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REVIEW PAPER

Refractive Errors Linked to Autism Spectrum Disorders in the Pediatric Population and Young Adults: A Systematic Review and Meta-Analysis

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Abstract

While previous studies have demonstrated significant eye problems in children with autism spectrum disorders (ASDs), refractive errors have not been extensively studied in the context of ASDs. We systematically reviewed twenty-eight articles to assess whether refractive errors are linked with ASDs, and to determine the prevalence of refractive errors in children with ASDs. We found no significant association between ASDs and myopia or hyperopia, but a significantly increased risk of astigmatism was observed in children with ASDs. Pooled results of single-arm studies revealed a 14.1% prevalence of myopia, a 9.8% prevalence of hyperopia, and a 16.5% prevalence of astigmatism in children with ASDs. Future studies should incorporate a prospective design with age-matched comparison groups.

Keywords Autism spectrum disorder · Autism · Refractive errors · Myopia · Hyperopia · Astigmatism

Autism spectrum disorders (ASDs) encompass a variety of neurodevelopmental anomalies with overlapping signs and symptoms including persistent social and communication difficulties, and restricted, repetitive behavioral patterns (American Psychiatric Association, 2013). Over the past 30 years, the incidence of ASDs has increased by approximately 0.06% per year (Li et al., 2022), possibly due to a rise in awareness and understanding, leading to better diagnosis, and they are estimated to affect 0.3% of the global population (Solmi et al., 2022). ASDs have transitioned from rare childhood conditions with narrow diagnostic parameters to widely recognized, extensively researched, and heterogeneous lifelong conditions (Lord et al., 2018).

Several neurological anomalies present with ocular manifestations because the eyes and brain develop from the same embryonic tissue (London et al., 2013). As structural brain alterations contribute to the pathogenesis of ASDs (Ecker, 2017), some of the clinical manifestations of ASDs — such as visual sensory alterations — may be attributable to visual defects (Simmons et al., 2009). ASDs are usually detected between 3 and 7 years of age (Mandell et al., 2005), and visually impaired children develop social deficits and repetitive behaviour analogous to children with ASDs (Wrzesińska et al., 2017). ASDs are also associated with poor eye contact, possibly linked to neural function (Chevallier et al., 2012; Hirsch et al., 2022; Senju & Johnson, 2009).

Uncorrected refractive errors are the leading cause of visual impairment globally (Dandona & Dandona, 2001; Flaxman et al., 2017). Refractive errors manifest in various forms, including myopia (difficulty seeing far objects), hyperopia (difficulty seeing near objects), and astigmatism (failure to converge light rays on a single point), and can negatively impact social development (Shah et al., 2020). Hyperopic eyes tend to have a shorter axial length that is usually corrected using convex (plus) lens, while myopic eyes tend to have a longer axial length that is usually corrected by concave (minus) lens. Astigmatism arises when the rays of lights in different meridians converge at different points. In simple hyperopic or myopic astigmatism, one meridian is focused on the retina while the other is hyperopic or myopic respectively. In compound hyperopic or myopic astigmatism, both meridians are hyperopic or myopic, respectively, but to different degrees. Mixed astigmatism arises when one meridian is hyperopic and the other is myopic. Children are hyperopic

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at birth due to a shorter axial length, but the axial length increases progressively starting around 2 years of age leading to emmetropia; children prone to myopia have a longer axial length at birth (Subudhi & Agarwal, 2023). Hyperopia and astigmatism may be of several types and etiologies (Gurnani & Kaur, 2023; Majumdar & Tripathy, 2023). Since refractive errors are widespread in children of school-going age (Tajbakhsh et al., 2022), they may exacerbate communication challenges, hinder social interactions, and deteriorate academic performance in children with ASDs. While a recent study revealed association of several eye problems in ASDs (Perna et al., 2023), it did not focus on refractive errors, and a concrete correlation with refractive errors has yet to be established. In this systematic review and meta-analysis, we aim to address whether refractive errors are linked to ASDs in children and young adults. Our secondary objective is to assess the prevalence of refractive errors in children with ASDs by analyzing single-arm studies. Our review may help in a timely diagnosis of these refractive errors, thereby improving the quality of life of children with ASDs.

Methods

This review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). We registered the protocol for this systematic review on the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42023433833).

Data Sources and Search Strategy

Two reviewers independently searched Medline (PubMed), Scopus, Science Direct, and Embase (Ovid) for relevant articles indexed from inception to May 2023. The searches were refreshed in October 2023 to identify any new articles of interest. No language restriction was applied. We combined the keywords "autism", "autism spectrum disorder", "refractive errors", "myopia", "hyperopia", "astigmatism", "child", and "adolescent" with other synonyms. The detailed search strategy for each database can be found in Online Resource 1. We eliminated the duplicate studies using Endnote 20.2.1. Two reviewers independently assessed the articles based on titles and abstracts. The full texts of the remaining articles were retrieved, and articles matching our eligibility criteria were included. Disputes were resolved by a third reviewer.

Study Selection

The studies were considered eligible for our systematic review and meta-analysis if they (a) were original studies including case reports, case series, cross-sectional studies, or cohort studies; (b) included children and young adults (< 20 years of age) with a diagnosis of ASDs; (c) evaluated at least one of the following refractive errors: myopia, hyperopia, and astigmatism. A study was excluded if it (a) was not concerned with ASD, (b) did not measure refractive errors, (c) included no children or young adults, or (d) was in a language other than English. Additionally, letters, editorials, short communications, review articles, conference abstracts, non-human studies, and book chapters were also excluded.

Data Extraction

The primary outcomes of interest were the number of subjects with ASDs having either myopia, hyperopia, or astigmatism. The total number of cases of non-autistic children with myopia, hyperopia, and astigmatism was also recorded in studies with a comparison (C) group. Demographic data including location, age, and gender, the criteria used to assess ASDs and refractive errors, and associated neurodevelopmental comorbidities were also extracted. Specific data on race and ethnicity, socioeconomic status, and educational attainment levels were not recorded, as such data was not available in most studies. All data was extracted by two reviewers independently, and a third reviewer cross-checked it.

Risk of Bias Assessment

The case reports, case series, and cross-sectional studies were assessed using the Joanna Brigg Institute's (JBI) critical appraisal tools, while the Newcastle–Ottawa Scale (NOS) was applied to the cohort studies. Two reviewers independently assessed the quality of included studies. Discrepancies were resolved by a third reviewer. The studies were rated good (low risk of bias), fair (moderate risk of bias), and poor (high risk of bias) quality based on their scores.

Statistical Analysis

We calculated the risk ratios (RRs) in a DerSimonian-Laird random effects model to address heterogeneity between the studies (Higgins et al., 2003). We used Arcsine-transformed prevalence data for one-arm studies to stabilize variance as recommended (Barendregt et al., 2013; Munn et al., 2015). However, due to recently raised concerns regarding this approach (Lin & Xu, 2020), we presented our data with 95% confidence intervals in forest plots. Percentages were converted into raw data, and a correction factor of 0.5 was applied to zero values. The meta-analysis of two-arm studies was conducted via Review Manager 5.4 (Nordic Cochrane Center, Copenhagen, Denmark) and of one-arm studies via OpenMeta[Analyst] (Center of Evidence-Based Medicine, Rhode Island, USA) (Wallace et al., 2012). We assessed heterogeneity using Higgin's I^2 statistic, and an I^2 value > 50% was considered significant (Higgins & Thompson, 2002). We used Comprehensive

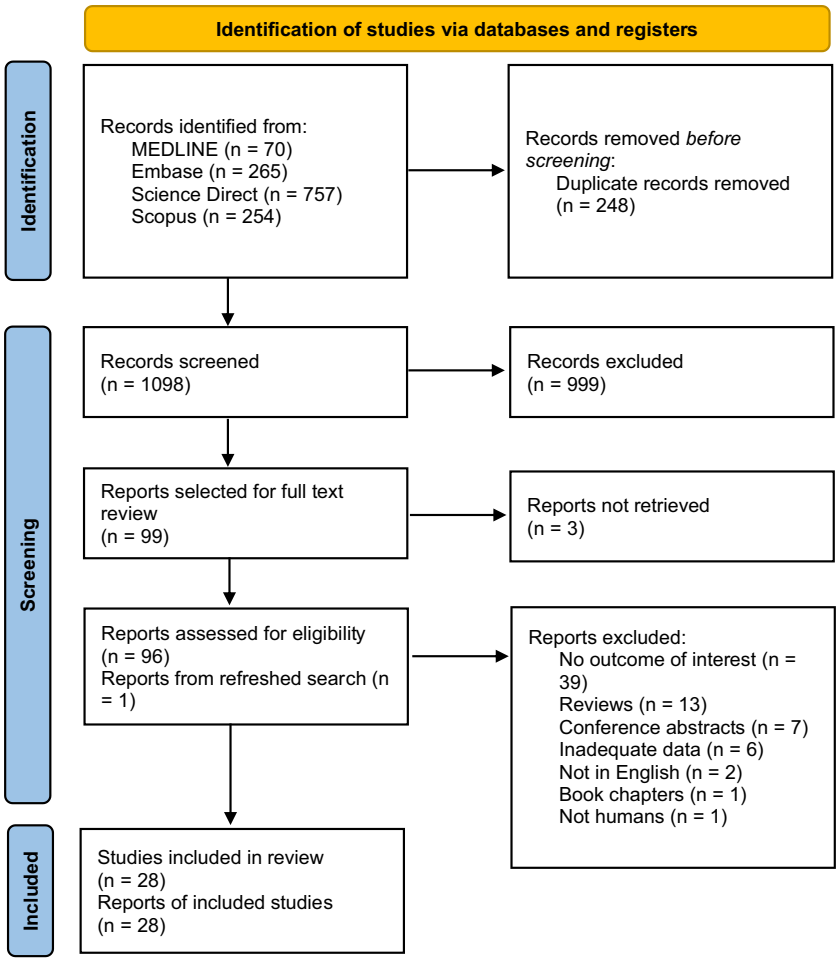

Fig. 1 PRISMA flow diagram of study selection

Meta Analyst (Biostat, Englewood, New Jersey, USA) to assess publication bias via funnel plots of standard error, and Egger's regression test (Egger et al., 1997). We conducted sensitivity analyses using a leave-one-out approach, i.e., omitting one study at a time to investigate the impact of each study on the overall effect estimates. Sensitivity analyses were also conducted by excluding the poor-quality studies to explore potential causes of heterogeneity. We conducted subgroup analyses by study design and meta-regression with the mean age of participants. All studies for which raw data could be obtained or calculated were included in the meta-analysis. Case reports were excluded from the quantitative synthesis.

Results

Literature Search

The initial search yielded 1346 papers, of which 248 were duplicates, leaving 1098 articles. The titles and abstracts of the remaining articles were assessed for eligibility, and 998 articles were excluded. The full texts of 3 papers could not be retrieved, and the full texts of 97 articles were subsequently reviewed. A secondary search yielded one additional relevant paper, and 28 papers were deemed eligible for our systematic review (ALGarzaie and Alsaqr, 2021; Amin et al., 2023; Anketell et al., 2016; Bhaskaran et al., 2018; Black et al., 2013; Cao et al., 2022a, 2022b; Chang et al., 2019; Dias et al., 2021; Ezegwui et al., 2014; Faron et al., 2021; Fryns et al., 1996; Gutiérrez et al., 2022; Ikeda et al., 2013; Kabatas et al., 2015; Kaur et al., 2016; Keith et al., 1972; Khanna et al., 2020; Lau et al., 2022; McCurry et al., 2013; Ozer et al., 2016; Pineles et al., 2010; Puri et al., 2015; Scharre & Creedon, 1992; Shen et al., 2011; Tsao et al., 2017; Tychsen et al., 2008; Wu et al., 2023; Zdonczyk et al., 2023). Figure 1 shows the PRISMA flow flowchart of the selection process.

Study Characteristics

Table 1 shows the characteristics of the included studies. The studies comprised eleven cohort studies, eleven cross-sectional studies, two case series, and four case reports published from 1972 to 2023. The studies varied in geographical

Table 1 Characteristics of included studies

Study	Study design	Country	Mean age ± standard deviation (years)	Criteria for ASDs	Criteria for significant refractive errors
Amin et al. (2023)	Cross sectional	Pakistan	3 to 20 [a]	Students from autism schools	–
Wu et al. (2023)	Cohort	Taiwan	–	ICD-9-CM	Myopia (ICD-9-CM code:367.1), Hyperopia (ICD-9-CM code:367.0), Astigmatism (ICD-9-CM code:367.2)
Zdonczyk et al. (2023)	Case series	USA	6.8, 13.3, 5.8 [c]	SRS-2	–
Gutiérrez et al. (2022)	Cohort	Spain	10.9 ± 8.1	Referred by the AMITEA Program	Hyperopia > + 2 D, Myopia > -0.50 D, Astigmatism > ± 0.75 D
Lau et al. (2022)	Cohort	Hong Kong	1 [b]	ICD 9, ICD 10	–
Cao et al., (2022b)	Case report	Canada	6 [c]	–	–
ALGarzaie & Alsaqr (2021)	Cross sectional	Kingdom of Saudi Arabia	ASD = 12.78 ± 4.49 C = 13.65 ± 3.56	–	–
Dias et al. (2021)	Cohort	USA	9.1	–	–
Faron et al. (2021)	Cohort	USA	9.9 ± 5.4	–	–
Khanna et al. (2020)	Cohort	France	5.6 [b]	DSM-5, ADOS-G, ADI-R	AAPOS age-based guidelines
Chang et al. (2019)	Cohort	USA	5.5	ICD-9, ICD-10, DSM-IV, DSM-V, ADOS-2	2017 AAO Preferred Practice Pattern guidelines for spectacle prescription
Bhaskaran et al. (2018)	Cross sectional	India	9.5	CARS	Myopia ≥ − 1.00 DS, Hyperopia ≥ + 1.0 DS, Astigmatism cylinder of ≥ 0.75
Tsao et al. (2017)	Cross sectional	Taiwan	7–18 [a]	–	Myopia ≤ − 1.0 D; High myopia ≤ − 6.0 D, Hyperopia ≥ + 1.0 D, Moderate hyperopia between + 3.0 D and + 5.0 D, Astigmatism ≥ + 0.5 D or ≤ − 0.5 D, High astigmatism ≥ + 2.0 D or ≤ − 2.0 D
Anketell et al. (2016)	Cross sectional	UK	ASD = 10.9 ± 3.3 C = 11.5 ± 3.1	Autism or Asperger's Syndrome according to ICD 10	Myopia ≤ − 0.50 D, Low hyperopia ≥ + 0.50 D or < + 2.00 D, Moderate hyperopia ≥ + 2.00 D, Astigmatism ≥ 1.00 DC
Kaur et al. (2016)	Cross sectional	India	9.5	–	Myopia ≤ − 0.5 D, Hyperopia ≥ + 1.0 D, Astigmatism ≥ ± 0.5 D
Ozer et al. (2016)	Cross sectional	Türkiye	8.85 ± 3.3	–	–
Kabatas et al. (2015)	Cohort	Türkiye	5	–	AAPOS referral criteria
Puri et al. (2015)	Cross sectional	Nepal	10.64 ± 4.12	–	Myopia < − 0.50 DS, Hyperopia > + 1.00 DS, Astigmatism ≥ 1.00 D
Ezegwui et al. (2014)	Cross sectional	Nigeria	10.28 ± 3.20	DSM-IV	Hypermetropia ≥ + 1.50 DS, Myopia > − 1.00 DS, Astigmatism ≥ ± 1.00 DC
Black et al. (2013)	Cohort	USA	–	Autism, pervasive developmental disorder, or Asperger's syndrome, reported by guardian and recorded on medical record	Necessitating a glasses prescription by the pediatric ophthalmologist (following the AAPOS guidelines for refractive correction in the pediatric population)

Table 1 (continued)

Study	Study design	Country	Mean age ± standard deviation (years)	Criteria for ASDs	Criteria for significant refractive errors
Ikeda et al. (2013)	Cohort	USA	3.25	–	Myopia and hyperopia > 3.00 D, Astigmatism > 2.00 D
McCurry et al. (2013)	Cross sectional	Peru	3 – 17 [a]	DSM-IV-TR, other ASDs, such as PDD-NOS and Asperger disorder not included	AAPOS Vision Screening Committee referral guidelines
Shen et al. (2011)	Case report	China	5 [c]	DSM-IV	–
Pineles et al. (2010)	Case series	USA	6, 13, 7 [c]	–	–
Tychsen et al. (2008)	Case series	USA	15 [c]	–	–
Fryns et al. (1996)	Case report	Denmark	6.33 [c]	–	–
Scharre and Creedon (1992)	Cross sectional	USA	7.5 [b]	DSM–III-R, board of education, multidisciplinary evaluations	Myopia ≥ 1D, Hyperopia ≥ 1D, Astigmatism ≥ 1D
Keith et al. (1972)	Case report	England	7 [c]	–	–

Age is presented as mean ± standard deviation, unless stated otherwise. *ASD*, Autism Spectrum Disorders group; *C*, Comparison group. All values in single-arm studies are for ASD groups. *ICD*, International Classification of Diseases; *CARS*, Childhood Autism Rating Scale; *DSM*, Diagnostic and Statistical Manual of Mental Disorders; *ADOS*, Autism Diagnostic Observation Schedule; *AMITEA*, Integral Medical Attention To Patients With Autism Spectrum Disorder; *ADI-R*, Autism Diagnostic Interview, Revised; *SRS*, Social Responsiveness Scale; *AAPOS*, American Association For Pediatric Ophthalmology And Strabismus; *AAO*, American Academy Of Ophthalmology

[a]Range

[b]Median

[c]Actual ages

distribution, with almost one-third of the studies originating from the USA (n = 9) (Black et al., 2013; Chang et al., 2019; Dias et al., 2021; Faron et al., 2021; Ikeda et al., 2013; Pineles et al., 2010; Scharre & Creedon, 1992; Tychsen et al., 2008; Zdonczyk et al., 2023). The population was predominantly male. The most used diagnostic criterion for ASD was the Diagnostic and Statistical Manual of Mental Disorders (DSM) (Chang et al., 2019; Ezegwui et al., 2014; Khanna et al., 2020; McCurry et al., 2013; Scharre & Creedon, 1992; Shen et al., 2011), followed by the International Classification of Diseases (ICD) (Anketell et al., 2016; Chang et al., 2019; Lau et al., 2022; Wu et al., 2023). Most studies considered refractive errors significant when necessitating spectacle prescription, but varying cutoff values were used. Only three studies compared the prevalence of refractive errors in children with ASDs with those without ASDs (ALGarzaie and Alsaqr, 2021; Anketell et al., 2016; Wu et al., 2023). The results of the included studies are depicted in Table 2.

Myopia

Of the twenty-eight included studies, nineteen reported raw data on myopia. Meta-analysis of three studies comparing ASD (1514/3710 participants) to C (14,797/35776 participants) groups yielded no significant association between myopia and ASD (RR 1.02, 95% CI 0.98 – 1.06; $p = 0.46$; $I^2 = 0\%$). Pooled estimates of sixteen studies without a comparison group showed a 14.1% (95% CI 0.082 – 0.213; $I^2 = 90.63\%$) incidence of myopia in the ASD group (165/1421 participants). The meta-analysis is depicted in Fig. 2.

No heterogeneity was present between the studies with a comparison group, while high heterogeneity was observed between the studies without a comparison group. Subgroup analysis by study design showed that the heterogeneity was lower for the cross-sectional studies (Fig. 2). Sensitivity analysis using the leave-one-out method revealed no substantial change in pooled effect estimates; RR 11.1% (95% CI 0.064 – 0.170) to RR 15.3% (95% CI 0.090 – 0.230). Sensitivity analysis omitting poor quality studies still presented considerable heterogeneity. Meta-regression with the mean age of participants showed no significant association ($p = 0.240$) with heterogeneity. We found no evidence of publication bias in the funnel plot (Egger's regression test, $p = 0.257$).

Hyperopia

Of the twenty-eight included studies, twenty reported raw data on hyperopia. Of the three studies with a comparison group, ALGarzaie and Alsaqr (2021) had zero incidence of hyperopia in both groups, so it could not be included in the two-arm meta-analysis. Meta-analysis of two studies comparing ASD (436/3710 participants) to C (1893/35776 participants) groups yielded no significant association between hyperopia and ASD (RR 1.27, 95% CI 0.46 – 3.45; $p = 0.65$; $I^2 = 99\%$). The pooled results of seventeen studies without a comparison group revealed a 9.8% (95% CI 0.066 – 0.136; $I^2 = 73.93\%$) incidence of hyperopia in the ASD group (176/1437 participants). The meta-analysis is depicted in Fig. 3.

High heterogeneity was present between the studies with a comparison group, while moderate heterogeneity was observed between the studies without a comparison group. Subgroup analysis by study design failed to show much difference (Fig. 3). Sensitivity analysis using the leave-one-out method revealed no substantial change in pooled effect estimates; RR 8.8% (95% CI 0.060 – 0.122) to RR 10.8% (95% CI 0.075 – 0.146). Sensitivity analysis omitting poor quality studies still presented considerable heterogeneity. Meta-regression with the mean age of participants showed no significant association ($p = 0.264$) with heterogeneity. We found evidence of publication bias in the funnel plot (Egger's regression test, $p = 0.032$).

Astigmatism

Of the twenty-eight included studies, nineteen reported raw data on astigmatism. Meta-analysis of three studies comparing ASD (825/3710 participants) to C (5468/35,776 participants) groups revealed that ASD significantly increases the risk of astigmatism (RR 1.63, 95% CI 1.26 – 2.12; $p = 0.0002$; $I^2 = 56\%$). Pooled results from the studies without a comparison group revealed a 16.5% (95% CI 0.108 – 0.232; $I^2 = 87.87\%$) incidence of refractive errors in the ASD group. The meta-analysis is depicted in Fig. 4.

Moderate heterogeneity was observed between the studies with a comparison group, and high heterogeneity was present between the studies without a comparison group. Subgroup analysis revealed no significant association of study design with heterogeneity (Fig. 4). Sensitivity analysis using the leave-one-out method revealed no substantial change in pooled effect estimates; RR 14.5% (95% CI 0.099 – 0.198) to RR 18.1% (95% CI 0.120 – 0.250). Sensitivity analysis omitting poor quality studies still presented considerable heterogeneity. Meta-regression with the mean age of participants showed no significant association (p = 0.134) with heterogeneity. We found no evidence of publication bias in the funnel plot (Egger's regression test, $p = 0.292$).

Case Reports

Keith et al. (1972) presented a case of a child with autism, myopia, and abnormal facial features. Fryns et al. (1996) presented a case report of two twin sisters with Cohen syndrome, having autistic features and high-grade myopia. Tychsen et al. (2008) presented a series of twelve children undergoing surgery for refractive errors, with one child having autism and

Table 2 Results of included studies

Study	Sample size, *n*	Myopia, *n* (%)	Hyperopia, *n* (%)	Astigmatism, *n* (%)	Comorbidities, *n*
Amin et al. (2023)	127 (77 M)	19 (14.96%)	15(11.81%)	9 (7.87%)	–
Wu et al. (2023)	ASD = 3551 (2910 M)	1499 (42.21%)	359 (10.11%)	775 (21.82%)	Down syndrome (19), Fragile X syndrome (5), Rett disorder (12), Prader Willi syndrome (4), others (12)
	C = 35,510 (29,100 M)	14,779 (41.62%)	1732 (4.88%)	5424 (15.27%)	Down syndrome (17), Fragile X syndrome (1), Rett disorder (3), Prader Willi syndrome (6), others (14)
Zdonczyk et al. (2023)	3	1 (33.33%)	1 (33.33%)	1 (33.33%)	–
Gutiérrez et al. (2022)	344 (257 M)	54 (7.85%) eyes	135 (19.62%) eyes	130 (18.90%) eyes	–
Lau et al. (2022)	100 (80 M)	36 (36%)	14 (14%)	46 (46%)	Developmental delay (32), ID (24), ADHD (31)
Cao et al., (2022b)	1 (F)	1 (100%)	0 (0%)	0 (0%)	Developmental delay, congenital hypothyroidism
ALGarzaie & Alsaqr (2021)	ASD = 31 (21 M)	1 (3.22%)	0 (0%)	5 (16.13%) (Simple), 1 (3.22%) (Mixed), 8 (25.81%) (Compound myopic), 9 (29.03%) (Compound hyperopic)	–
	C = 60 (33 M)	0 (0%)	0 (0%)	10 (16.67%) (Simple), 0 (0%) (Mixed), 27 (45%) (Compound myopic), 17 (28.33%) (Compound hyperopic)	–
Dias et al. (2021)	4	2 (50%)	0 (0%)	0 (0%)	De novo variants in TCF7L2
Faron et al. (2021)	9	9 (100%)	0 (0%)	0 (0%)	–
Khanna et al. (2020)	51 (43 M)	2 (3.92%)	2 (3.92%)	8 (15.69%) (Compound hypermetropic), 2 (3.92%) (Compound myopic), 3 (5.88%) (Mixed)	–
Chang et al. (2019)	380 (291 M)	50 (13.16%)	62 (16.32%)	59 (15.53%)	–
Bhaskaran et al. (2018)	30 (25 M)	3 (10%)	0 (0%)	3 (10%) (Myopic)	–
Tsao et al. (2017)	16	9 (28.13%) eyes	0 (0%)	20 (63%) eyes	–
Anketell et al. (2016)	ASD = 128 (104 M)	14 (10.94%)	58 (45.31%) (low), 19 (14.84%) (moderate)	27 (21.09%)	–
	C = 206 (113 M)	18 (8.74%)	138 (67%) (low), 23 (11.17%) (moderate)	17 (3.4%)	–
Kaur et al. (2016)	35	0 (0%)	3 (8.57%)	0 (0%)	
Ozer et al. (2016)	41 (31 M)	8 (19.51%)	15 (36.59%)	18 (43.90%)	–
Kabatas et al. (2015)	324 (267 M)	6 (1.85%)	27 (8.33%)	13 (4.01%) (Simple hyperopic), 11 (3.40%) (Simple myopic), 8 (2.47%) (Compound hyperopic), 5 (1.54%) (Compound myopic), 1 (0.31%) (Mixed)	Mental retardation (16), Epilepsy (9), Cerebral palsy (5), Congenital sensorineural hearing loss (5), Hypotonia (4), Microcephaly (3), Auricular atresia (2), Ventricular septal defect (2), Down syndrome (2), Di-George syndrome (1)
Puri et al. (2015)	30	6 (20%)	0 (0%)	6 (20%)	–

Table 2 (continued)

Study	Sample size, *n*	Myopia, *n* (%)	Hyperopia, *n* (%)	Astigmatism, *n* (%)	Comorbidities, *n*
Ezegwui et al. (2014)	15	0 (0%)	2 (13.33%)	4 (26.67%)	–
Black et al. (2013)	44 (M:F = 3:1)	4(9.1%)	0 (0%)	4 (9.1%) (hyperopia and astigmatism), 3 (6.82%) (myopia and astigmatism), 1 (2.27%) (myopia, astigmatism, and hyperopia)	–
Ikeda et al. (2013)	154 (122 M)	9 (5.84%)	26 (16.88%)	6 (3.90%)	–
McCurry et al. (2013)	43 (34 M)	8 (18.60%)	4 (9.30%)	11 (25.58%)	–
Shen et al. (2011)	1	1 (100%)	0 (0%)	0 (0%)	16p11.2 deletion
Pineles et al. (2010)	3 (M)	0 (0%)	2 (66.67%)	0 (0%)	Vitamin B12 Optic Neuropathy
Tychsen et al. (2008)	1	1 (100%)	0 (0%)	0 (0%)	DD, CP, Hydrocephalus, Encephalopathy
Fryns et al. (1996)	2 (F)	2 (100%)	0 (0%)	0 (0%)	Cohen Syndrome
Scharre and Creedon (1992)	34 (32 M)	3 (8.82%)	6 (17.65%)	6 (17.65%)	–
Keith et al. (1972)	1 (M)	1 (100%)	0 (0%)	0 (0%)	–

ASD, Autism Spectrum Disorders group; *C*, Comparison group. All values in single-arm studies are for ASD groups. *M*, males; *F*, females

myopia. Pineles et al. (2010) presented a case report of three children with vitamin B12 optic neuropathy and autism, two of whom presented with myopia. Shen et al. (2011) reported a family with 16p11.2 deletion, having a child with autism and bilateral myopia. Cao et al. (2022b) reported a case of high myopia in a child with autism who developed neurotrophic keratopathy after laser retinopexy. Zdonczyk et al. (2023) presented a prospective case series including three children with autism spectrum disorder, with one case each of myopia, hyperopia, and astigmatism.

Risk of Bias Assessment

The JBI critical appraisal checklists rated the case reports 3 to 7 points: two good, two fair, and one poor quality; the case series were both rated 10: considered good quality; the cross-sectional studies were rated 3 to 6: two poor, four fair, and five good quality studies. The NOS scores for the cohort studies range from 3 to 5: one good and nine poor quality studies. The detailed quality assessment can be found in Online Resource 1.

Discussion

Our pooled analysis of twenty-eight studies suggests a significant association of astigmatism with ASDs, while associations with myopia and hyperopia remain unclear. These findings align with a previous study that suggested 22 to 44% of all children with autism also have refractive errors (Reynolds & Culican, 2023). Our results revealed a 16.5% prevalence of astigmatism, followed by a 14.1% prevalence of myopia and a 9.8% prevalence of hyperopia in children with ASD.

We could not establish a clear association between myopia and ASDs. Recent studies have observed a rise in the incidence of acquired myopia (Morgan et al., 2018). Furthermore, myopia shows variable prevalence in different ethnicities, geographical regions, and age groups (Foster & Jiang, 2014), and is affected by a multitude of environmental factors (Ramamurthy et al., 2015), which might explain the lack of a conclusive relationship.

We could not find evidence of an association between hyperopia and ASDs. Hyperopia is generally less prevalent than other refractive errors; however, young children are generally hyperopic (Jiang et al., 2019; Majumdar & Tripathy, 2023). Emmetropization occurs in the majority of hyperopic children in the first year of life, but some children may remain hyperopic (Mutti, 2007). A previous meta-analysis showed an 8.4% incidence of hyperopia in typically developing 6-year-olds that decreases with age (Castagno et al., 2014), which is comparable to our findings in children with ASDs.

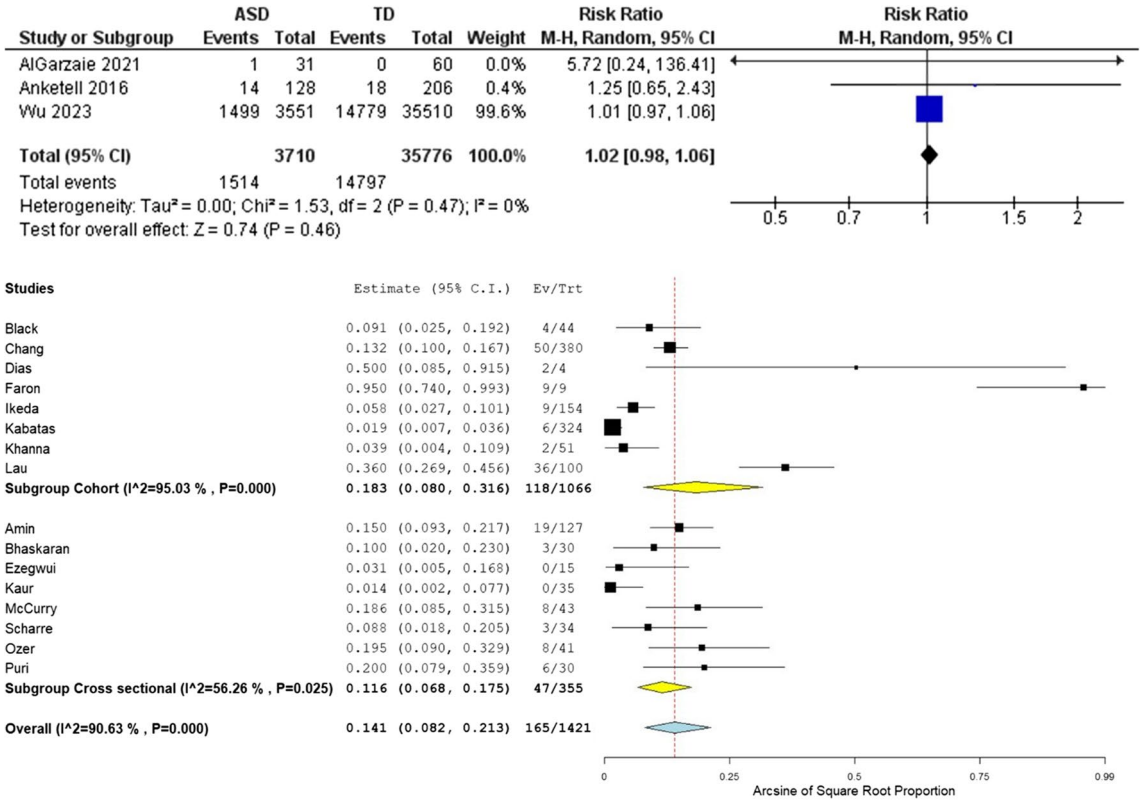

Fig. 2 Meta-analysis of myopia for studies with comparison group (top) and without (bottom)

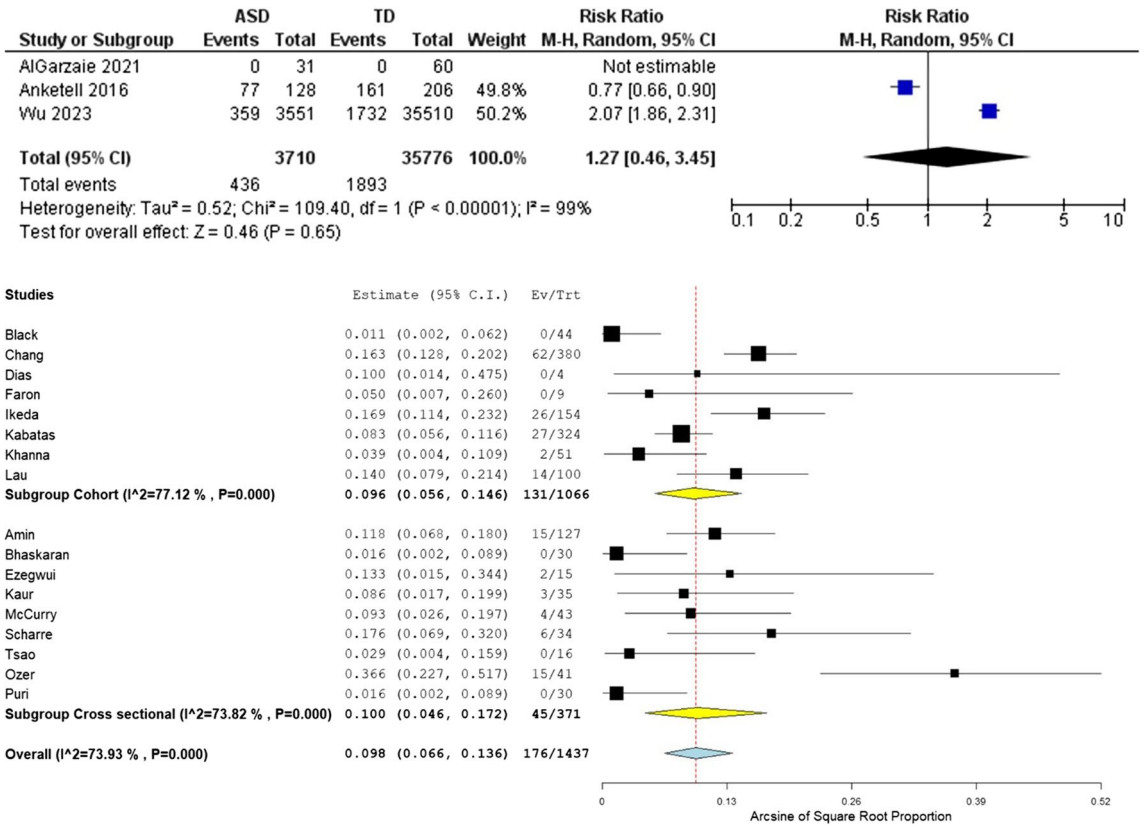

Fig. 3 Meta-analysis of hyperopia for studies with comparison group (top) and without (bottom)

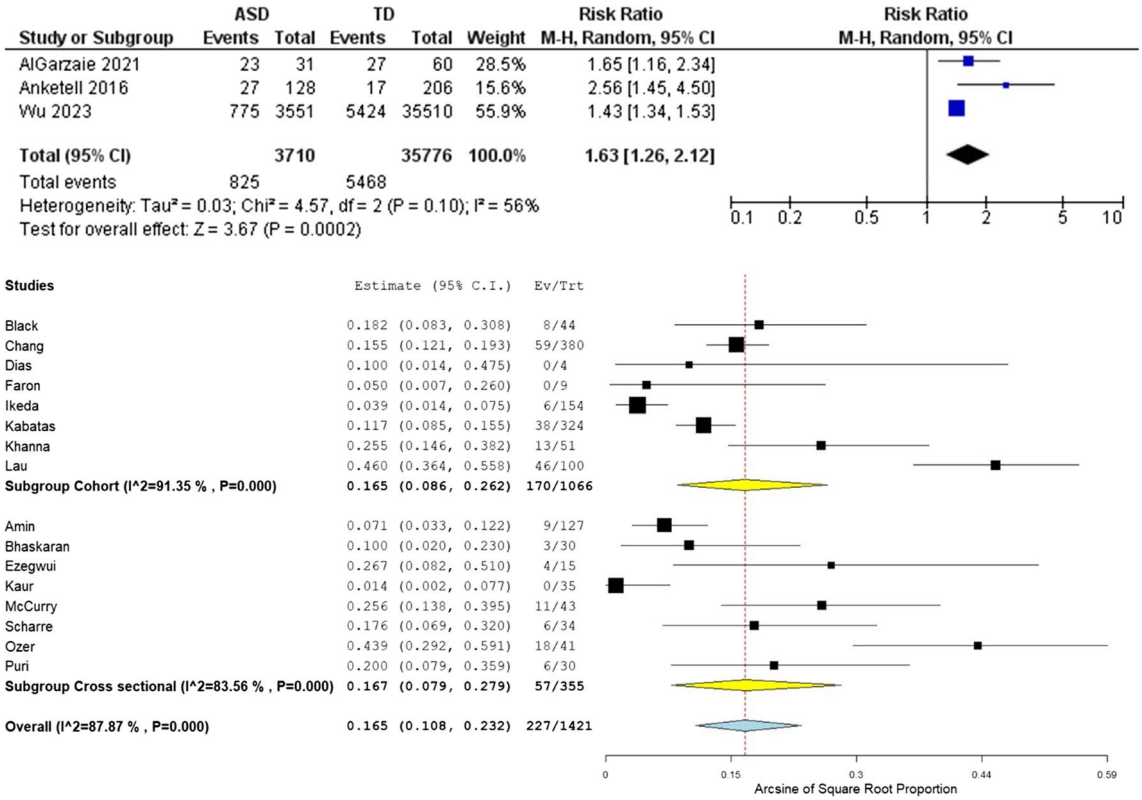

Fig. 4 Meta-analysis of astigmatism for studies with comparison group (top) and without (bottom)

The higher incidence of astigmatism in children with ASD is similar to its incidence in other neurodevelopmental disorders, such as Down's syndrome (Little et al., 2009; Woodhouse et al., 1997), attention-deficit/hyperactivity disorder (ADHD) (Bellato et al., 2023; Reimelt et al., 2021), developmental delay (Nielsen et al., 2007), and hydrocephalus (Biglan, 1990; Patel et al., 2021). Astigmatism is generally more common in adults (Hashemi et al., 2014; Zhang et al., 2023); however, it remains a cause of concern in children (H. Cao et al., 2022a). In typically developing individuals, emmetropization occurs early in life (Abrahamsson et al., 1988). A failure in emmetropization might explain the higher incidence of astigmatism in younger populations with ASDs and other neurodevelopmental disorders (Doyle et al., 1998). Genetic and epigenetic components may be responsible in some cases: greater prevalence of astigmatism has been observed in Native American children (Harvey et al., 2010), and gene loci such as (2p16.3) downstream of the neurexin-1 gene and 2p13.3 in the VAX2 gene have been linked to astigmatism in Europeans (Li et al., 2015; Lopes et al., 2013). In our included studies, European Caucasian children were studied by Anketell et al. (2016). Other studies reported the country of origin, but specific racial/ethnicity data was not reported, nor were participants stratified by socioeconomic or educational levels.

We found several comorbidities — ranging from genetic variations to neurodevelopmental disorders — which could affect the visual function in children with ASDs. Previous studies have also demonstrated that ASDs can present with several comorbidities, including genetic and chromosomal abnormalities (Bergbaum & Ogilvie, 2016; Genovese & Butler, 2020), anxiety, ADHD, and other psychiatric disorders (Hossain et al., 2020). Furthermore, visual impairments, including refractive errors, have also been observed in psychomotor disorders (Sobrado et al., 1999) and other neural disorders such as Fragile X syndrome and Prader-Willi syndrome (Van Splunder et al., 2003). Cerebral visual impairment is associated with vision defects (Fazzi et al., 2007) and is closely related to ASDs and intellectual disability (Chokron et al., 2020). ASDs show a multifactorial pattern of inheritance with complex interactions between genetic, environmental, and epigenetic factors (Genovese & Butler, 2020), and similar patterns have been observed for refractive errors (Harb & Wildsoet, 2019). All this evidence points to shared etiological factors contributing to ASDs and refractive errors.

Our study should be viewed in the context of some limitations. First, the generalizability of our findings might be limited due to the lack of a comparison group in most of the included studies. Second, our review did not include

conference abstracts and unpublished studies, which might contribute to publication bias. Third, our studies encompassed a broad time period, and the diagnostic criteria for ASDs and refractive errors differ dramatically across the studies, potentially introducing heterogeneity. Lastly, all the included studies were observational, which might pose a risk of confounding bias.

We found no association between myopia and ASDs, but the prevalence of myopia and astigmatism is very similar in children with ASDs; optometrists should be mindful, and test for both whenever possible in children with ASDs. Drugs such as anticonvulsants are often prescribed to children with ASDs (Oswald & Sonenklar, 2007), which may cause transient refractive errors (Hadjikoutis et al., 2005). Acetazolamide has been reported to improve symptoms of ataxia in autistic patients (Martorell et al., 2022), but it is also a known risk factor for refractive errors (Garland et al., 1962; Hadjikoutis et al., 2005) Clinicians should exercise caution when prescribing such medications, and alternative drugs should be considered if possible. Children with ASDs are less likely to have access to eye care — in the USA, estimates from the National Survey of Children's Health revealed that about 50% of children with ASDs have been evaluated by an eye care provider, which should ideally be increased to 100% (Swanson et al., 2020), and lower rates of vision screening have been observed in children with ASDs compared to those without ASDs, particularly in Black and younger children (Hoover et al., 2023). Regular eyecare is important to ensure that the visual impairment does not impact the development of children with ASDs.

There is a noticeable lack of studies comparing refractive errors in children with and without ASDs, with only three such included studies in our systematic review (ALGarzaie and Alsaqr, 2021; Anketell et al., 2016; Wu et al., 2023). Future research should incorporate robust prospective designs with age-matched comparison groups while adjusting for confounding factors and comorbid conditions such as ADHD. Furthermore, standardized metrics should be used for refractive errors and ASDs. As research on novel methods to slow or halt the progression of myopia continues (Agyekum et al., 2023), it would be prudent to look into its cost-effectiveness and develop cheaper and more widely applicable methods, as the families or caretakers of children with ASDs may be financially strained (Cidav et al., 2012). Lastly, future research should be expanded to include different demographics and ethnicities to get a broader picture.

To conclude, ASDs seem to be associated with a significantly higher risk of astigmatism, but no significant associations were observed for myopia and hyperopia. The retrospective nature of the included studies and lack of comparison groups are noteworthy limitations, and more robust studies should be designed in the future. Timely diagnosis and management may slow the progression of refractive errors in children with ASDs and lessen the impact on their everyday lives.

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Declarations

Ethics Approval This study was registered with PROSPERO (CRD42023433833).

Conflict of Interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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