Int J Clin Exp Med 2017;10(8):11349-11359
www.ijcem.com /ISSN:1940-5901/IJCEM0049984

Review Article

Less fixation on the eyes is associated with severe social disability in individuals with autism spectrum disorder

Yun Tang[1*], Shu-Xian Xu[1,2*], Xin-Hui Xie[1], Ying-Hui Hu[3], Tie-Bang Liu[1], Han Rong[1]

[1]Shenzhen Key Laboratory of Psychological, Shenzhen, China; [2]Shenzhen Psychiatric College, Anhui Medical University, Shenzhen, China; [3]Department of endocrinology, Zhujiang Hospital, Southern Medical University, Guangzhou, China. [*]Equal contributors.

Received February 2, 2017; Accepted March 17, 2017; Epub August 15, 2017; Published August 30, 2017

Abstract: Objective: Previous studies' findings regarding fixation on the eyes or mouth and level of social disability in people with autism spectrum disorder (ASD) are controversial. This meta-analysis aimed to assess the association between eye gaze patterns and social impairments. Methods: We searched the PubMed, Embase, and PsycINFO databases for studies that reported the Pearson's correlation coefficient (*r*) between time fixated on the eyes or/and mouth in an eye-tracking experiment and level of social disability in people with ASD. Subgroup analyses were conducted according to stimuli type. Results: Twelve cross-sectional studies comprising 15 study groups with 317 participants were included. The amount of time fixated on the eyes was linked to the level of social disability (*r* = -0.300, 95% CI -0.397 to -0.197). The result was more pronounced when the patients viewed image stimuli (*r* = -0.414, 95% CI -0.565 to -0.236, I^2 = 0%). Furthermore, we found a significant relationship between mouth fixation and social disability when patients viewed images (*r* = 0.319, 95% CI -0.080 to 0.530, I^2 = 0%), but not when they viewed videos (*r* = -0.197, 95% CI -0.178 to 0.523, I^2 = 80.4%). Conclusions: This study showed that less eye fixation was associated with greater social impairment in individuals with ASD, providing further evidence that reduced eye fixation is a strong hallmark of the early detection, diagnosis and prediction of social deficits in ASD. Future studies should further investigate the relationship between mouth fixation and social impairment.

Keywords: Autism spectrum disorder, social disability, eye tracking, fixation

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is characterized by impaired social interaction and restricted and repetitive behaviour [1, 2]. It was initially described by Kanner in 1943. Atypical social behaviours are a core diagnostic feature of ASD. As the current diagnostic tools for autism, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) [1], Autism Diagnostic Observation Schedule (ADOS) [3], Childhood Autism Rating Scale (CARS) [4] and Autism Diagnostic Interview-Revised (ADI-R) [5], are primarily based on direct or indirect observations of behaviour, which can be influenced by subjective assessment and varying symptoms, objective physiological response indicators must be collected.

In recent decades, eye-tracking technology has been widely used to research social attention and behaviours. Studies have research eye gaze duration and the specific eye gaze fixation on the eyes and/or the mouth in people with ASD compared to controls [6-8]. However, findings in the past decades have been contradictory. Recently, Papagiannopoulou et al. [9] published a systematic review and meta-analysis of eye-tracking studies and reported that children with ASD have significantly reduced gaze fixation on the eye region of the face than controls. However, no significant difference was found in terms of fixation on the mouth region. Chita-Tegmark's systematic review and meta-analysis [10] showed that individuals with autism spend less time than typically developing controls attending to social stimuli. Another study characterized 700 complex natural scene

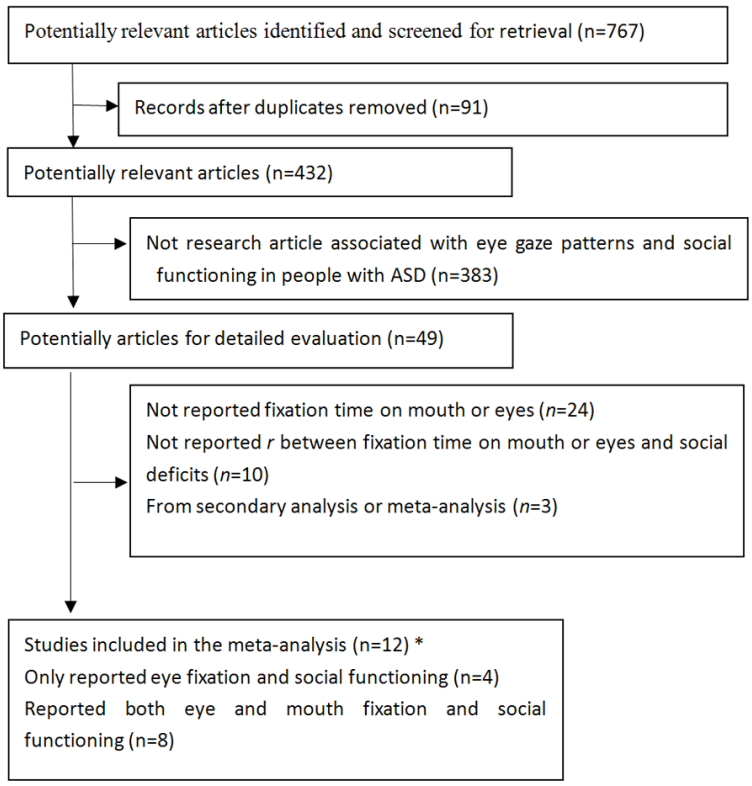


Figure 1. Flow of selection for studies. ASD: Autism spectrum disorder *In Gillespie-Smith 2014 [23] and Fujioka 2016 [20], each patient was involved in two different stimuli trials (familiar vs. unfamiliar faces, image vs. video), while in Falck-Ytter's study [26], two samples completed the same stimuli trials.

images using model-based eye tracking and found that, faces and locations had less salience for people with ASD than for matched controls, as indicated by their social gaze [11].

However, the association between the absence of preferential looking towards the eyes or mouth and an individual's level of social disability remains a topic of debate. Jones and Klin [12] uncovered a highly significant negative correlation between the time spent looking at the eyes and social competence, where less fixation on the eyes predicted greater social disability. Another study with a larger sample was consistent with this finding [13]. However, Birmingham et al. [14] indicated that participants with ASD who displayed more impaired communication spent more time looking at the eyes. Other studies failed to find any significant association between these variables [15, 16]. Correlational analyses of fixation patterns to the mouth area and social functioning are also ambiguous.

Given that previous studies found inconsistent results, a meta-analysis might help to clarify these relationships. Therefore, the present study aims to assess the relationship between eyes or mouth fixation and social functioning in adults with ASD.

Methods

Search strategy and selection criteria

Following the proposals of the Meta-Analysis of Observational Studies in Epidemiology Group [17], we conducted a literature search for potentially relevant papers in PubMed, Embase and PsycINFO through October 31, 2016 using the following terms: "Autistic disorder", "Autism spectrum disorder", "Autism", "Asperger", "ASD", "Eye movement", "Eye tracking", "Eye gaze", "Fixation", "Visual scanning", "Social Behavior Disorders", "Communicative competence", "Social competence", "Social attention", "Social interaction", "Social engagement", and "Social deficits". Additionally, original articles and reviews were searched to identify potentially suitable studies. Details about the search strategy in PubMed are presented in Supplementary Table 1.

We included studies that met the following criteria: (1) the patient group had a diagnosis of high- or low-functioning autism disorder, Asperger's syndrome or pervasive developmental disorder; (2) an eye-tracking experiment was performed to measure facial processing and response to social and non-social stimuli; (3) social functioning was measured by social functioning scales (if the study reported several results of different scales, we preferentially selected the results of the Autism Diagnostic Observation Schedule (ADOS) or Autism Diagnostic Interview-Revised (ADI-R)); and (4) the number (*n*) of patients and the Pearson's correlation coefficient (*r*) between the percentage

Table 1. Study characteristics

Study	Sample (women)	Age (y), average (range or SD)	Stimuli type	Fixation time	Diagnostic criteria	Developmentallevel	Social function measures	Comorbidity
Fujioka 2016	21 (0)	27.6 (7.7)	Images/video	Percentage of time fixation to the eyes and mouth	DSM-IV-TR and DISCO	High function, IQ > 85	SRS	No
Amestoy 2015	27 (4)	17.3 (U)	Images	Total time fixation to the eyes and mouth	DSM-IV-TR, ADI-R, ADOS	High function, IQ > 85	ADOS	No
Hanley 2015	11 (4)	26 (8.1)	Video	Percentage of time fixation to the eyes and mouth	DSM-IV-TR	High function, IQ > 110	SRS	NA
Gillespie-Smith 2014	21 (1)	13.6 (2.4)	Images	Percentage of time fixation to the eyes	CARS	Low, mild and high function	SCQ	NA
Jones 2013	11 (0)	1.1 (2-24 m)	Video	Percentage of time fixation to the eyes	ADOS	NA	ADOS	NA
Rice 2012	109 (26)	10.1 (NA)	Video	Percentage of time fixation to the eyes and mouth	DSM-IV-TR, ADOS, ADI-R	High function, IQ > 85	ADOS	No
Kirchner 2011	20 (5)	31.9 (7.6)	Images	Percentage of time fixation to the eyes and mouth	DSM-IV-TR, ADI-R	IQ > 100	ADI-R	NA
Falck-Ytter 2010a	15 (3)	5.2 (0.9)	Video	Total time fixation to the eyes and mouth	DSM-IV-TR	NA	ADI-R	NA
Falck-Ytter 2010b	12 (1)	6.6 (0.7)	Video	Total time fixation to the eyes and mouth	DSM-IV-TR	High function	SCQ	NA
Norbury 2009	28 (1)	14.9 (U)	Video	Percentage of time fixation to the eyes	DSM-IV-TR, ADI-R, ADOS	NA	ADOS	No
Jones 2008	15 (4)	2.3 (0.6)	Video	Percentage of time fixation to the eyes	ADI-R, ADOS	NA	ADOS	NA
Speer 2007	12 (0)	13.6 (2.7)	Video	Total time fixation to the eyes and mouth	ADI-R, ADOS	IQ > 95	ADOS	NA
Klin 2002	15 (0)	15.4 (7.2)	Video	Total time fixation to the eyes and mouth	DSM-IV-TR, ADI-R, ADOS	IQ > 100	ADOS	NA

SRS: Social Responsiveness Scale; SCQ: Social Communication QuestionUire; ADOS: Autism Diagnostic Observation Schedule; CARS: Childhood Autism Rating Scale; ADI-R: Autism Diagnostic Interview-Revised; U: Not Available; DISCO: Diagnostic Interview for Social and Communication Disorders; DSM: Diagnostic and Statistical Manual of Mental Disorders.

Table 2. The quality assessment of included studies

Study	1	2	3	4	5	6	7	8	9	10	11	Total
Fujioka 2016	Y	Y	N	U	U	Y	Y	Y	N	Y	U	6
Amestoy 2015	Y	Y	N	N	U	Y	N	Y	N	N	U	4
Hanley 2015	Y	Y	Y	N	U	N	N	Y	N	Y	U	5
Gillespie-Smith 2014	Y	Y	Y	N	U	Y	N	Y	N	N	U	5
Jones 2013	Y	Y	Y	N	U	Y	Y	Y	N	Y	Y	8
Rice 2012	Y	Y	N	U	U	Y	Y	Y	N	Y	U	6
Kirchner 2011	Y	Y	N	U	U	Y	N	Y	N	N	U	4
Falck-Ytter 2010a	Y	Y	N	U	U	Y	N	Y	N	Y	U	5
Falck-Ytter 2010b	Y	Y	N	U	U	N	N	N	N	Y	U	3
Norbury 2009	Y	Y	Y	U	U	Y	Y	Y	N	Y	U	6
Jones 2008	Y	Y	N	U	U	N	Y	Y	N	Y	U	5
Speer 2007	Y	Y	Y	U	U	Y	N	Y	N	N	U	5
Klin 2002	Y	Y	Y	U	U	Y	N	Y	N	Y	U	6

of time fixated on the eyes or/and mouth and the level of social disability were reported.

The exclusion criteria were as follows: (1) the participants suffered from other psychiatric disorders (e.g., schizophrenia, bipolar disorder, or obsessive-compulsive disorder); (2) the number of subjects was fewer than 10; and (3) an inverted image or cued gaze following was used in the experimental design.

Data extraction and quality assessment

Potentially relevant studies were selected independently by two authors according to the aforementioned criteria. We recorded the study information such as the number of participants, diagnostic criteria and social function scale employed for each included study.

The quality of the included cross-sectional studies was evaluated based on the criteria developed by the Agency for Healthcare Research and Quality (AHRQ) and measured with 11 items. An item was scored as '1' if it was answered 'Yes'. If it was answered 'No' or 'Unclear', the item was scored '0'. Article quality was assessed as follows: high quality = 8-11; moderate quality = 4-7; and low quality = 0-3 [18]. The detailed assessment list is presented in Supplementary Table 2.

Statistical analysis

For the Pearson's correlation coefficients, all the computations were performed using Fisher's *z*-values and 95% confidence intervals (CIs) [19]. First, each effect size *r* was transformed into a Fisher's *z*-value using the following formula:

$$\text{Fisher's } z = 0.5 * \ln((1 + r)/(1 - r)) \quad \text{Formula 1}$$

Then, we calculated the standard errors (SEs) as follows:

$$SE = SQRT(1/(n - 3)) \quad \text{Formula 2}$$

Third, data (Fisher's *z* and 95% CI) from the various studies were combined using random- or fixed-effects meta-analysis. Finally, the summary Fisher's *z*-value was back-transformed into the summary Pearson's *r* value using the following formula:

$$\text{Summary } r = (\exp(2Z) - 1)/(\exp(2Z) + 1), \text{ where } Z = \text{the summary Fisher's } z\text{-value} \quad \text{Formula 3}$$

The I^2 statistic was used to test the heterogeneity ($P < 0.10$ or $I^2 > 50\%$ was regarded as significant). The results of studies were pooled using a fixed-effects model if the heterogeneity was non-significant. Otherwise, a random-effects model was used. To explain the heterogeneity in the meta-analysis, we conducted subgroup analyses using stimuli materials.

A sensitivity analysis was performed by computing the summary Pearson's *r* values when one study was removed from the meta-analysis, and publication bias was assessed by inspecting the funnel plots. We used Stata version 12.0 (Stata Corp LP, College Station, TX) to perform all the analyses. The *p*-values were 2-tailed, and the statistical significance level was set at 0.05.

Results

Selected studies and characteristics

The search initially yielded 767 potential references, and 49 of them qualified for full review. Ultimately, 12 articles [8, 12, 13, 15, 16, 20-26] with 15 study groups met all the criteria and were analysed (**Figure 1**).

Table 1 provides a detailed description of the 15 study groups from the 12 papers. These papers included a total of 317 ASD patients who ranged in age from 2 months to 55 years and met the diagnostic criteria of the DSM-IV-

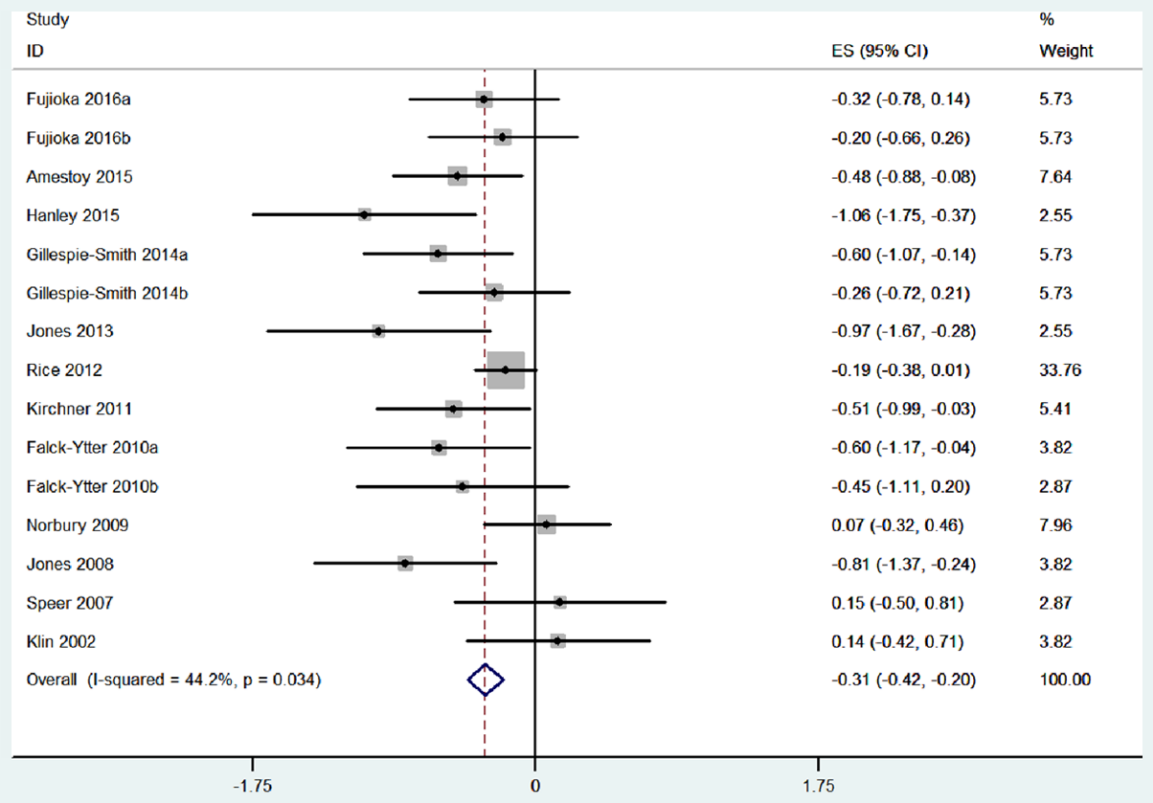


Figure 2. Forest plot of the association between the time spent looking at the eyes and social impairment in individuals with ASD. The square box in the graph portrays the weight of each study contributed to the analysis. The overall summary Fisher's *z*-value is shown on the last row of the graph. CI: confidence interval.

TR, ADOS, ADI-R or CARS. Most participants were high-functioning, with a mean IQ > 85. Their social function was measured by the SRS, ADOS, SRS, SCQ or ADI-R. The quality assessment of the included studies is presented in **Table 2**. One study group was low-quality [26], one study group was high-quality [12], and the others were moderate in quality.

Overall correlation between eyes or mouth fixation and social ability

The correlation coefficient (*r*) between eye fixation and social ability was reported for all the study groups, whereas the correlation coefficient (*r*) between mouth fixation and social disability was reported for only ten study groups that included 258 individuals [13, 15, 16, 20-22, 25, 26]. The data were pooled and calculated using the fixed-effects model in the eyes groups, as the heterogeneity (I^2 = 44.2%) was non-significant. **Figure 2** shows the negative correlation between the percentage of time fixated on the eyes and the level of social disability (*r* = -0.300, 95% CI -0.397 to -0.197), which was transformed from the Fisher's *z*-value. As shown in **Figure 3**, the correlation between the degree of mouth fixation and the level of social impairment was insignificant (*r* = 0.226, 95% CI -0.050 to 0.470); however, the heterogeneity (I^2 = 75.0%) was significant. Furthermore, no evidence of publication bias was detected by the visual inspection of the funnel plot (Supplementary Figures 1, 2).

Subgroup analyses and sensitivity analyses

We performed a subgroup analysis on stimuli materials, as different stimuli may influence the results. As shown in **Figure 4**, a more pronounced significant relationship was observed between the time spent looking at the eyes and social impairment when the patients viewed image stimuli (*r* = -0.414, 95% CI -0.565 to -0.236, I^2 = 0%). A significant result was also found when video stimuli were used (*r* = -0.327, 95% CI -0.523 to -0.100), but the heterogeneity rose to 57.9%. On the other hand, we found a

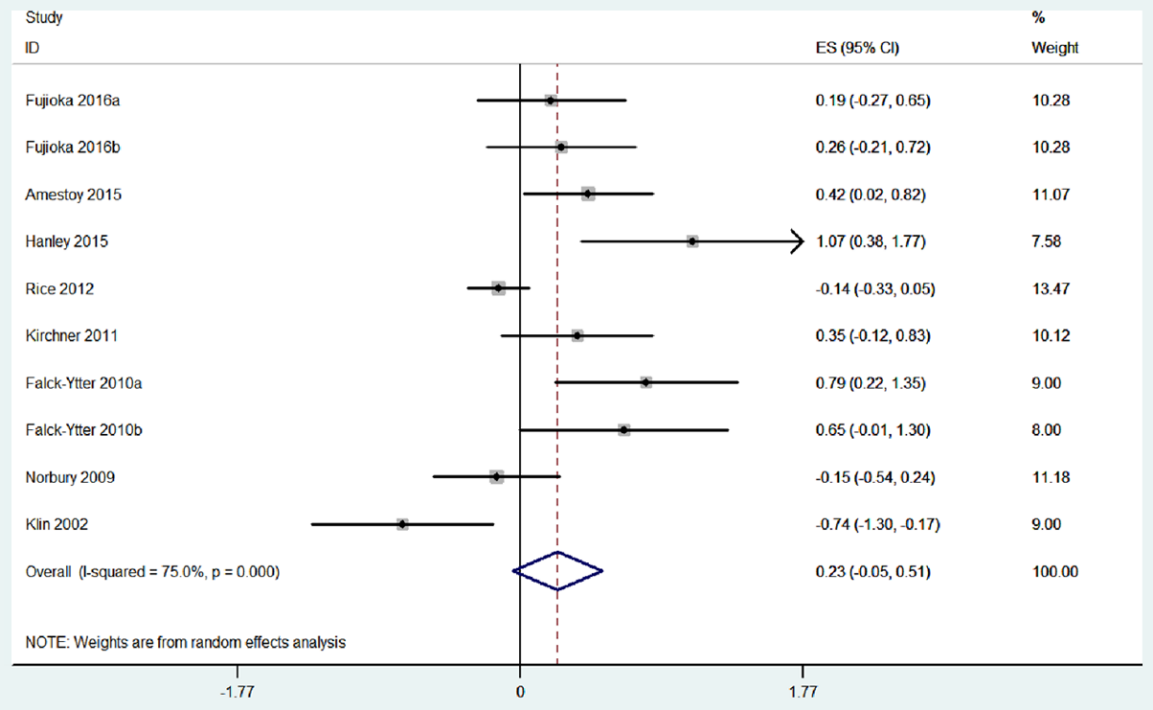


Figure 3. Forest plot of the association between the time spent looking at the mouth and social impairment in individuals with ASD. The square box in the graph portrays the weight of each study contributed to the analysis. The overall summary Fisher's *z*-value is shown on the last row of the graph. CI: confidence interval.

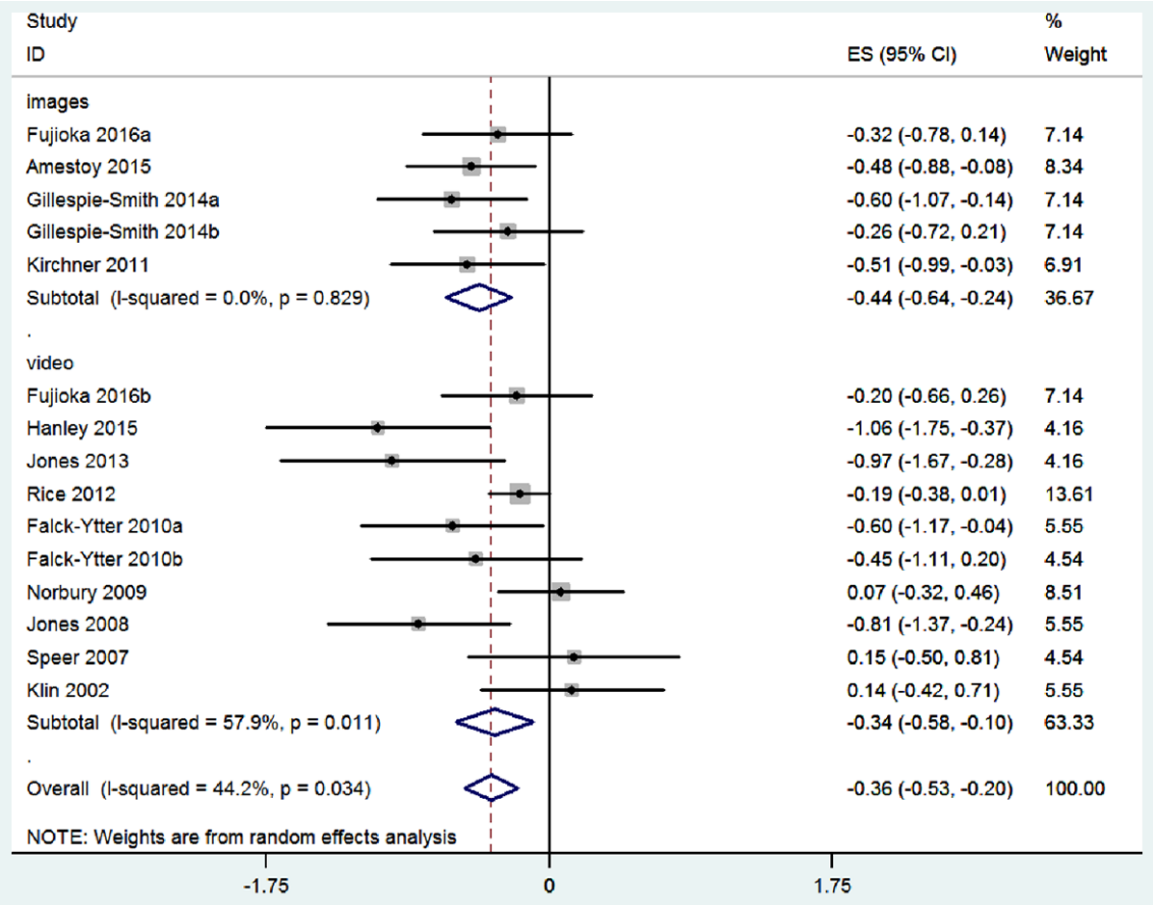


Figure 4. Forest plot of subgroup analyses according to stimuli material, outcome: fixation on the eyes. The square box in the graph portrays the weight of each study contributed to the analysis. The overall summary Fisher's *z*-value is shown on the last row of the graph. CI: confidence interval.

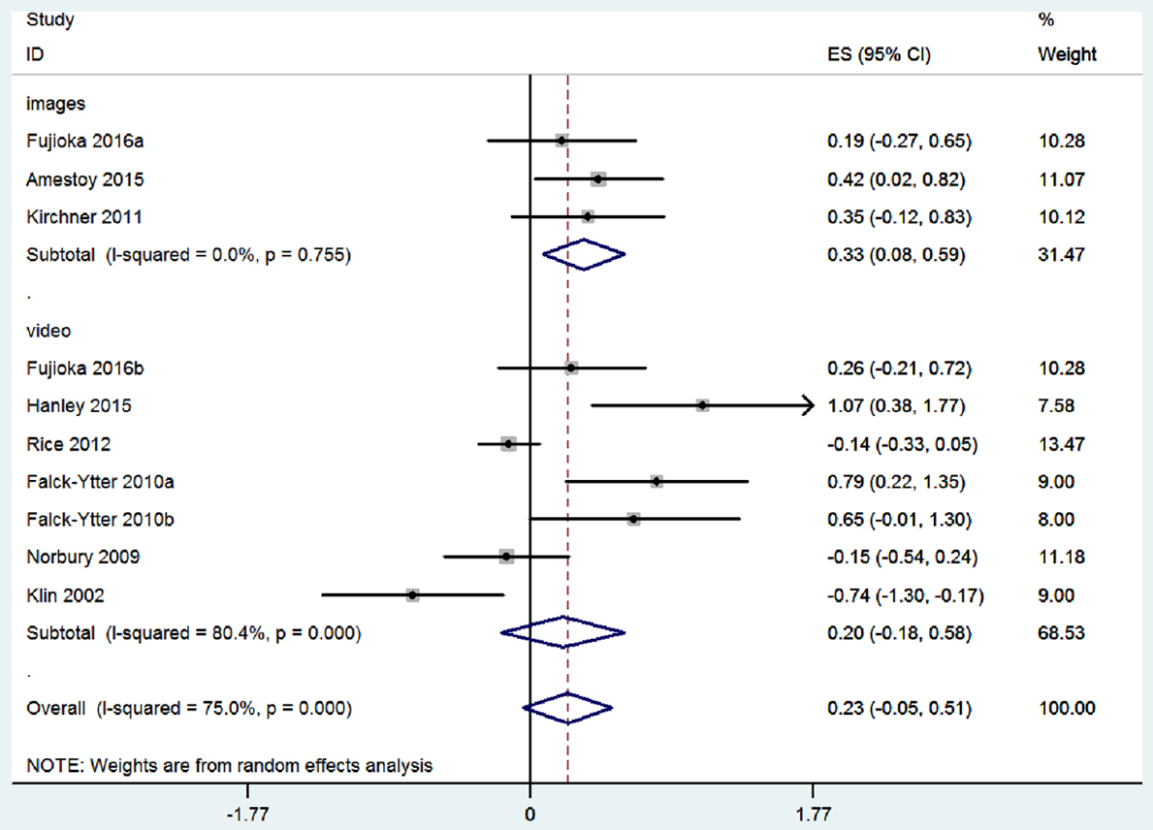


Figure 5. Forest plot of subgroup analyses according to stimuli material, outcome: fixation on the mouth. The square box in the graph portrays the weight of each study contributed to the analysis. The overall summary Fisher's *z*-value is shown on the last row of the graph. CI: confidence interval.

significant relationship between mouth fixation and social disability in the image (r = 0.319, 95% CI -0.080 to 0.530, I^2 = 0%), but not in the video (r = -0.197, 95% CI -0.178 to 0.523, I^2 = 80.4%) trial (**Figure 5**).

Several methods were used to test the sensitivity and confirmed that the outcomes were not influenced by the use of a fixed- or random-effects model.

Discussion

In this study, we found a significant negative correlation between the percentage of time fixated on eyes and the level of social disability in individuals with ASD, indicating that reduced eye fixation is linked to poor social awareness. However, the degree of mouth fixation was not related to social disability. These findings are consistent with the results of an aforementioned meta-analysis [9] that indicated that ASD patients have significant impairments in gaze fixation on the eyes but no significant difference in terms of fixation on the mouth region. Consequently, we can infer that eye fixation plays a more important role as a biomarker of early detection and diagnosis and even a predictor of social deficit in ASD than mouth fixation. To the best of our knowledge, this is the first meta-analysis to evaluate the association between eye gaze pattern and social impairments.

The underlying mechanisms of atypical eye gaze in people with ASD are poorly understood. According to previous studies, dysfunctions in several brain regions can lead to atypical eye

gaze. The fusiform face area (FFA) has been specifically highlighted in the last two decades [27, 28]. Scholars speculated that significantly diminished activity in the FFA in response to facial stimuli correlated with facial processing deficits in individuals with ASD [29, 30]. Another brain region that has received considerable research attention is the amygdala, which has been closely tied to ASD and to abnormal eye gaze in a number of studies [31, 32]. Evidence from magnetic resonance imaging (MRI) studies has shown that individuals with ASD display abnormal amygdala activation when they fixate on the eyes of faces [33]. Amygdala damage also impairs social judgements about people's faces within complex scenes [14]. Differences in other regions such as the superior temporal sulcus, cerebellum, and temporal lobe have also been reported between ASD subjects and controls during facial expression tasks [34, 35]. These differences have also been associated with the level of social impairment.

Another debatable topic is the relationship between mouth fixation and social disability. Chawarska et al. [36] found decreased attention to the mouth in children with ASD compared to typically developing children. However, Papagiannopoulou et al. [9] revealed that no significant effect was found for the patterns of eye movements that involved looking at the mouth between people with ASD and healthy controls. These results are not surprising, given that a positive correlation was found between the amount of mouth fixation and verbal development in toddlers [36] and adolescents [16] with ASD and in infants at risk of autism [37]. Additionally, Norbury et al. [16] demonstrated that increased fixations on the mouth were associated with variation in language acquisition and greater communicative competence in children with ASD. The participants in Papagiannopoulou's meta-analysis were mostly those with high-functioning autism who had a higher IQ and language skills compared to people with low- and mild-functioning autism, which yielded a nonsignificant result between people with ASD and healthy controls [1, 9]. Our study included mostly high-functioning people with autism. We discovered that the degree of mouth fixation was not related to social disability either. However, it should be noted that the lack of a finding of a significant difference relating to mouth fixation might be influenced by high heterogeneity. After performing a subgroup analysis for stimulus type in our study, we discovered a positive significant relationship between mouth fixation and social disability in the image group, meaning that greater fixation on the mouth predicted greater social disability in people with ASD when they looked at pictures. This may be due to their compensating for reduced eye fixation and, thus, their taking more time to look at the mouth and other regions of the face to collect information [38, 39]. However, the contradictory results should be further clarified in the future.

How to choose a stimulus type for an eye-tracking study is also commonly debated. The results vary in terms of how sensitive they are to the deficits of people with ASD. Both static images and dynamic stimuli were used widely in previous decades; however, dynamic stimuli have become increasingly more popular recently. Data from Speer et al. [8] showed that individuals with autism fixated less on the eyes when they viewed social-dynamic stimuli but not isolated-static stimuli. Data from a more recent study with a larger sample size revealed that the interactive task has significant classification power between ASD and control groups [40]. They argued that slowing down the facial dynamics' presentation tended to enhance facial exploration of the mouth and/or eyes in toddlers with ASD [41]. Static stimuli neither consistently produced group differences nor were as effective as dynamic stimuli at eliciting individual differences in social attention. However, our study uncovered different results. A more pronounced significant relationship was found between the time spent looking at the eyes/mouth and social impairment when the patients viewed static image stimuli but not social-dynamic stimuli. Additionally, the heterogeneity in the dynamic stimuli study was significant. In our opinion, although dynamic stimuli might produce a more complicated and realistic social environment [15, 42], they should be used with caution, as they also increase the heterogeneity among studies. Digitized colour video clips, including a story with a social interaction, emotional responses [16] and complicated backgrounds, are all confounding factors that lead to inconsistent results. In short, eye-tracking stimulus materials vary across studies, as there was no standard paradigm. The unstructured, natural test paradigm with con-

trol variables should be developed for further research.

Although this study yielded promising results, it suffers from several limitations. First, the number of participants who were enrolled is limited, although it is large compared to ASD studies to some extent because it is difficult to include people with ASD in research. The association between mouth fixation and social disability was not significant, which might be due to the limited number of included studies and participants. Therefore, this finding should be interpreted with caution. Second, the findings are largely based on high-functioning people with autism, whereas low-functioning people with autism might experience greater benefits from early detection and diagnosis. Clinically and technically, children with lower functioning generally have moderate to severe ASD and often present with one or several comorbid disorders (attention disorders, motor disorders, language disorders, emotional disorders, etc.) [43]. Therefore, they generally cannot participate in eye-tracking studies. Future research is needed to determine whether the results can be extended to individuals with autism who demonstrate lower cognitive functioning. Third, in most of the studies, the association between eyes/mouth fixation and social impairment was measured at a single time point. Data from Jones and Klin [24] revealed that the results might change as they grow. Rutherford and Towns [44] also demonstrated that social skills training can impact the facial processing strategy and tests performed. Thus, follow-up research is necessary to examine the stability of the results.

Conclusion

In conclusion, this study showed that less eye fixation was associated with greater social impairment in individuals with ASD. Our findings provide additional evidence that reduced eye fixation is a strong hallmark of the early detection, diagnosis and prediction of social deficits in individuals with ASD. Therefore, intervention and treatment aimed at improving social responsiveness can be conducted at an early stage of the disorder. The relationship between mouth fixation and social impairments should be further investigated in future research.

Acknowledgements

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Disclosure of conflict of interest

None.

Authors' contribution

S.X and X.X were responsible for the initial plan, study design, conducting the study, data interpretation, and manuscript drafting. X.X and S.X was responsible for statistical analysis. T.L and H.R were responsible for data collection, and data extraction. Y.T, S.X, and Y.H were responsible for data interpretation and manuscript drafting.

Address correspondence to: Drs. Shu-Xian Xu and Tie-Bang Liu, Shenzhen Key Laboratory of Psychological, Shenzhen, China; Shenzhen Psychiatric College, Anhui Medical University, Shenzhen, China. E-mail: shuxianxu@outlook.com (SXX); liutbsz@sina.com (TBL)

References

[1] Association AP. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub 2013.

[2] Volkmar FR, Lord C, Bailey A, Schultz RT and Klin A. Autism and pervasive developmental disorders. J Child Psychol Psychiatry 2004; 45: 135-170.

[3] Lord C, Rutter M, DiLavore P and Risi S. Autism diagnostic observation schedule-WPS (ADOS-WPS). Los Angeles, CA; Western Psychological Services 1999.

[4] Schopler E, Reichler RJ and Renner BR. The childhood autism rating scale (CARS). Western Psychological Services Los Angeles 2002.

[5] Lord C, Rutter M and Le Couteur A. Autism diagnostic interview-revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord 1994; 24: 659-685.

[6] Swettenham J, Baron-Cohen S, Charman T, Cox A, Baird G, Drew A, Rees L and Wheelwright S. The frequency and distribution of spontaneous attention shifts between social and nonsocial stimuli in autistic, typically developing, and nonautistic developmentally delayed infants. J Child Psychol Psychiatry 1998; 39: 747-753.

[7] Sasson NJ and Touchstone EW. Visual attention to competing social and object images by

preschool children with autism spectrum disorder. J Autism Dev Disord 2014; 44: 584-592.
[8] Speer LL, Cook AE, McMahon WM and Clark E. Face processing in children with autism effects of stimulus contents and type. Autism 2007; 11: 265-277.
[9] Papagiannopoulou EA, Chitty KM, Hermens DF, Hickie IB and Lagopoulos J. A systematic review and meta-analysis of eye-tracking studies in children with autism spectrum disorders. Soc Neurosci 2014; 9: 610-632.
[10] Chita-Tegmark M. Social attention in ASD: a review and meta-analysis of eye-tracking studies. Res Dev Disabil 2016; 48: 79-93.
[11] Wang S, Jiang M, Duchesne XM, Laugeson EA, Kennedy DP, Adolphs R and Zhao Q. Atypical visual saliency in autism spectrum disorder quantified through model-based eye tracking. Neuron 2015; 88: 604-616.
[12] Jones W, Carr K and Klin A. Absence of preferential looking to the eyes of approaching adults predicts level of social disability in 2-year-old toddlers with autism spectrum disorder. Arch Gen Psychiatry 2008; 65: 946-954.
[13] Rice K, Moriuchi JM, Jones W and Klin A. Parsing heterogeneity in autism spectrum disorders: visual scanning of dynamic social scenes in school-aged children. J Am Acad Child Adolesc Psychiatry 2012; 51: 238-248.
[14] Birmingham E, Cerf M and Adolphs R. Comparing social attention in autism and amygdala lesions: effects of stimulus and task condition. Soc Neurosci 2011; 6: 420-435.
[15] Klin A, Jones W, Schultz R, Volkmar F and Cohen D. Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. Arch Gen Psychiatry 2002; 59: 809-816.
[16] Norbury CF, Brock J, Cragg L, Einav S, Griffiths H and Nation K. Eye-movement patterns are associated with communicative competence in autistic spectrum disorders. J Child Psychol Psychiatry 2009; 50: 834-842.
[17] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA and Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA 2000; 283: 2008-2012.
[18] Hu J, Dong Y, Chen X, Liu Y, Ma D, Liu X, Zheng R, Mao X, Chen T and He W. Prevalence of suicide attempts among Chinese adolescents: a meta-analysis of cross-sectional studies. Compr Psychiatry 2015; 61: 78-89.
[19] Borenstein M, Hedges LV, Higgins JPT and Rothstein HR. Introduction to meta-analysis. 2009.
[20] Fujioka T, Inohara K, Okamoto Y, Masuya Y, Ishitobi M, Saito DN, Jung M, Arai S, Matsumura Y, Fujisawa TX, Narita K, Suzuki K, Tsuchiya KJ, Mori N, Katayama T, Sato M, Munesue T, Okazawa H, Tomoda A, Wada Y and Kosaka H. Gazefinder as a clinical supplementary tool for discriminating between autism spectrum disorder and typical development in male adolescents and adults. Mol Autism 2016; 7: 19.
[21] Hanley M, Riby DM, Carty C, McAteer AM, Kennedy A and McPhillips M. The use of eye-tracking to explore social difficulties in cognitively able students with autism spectrum disorder: a pilot investigation. Autism 2015; 19: 868-73.
[22] Amestoy A, Guillaud E, Bouvard MP and Cazalets JR. Developmental changes in face visual scanning in autism spectrum disorder as assessed by data-based analysis. Front Psychol 2015; 6: 989.
[23] Gillespie-Smith K, Doherty-Sneddon G, Hancock PJ and Riby DM. That looks familiar: attention allocation to familiar and unfamiliar faces in children with autism spectrum disorder. Cogn Neuropsychiatry 2014; 19: 554-569.
[24] Jones W and Klin A. Attention to eyes is present but in decline in 2-6-month-old infants later diagnosed with autism. Nature 2013; 504: 427-431.
[25] Kirchner JC, Hatri A, Heekeren HR and Dziobek I. Autistic symptomatology, face processing abilities, and eye fixation patterns. J Autism Dev Disord 2011; 41: 158-167.
[26] Falck-Ytter T, Fernell E, Gillberg C and Von Hofsten C. Face scanning distinguishes social from communication impairments in autism. Dev Sci 2010; 13: 864-875.
[27] Madipakkam AR, Rothkirch M, Guggenmos M, Heinz A and Sterzer P. Gaze direction modulates the relation between neural responses to faces and visual awareness. J Neurosci 2015; 35: 13287-13299.
[28] Slotnick SD and White RC. The fusiform face area responds equivalently to faces and abstract shapes in the left and central visual fields. Neuroimage 2013; 83: 408-417.
[29] Volkmar FR. Understanding the social brain in autism. Dev Psychobiol 2011; 53: 428-434.
[30] Schultz RT. Developmental deficits in social perception in autism: the role of the amygdala and fusiform face area. Int J Dev Neurosci 2005; 23: 125-141.
[31] Kliemann D, Dziobek I, Hatri A, Baudewig J and Heekeren HR. The role of the amygdala in atypical gaze on emotional faces in autism spectrum disorders. J Neurosci 2012; 32: 9469-9476.
[32] Kleinhans NM, Richards T, Sterling L, Stegbauer KC, Mahurin R, Johnson LC, Greenson J, Dawson G and Aylward E. Abnormal function-

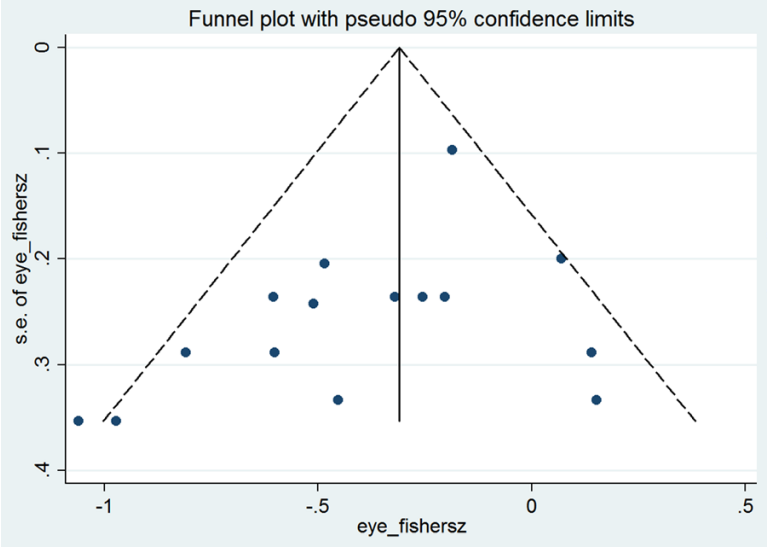
al connectivity in autism spectrum disorders during face processing. Brain 2008; 131: 1000-1012.
[33] Adolphs R, Gosselin F, Buchanan TW, Tranel D, Schyns P and Damasio AR. A mechanism for impaired fear recognition after amygdala damage. Nature 2005; 433: 68-72.
[34] Pelphrey KA and Carter EJ. Brain mechanisms for social perception: lessons from autism and typical development. Ann N Y Acad Sci 2008; 1145: 283-299.
[35] Critchley HD, Daly EM, Bullmore ET, Williams SC, Van Amelsvoort T, Robertson DM, Rowe A, Phillips M, McAlonan G, Howlin P and Murphy DG. The functional neuroanatomy of social behaviour: changes in cerebral blood flow when people with autistic disorder process facial expressions. Brain 2000; 123: 2203-2212.
[36] Chawarska K, Macari S and Shic F. Context modulates attention to social scenes in toddlers with autism. J Child Psychol Psychiatry 2012; 53: 903-913.
[37] Young GS, Merin N, Rogers SJ and Ozonoff S. Gaze behavior and affect at 6 months: predicting clinical outcomes and language development in typically developing infants and infants at risk for autism. Dev Sci 2009; 12: 798-814.
[38] Back E, Ropar D and Mitchell P. Do the eyes have it? Inferring mental states from animated faces in autism. Child Dev 2007; 78: 397-411.
[39] Joseph RM and Tanaka J. Holistic and part-based face recognition in children with autism. J Child Psychol Psychiatry 2003; 44: 529-542.
[40] Chevallier C, Parish-Morris J, McVey A, Rump KM, Sasson NJ, Herrington JD and Schultz RT. Measuring social attention and motivation in autism spectrum disorder using eye-tracking: Stimulus type matters. Autism Res 2015; 8: 620-628.
[41] Charrier A, Tardif C and Gepner B. [Slowing down the flow of facial information enhances facial scanning in children with autism spectrum disorders: a pilot eye tracking study]. Encephale 2017; 43: 32-40.
[42] Klin A. Attributing social meaning to ambiguous visual stimuli in higher-functioning autism and asperger syndrome: the social attribution task. J Child Psychol Psychiatry 2000; 41: 831-846.
[43] Eagle RS. Accessing and assessing intelligence in individuals with lower functioning autism. J Dev Disabil 2002; 9: 45-53.
[44] Rutherford MD and Towns AM. Scan path differences and similarities during emotion perception in those with and without autism spectrum disorders. J Autism Dev Disord 2008; 38: 1371-1381.

Supplementary Table 1. Literature search strategy for Pubmed

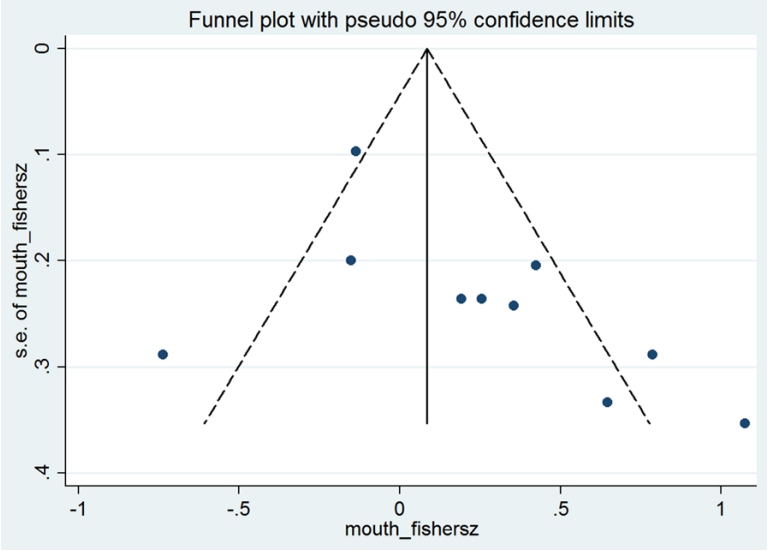
#1	"Autistic Disorder" [Mesh] OR "Autism Spectrum Disorder" [Mesh]
#2	((((("Autistic Disorder") OR "Autism Spectrum Disorder") OR Autism) OR Asperger) OR ASD
#3	#1 OR #2
#4	"Eye Movements" [Mesh] OR "Eye Movement Measurements" [Mesh]
#5	((((("Eye movement") OR "Eye tracking") OR "Eye gaze") OR Fixation) OR "Visual Scanning"
#6	#4 OR #5
#7	"Social Behavior Disorders" [Mesh]
#8	((((("Communicative competence") OR "Social competence") OR "Social attention") OR "Social interaction") OR "Social engagement") OR "Social deficits"
#9	#7 OR #8
#10	#3 AND #6 AND #9
#11	Humans [MeSH]
#12	#10 AND #11

Supplementary Table 2. AHRQ quality assessment criteria for Cross-Sectional

Item	Yes	No	Unclear
1) Define the source of information (survey, record review)			
2) List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications			
3) Indicate time period used for identifying patients			
4) Indicate whether or not subjects were consecutive if not population-based			
5) Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants			
6) Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements)			
7) Explain any patient exclusions from analysis			
8) Describe how confounding was assessed and/or controlled.			
9) If applicable, explain how missing data were handled in the analysis			
10) Summarize patient response rates and completeness of data collection			
11) Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained			



Supplementary Figure 1. Funnel plot, outcome: fixation on eyes.



Supplementary Figure 2. Funnel plot, outcome: fixation on mouth.