**Association between Autism Spectrum Disorder (ASD) and vision problems. A systematic review and meta-analysis**

John Perna, MD 1,2\*, Alessio Bellato, PhD 3\*, Preethi S. Ganapathy, MD, PhD 4, Marco Solmi, MD, PhD 5-10, Andrea Zampieri, MD 11, Stephen V. Faraone, PhD 1,#, Samuele Cortese, MD, PhD 9, 12-15,#

1 Department of Psychiatry and Behavioral Sciences, Norton College of Medicine at SUNY Upstate Medical University, Syracuse NY, USA

2 Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta GA, USA

3 School of Psychology, University of Nottingham Malaysia, Selangor, Malaysia

4 Department of Ophthalmology & Visual Sciences, Norton College of Medicine at SUNY Upstate Medical University, Syracuse NY USA

5 Department of Psychiatry, University of Ottawa, Ontario, Canada

6 On Track: The Champlain First Episode Psychosis Program, Department of Mental Health, The Ottawa Hospital, Ontario, Canada

7 Ottawa Hospital Research Institute (OHRI) Clinical Epidemiology Program University of Ottawa, Ontario, Canada

8 School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, Canada

9 Centre for Innovation in Mental Health, School of Psychology, Faculty of Environmental and Life Sciences, University of Southampton, Southampton, UK

10 Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany

11 Vittorio Emanuele III Hospital - Montecchio Maggiore, Vicenza, Italy

12 Solent NHS Trust, Southampton, UK

13 Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, Southampton, UK

14 Hassenfeld Children's Hospital at NYU Langone, New York University Child Study Center, New York City, New York, USA

15 Division of Psychiatry and Applied Psychology, School of Medicine, University of Nottingham, Nottingham, UK

\*Shared co-first authorship

# Shared senior authorship

**Corresponding author:** Prof Stephen V. Faraone, Distinguished Professor of Psychiatry and of Neuroscience & Physiology, SUNY Upstate Medical University, 750 East Adams Street, Syracuse, NY 13210, Phone: 315-464-3113, Fax: 315-464-3279, SVFaraone@upstate.edu

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# ABSTRACT

**Aim:** To conduct a systematic review and meta-analysis assessing whether vision and/or eye disorders are associated with Autism Spectrum Disorder (ASD). **Method:** Based on a pre-registered protocol **(**PROSPERO: CRD42022328485), we searched PubMed, Web of Knowledge/Science, Ovid Medline, Embase and APA PsycINFO up to 5th February 2022, with no language/type of document restrictions. We included observational studies 1) reporting at least one measure of vision in people of any age with a diagnosis of ASD based on DSM or ICD criteria, or ADOS; or 2) reporting the prevalence of ASD in people with and without vision disorders. Study quality was assessed with the Appraisal tool for Cross-Sectional Studies (AXIS). Random-effects meta-analyses were used for data synthesis. **Results:** We included 49 studies in the narrative synthesis and 46 studies in the meta-analyses (15,629,159 individuals distributed across multiple different measures). We found meta-analytic evidence of increased prevalence of strabismus (OR=4.72 [95% CI:4.60,4.85]) in people with versus those without ASD (non-significant heterogeneity: Q = 1.0545, p = 0.7881). We also found evidence of increased accommodation deficits (Hedge’s g=0.68 [CI:0.28,1.08]) (non-significant heterogeneity: Q = 6.9331, p = 0.0741), reduced peripheral vision (-0.82 [CI:-1.32,-0.33]) (non-significant heterogeneity: Q = 4.8075, p = 0.4398), reduced stereoacuity (0.73 [CI:-1.14,-0.31]) (non-significant heterogeneity: Q = 0.8974, p = 0.3435), increased color discrimination difficulties (0.69 [CI:0.27,1.10]) (non-significant heterogeneity: Q = 9.9928, p = 0.1890), reduced contrast sensitivity (0.45 [CI:-0.60,-0.30]) (non-significant heterogeneity: Q = 9.9928, p = 0.1890) and increased retinal thickness (=0.29 [CI: 0.07,0.51]) (non-significant heterogeneity: Q = 0.8113, p = 0.9918) in ASD. **Discussion:** ASD is associated with some self-reported and objectively measured functional vision problems, and structural alterations of the eye, even though we observed several methodological limitations in the individual studies included in our meta-analyses. Further research should clarify the causal relationship, if any, between ASD and problems of vision and if problems of vision during early life.

# INTRODUCTION

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder affecting on average 0.3% of the population globally, with a 3:1 male-to-female ratio[1]. It is characterized by impaired social communication and social reciprocity, alongside rigid/repetitive patterns of interest, behavior or activities[2]. ASD can also be associated with sensory processing abnormalities, often including vision, that can manifest as hypo and/or hypersensitivity to certain stimuli and sensory input such as light, colors, and motion[3, 4]. These sensory sensitivities have a significant negative impact on the personal life and wellbeing of individuals with ASD[5].

Beyond sensory processing abnormalities in vision, ASD may be associated with a broad range of vision problems. Of note, children with significant visual impairments develop deficits in social development and repetitive stereotypical behaviors[6, 7] similar to those seen in individuals diagnosed with ASD. As the dominant human sensory modality, vision provides developmentally critical input to navigate social environments[8]. Considering that vision problems, including not only vision loss, but also blurred vision and strabismus, are influenced by biological risk factors (e.g. pre-term birth, congenital infections, nutritional deficiencies)[9-11], and given the established evidence on the involvement of these environmental risk factors in the etiology of ASD [12-14], it is possible that altered neurodevelopment concurrently leads to the onset of ASD and vision disorders. Additionally, ASD is significantly associated with many rare genetic syndromes (e.g., Fragile X, epilepsy, Down syndrome, Noonan Syndrome, Tuberous Sclerosis, neurofibromatosis type 1) that increase the risk of both ASD and disorders of vision[15, 16]. Lastly, structures of the eye develop from the same embryological tissue as the brain[17] and ASD is a neurodevelopmental disorder presenting with structural brain abnormalities[18, 19]. Therefore, the development of ocular structures (including major structures of the eye and neural connections with brain networks involved in visual information processing and perception) might be affected by the same processes that ultimately lead to the development of ASD[20].

Such observations, in conjunction with the early work of Ornitz an Ritvo who established the research paradigm for investigating perceptual alterations in ASD [21], have motivated extensive research into the relationship between ASD and vision problems[22-24]. It has been reported that individuals with ASD may present with impaired global motion processing[25], altered oculomotor control[26], and increased prevalence of various disorders of vision[27] compared to neurotypical controls. Reciprocally, it has been shown there is an increased relative risk of ASD in severely visually impaired children compared to children from the general population. While this research has been described in narrative reviews[22-24], as of today no meta-analysis has been conducted to summarize quantitatively and comprehensively the data on the possible relationship between ASD and a broad range of vision problems.

Therefore, the current study aimed to: (a) investigate if the prevalence of ASD differs in people with and without vision problem and, vice versa, if the prevalence of vision problems/conditions differs in people with and without ASD; and (b) assess possible differences in objective measures of vision (e.g., structural ocular measures, visual acuity, contrast sensitivity and color vision) between people with and without ASD.

 METHODS

We pre-registered the study on PROSPERO (CRD42022328485) and followed the 2020 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[28].ThePRISMA Checklist can be found in Supplement 1.

## Search strategy

We systematically searched Pubmed, Web of Knowledge/Science, Ovid Medline, Embase and APA PsycInfo until 5th February 2022, with no language/type of document restrictions. The search strategy/syntax included keywords associated with a) ASD and b) vision (more details in Supplement 2).

## Selection criteria

Inclusion criteria: (1) original, observational studies (case studies and previous systematic or narrative reviews were not included, but reference lists were searched to identify any additional eligible studies); (2) including people of any age with a diagnosis of ASD or equivalent – such as Pervasive Developmental Disorder or Asperger's – based on DSM/ICD criteria or based on the Autism Diagnostic Observation Schedule (ADOS), that has shown acceptable diagnostic accuracy in research settings[29] (self-report or above-threshold scores on clinical instruments were permitted for the diagnosis of autism in population studies); and (3) comparing at least one measure of vision in people with vs. those without ASD. Moreover, we also included studies reporting the prevalence of ASD in people with and without any disorders of vision; and studies reporting the prevalence of vision disorders in people with and without ASD.

## Data selection, extraction and coding

Titles and abstracts of the retrieved references were screened independently by two authors (AB and JP) to identify potentially eligible studies; disagreements were resolved through discussion between authors and consultation with project supervisors. The full text of each article marked as eligible was assessed for final inclusion. The information extracted from retained studies was: study design, sample characteristics (size, age, sex, socio-demographic background), clinical characteristics (ascertainment of clinical diagnosis, presence of co-occurring conditions), outcome measures (type of measure, unit of measure, method and tool used, mean and standard deviation, SD). Data not available from the publication were systematically requested from corresponding, first or senior authors via e-mail. Publications for which data were initially not available and were received by the authors are indicated in Table 1. Supplement 3 reports a list of reviews we screened to detect any eligible study that could have been missed via the electronic search.

## Outcomes and assessment of study quality

We calculated the standardized mean difference (Hedge’s g) and its variance for studies that reported the mean and SD of any eligible outcome measure, in people with and without ASD. The natural logarithm of the odds ratio (LogOR) and its variance were calculated for studies that reported the prevalence of vision disorder/problem in people with and without ASD, or the prevalence of ASD in people with and without vision problems/disorders[30]. Study quality was rated with the Appraisal tool for Cross-Sectional Studies (AXIS[31]) (see Supplement 4).

## Data synthesis and analysis

A narrative synthesis was performed for all studies included in the systematic review. Meta-analyses were conducted in *R 4.1.0* to estimate the pooled effect size across studies for each outcome, whenever at least two studies reporting on the same outcome were available. Random-effects meta-analytic models were fitted to the data in *metafor,[32]* with effect sizes nested within studies for those that reported multiple effect sizes for the same component, to account for non-independence of data (multivariate models). The Restricted Maximum-Likelihood (REML) estimator was used with Knapp-Hartung confidence interval adjustment[33]. The Cochran’s Q test, H2 and I2 were used to investigate heterogeneity[34]. Publication (small study) bias was assessed visually using funnel plots and quantitatively with the Egger’s test[35], whenever at least 10 effect sizes were included in the meta-analysis, as suggested by Borenstein and colleagues[36]. For multivariate meta-analytic models, the rank correlation test for funnel plot asymmetry was used[37]. Trim and fill analyses were performed – when publication bias was detected – to re-estimate the effect size considering the effect of any potentially missing studies due to this bias[38]. We planned to conduct meta-regressions to investigate potential confounding effects of age, when feasible.

# RESULTS

Out of 15,739 de-duplicated references initially retrieved, we screened 229 potentially eligible full texts. Forty-four studies met inclusion criteria (reasons for exclusion of studies for which we checked the full text are in Supplement 3) and were included in the review, together with five additional studies identified from references of retrieved articles (Figure 1, Table 1). Forty-six studies (encompassing 15,629,159 individuals, 88,370 with ASD; 28.2 % females) were included in the meta-analyses. Results of the narrative synthesis and meta-analyses are reported below, grouped by type of study/outcome. Results of the meta-analysis across outcomes are also summarized in Table 2.

[Figure 1 approximately here]

[Table 1 approximately here]

[Table 2 approximately here]

## Prevalence of vision disorders in people with vs. without ASD

Thirteen studies investigated the prevalence of vision disorders in children and adolescents with and without ASD and were included in the meta-analyses. Three studies investigated anisometropia[39-41], four astigmatism[39-42], two hyperopia[40, 41], three myopia[39-41], four strabismus[27, 39, 41, 43], and two phoria[44, 45]. Six studies investigated general vision problems/disorders; of these, four were on children and adolescents[27, 43, 46, 47], one on adults[48] and one[49] included children, adolescents and adults.

We found an increased prevalence of strabismus in children with vs. those without ASD (logOR = 1.5521, SE = 0.0134, 95% CI = [1.5258; 1.5783], *z* = 115.9041, *p* < 0.0001; non-significant heterogeneity: I2 = 0.0%, H2 = 1.00, Q = 1.0545, p = 0.7881; publication bias was not detected: Test for Funnel Plot Asymmetry: z = 1.0121, p = 0.3115; Table S2, Figure S1 and S2). A significantly increased prevalence of general/unspecified vision or eye problems/disorders was found in people with compared to those without ASD (logOR = 1.4811, SE = 0.1952, 95% CI = [1.0558; 1.9064], *t* = 7.5882, *p* < 0.0001; significant heterogeneity: Q = 568.4288, p < 0.0001; publication bias was not detected: Kendall's tau = 0.2821, p = 0.2044; Table S3, Figure S3 and S4). This result was not moderated by age (F2,10 = 0.6557, p = 0.5400). The risk of other vision disorders did not significantly differ between people with and without ASD (see supplements 6-12).

It was not possible to meta-analyze outcomes reported in less than two studies. Among these, Anketell et al[50] found a similar prevalence of uncorrected refractive error in those with compared to those without ASD (OR = 1.2819, 95 % CI = [0.6305; 2.6062]). Chang et al.[27], in a population study including more than 10 million children, found increased prevalence of amblyopia (adjusted OR = 2.45, 95% CI = [2.35; 2.56]) and nystagmus (adjusted OR = 4.88, 95% CI = [4.57; 5.22]) in autistic children compared to neurotypical controls. Another study,[51] using the Structured Interview for Assessing Perceptual Anomalies-Child Version (SIAPA-CV) to compare self-reported vision problems in children with and without ASD, found an increased prevalence of self-reported sensory anomaly in the visual domain in children with compared to those without ASD.

## Differences in measures of visual acuity between individuals with and without ASD

Twenty studies analyzed measures of visual acuity in people with and without ASD and were included in the meta-analyses: twelve studies investigated visual acuity[39, 44, 45, 52-60], six refractive errors[39-42, 45, 50], two stereoacuity[61, 62], four accommodation problems[45, 49, 50, 61], and three peripheral vision[44, 63, 64].

The meta-analysis on visual acuity did not show any statistically significant differences between people with ASD and neurotypical controls (Hedge’s g = 0.2257, SE = 0.3420, 95% CI = [-0.4900; 0.9415], *t* = 0.6601, p = 0.5171; significant heterogeneity: Q = 84.7669, p < 0.0001; publication bias was not detected: Kendall's tau = -0.2000, p = 0.7194; Table S9, Figure S15 and S16). This result was not moderated by age (F1,18 = 0.2777, p = 0.6046).

Conversely, we found evidence of increased refractive errors (Hedge’s g = 0.2364, SE = 0.0836, 95% CI = [0.0437; 0.4291], *t* = 2.8285, p = 0.0222; significant heterogeneity: Q = 18.8589, p = 0.0156; publication bias was not detected: Kendall's tau = 0.5000, p = 0.0752; Table S10, Figure S17 and S18) and worse peripheral vision (Hedge’s g = -0.8232, SE = 0.1917, 95% CI = [-1.3159; -0.3304], *t* = -4.2946, p = 0.0078; non-significant heterogeneity: Q = 4.8075, p = 0.4398; publication bias was not detected: Kendall's tau = -0.2000, p = 0.7194; Table S11, Figure S19 and S20) in children and adolescents with ASD compared to neurotypicals. Increased accommodation deficits (Hedge’s g = 0.6809, SE = 0.2057, 95% CI = [0.2776; 1.0841], *z* = 3.3049, *p* = 0.0009; non-significant heterogeneity: I2 = 57.06%, H2 = 2.33, Q = 6.9331, p = 0.0741; publication bias was not detected, Test for Funnel Plot Asymmetry: z = -0.2545, p = 0.7991; Table S12, Figure S21 and S22) were found in people with ASD vs. neurotypical controls, regardless of age (QM = 0.0254, p = 0.8734). Lastly, we found poorer stereoacuity (Hedge’s g = -0.7284, SE = 0.2115, 95% CI = [-1.1430; -0.3139], *z* = -3.4438, p = 0.0006; non-significant heterogeneity: Q = 0.8974, p = 0.3435; Table S13, Figure S23 and S24) in people with ASD vs. neurotypical controls. Meta-regression to investigate effect of age could not be conducted for this meta-analysis, since only two studies were included.

## Anatomical ocular measures and electroretinogram in people with and without ASD

Two studies investigating retinal thickness in people with and without ASD[65, 66] and two investigating RNFL[65, 67], were included in the meta-analyses on anatomical measures. Lastly, three studies (all from the same research group) investigating electroretinogram (ERG) patterns (i.e., a-wave and b-wave amplitudes) in autistic people and neurotypicals were included[68-70].

We found statistically significantly increased retinal thickness in people with ASD vs. without (Hedge’s g = 0.2883, SE = 0.0910, 95% CI = [0.0657; 0.5110], *t* = 3.1686, p = 0.0194; non-significant heterogeneity: Q = 0.8113, p = 0.9918; Table S16, Figure S29 and S30). A meta-regression to investigate the moderating effects of age could not be conducted, since only two studies were included in this meta-analysis. We did not find any statistically significant differences on RNFL (Hedge’s g = -0.0170, SE = 0.2904, 95% CI = [-0.6562; 0.6222], *t* = -0.0585, p = 0.9544; significant heterogeneity: Q = 21.9618, p = 0.0247; Table S17, Figure S31 and S32) between young adults with and without ASD.

The meta-analysis showed no statistically significant differences on ERG measures between people with and without ASD (Hedge’s g = -0.7655, SE = 0.4435, 95% CI = [-1.6725; 0.1415], *t* = -1.7262, p = 0.0949; significant heterogeneity: Q = 508.4720, p < 0.0001; publication bias detected: Kendall's tau = -0.3465, p = 0.0077; Table S18, Figure S33 and S34a). This result was not moderated by age (F1,28 = 0.1808, p = 0.6740). Estimation from trim and fill analyses showed that no study was missing due to publication bias in the meta-analysis conducted on ERG measures (Figure S34b). In line with these findings, Tebartz van Elst[60] (not included in meta-analysis, since it was the only study to investigate retinal background noise and contrast gain) did not find any evidence of alterations in electrophysiological retinal contrast processing between adults with ASD and neurotypical controls.

Five studies investigated other anatomical parameters[39, 42, 61, 65, 66], but could not be included in the meta-analysis since there were not at least two studies reporting on the same measure. One study could not be included[71] due to reporting data in format incompatible with meta-analysis. Little et al.[66] found increased axial length in children with ASD vs. neurotypicals. AlGarzaie et al.[39] investigated corneal characteristics in autistic children and adolescents and found no statistically significant group differences on corneal shape descriptors (e.g., corneal asphericity, inferior superior index, opposite sector index, and differential sector index). Little et al.[42] assessed corneal power parameters, and, similarly, found no significant group differences on such measures. Coulter et al.[61] reported statistically significant differences in near point of convergence (NPC) between children and adolescents with ASD and neurotypical controls (with larger NPC in controls), but not any group differences on near fusional divergence and convergence. Garcia Medina[71] investigated retinal thickness, and RFNL thickness, and found no significant group differences between autistic adolescents and neurotypicals.

## Differences in functional measures of vision between people with and without ASD

Five studies investigating color vision[72-76] and ten assessing contrast sensitivity were included in the meta-analyses[39, 77-85].

The meta-analysis on color vision showed significantly increased difficulties/errors and reduced accuracy in color discrimination in people with ASD compared to those without (Hedge’s g = 0.6879, SE = 0.1758, 95% CI = [0.2721; 1.1037], *t* = 3.9122, *p* = 0.0058; non-significant heterogeneity: Q = 9.9928, p = 0.1890; publication bias was not detected, Kendall's tau = 0.5714, p = 0.1890; Table S14, Figure S25 and S26). We found reduced contrast sensitivity and increased difficulties/errors in contrast discrimination in people with ASD, compared to those without (Hedge’s g = -0.4523, SE = 0.0728, 95% CI = [-0.6032; -0.3014], *t* = -6.2156, *p* < 0.0001; non-significant heterogeneity: Q = 21.8909, p = 0.4664; publication bias was not detected, Kendall's tau = -0.0514, p = 0.7540; Table S15, Figure S27 and S28). Both effects were not moderated by age (color: F1,6 = 1.6604, p = 0.2450; contrast: F2,20 = 0.2033, p = 0.8177), suggesting that both children/adolescents and adults with ASD showed alterations on functional measures of vision, compared to those without ASD.

One study on color vision[86] could not be included in the meta-analysis. In this study, children with ASD showed similar contrast sensitivity profiles for flickering stimuli compared to neurotypical peers. Another study [87] found no group differences in contrast sensitivity on detection of luminance gratings, detection of chromatic gratings or direction-of-motion discrimination of chromatic gratings, but increased contrast sensitivity in neurotypical vs. ASD on direction-of-motion discrimination of luminance gratings.

We did not find any study investigating the prevalence of ASD in people with vision disorders.

# DISCUSSION

We conducted the first comprehensive meta-analysis investigating the relationship between ASD and a broad range of disorders of vision, as well as functional and structural measures of vision. While meta-analyses can provide a definitive answer to a research question, more often their main value is to quantitatively synthesize the available literature while pointing to areas that deserve further research and methodological improvement. The latter is certainly the case for our meta-analysis. We will now discuss, in turn, the results for vision disorders and visual acuity, for anatomical and electroretinogram measures and, finally, for color vision and contrast sensitivity.

We found evidence of an association between ASD and strabismus. Being an impairment of the parallel alignment of the eyes due to weak control of vergence movements[88], strabismus is likely to affect stereoacuity and accommodation, which our study also found altered in individuals with ASD. These findings are in line with and extend previous literature suggesting that ASD is associated with weak oculomotor control arising from atypical functioning of multiple neural circuits[26]. Our meta-analysis also found increased refractive error in people with ASD but did not find evidence of increased prevalence of disorders of refraction, which often arise from abnormalities of the lens, cornea and globe. One possible explanation for this conflicting result is that categorical diagnoses require a cut-off in terms of refractive error[89]. Moreover, as ASD is a condition with heterogeneous presentations, it is possible that refractive errors below these diagnostic thresholds characterize some people (but not everyone) with ASD. Similarly, this might explain why we found evidence of more severe accommodation problems but not increased prevalence of disorders of refractive error in people with ASD. Accommodation is a process that helps to adjust for near vision and to maintain attentional focus, and it is partly modulated by the parasympathetic nervous system[90]. In line with our results, multiple autonomic, pupillary and convergence dysfunctions have been indeed reported in those with ASD[43, 61, 91-93] and may contribute to the attentional and sensory processing abnormalities typically reported in people with this condition.

Our study also highlighted that people with ASD experience problems in peripheral vision, which could contribute to the well-known local processing bias observed in this condition. While some authors have proposed that the local processing bias in ASD may arise from impaired rod-function in the retina[63], others suggested that it may emerge from abnormal magnocellular pathway function[64] or from altered cortically-mediated integration of spatiotemporal information[94]. It is therefore not clear what causes problems in peripheral vision in people with ASD. Further studies should assess if they arise from atypical functioning of retinal structures or if they are driven by higher order attentional mechanisms. Interestingly, we did not find any evidence of reduced visual acuity in people with vs. without ASD. There was, however, significant heterogeneity due to the variety of methodologies employed by the included studies to measure visual acuity.

In relation to anatomical measures, we found increased retinal thickness in people with ASD vs. neurotypical controls, but no differences in retinal nerve fiber layer thickness or electroretinogram patterns. However, the meta-analyses on retinal thickness and retinal nerve fiber layer thickness were based only on two studies each, and the meta-analysis on electroretinogram patterns included three studies, all from the same research group. Further studies from independent using ocular coherence tomography[95] and electroretinogram may prove fruitful to fully clarify if ASD is characterized by anatomical and electroretinogram alterations.

Lastly, when investigating functional measures of vision, we found that people with ASD show impairments in color vision and contrast discrimination. Impairments in these functions can arise from functional alterations in the retina (e.g., detected by electroretinogram)[96-98]. As reported above, however, we did not find any significant difference in electroretinogram patterns between people with and without ASD. It is therefore possible that problems in color discrimination and reduced contrast sensitivity arise from impairments in top-down visual processing in ASD, as suggested by several theoretical models of the condition. For example, the Weak Central Coherence Theory[99] posits that functional vision impairments may be due to a detail-focused processing style that characterizes those with ASD and leads to reduced ability to process visual stimuli as a whole. Conversely, the Enhanced Perceptual Functioning model[100] proposes that atypical early visual and spatial processing mechanisms may lead to functional problems of vision in ASD. As we did not find any anatomical or electroretinogram differences between people with and without ASD we speculate that problems in color vision and reduced contrast sensitivity are likely to emerge from higher-order cognitive mechanisms that are affected in those with ASD. However, these findings are only preliminary due to paucity of studies included in the meta-analyses.

In summary, our study corroborates and extends findings from previous narrative reviews in the field[6, 22-24], providing quantitative evidence of a relationship between ASD and disorders of vision, and adding up to the literature documenting problems in higher order visual processing[101, 102], motion perception[25, 103], gaze patterns[104, 105], oculomotor disturbances[26] and pupil dynamics[93] in those with ASD. Taken together, our findings suggest that both lower- and higher-order visual mechanisms are likely to be affected in ASD (or, at least, in a sizeable portion of them), and they could partly explain (together with alterations in other sensory domains) the core symptoms of the condition, including social and interaction difficulties and restricted/repetitive behaviors[106, 107].

Disentangling the specific effects of ASD and the effects of conditions that co-occur with ASD, on visual functioning, has however proven difficult. ASD is known to emerge, in some cases, from genetic syndromes that directly affect the structural and functional development of neural systems (including the visual system)[16]. In these cases, problems of vision and socio-communication deficits may arise as consequences of atypical brain development due to genetic factors[108, 109]. Moreover, while there is evidence that atypical visual processing characterizes infants later diagnosed with ASD[110] – therefore, preceding the development of social attention deficits[111] – there is also evidence of people with visual impairment (without ASD) experiencing difficulties in social interactions and communications[7, 112, 113]. This makes it difficult to understand what causal relationship (if any) exists between ASD and vision disorders. Lastly, ASD co-occurs with several neurodevelopmental and psychiatric disorders[114], including Attention-Deficit/Hyperactivity Disorder (ADHD), schizophrenia and intellectual disability, which have been proposed to be associated with vision disorders themselves[115-117]. While there is no meta-analytic evidence of this hypothesis for schizophrenia or intellectual disability, we recently conducted a systematic review and meta-analysis on the association between ADHD and vision disorders[115]. We found that ADHD, partly in line with our findings on ASD, was associated with increased prevalence of strabismus, general vision problems, impaired accommodation, and deficits in color and contrast discrimination. This is not surprising, considering the high co-occurrence between ADHD and ASD[118] and the fact that these conditions are likely to arise from shared etiological factors[119, 120]. Similarly, we found no association with myopia, retinal thickness, and visual acuity in neither ASD nor ADHD. However, there were also some discrepancies between ASD and ADHD. We found an association with increased refractive error and retinal nerve fiber layer thickness in ASD, but not ADHD. Reciprocally, we found an association with increased prevalence of astigmatism and hyperopia in ADHD, but not ASD.

Based on the neuro-constructivist model[121], it could be speculated that atypical functioning of sensory systems - not just limited to the visual domain - during critical developmental periods (e.g., early infancy) may impact the acquisition of crucial skills and abilities, e.g., in the social and cognitive domains, partly facilitating the emergence of symptoms of neurodevelopmental conditions such as ASD or ADHD. In the case of ASD, vision problems from an early age - especially if not appropriately and promptly treated - may exacerbate socio-communication difficulties and restricted/repetitive behaviors. This theoretical concern is well supported given that visual impairments has been shown to be a significant risk factor for the development of ASD and autistic traits [6-8]. Therefore, evidence from this systematic review and meta-analysis provides a rationale for a systematic visual examination in people with ASD [47, 122]. Furthermore, to complement evidence showing the effectiveness of early intervention in improving function and prognosis in ASD [123], our findings provide a strong rationale to test interventions aimed at addressing vision disorders in infants and young children with suspected or diagnosed ASD.

Our study should be considered in light of its limitations. A relatively low number of eligible studies were retrieved. Moreover, due to methodological issues observed in individual studies included in our meta-analysis, some of our conclusions need to be taken with caution. We were not able to control for IQ (even though we planned to do, considering the proposed association between intellectual disability and vision problems), because an insufficient number of included studies reported this data. Moreover, although initially planned, we could not properly assess, across all meta-analyses, the effects of age on the association between ASD and problems of vision. Longitudinal studies (e.g., on infants at risk of developing ASD) should be conducted to shed light on the factors associated with the early emergence of symptoms of ASD, visual problems and cognitive difficulties. Further research should also consider additional common risk factors associated with both ASD and disorders of vision including low birth weight[124, 125], prematurity[9, 125], congenital infections[10, 126, 127], and nutritional deficiencies[11, 12]. Additionally, many included studies did not address the possible role of medications. While there are no approved medications that directly target the symptoms of ASD, many children with ASD are prescribed antipsychotics, psychostimulants and other off-label use medications to target behavioral problems[128]. Antipsychotics and psychostimulants act on dopaminergic and cholinergic neurons, which are involved in functioning of the visual system, central and autonomic nervous systems[129]. For example, antipsychotic medications are known to produce, in some cases, blurred vision, ocular movement disorders, color and contrast discrimination abnormalities, retinopathy and glaucoma[130]. Similarly, psychostimulants affect vision, at least in some cases, leading to changes in visual function[131-133] and changes at the level of the retina[98]. An important achievement for future research would therefore be to clarify whether medications commonly used to target co-occurring symptoms in ASD affect vision functioning in people with this condition.

Cross-study heterogeneity was significant for the meta-analyses on visual acuity, refractive error, astigmatism, general vision problem, RNFL and, ERG. This heterogeneity is probably due to differences in the methods used for obtaining anatomical measures, different paradigms used to measure visual acuity and refractive error, and heterogeneity in the ascertainment and diagnosis of study participants. Additionally, the data were extracted from low powered case control studies and high-powered population studies, however the random-effects model we used decreases the weight of the high-powered population studies. Moreover, high heterogeneity in some of our meta-analyses could be explained by the fact that studies were uncontrolled or controlled for different set of confounders, and this is likely to have led to high heterogeneity in some of the meta-analyses.

The studies in our meta-analyses varied in terms of the criteria used to define ASD and the cut-offs used to make categorical diagnoses of vision disorders, which suggests the need, in future research, for more standardized diagnostic measures. Publication bias was detected for the meta-analysis on ERG, but the trim and fill analysis did not detect any missing publications. Lastly, because most of the studies we included were based on clinically referred populations, the generalizability of our results is limited to such samples due to Berkson's bias[134] (i.e., a selection bias that can arise when the sample is taken not from the general population, but from a subpopulation). We could not address potential confounding variables as there were not provided in most of the constituent studies. Thus, our findings should be viewed cautiously, and future work should adjust for potential clinical differences between cases and controls.

In conclusion, we found meta-analytic evidence of a significant association between ASD and several vision problems, and some structural or anatomical alterations of the eye and the visual system. Further studies are needed to clarify what type of causal relationship (if any) exists between ASD and problems of vision. Such work may eventually show that problems of vision from an early age may provide bio-markers for ASD.

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# Conflict of Interest

In the past year, Dr. Faraone received income, potential income, travel expenses continuing education support and/or research support from Aardvark, Aardwolf, Akili, Atentiv, Corium, Genomind, Ironshore, Medice, Noven, Otsuka, Sandoz, Sky Therapeutics, Supernus, Tris, and Vallon. With his institution, he has US patent US20130217707 A1 for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. In previous years, he received support from: Alcobra, Arbor, Aveksham, Axsome, CogCubed, Eli Lilly, Enzymotec, Impact, Janssen, KemPharm, Lundbeck/Takeda, Shire/Takeda, McNeil, NeuroLifeSciences, Neurovance, Novartis, Pfizer, Rhodes, Shire, and Sunovion. He also receives royalties from books published by Guilford Press: *Straight Talk about Your Child’s Mental Health*; Oxford University Press: *Schizophrenia: The Facts;* and Elsevier: *ADHD:* *Non-Pharmacologic Interventions.* In addition, he is the program director of www.adhdinadults.com. Dr. Faraone is supported by the European Union’s Horizon 2020 research and innovation programme under grant agreement No 965381; NIMH grants U01AR076092-01A1, 1R21MH1264940, R01MH116037; 1R01NS128535 – 01; Oregon Health and Science University, Otsuka Pharmaceuticals, Noven Pharmaceuticals Incorporated, and Supernus Pharmaceutical Company.

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All other authors declare no conflict of interest.

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FIGURE LEGENDS

## Figure 1. PRISMA flowchart. *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

**TABLE LEGENDS**

**Table 1.** Characteristics of studies investigating vision in ASD

**Table 2.** Summary of meta-analytic results for each outcome

# TABLES

## Table 1. Characteristics of studies investigating vision in ASD

| **Study** | **Sample characteristics** | **Measure(s) investigated** | **Main findings** |
| --- | --- | --- | --- |
| Albrecht, 2014 a | Children/Adolescents. Clinical group: n=31 (Mean age: 10.6 years; 16% F); Control group: n=33 (Mean age: 10.6 years; 21% F) | Visual Acuity | No significant group difference in visual acuity |
| AlGarzaie, 2021 | Children/Adolescents. Clinical group: n=31 (Mean age: 12.78 years; 68% F); Control group: n=60 (Mean age: 13.65 years; 55% F) | Vision or Eye Disorders, Contrast Discrimination, Visual Acuity, Anatomical measures | No significant group difference in visual acuity, corneal power, corneal shape indices or contrast discriminationIncreased prevalence of astigmatism in ASD group |
| Anketell, 2016 | Children/Adolescents. Clinical group: n=105 (Mean age: 10.9 years; 19% F); Control group: n=202 (Mean age: 11.5 years; 45% F) | Vision or Eye Disorders, Visual Acuity | No significant group difference in refractive errorIncreased incidence of astigmatism in ASD group |
| Anketell, 2015 | Children/Adolescents. Clinical group: n=113 (Mean age: 10.9 years; 19% F); Control group: n=206 (Mean age: 11.5 years; 45% F) | Visual Acuity | No significant group difference in visual acuity |
| Anketell, 2018 | Children/Adolescents. Clinical group: n=95 (Mean age: 10.9 years; 19% F); Control group: n=202 (Mean age: 11.5 years; 45% F) | Visual Acuity, Vision Disorders | No significant group difference in refractive errorIncreased lag of accommodation and near visual acuity in ASD group |
| Ashwin, 2009 | Adults. Clinical group: n=15 (Mean age: 38.93 years; 0% F); Control group: n=15 (Mean age: 27.6 years; 0% F) | Visual Acuity | Increased visual acuity in ASD group |
| Bertone, 2005 b | Young Adults. Clinical group: n=13 (Mean age: 20.5 years; % F not reported); Control group: n=13 (Mean age: 22.3 years; % F not reported) | Contrast Discrimination | No significant group difference in contrast discrimination |
| Bölte, 2012 | Young adults. Clinical group: n=34 (Mean age: 19.8 years; 12% F); Control group: n=26 (Mean age: 20.1 years; 15% F) | Visual Acuity | No significant group difference in visual acuity. |
| Brosnan, 2012 | Children/Adolescents. Clinical group: n=13 (Mean age: 13.85 years; 0% F); Control group: n=13 (Mean age: 14.69 years; 0% F) | Visual Acuity | Increased visual acuity in ASD group. |
| Chang, 2021 b | Children. Clinical group: n=61167 (Mean age: 7.4 years; 20% F); Control group: n=10815576 (Mean age: 8.1 years; 50% F) | Vision or Eye Disorders | Increased prevalence of optic neuropathy, retinopathy of prematurity, amblyopia, nystagmus and strabismus in children with ASD. |
| Classen, 2013 | Children/Adolescents. Clinical group: n=22 (Mean age: 15.05 years; 23% F); Control group: n=22 (Mean age: 14.32 years; 41% F) | Vision or Eye Disorders, Visual Acuity | Decreased right eye visual acuity and depth perception in ASD group. No significant group difference in binocular visual acuity, left eye visual acuity, peripheral field or prevalence of phoria |
| Constable, 2020 | Children and Young Adults. Clinical group: n=90 (Mean age: 13 years; 27% F); Control group: n=87 (Mean age: 13.8 years; 53% F) | Electroretinogram, Anatomical measures | Decreased b-wave and a-wave amplitudes at high flash strengths and slower b-wave peak times in ASD group. |
| Constable, 2021 a | Children and Young Adults. Clinical group: n=55 (Mean age: 13.6 years; 25% F); Control group: n=87 (Mean age: 14 years; 49% F) | Electroretinogram, Anatomical measures | Significant interaction between groups and flash strengths for b-wave amplitude. No significant interaction between groups for photopic negative response measures of amplitude or time. |
| Constable, 2016 | Adults. Clinical group: n=11 (Mean age: 37.2 years; 9% F); Control group: n=15 (Mean age: 36.9 years; 27% F) | Electroretinogram, Anatomical measures | Reduced b-wave amplitudes related to cone-ON-bipolar cell synapse in ASD group. No group difference in a-wave parameters that indicate normal phototransduction. |
| Coulter, 2021 | Children/Adolescents. Clinical group: n=24 (Mean age: 11.7 years; 41% F); Control group: n=27 (Mean age: 11.2 years; 33% F) | Visual Acuity, Anatomical measures | Decreased near point convergence and stereoacuity in ASD group. No significant group difference in negative fusional vergence, positive fusional vergence, refractive error, near phoria or distance phoria. |
| Davis, 2006 | Children/Adolescents. Clinical group: n=9 (Mean age: 12.3 years; 0% F); Control group: n=9 (Mean age: 11.9 years; 33.3% F) | Contrast Discrimination, Vision or Eye Disorders | Decreased contrast sensitivity in ASD group. Increased visual perceptual anomalies in ASD group |
| De Jonge, 2007 | Children and Young Adults. Clinical group: n=29 (Mean age: 16.6 years; % F not reported); Control group: n=32 (Mean age: 17.6 years; % F not reported) | Contrast Discrimination | No significant group difference in contrast sensitivity. |
| Emberti Gialloreti, 2014 | Adults. Clinical group: n=24 (Mean age: 23 years; 17% F); Control group: n=24 (Mean age: 23.9 years; 17% F) | Anatomical measures | No significant group difference in global retinal nerve fiber layer thickness or superior, inferior, or temporal quadrants. Decreased nasal quadrant retinal nerve fiber layer thickness in ASD group. |
| Falkmer, 2011 | Adults. Clinical group: n=24 (Mean age: 24.9 years; 29% F); Control group: n=25 (Mean age: 26.5 years; 68% F) | Visual Acuity | No significant group difference in visual acuity. |
| Franklin, 2010 | Children/Adolescents. Clinical group: n=14 (Mean age: 13.71 years; 0% F); Control group: n=14 (Mean age: 13.93 years; 0% F) | Color Vision | Increased errors in color discrimination task and increased chromatic discrimination thresholds in ASD group. |
| Franklin, 2008 | Children/Adolescents. Clinical group: n=19 (Mean age: 10.9 years; 0% F); Control group: n=14 (Mean age: 9.8 years; 0% F) | Color Vision | Decreased color memory, color search and chromatic discrimination in ASD group. No significant group difference in categorical perception of color. |
| Garcia-Medina, 2020 | Young Adults. Clinical group: n=13 (Mean age: 16.6 years; 23% F); Control group: n=14 (Mean age: 16.9 years; 29% F) | Anatomical measures | Increased macular and optic nerve perfusion density and increased macular optic nerve flux at peripapillary inferior quadrant in ASD group, no difference in temporal, superior and nasal quadrants.Increased macular and pRNFL thickness in inferior sector in ASD group, no difference in temporal, superior or nasal sector. |
| Garcia-Medina, 2017 | Young Adults. Clinical group: n=27 (Mean age: 13.7 years; 17% F); Control group: n=27 (Mean age: 13.7 years; 17% F) | Anatomical measures | Increased foveal thickness at total retina, total inner retina, inner plexiform and inner nuclear in ASD group, but no group difference in retinal nerve fiber layer, ganglion cell, total outer retina, outer plexiform or photoreceptors.Increased macular thickness at total retina, total inner retina in ASD group, but no difference retinal nerve fiber layer, ganglion cell, inner plexiform, inner nuclear, total outer retina, outer plexiform and photoreceptors.Increased peripapillary retinal nerve fiber layer thickness in inferior quadrant of ASD group, but no difference in superior, nasal or temporal quadrants. |
| Greenaway, 2013 | Children/Adolescents. Clinical group: n=17 (Mean age: 12 years; 30% F); Control group: n=17 (Mean age: 12 years; 30% F) | Contrast Discrimination | Decreased contrast discrimination in ASD in steady pedestal task in ASD but no significant group difference in contrast discrimination in pulsed pedestal task. |
| Guy, 2016 | Children/Adolescents. Clinical group: n=34 (Mean age: 11 years; 3% F); Control group: n=55 (Mean age: 10.5 years; 36% F) | Contrast Discrimination | Decreased contrast sensitivity in ASD group for children at age six. Decreased contrast sensitivity in ASD group for children at age ten. No significant group difference in contrast sensitivity for children at age thirteen. |
| Heaton, 2008 | Children/Adolescents. Clinical group: n=13 (Mean age: 11.4 years; % F not reported); Control group: n=13 (Mean age: 11 years; % F not reported) | Color Vision | Decreased color discrimination in ASD group. |
| Kéïta, 2010 a | Children and Young Adults. Clinical group: n=19 (Mean age: 19.63 years; % F not reported); Control group: n=15 (Mean age: 19.4 years; % F not reported) | Visual Acuity | No significant group difference in visual acuity. |
| Kéïta, 2014 b | Children and Young Adults. Clinical group: n=21 (Mean age: 20.4 years; % F not reported); Control group: n=15 (Mean age: 19.4 years; % F reported) | Contrast Discrimination | Increased contrast discrimination for luminance defined high spatial frequency gratings in ASD but no significant group difference for luminance defined low spatial frequency gratings. No significant group difference in contrast discrimination in texture defined high and low frequency gratings. |
| Koh, 2010 (Neuropsychologia) a | Adolescents. Clinical group: n=17 (Mean age: 14.83 years; 6% F); Control group: n=39 (Mean age: 15.25 years; 44% F) | Contrast Discrimination | Increased contrast sensitivity on direction-of-motion discrimination of luminance gratings. No significant group difference in contrast sensitivity on detection of luminance gratings, detection of chromatic gratings or direction-of-motion discrimination of chromatic gratings. |
| Koh, 2010 (JADD) b | Children/Adolescents. Clinical group: n=10 (Mean age: 15.08 years; 0% F); Control group: n=25 (Mean age: 15.58 years; 44% F) | Contrast Discrimination | No significant group difference in visual acuity as measured by highest perceivable spatial frequency. No significant group different in any contrast sensitivity measures including low spatial frequency, spatial frequency producing peaking contrast sensitivity and peak contrast sensitivity. |
| Little, 2014 a | Children/Adolescents. Clinical group: n=27 (Mean age: 13.28 years; 15% F); Control group: n=39 (Mean age: 12.27 years; 64% F) | Vision or Eye Disorders, Visual Acuity | No significant group difference in visual acuity. Increased accommodative gain slopes in ASD group. Increased prevalence of phoria in ASD. |
| Little, 2013 a | Children/Adolescents. Clinical group: n=89 (Mean age: 10.9 years; 19% F); Control group: n=204 (Mean age: 11.5 years; 45% F) | Vision or Eye Disorders, Visual Acuity, Anatomical measures | Increased refractive error of refractive astigmatism and corneal astigmatism in ASD. Increased J0 refractive vector in ASD group but no significant group difference in J0 corneal power vector. |
| Little, 2016 a | Children/Adolescents. Clinical group: n=27 (Mean age: 13.2 years; 15% F); Control group: n=64 (Mean age: 12.4 years; 64% F) | Anatomical measures | No significant group difference in retinal thickness or axial length. |
| Maule, 2017 | Adults. Clinical group: n=21 (Mean age: 24.9 years; 48% F); Control group: n=16 (Mean age: 24.5 years; 63% F) | Color Vision | Decreased accuracy in ASD group for color averaging task in four element ensembles no significant group difference in eight or sixteen element ensembles. Increased accuracy for color membership identification task in ASD group. |
| Milne, 2009 | Children/Adolescents. Clinical group: n=51 (Mean age: 12.1 years; 14% F); Control group: n=44 (Mean age: 11.5 years; 70% F) | Vision or Eye Disorders, visual acuity | Increased prevalence of unspecified disorders of vision and the eye in ASD group. No significant group difference in prevalence of strabismus.Decreased visual acuity in both HF (high functioning) ASD and LF (low functioning) ASD. No significant difference in stereoacuity, convergence and divergence in both HF ASD and LF ASD. Increased near point convergence in LF ASD but no significant difference in near point convergence in HF ASD group. |
| Milne, 2013 | Adolescents and Children. Clinical group: n=11 (Mean age: 14 years; % F not reported); Control group: n=21 (Mean age: 14.4 years; % F not reported) | Visual Acuity | Decreased accuracy in peripheral vision task in ASD group, with deficits most pronounced in in nasal hemifield. |
| Mouridsen, 2017 | Adults. Clinical group: n=118 (Mean age: 49.6 years; 28% F); Control group: n=336 (Mean age: 49.6 years; 27% F) | Vision or Eye Disorders, Visual Acuity | No group difference in prevalence of unspecified eye disorders. Increased prevalence of disorders of lens, choroid, retina, vitreous body, globe and visual impairment in ASD group. |
| Norton, 2021 | Young Adults. Clinical group: n=13 (Mean age: 15.7 years; 23% F); Control group: n=18 (Mean age: 15.7 years; 28% F) | Contrast Discrimination | No significant group difference in contrast discrimination. |
| Pellicano 2005 b | Children/Adolescents. Clinical group: n=20 (Mean age: 9.5 years; 10% F); Control group: n=20 (Mean age: 9.75 years; 10% F) | Contrast Discrimination | No significant group difference in contrast discrimination. |
| Robertson, 2013 | Adults. Clinical group: n=20 (Mean age: 32.6 years; 35% F); Control group: n=20 (Mean age: 30.1 years; 75% F) | Contrast Discrimination | No significant group difference in contrast discrimination. |
| Rydzewska, 2019 | Children. Clinical group: n=17348 (Age: 0-15 years; 20% F); Control group: n=898983 (Age: 0-15 years; 49% F) | Vision or Eye Disorders | Increased prevalence of blindness and partial sight loss in children with ASD. |
| Rydzewska, 2018 | Adults. Clinical group: n=6649 (Age: 25+ years; 31% F); Control group: n=3739935 (Age: 25+ years; 53% F) | Vision or Eye Disorders | Increased prevalence of blindness and partial sight loss in adults with ASD. |
| Smith, 2017 b | Young Adults. Clinical group: n=22 (Mean age: 21.8 years; % F not reported); Control group: n=23 (Mean age: 23.6 years; % F not reported) | Visual Acuity | No significant group difference in stereoacuity. |
| Song, 2015 | Children/Adolescents. Clinical group: n=13 (Mean age: 11.46 years; 8% F); Control group: n=13 (Mean age: 11.38 years; 0% F) | Visual Acuity | Decreased functional field of view in ASD group. |
| Swanson, 2020 | Children/Adolescents. Clinical group: n=1624 (Mean age: 10.3 years; 19% F); Control group: n=83858 (Mean age: 9.6 years; 49% F) | Vision or Eye Disorders | Increased prevalence of unspecified visual impairment in ASD group. |
| Tavassoli, 2011 | Adults. Clinical group: n=20 (Mean age: 30.4 years; 45% F); Control group: n=20 (Mean age: 30.7 years; 65% F) | Visual Acuity | No significant group difference in visual acuity. |
| Tebartz van Elst, 2015 | Adults. Clinical group: n=33 (Mean age: 39.5 years; 33% F); Control group: n=33 (Mean age: 34.4 years; 36% F) | Visual Acuity, Anatomical measures | No significant group difference in visual acuity, PERG contrast gain, and retinal background noise. |
| Wang, 2017 | Children. Clinical group: n=168 (Mean age: 5.01 years; 15% F); Control group: n=264 (Mean age: 5.19 years; 28% F) | Vision or Eye Disorders, Visual Acuity | No significant group difference in visual acuity, and refractive error. No significant group difference prevalence in hyperopia, myopia, astigmatism, anisometropia.Increased prevalence of strabismus in ASD group |
| Zachi, 2017 | Children/Adolescents. Clinical group: n=20 (Mean age: 9.9 years; 5% F); Control group: n=36 (Mean age: 9.64 years; 6% F) | Color Vision | Decreased color discrimination in ASD group but no specific defect found in tritan, protan or deutan axis. |

a Data not available in the original paper, gathered via email from the authors. b Study manually added to the review (retrieved from screening of reference lists).

## Table 2. Summary of meta-analytic results for each outcome

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Outcome** | **N of studies** | ***logOR*** | ***95% CI*** | ***p*** | **Heterogeneity** | **Publication bias** | **Moderating effect of age** | **Average quality of studies included a** |
| **Prevalence of Vision Disorders** |
| Anisometropia | 3 | 1.4997 | -0.0389; 3.0383 | 0.0561 | Non-significant | Not detected | n/a. All studies conducted on children/adolescents |  16.3 |
| Astigmatism | 4 | 0.3056 | -0.4069; 1.0180 | 0.3443 | Significant | Not detected | n/a. All studies conducted on children/adolescents |  15.3 |
| General vision problems\* | 6 | 1.4811 | 1.0558; 1.9064 | < 0.0001 | Significant | Not detected | Non-significant |  18.7 |
| Hyperopia | 2 | 0.4381 | -0.1621; 1.0383 | 0.1525 | Non-significant | n/a. Only two studies included | n/a. All studies conducted on children/adolescents |  16.0 |
| Myopia | 3 | 0.4564 | -0.2364; 1.1492 | 0.1966 | Non-significant | Not detected | n/a. All studies conducted on children/adolescents |  16.3 |
| Phoria | 2 | 0.2566 | -4.6456; 5.1588 | 0.8427 | Non-significant | n/a. Only two studies included | n/a. All studies conducted on children/adolescents |  13.5 |
| Strabismus\* | 4 | 1.5521 | 1.5258; 1.5783 | < 0.0001 | Non-significant | Not detected | n/a. All studies conducted on children/adolescents |  16.4 |
| **Outcome** | **N of studies** | ***Hedge's g*** | ***95% CI*** | ***p*** | **Heterogeneity** | **Publication bias** | **Moderating effect of Age** | **Average quality of studies included a** |
| **Visual acuity** |
| Accommodation deficits\* | 4 | 0.6809 | 0.2776; 1.0841 | 0.0009 | Non-significant | Not detected | Non-significant |  15.3 |
| Peripheral vision\* | 3 | -0.8232 | -1.3159; -0.3304 | 0.0078 | Non-significant | Not detected | n/a. All studies conducted on children/adolescents |  15.7 |
| Refractive Error\* | 6 | 0.2364 | 0.0437; 0.4291 | 0.0222 | Significant | Not detected | n/a. All studies conducted on children/adolescents |  15.0 |
| Stereoacuity\* | 2 | -0.7284 | -1.1430; -0.3139 | 0.0006 | Non-significant | n/a. Only two studies included | n/a. Only two studies included |  16.5 |
| Visual acuity | 12 | 0.2257 | -0.4900; 0.9415 | 0.5171 | Significant | Not detected | Non-significant |  15.3 |
| **Functional measures of vision** |
| Color discrimination difficulties\* | 5 | 0.6879 | 0.2721; 1.1037 | 0.0058 | Non-significant | Not detected | Non-significant |  15.2 |
| Contrast sensitivity\* | 10 | -0.4523 | -0.6032; -0.3014 | < 0.0001 | Non-significant | Not detected | Non-significant |  16.5 |
| **Anatomic ocular measures and electroretinogram** |
| Retinal thickness\* | 2 | 0.2883 | 0.0657; 0.5110 | 0.0194 | Non-significant | n/a. Only two studies included | n/a. Only two studies included |  14.5 |
| RFNL | 2 | -0.0170 | -0.6562; 0.6222 | 0.9544 | Significant | n/a. Only two studies included | n/a. Only two studies included |  16.5 |
| ERG | 3 | -0.7655 | -1.6725; 0.1415 | 0.0949 | Significant | Detected (no study missing based on trim-and-fill analysis) | Non-significant |  16.7 |

\*: statistically significant result.

a: based on AXIS scale scores.

Legend. logOR: natural logarithm of odds ratio; CI: confidence interval; RNFL: Retinal nerve fiber layer thickness; ERG: electroretinogram