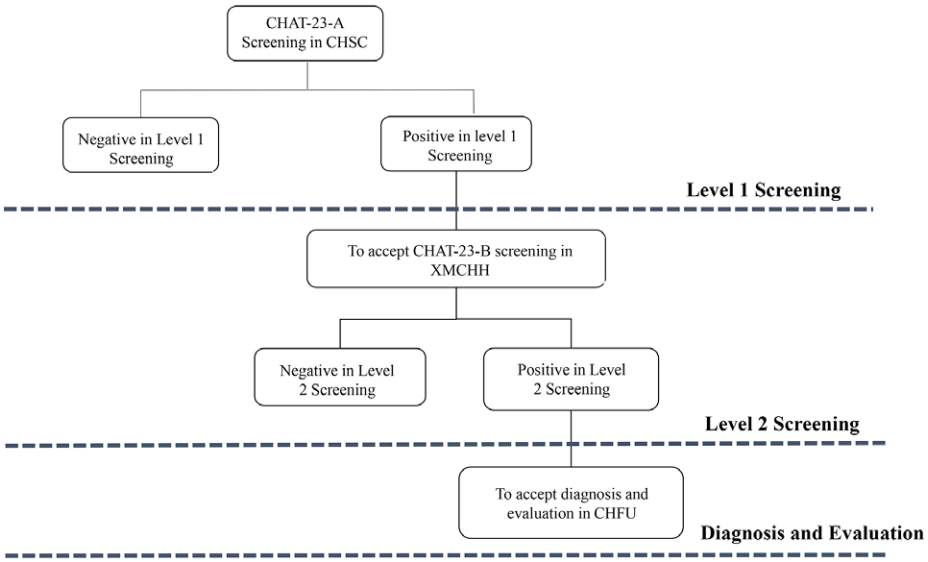

Figure 1. Flow chart of the basic screening model in Stage I. CHAT-23, Chinese-validated version of the Checklist for Autism in Toddlers; CHSC, community healthcare service center; XMCHH, Xuhui Maternal and Child Healthcare Hospital; CHFU, Children's Hospital of Fudan University.

termed level 2 referral. The diagnostic assessment was usually completed within 1 week.

Developmental pediatricians at CHFU clinically evaluated children who met the criteria of CHAT-23-B (level 2 referral) and made the final diagnosis in accordance with the Diagnostic and Statistical Manual of Mental Disorders (5th edition) and the Autism Diagnostic Observation Schedule, Second Edition (ADOS, 2nd edition) [Lord, Rutter, Labore, Risi, & Gotham, 2012]. The ADOS assessors were blind to the screening status. Relevant examinations and cognitive functioning evaluations such as the Developmental Screen Test for children under six [Zheng et al., 1997] were completed as required.

Screening procedure in Stage II—improved model

Based on the basic screening model in Stage I, we added the following three improvement measures to Stage II (Fig. 2).

1. Observational tests were added to the level 1 screening. After caregivers completed the questionnaire, CHSC physicians administered behavioral tests for two early signs of ASD risk: response to name calling and the ability to follow simple commands. For assessment of the first sign, the physician called the child's name twice in a clear voice at a normal volume. If the child did not respond or look at the physician even once, then he or she failed the test. For the sign of ability to follow a simple command, the child was required to complete two simple instructions such as waving goodbye, blowing a kiss, or bring an object to their caregiver. If the child could not follow both instructions, then he or she failed the test. Failure in both tests indicated a positive screen in the observational test component of level 1 screening (Fig. 3). Children who screened positive in the questionnaire, the observational tests, or both were deemed positive in level 1 screening.

2. A telephone follow-up was added to level 2 screening and referral to strengthen communication with the

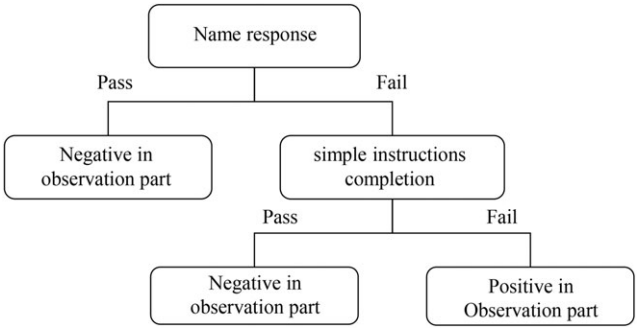

Figure 2. Implementation of the observational tests in level 1 screening.

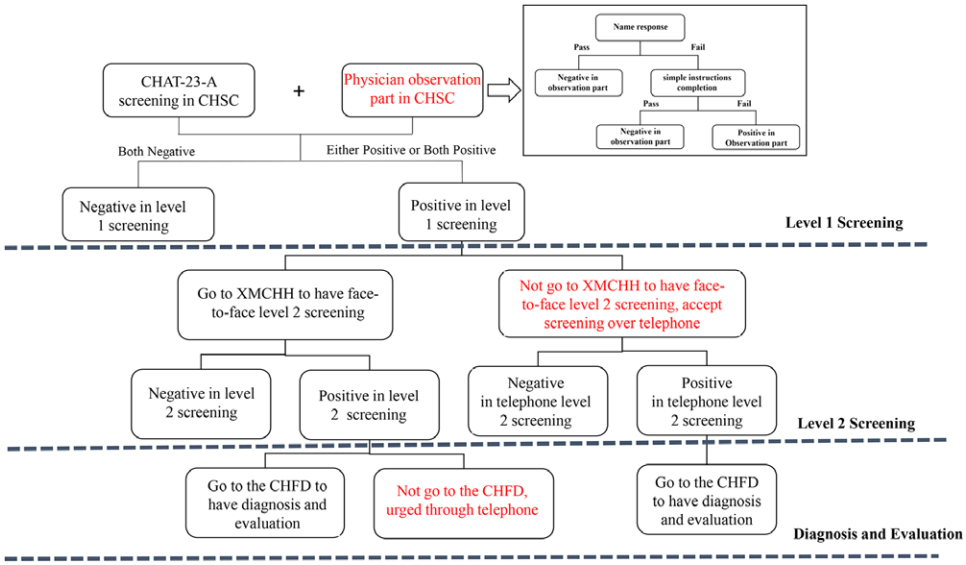

Figure 3. Flow chart of the improved screening model in Stage II. CHAT-23, Chinese-validated version of the Checklist for Autism in Toddlers; CHSC, community healthcare service center; XMCHH, Xuhui Maternal and Child Healthcare Hospital; CHFU, Children's Hospital of Fudan University.

families of screen-positive children and to improve the show rate for the referral. First, screen-positive children in level 1 screening who did not complete the face-to-face level 2 screening at XMCHH were screened via telephone by well-trained research assistants in accordance with the CHAT-23-B. The caregivers of screen-positive children were instructed to go directly to CHFU for diagnosis and evaluation. Second, the screen-positive children in face-to-face level 2 screening who did not complete the subsequent diagnosis and evaluation step were contacted by well-trained research assistants by telephone and urged to seek medical advice at CHFU.

3. ASD-related knowledge was promoted among the caregivers. A set of social skills-development guidelines for children was included in a brochure distributed to the caregivers when they brought their children to routine well-child visits. Moreover, since January 2015, our research group has offered face-to-face lectures semi-annually to the caregivers of children aged 0–3 years within the community to explain the early behavioral indicators of ASD as well as family guidance strategies for developing children's social skills.

Interventions for ASD children

For children ultimately diagnosed with ASD in this study, the families were offered four interventions by CHFU: (a) 8 hr of early start Denver model (ESDM) parent training, (b) an 8-week parent skills training (PST) group class, (c) 6 months of ESDM individual training, and (d) parent training in a regular outpatient service. In addition to the interventions offered by CHFU, the community ASD rehabilitation agency training could also be selected. Intervention data from the ESDM parent class, PST group class, and ESDM individual training were collected from the training records of our department, while outpatient follow-up data were collected from the outpatient system of our hospital. Community agency training information was acquired during the telephone interviews with the caregivers. The families receiving any one of the five interventions were regarded as accepting early intervention.

Statistical analysis

Data analysis was conducted using SPSS 24.0 statistical software. Measurement data such as age are expressed as the mean ±SD ($x \pm S$), and numerical data such as the number of patients are expressed as numbers and percentages. The *t*-test was used to detect differences in measurement data between groups, the Chi-Square test to analyze differences in numerical data, and a trend Chi-Square test to compare changes in rates. A $P < 0.05$ was considered statistically significant for all tests.

Results

Results of the basic screening model in Stage I

In Stage I, 4,954 of 6,997 children (70.8%) in the targeted community were screened throughout 2014. Seventy-one (1.43%) were positive according to level 1 screening at CHSC. Among them, 33 (33/71, 46.48%) completed level 2 screening at XMCHH and 17 (17/33, 51.52%) were again considered as positive. Twelve of 17 children who were positive according to the level 2 screen (12/17, 70.59%) completed the diagnostic evaluation at CHFU

and 5 (5/12, 41.67%) were diagnosed with ASD, for a final ASD diagnosis rate of 1.0/1,000. Among the seven children who did not meet the diagnostic criteria for ASD, three were diagnosed with intellectual disability, and four with developmental language disorder.

Results of the improved model in Stage II

Due to the lower than expected positive rate and diagnosis rate in Stage I, we conducted Stage II with three additional improvements: observational component, telephone follow-ups and dissemination of ASD-related scientific knowledge. In the Stage II, a total of 17,293 children aged 18–24 months (94.90% of the targeted population) were screened from 2015 to 2017. A total of 437 (2.53%) children were positive according to level 1 screening. Among the positive cases from level I screening, 364 children (364/437, 83.30%) completed the level 2 screening and 110 (110/364, 30.22%) were deemed positive. A total of 81 positive cases from level 2 screening (81/110, 73.64%) underwent ASD diagnostic assessment and 37 (37/81, 45.68%) were confirmed with a diagnosis of ASD. In this stage, the diagnosis rate of ASD was 2.1/1,000. Among 44 children who did not meet the diagnostic criteria for ASD, 22 were diagnosed with intellectual disability (ID), 16 with language developmental disorder, and six were considered developmentally normal.

Comparison of screening results from two stages

The coverage rate was significantly improved from 70.80% in stage I to 94.09% in Stage II ($P < 0.0001$), a growth of 32.90%. The positive rate in level 1 screening increased from 1.43% in stage I to 2.53% in stage II, a growth rate of 76.92%. The show rate of level 1 referral in Stage II was improved from 46.48% in stage I to 73.64% in stage II, a growth rate of 58.43% (Table 1).

The ASD diagnosis rate over the entire 4 years showed significant growth ($P = 0.011$ by trend Chi-square test), increasing from 1.0/1,000 in stage I to 2.1/1,000 in stage II, a growth rate of 110% (Table 2).

Effect of the observational test component in level 1 screening in Stage II

The positive children in level 1 of Stage II were divided into three groups: positive in both the questionnaire and the observational tests (dual-positive), positive only in the questionnaire (questionnaire-positive), and positive only in the observational tests section (observation-positive). The show rate of level 1 referral for the dual-positive group was significantly higher than that of the observation-positive group ($P = 0.023$), and show rates of level 2 referral were significantly higher in both dual-positive and observation-positive groups compared to the questionnaire-positive group ($P < 0.0001$ and $P = 0.018$, respectively). In addition, the observation-positive group in level 1 had a significantly higher positive rate in level 2 screening than that questionnaire-positive group ($P = 0.005$).

In Stage II, among children who screened positive in the observational test component but negative in the questionnaire, three were ultimately diagnosed with ASD. These children accounted for 8.11% of all ASD patients identified during Stage II (Table 3).

Effect of telephone follow-up during Stage II

In Stage II, 437 children screened positive in level 1. Among them, 154 children who declined face-to-face level 2 screening were offered telephone screening. In addition, 30 children who screened positive according to face-to-face level 2 screening but who did not complete level 2 referral were urged to seek medical advice via telephone. In these telephone follow-ups, five children were diagnosed with ASD, accounting for 13.51% of all the diagnosed ASD children in Stage II (Fig. 4).

Positive predictive value of each positive type during Stage II screening

The positive predictive values (PPVs) of the each positive classification in levels 1 and 2 screening were determined and compared. The results showed that the PPV of level 1 screening was 11.04%. Dual-positive group and observation-positive group had significantly higher PPV than questionnaire-positive group ($P < 0.0001$ and $P = 0.005$, respectively). The total PPV of level 2 screening was 45.68%. The PPVs of face-to-face and telephone level 2 screening were 47.30% and 28.60%, respectively, with no significant difference (Table 4).

Age at diagnosis and the intervention rate of ASD children

From 2014 to 2017, 42 children were diagnosed by the community-based early ASD screening model (The clinical characteristics are shown in Table 5). Among them, 35 were male, and seven were female (sex ratio of 5:1) and average age at diagnosis was 25.19 ± 6.84 months. During the same period, 460 ASD children in the voluntary visit group were first diagnosed, including 403 males and 57 females (ratio of 7:1), but the average age at diagnosis was 39.24 ± 16.55 months. The community screening group was significantly younger than the voluntary visit group ($P < 0.0001$); on average, the former was diagnosed 14 months earlier than the latter. No significant difference in sex ratio was observed between the two groups (Table 6).

Among the 42 children diagnosed with ASD through the community-based early screening model, 36 received the early interventions (early intervention rate of 85.71%). Among them, 15 (35.71%) attended the ESDM parent

Table 1. Comparison of Screen-Positive Rates and Referral Arrival Show Rates in Level 1 Screening

Stage of screening	Year of screening	Total sample in level 1 screening *n*	Number (Rate) of positive cases in level 1 screening *n* (%)	Number (Rate) of show for referral in level 1 *n* (%)		
				Face-to-face screening in level 2 *n* (%)	Telephone screening in level 2 *n* (%)	Total show rate for referral *n* (%)
Stage I	2014	4,954	71 (1.43%)	33 (46.48%)	/	33(46.48%)[a]
Stage II	2015	6,226	116 (1.86%)	69 (59.48%)	29 (25%)	98(84.48%)***
	2016	6,005	156 (2.60%)	98 (62.82%)	21 (13.46%)	119(76.28%)***
	2017	5,062	165 (3.26%)	116 (70.30%)	31 (18.79%)	147(89.09%)***
χ^2			6.69[b]	3.42[b]	5.88[c]	
P			<0.0001***	0.0003***	0.053	

[a]In the comparison of show for referral in level 1 between 2014 and 2015, 2016, and 2017, χ^2 values were 30.32, 19.59, and 49.80, respectively, and *P* values were all <0.0001.
[b]Cochran-Armitage trend chi-square test.
[c]Chi-square test.
***$P < 0.001$.

Table 2. Comparison of Screen-Positive Rates, Referral Show Rates, and Final Diagnoses of ASD in Level 2 Screening

Stage of screening	Year of screening	Number (Rate) of positive cases in level 2 screening *n* (%)			Number (Rate) of show for referral in level 2 *n* (%)	Number (Rate) of ASD cases *n* (%)	Diagnosis rate of ASD
		Positive in face-to-face screening *n* (%)	Positive in telephone screening *n* (%)	Total positive cases *n* (%)			
Stage I	2014	17 (51.52%)[a]	/	17 (51.52%)[b]	12 (70.59%)	5 (41.67%)	1.0/1,000
Stage II	2015	22 (31.88%)**	3 (10.34%)	25 (25.51%)**	20 (80%)	11 (55.00%)	1.8/1,000
	2016	35 (35.71%)*	3 (14.29%)	38 (31.93%)*	28 (73.68%)	10 (35.71%)	1.7/1,000
	2017	43 (37.07%)*	4 (19.05%)	47 (31.97%)*	33 (70.21%)	16 (48.48%)	3.2/1,000
χ^2			0.19[c]		0.87[c]	2.0[c]	2.29[d]
P			0.91		0.83	0.57	0.011

[a]In the comparison of the screen-positive rate of face-to-face screening in 2014 with that in 2015, 2016, and 2017, χ^2 values were 9.97, 5.61, and 6.01, respectively, and *P* values were 0.002, 0.018, and 0.014, respectively.
[b]In the comparison of the total positive rate of level 2 screening in 2014 with that in 2015, 2016, and 2017, χ^2 values were 7.66 4.29, and 4.49, respectively, and *P* values were 0.006, 0.038, and 0.034, respectively.
[c]Chi-square test.
[d]Cochran-Armitage trend Chi-square test.
*$P < 0.05$.
**$P < 0.01$.

Table 3. Comparison of Screening Indicators Among the three Positive Status Groups

Positive type in level 1 screening	Number of positive cases in level 1 screening *n*	Number (Rate) of show for referral in level 1 *n* (%)	Number (Rate) of positive cases in level 2 screening *n* (%)	Number (Rate) of show for referral in level 2 *n* (%)	Number (Rate) of ASD cases *n* (%)
Dual questionnaire- and observation-positive	118	103 (87.29%)[a,*]	60 (58.25%)[b,***]	50 (83.33%)[b,*]	26 (52.00%)
Questionnaire- Positive only	297	246 (82.83%)	43 (17.48%)[c,**]	27 (62.79%)	8 (29.62%)
Observation-positive only	22	15 (68.18%)	7 (46.67%)	4 (57.14%)	3 (75%)
Total	437	364 (83.30%)	110 (30.22%)	81 (73.64%)	37 (45.68%)

[a]Comparison of the dual-positive and observation-positive group with the observation-positive group, χ^2 was 5.11 and the *P* value was 0.023.
[b]Comparison of the dual-positive group with the questionnaire-positive group and observation-positive group. χ^2 values were 58.01 and 5.60, respectively, and *P* values were < 0.0001 and 0.018, respectively.
[c]Comparison of the questionnaire-positive group with the observation-positive group, χ^2 was 7.78 and the P value was 0.005.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

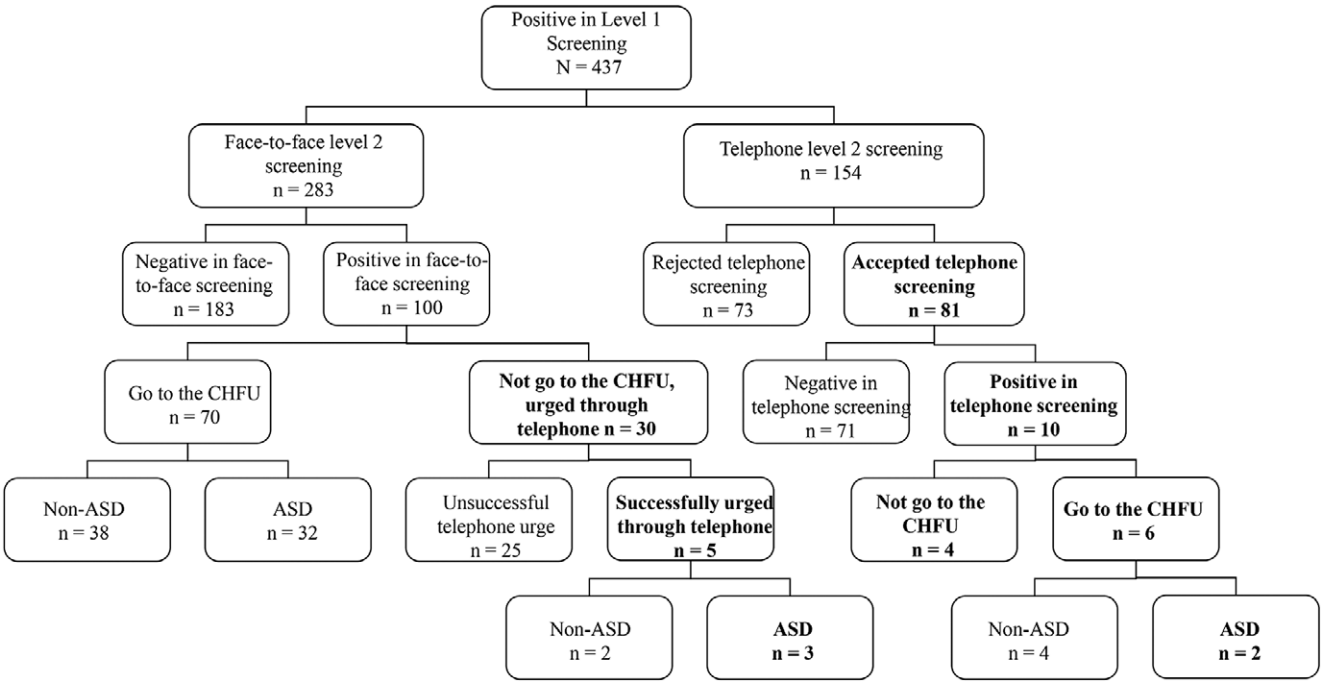

Figure 4. Effect of telephone follow-up in Stage II. CHFU, Children's Hospital of Fudan University; ASD, autism spectrum disorder.

training class, 11 (26.19%) attended ESDM individual training, two (4.76%) attended the PST group class, 30 (71.43%) received family training through outpatient service, and 27 (64.29%) received rehabilitation training at community ASD rehabilitation agencies. Of these 36 children, 28 received continued early intervention. The average age of initial intervention was 27.20 ± 6.12 months and the rate of continued early intervention was 66.67% (28/42).

Discussion

This is the first study on an early ASD screening program integrated into the three-level child healthcare network in China. Screening was included in routine well-child visits and achieved lasting quality of monitoring. In this study, 22,247 children were screened, and 42 were ultimately diagnosed with ASD. This is the largest and longest early ASD screening study to date in China. After conducting screening in two stages, we established a feasible, flexible, and efficient ASD screening model. The improved model in Stage II demonstrated a significantly higher level 1 positive rate, show rate of level 1 referral to level 2, and final ASD diagnosis rate than the basic model in Stage I. Notably, the age at first diagnosis was significantly younger than in a comparable group. In addition, among the children ultimately diagnosed with ASD in the screening project, the early intervention rate was

Table 4. Positive Predictive Value of each Positive Status Type During Stage II

Screening level	Positive type in screening	Number of Screening positive children(Excluding the lost to follow-up)	Number of ASD cases	Positive predictive value(%)
Level 1 screening	Both questionnaire and observation positive	93	26	27.96[a,***]
	Only questionnaire positive	230	8	3.48
	Only observation positive	12	3	25.00[b,**]
	Total	335	37	11.04
Level 2 screening	Positive in face-to-face screening	74	35	47.30
	Positive in telephone screening	7	2	28.60
	Total	81	37	45.68

[a]Comparison of the PPV of both questionnaire and observation positive group and only questionnaire positive group, χ^2 was 42.13 and the *P* value was <0.0001.
[b]Comparison of the PPV of only observation positive group and only questionnaire positive group, χ^2 was 7.72 and the *P* value was 0.005.
**$P < 0.01$.
***$P < 0.001$.

Table 5. Clinical Characteristics of Children with ASD

ADOS Score	N	Mean ± SEM		
SA	36	14.53 ± 4.75		
RRB	36	1.83 ± 1.65		
Severity Score	36	5.81 ± 2.21		
DST DQ	N	DQ ($\bar{x} \pm s$)	DQ<70 *n* (%)	DQ ≥ 70 *n* (%)
Locomotor	41	84.04 ± 20.11	9(21.95%)	32(78.05%)
Personal–social	41	58.57 ± 20.23	31(75.61%)	10(24.39%)
Intelligence	41	53.24 ± 14.70	38(92.68%)	3(7.32%)

ADOS, autism diagnostic observation schedule; SA, social affect; RRB, restricted, repetitive patterns of behavior; DST, Developmental Screen Test for children under six.

85.71% and the rate of continued early intervention was 66.67%, indicating that this program offers a promising opportunity to improve both prognosis and quality of life.

Integrating ASD screening into routine well-child visits is helpful for the systematic monitoring of early ASD symptoms and the promotion of early diagnosis and intervention [Daniels & Mandell, 2013]. Guevara et al. randomize over 2,000 children into a screening group and a monitoring group. In the screening group, children were screened with the Ages and Stages Questionnaire during routine well-child visits at 9, 18, and 30 months of age and with the M-CHAT at 18 and 24 months of age. In the monitoring group, the children received only routine healthcare monitoring at the same ages. The results suggested that developmental behavior problems were identified earlier in the screening group by 59%, and the early intervention referral rate was increased by 24% [Guevara et al., 2013]. Likewise, by creating an early ASD screening model, Koegel et al. report an increase of the ASD show rate of referral from 36 to 57% and reduced the age at early invention acceptance from 32.3 to 29.6 months [Koegel et al., 2005]. This study utilized the existing child healthcare system in China to combine early ASD screening with routine well-child visits for 18–24-month-old children. During the four-year study, 42 children were diagnosed with ASD. The average age at diagnosis was 25.19 ± 6.84 months, 14 months earlier than in a voluntary visit group, consistent with a previous report [Wingate et al., 2014].

Among seven domestic and international studies on early ASD screening with CHAT-related instruments during routine well-child visits, the positive rate of level 1 screening ranged from 1.37% to 17.23%, the show rate of referral from 9.80% to 81.90%; the level 2 positive rate from 18.75% to 56.67%, the show rate of referral from 63.50% to 100%, and the ASD diagnosis rate from 1.2/1,000 to 11/1,000 [Barid et al., 2000; VanDenHeuvel, Fitzgerald, Greiner, & Perry, 2007; Wu, Xu, Liu, & Cao, 2010; Chlebowski et al., 2013; Kamio et al., 2014; Robins et al., 2014; Baduel et al., 2017] (see Table 7 for details). The variance among studies may stem from differing research methods and objectives. For example, in the study of Kamio et al., the criterion for positivity on the M-CHAT was failing any 3 of the 23 items or any 1 of the 10 critical items [Kamio et al., 2014], while in the studies of Chlebowski et al. and Baduel et al., a positive screen was indicated by failure on 3 of the 23 items or 2 of 6 critical items [Chlebowski et al., 2013; Baduel et al., 2017]. These different criteria may partly explain why the positive rate of level 1 screening in the study by Kamio et al. was 17.23%, almost two-fold higher than that in the studies of Chlebowski et al. and Baduel et al. In addition, differences in cultural background of the screened population and screening age appear to influence outcomes [Khowaja, Hazzard, & Robins, 2015]. In this study, the positive rate and referral show rate of level 1 screening during Stage I were lower than those in most previous studies, and the ASD diagnosis rate was lower than in all previous studies [Barid et al., 2000; VanDenHeuvel et al., 2007; Wu et al., 2010; Chlebowski et al., 2013; Kamio et al., 2014; Robins et al., 2014; Baduel et al., 2017]. The three aforementioned modifications in Stage II significantly increased these rates. In 2017, the level 1 show rate of referral was higher than in all previous studies, while the ASD diagnosis rate (3.2/1,000) was consistent with several studies [Barid et al., 2000; VanDenHeuvel et al., 2007; Wu et al., 2010]. But still lower than studies conducted in America, Japan, and France [Chlebowski et al., 2013; Kamio et al., 2014; Robins et al., 2014; Baduel et al., 2017]. In this study, the positive rate of level 1 screening was relatively low. In the early stage, we initially applied the CHAT-23 for ASD screening among 484 children aged 18–24 months in the Luwan District of Shanghai, and the resulting level 1 positive rate was 11.98% [Wu et al., 2010]. Possible explanations may include the larger sample size in this study and the implementation of screening as part of the well-child visit, which may have caused caregivers to pay less attention to the questionnaire.

Table 6. Comparison of Sex Distribution and Age at Diagnosis between ASD Children Identified by the Community Screening Group and the Voluntary Visit Group

	Sex *n*			Age at diagnosis ($\bar{x} \pm s$)
Group Category	Males	Females	Male/female	
Community screening	35	7	5.00	25.19 ± 6.84
Voluntary visit	403	57	7.07	39.24 ±16.55
χ^2/t			0.63[a]	5.46[b]
P			0.43	<0.0001

[a]Is the value of χ^2.
[b]Is the value of *t*.

Table 7. Summary of the Early ASD Screening Studies Applying CHAT-Related Instruments

	Screening instrument	Screening age (months)	Sample size (*n*)	Screen-positive rate/show rate of referral in level 1 (%)	Screen-positive rate/ show rate of referral in level 2 (%)	Diagnosis rate of ASD	Positive predictive value (%)
Baird et al. 2000, UK	CHAT	18.7 ± 1.1	16235	2.51%/9.80%	56.67%/100%	1.2/1,000	58.8
VanDenHeuveld et al. 2007, Ireland	CHAT	18–20	2117	1.37%/65.52%	36.84%/100%	3.3/1,000	58.3
Chlebowski et al., 2013, US	M-CHAT-F	20	18989	9.15%/74.55%	21.00%/76.10%	5.2/1,000	54
Kamio et al., 2014, Japan	M-CHAT-F	17–26	1851	17.23%/61.13%	22.56%/100%	11/1,000	45.5
Baduel et al., 2017, France	M-CHAT-F	24	1250	8.64%/78.70%	23.53%/100%	9.6/1,000	60
Robins et al., 2014, US	M-CHAT-R/F	16–30	16115	7.17%/81.90%	36.79%/63.50%	6.5/1,000	48
Wu et al. 2010, China	CHAT-23	18–24	484	11.98%/55.17%	18.75%/100%	4.1/1,000	50
Stage I of present study, 2014, China	CHAT-23	18–24	4954	1.43%/46.48%	51.52%/70.59%	1.0/1,000	41.7
Stage II of present study, 2017, China	CHAT-23	18–24	5062	3.26%/89.09%	31.97%/70.21%	3.2/1,000	48.5

Abbreviations: CHAT, Checklist for Autism in Toddlers; M-CHAT-F, Modified Checklist for Autism in Toddlers with follow-up; M-CHAT-R/F, Modified Checklist for Autism in Toddlers, revised with follow-up; CHAT-23, Chinese-validated version of the Checklist for Autism in Toddlers; ASD, autism spectrum disorder.

Although ASD presentation appears to be extremely heterogeneous in the early stage, prospective studies have found compelling evidence that certain behavioral manifestations in children aged 12 to 24 months [Zwaigenbaum, Bauman, Fein, et al. 2015b], including name unresponsiveness [Wetherby et al., 2004], decreased visual attention [Jones and Klin, 2013], and joint attention deficit [Sullivan et al., 2007; Yoder, Stone, Walden, & Malesa, 2009], are early signs of ASD risk. In this study, we selected name response and simple instruction completion as two early warning indicators for ASD. Name unresponsiveness is among the earliest manifestations of ASD recognized by parents, and some evidence suggests that this feature distinguishes ASD children not only from normal children but also from children suffering from other developmental disorders [Wetherby et al., 2004]. Miller et al, found that infants eventually diagnosed with ASD more frequently failed to orient in response to their names at 9 months of age and that this deficit persisted at 24 months. They recommended that response to name should be regularly monitored in infants at risk for ASD [Miller et al., 2017]. Meanwhile, inability to follow verbal commands was found as a clinical characteristic in a retrospective study of toddlers with ASD [Malhi & Singhi, 2014]. Simple instruction completion is also included in many ASD screening scales [Nah, Young, Brewer, & Berlingeri, 2014]. In the *Early Warning Signs for Psycho-Behavioral Developmental Disorders Among Children* [Huang Xiaona, 2017], drafted by senior experts in child psychology and development fields in China, "failure to point at people or object as required" and "failure to do simple things as instructed" are indicative of abnormal social interaction and communication functions among children aged 18 to 24 months. Moreover, Nah et al. developed a brief (five-item) early childhood ASD detection scale including the similar two observational items used in Stage II [Nah, Young, & Brewer, 2018]. In Stage II screening, 8.11% of all the ASD children diagnosed during Stage II were negative according to the questionnaire but failed the two early warning indicator tasks.

We divided early ASD screening into two steps, levels 1 and 2, and implemented these two steps at CHSC and XMCHH with the aim of utilizing the existing three-level child healthcare system for greater resource efficiency and lower cost. However, this division was found to reduce the referral show rates for level 2 and diagnosis. In Stage I, among the children who screened positive in level 1, only 46.48% completed level 2 screening. Meanwhile, the no-show rate for the diagnosis and evaluation step was approximately 30%. Possible reasons are the required time commitment, long commutes, insufficient awareness of early ASD signs, and caregivers' belief that their children did not exhibit abnormal social interactions. Therefore, we added a telephone follow-up in Stage II. In previous screening studies, researchers have typically used telephone follow-ups to eliminate false-positive diagnoses caused by caregivers' misunderstanding or mistakes when completing the questionnaires. The success rate of telephone interviews ranged from 60 to 80% [Chlebowski et al., 2013; Kamio et al., 2014; Robins et al., 2014; Baduel et al., 2017]. Nevertheless, the author of the CHAT-23 believed that the answers provided by caregivers over the telephone were not completely

reliable and that a face-to-face interview was still required [Wong et al., 2004]. For families that refuse face-to-face screening, however, telephone interview remains a simple and efficient strategy. When calling the caregivers of screen-positive children, they should be informed of the importance of referral and the detailed referral process. In this study, the success rates of telephone level 2 screening and completion of diagnosis and evaluation were 52.59% (81/154) and 16.67% (5/30), respectively, which are still relatively low. However, the diagnoses of five ASD children in Stage II were dependent on the telephone follow-up measure, accounting for 13.51% of all children diagnosed with ASD. Despite the poor completion rate, the cost of this measure was low. In future studies, the telephone follow-up frequency may be increased to elevate caregivers' mindfulness regarding ASD, which can be regarded as one measure to improve screening quality.

Public awareness of ASD can substantially improve identification, diagnosis, and intervention [Zwaigenbaum, Bauman, Stone, et al., 2015a]. To increase the public's awareness of ASD, the Centers for Disease Control and Prevention in US initiated "Learn the Signs, Act Early" in 2004–2007 offering scientific education on ASD using various approaches. After this 3-year program, the proportion of caregivers able to identify the early signs of ASD increased from 37% to 52%, and the proportion of caregivers who were unaware of the optimal time for intervention was reduced from 57% to 42% [King et al., 2010]. In China, the first case report of autism has been published in 1982 [Guotai, 1982]. However, the public awareness has not really emerged until recently. Wang et al. found that although 93.9% of parents with children aged 3–6 years had heard about ASD, only 57.8% were somewhat aware of the associated clinical manifestations [Wang et al., 2012]. In Stage II of this study, we provided ASD-related information to caregivers in the community through talks and brochures, and during these 3 years the positive rate during level 1 screening and the completion rate of face-to-face level 2 screening increased yearly, reflecting increasing attention to social skill development and an improved awareness of ASD.

Our present study established a feasible, flexible, and efficient early screening model for ASD in China using the three-level child healthcare system of China. Implementing two-level screening and referral with fundamental supportive measures such as telephone follow-up and knowledge promotion may increase the chances of ASD patients receiving early intervention. Screening should be advocated in other areas to identify more ASD children in the early stage and provide treatment as soon as possible.

The major limitation of this study is that there was no follow-up for the screen-negative children and no measures for identification of potential false-negative children. Further, the reliability and validity of the observational tests added to level 1 screening require further evaluation in a large-scale longitudinal population-based screening sample. In addition, after improvements were implemented, the positive rate in level 1 screening remained low, and loss to follow-up for referral was still evident in both two screening levels.

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Conflict of Interest

The authors declare that they have no competing interests.

References

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders(DSM 5). Washington, DC: American Psychiatric Publishing.

Amihaesei, I. C., & Stefanachi, E. (2013). Autism, an overwhelming condition: History, etiopathogenesis, types, diagnosis, therapy and prognosis. Revista Medico-Chirurgicala A Societatii de Medici si Naturalisti din Iasi, 117(3), 654–661.

Baduel, S., Guillon, Q., Afzali, M. H., Foudon, N., Kruck, J., & Rogé, B. (2017). The French version of the modified-checklist for autism in toddlers (M-CHAT): A validation study on a french sample of 24 month-old children. Journal of Autism and Developmental Disorders, 47(2), 297–304.

Barid, G., Charman, T., Baron-Cohen, S., Cox, A., Swettenham, J., Wheelwright, S., & Drew, A. (2000). A screening instrument for autism at 18 months of age: A 6-year follow-up study. Journal of the American Academy of Child & Adolescent Psychiatry, 39(6), 694–702.

Chlebowski, C., Robins, D. L., Barton, M. L., & Fein, D. (2013). Large-scale use of the modified checklist for autism in low-risk toddlers. Pediatrics, 131(4), e1121–e1127.

Church, B. A., Rice, C. L., Dovgopoly, A., Lopata, C. J., Thomeer, M. L., Nelson, A., … Mercado, E. R. (2015). Learning, plasticity, and atypical generalization in children with autism. Psychonomic Bulletin & Review, 22(5), 1342–1348.

Daniels, A. M., & Mandell, D. S. (2013). Children's compliance with American academy of pediatrics' well-child care visit guidelines and the early detection of autism. Journal of Autism and Developmental Disorders, 43(12), 2844–2854.

Dawson, G., Jones, E. J., Merkle, K., Venema, K., Lowy, R., Faja, S., … Webb, S. J. (2012). Early behavioral intervention is

associated with normalized brain activity in young children with autism. Journal of the American Academy of Child and Adolescent Psychiatry, 51(11), 1150–1159.

Dawson, G., S. Rogers, J. Munson, M. Smith, J. Winter, J. Greenson, J. Varley (2010). Randomized, controlled trial of an intervention for toddlers with autism: the early start denver model. Pediatrics 125 (1): e17.

Guevara, J. P., Gerdes, M., Localio, R., Huang, Y. V., Pinto-Martin, J., Minkovitz, C. S., & Pati, S. (2013). Effectiveness of developmental screening in an urban setting. Pediatrics, 131(1), 30–37.

Guotai, T. (1982). Diagnosis and attribution of autism in infants. Chinese Journal of Psychiatry, 15(02), 104–107.

Huang Xiaona, Z. Y. F. W. (2017). Reliability and validity of warning signs checklist for screening psychological, behavioral and developmental problems of children. Chin J Pediatr, 6(55), 445–450.

Johnson, C. P., & Myers, S. M. (2007). Identification and evaluation of children with autism spectrum disorders. Pediatrics, 120(5), 1183–1215.

Jones, W., & Klin, A. (2013). Attention to eyes is present but in decline in 2–6-month-old infants later diagnosed with autism. Nature, 504(7480), 427–431.

Kamio, Y., Inada, N., Koyama, T., Inokuchi, E., Tsuchiya, K., & Kuroda, M. (2014). Effectiveness of using the modified checklist for autism in toddlers in two-stage screening of autism spectrum disorder at the 18-month health check-up in Japan. Journal of Autism and Developmental Disorders, 44(1), 194–203.

Khowaja, M. K., Hazzard, A. P., & Robins, D. L. (2015). 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, 45(6), 1797–1808.

Kim, Y. S., Leventhal, B. L., Koh, Y. J., Fombonne, E., Laska, E., Lim, E. C., … Grinker, R. R. (2011). Prevalence of autism spectrum disorders in a total population sample. The American Journal of Psychiatry, 168(9), 904–912.

King, T. M., Tandon, S. D., Macias, M. M., Healy, J. A., Duncan, P. M., Swigonski, N. L., … Lipkin, P. H. (2010). Implementing developmental screening and referrals: Lessons learned from a national project. Pediatrics, 125(2), 350–360.

Koegel, L. K., Koegel, R. L., Nefdt, N., Fredeen, R., Klein, E. F., & Bruinsma, Y. (2005). First STEP - A Model for the early identification of children with autism spectrum disorders. Journal of Positive Behavior Interventions, 7(4), 247–252.

Lai, M. C., Lombardo, M. V., & Baron-Cohen, S. (2014). Autism. Lancet, 383(9920), 896–910.

Lord, C. M., Rutter P.D., Labore S., Risi K., Gotham S. & Bishop, (2012). Autism diagnostic observation schedule, second edition (ADOS-2). Los Angeles, CA: Western Pschological Services.

Malhi, P., & Singhi, P. (2014). A retrospective study of toddlers with autism spectrum disorder: Clinical and developmental profile. Annals of Indian Academy of Neurology, 17(1), 25–29.

Mao, M. (2015). China child health care discipline: Distinguishing feature and development. Zhonghua Erke Zazhi, 53(12), 881–883.

Miller, M., Iosif, A. M., Hill, M., Young, G. S., Schwichtenberg, A. J., & Ozonoff, S. (2017). Response to name in infants developing autism spectrum disorder: A prospective study. The Journal of Pediatrics, 183, 141–146.e1.

Nah, Y., Young, R. L., Brewer, N., & Berlingeri, G. (2014). Autism Detection in Early Childhood (ADEC): Reliability and validity data for a level 2 screening tool for autistic disorder. Psychological Assessment, 26(1), 215–226.

Nah, Y. H., R. L. Young and N. Brewer (2018). Development of a brief version of the Autism Detection in Early Childhood. Autism. doi: 10.1177/1362361318757563.

Noland, R. M., & Gabriels, R. L. (2004). Screening and identifying children with autism spectrum disorders in the public school system: The development of a model process. Journal of Autism and Developmental Disorders, 34(3), 265–277.

Reichow, B., Barton, E. E., Boyd, B. A., & Hume, K. (2012). Early intensive behavioral intervention (EIBI) for young children with autism spectrum disorders (ASD). Cochrane Database of Systematic Reviews, 10, CD009260.

Robins, D. L. (2008). Screening for autism spectrum disorders in primary care settings. Autism 12 (5).

Robins, D. L., Casagrande, K., Barton, M., Chen, C. M., Dumont-Mathieu, T., & Fein, D. (2014). Validation of the modified checklist for Autism in toddlers, revised with follow-up (M-CHAT-R/F). Pediatrics, 133(1), 37–45.

Sullivan, M., J. Finelli, A. Marvin, E. Garrett-Mayer, M. Bauman, R. Landa (2007). Response to joint attention in toddlers at risk for autism spectrum disorder: A prospective study. Journal of Autism and Developmental Disorders 37 (1): 37–48.

VanDenHeuvel, A., Fitzgerald, M., Greiner, B., & Perry, I. J. (2007). Screening for autistic spectrum disorder at the 18-month developmental assessment: A population-based study. Irish Medical Journal, 100(8), 565–567.

Wang, J., Zhou, X., Xia, W., Sun, C., Wu, L., & Wang, J. (2012). Autism awareness and attitudes towards treatment in caregivers of children aged 3–6 years in Harbin, China. Social Psychiatry and Psychiatric Epidemiology, 47(8), 1301–1308.

Wetherby, A. M., Woods, J., Allen, L., Cleary, J., Dickinson, H., & Lord, C. (2004). Early indicators of autism spectrum disorders in the second year of life. Journal of Autism and Developmental Disorders, 34(5), 473–493.

Wingate, M., Kirby, R. S., & Pettygrove, S. (2014). Prevalence of autism spectrum disorder among children aged 8 years — Autism and developmental disabilities monitoring network, 11 Sites, United States, 2010. MMWR Surveill Summary, 63(2), 1–21.

Wong, V., L. S. Hui, W. Lee, L. J. Leung, P. P. Ho, W. C. Lau,... B. Chung (2004). A modified screening tool for autism (checklist for autism in toddlers [CHAT-23]) for Chinese children. 114 (2): e166–e176.

Wu, F., Xu, X., Liu, J., & Cao, L. (2010). Study on the application of autism screening scale (CHAT-23). Chinese Journal of Child Health Care, 18(04), 288–291.

Yoder, P., Stone, W. L., Walden, T., & Malesa, E. (2009). Predicting social impairment and ASD diagnosis in younger siblings of children with autism spectrum disorder. Journal of Autism and Developmental Disorders, 39(10), 1381–1391.

Zheng, M., L. Feng, X. Liu, X. Xu, H. Li, K. Wang (1997). Development of national urban norm for intelligent development screening test for children aged 0 to 6. Chinese Journal of Pediatrics, 35(03): 6–9

Zwaigenbaum, L., Bauman, M. L., Fein, D., Pierce, K., Buie, T., Davis, P. A., & Wagner, S. (2015a). Early screening of autism spectrum disorder: Recommendations for practice and research. Pediatrics, 136(Suppl 1), S41–S59.

Zwaigenbaum, L., Bauman, M. L., Stone, W. L., Yirmiya, N., Estes, A., Hansen, R. L., … Wetherby, A. (2015b). Early identification of autism spectrum disorder: Recommendations for practice and research. Pediatrics, 136(Suppl 1), S10–S40.