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# Risk of retinal disease in patients with autism spectrum disorder

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## Original Research

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## Abstract

**Background.** Ocular abnormalities and visual dysfunction have been associated with autism spectrum disorder (ASD). Our study assessed the risks of developing retinal diseases in individuals with ASD.

**Methods.** In all, 18 874 patients with ASD and 188 740 controls were selected from the Taiwan National Health Insurance Research Database between 2001 and 2009. The control group was matched based on demographic characteristics and medical and ophthalmological comorbidities. The hazard ratios (HRs) with 95% confidence intervals were calculated with Cox-regression analyses adjusted for selected confounders.

**Results.** Individuals with ASD had a higher incidence of developing retinal diseases (1.48‰ vs 0.73‰, $P < .001$), and the diagnosis of retinal diseases occurred earlier than the controls (3.73 vs 6.28 years, $P < .001$). When compared to the control group, the HR of developing retinal diseases in the ASD group was 1.75 (95%: 1.04-2.94) and 7.84 (95%: 3.51-17.47) for retinal detachment. There was no association between the cumulative daily dose of atypical antipsychotics and the incidence of retinal diseases in the ASD group.

**Conclusion.** Individuals with ASD have a higher risk of developing retinal detachment and are diagnosed with retinal diseases earlier than controls. Future research is needed to elucidate the mechanisms mediating the progression of retinal diseases in the ASD population.

## Introduction

Autism spectrum disorder (ASD) is a heterogeneous group of neurodevelopmental disorders characterized by deficits in social interactions and communication and abnormal sensory-motor behaviors.[1,2] Early testing can screen for ASD as early as 14 months of age, although the average age of diagnosis remains around 4 to 5 years of age.[2] Males are more commonly affected than females, and recent evidence estimates the prevalence of ASD to be around 1.5% in developed countries, which has been rising over the past few decades.[3-5]

The retina shares the same embryological origin with the ectoderm-derived central nervous system and may shed light on pathological processes in the brain. For example, pronounced thinning of the retinal nerve fiber layer (RNFL) has been described in various neurological disorders, such as multiple sclerosis, Lewy body dementia, dementia associated with Parkinson's disease, and Alzheimer's disease.[6,7]

ASD has also been associated with retinal abnormalities and visual dysfunction, although the pathogenesis has yet to be determined. Individuals with ASD commonly present with astigmatism and refractive errors in addition to atypical eye movements, all of which may play a role in the manifestation of visuomotor deficits.[8] Chang et al reported a high prevalence (71%) of ophthalmological disorders in 2555 children with ASD at an ophthalmological clinic over a 10-year follow-up period, and a recent claims review noted a higher (12.5%) prevalence of ophthalmological diagnosis, including amblyopia, strabismus, optic neuropathy, nystagmus, or retinopathy of prematurity (ROP), compared to a 3.5% prevalence in typically developing children.[9,10] A higher prevalence of ASD symptoms was more commonly observed in children with blindness due to ROP, which was posited to result from brain damage.[11] In 83 children with optic nerve hypoplasia or septo-optic dysplasia, Parr et al noted a 31% prevalence of concurrent ASD.[12] Emberti Gialloreti et al have reported thinning of the RNFL in the nasal quadrant in 24 individuals with ASD.[13] In contrast, another study of 54 individuals with ASD showed selectively thickened foveal, macular, and peripapillary RNFL in the inferior sector when compared with neurotypical controls.[14]

Nevertheless, existing evidence on the association between retinopathies in ASD is limited by small sample sizes. The aforementioned retinal abnormalities in individuals with ASD can be reflected in a population-based incidence and prevalence analysis. It is also crucial to adjust for other ophthalmological diseases and to exclude secondary retinopathies, such as diabetic retinopathy and hypertensive retinopathy, to elucidate the association between ASD and retinal diseases. Therefore, we conducted a retrospective case-control study using the Taiwan National Health Insurance Research Database (NHIRD) to ascertain the risks of developing retinal diseases in individuals with and without ASD and adjusted for demographic characteristics, medical and ophthalmological comorbidities, and intellectual disability. It is our hypothesis that there is an increased risk of developing retinal diseases in individuals with ASD after adjusting for demographic characteristics and medical and ophthalmological comorbidities.

## Methods

### Data source

The Taiwan NHIRD is audited and released by the National Health Research Institute for scientific and study purposes upon the formal application. The database contains comprehensive medical information about the insured patients, such as demographics (birthdate, sex, and residential location), clinical visits (dates and diagnoses), and prescriptions. Claims data of subjects included in the NHIRD are anonymous to maintain individual privacy. Each patient is assigned a unique and anonymous identifier upon enrollment by the National Health Research Institute (NHI), which allows researchers to follow their diseases and outcomes. In the current study, we linked two databases together for the analysis. The first is the specialized dataset of mental disorders, which includes all medical (mental and nonmental) records of all insured individuals with mental disorders. The second is the Longitudinal Health Insurance Database, which includes all medical records of 3 000 000 insured individuals that are randomly selected from entire Taiwanese people (~28 000 000), and was used for the identification of control groups in the current study. Diagnoses were captured using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The NHIRD has been used extensively for epidemiologic studies.[15-18] This study was approved by the Taipei Veterans General Hospital institutional review board.

### Inclusion criteria for patients with ASD and control groups (study 1)

Patients with ASD (ICD-9-CM code: 299) by board-certified psychiatrists between January 1, 2001, and December 31, 2009, and who had no history of any retinal disease (ICD-9-CM codes: 361 and 362) before enrollment were included in the ASD cohort. The time of enrollment was defined as the time of ASD diagnosis. The age, sex, time of enrollment, residence, and medical and ophthalmological comorbidities-matched (1:10) control cohort was randomly identified after eliminating the study cases, individuals who had been given a diagnosis of ASD at any time, and individuals with any retinal disease before enrollment.[19] Medical and ophthalmological comorbidities, including glaucoma, uveitis, hypertension, dyslipidemia, diabetes mellitus (DM), obesity, smoking, cerebrovascular diseases, and chronic kidney disease, were also identified and matched between case and control cohorts. Furthermore, intellectual disability was assessed for the ASD and the matched-control cohorts. The use of atypical antipsychotics during the follow-up was also examined, and the study cohort was divided into 3 subgroups: nonusers (cumulative defined daily dose [cDDD] during the follow-up <30), short-term users (cDDD = 30-364), and long-term users (cDDD ≧ 365). Atypical antipsychotics included aripiprazole, risperidone, paliperidone, olanzapine, amisulpride, ziprasidone, clozapine, and quetiapine.

### Outcome assessment

Three retinal diseases, including retinal detachment (ICD-9-CM codes: 361.0, 361.1, 361.2, 361.8, 361.9, and 362.40), primary retinopathy (ICD-9-CM codes: 362.10, 362.12, 362.13, 362.14, 362.15, 362.16, 362.17, 362.41, 362.42, 362.43, 362.82, 362.83, and 362.89), and retinal vascular complications (ICD-9-CM codes: 362.3, 362.81, and 362.84), were assessed as the primary outcome variables in the current study. To exactly investigate the association between ASD and primary retinopathy, ROP (ICD-9-CM code: 362.2), diabetes retinopathy (ICD-9-CM code: 362.0), and hypertensive retinopathy (ICD-9-CM code: 362.11) were excluded in the current study. The diagnoses of retinal diseases were given at least twice based on board-certified ophthalmologists during the follow-up period (from enrollment to December 31, 2011, or death).

### Study 2

To avoid artificially increasing the statistical power, our study was reexamined based on a new cohort of patients with ASD and 1:1 matched control groups. Case and control groups were matched based on age, sex, time of enrollment, residence, and medical and ophthalmological comorbidities.

### Statistical analysis

For between-group comparisons, the *F*-test was used for continuous variables and Pearson's $\chi^2$ test for nominal variables. Cox-regression analyses with adjustment for demographic data, medical and ophthalmological comorbidities, and intellectual disability were applied to investigate the hazard ratios (HRs) and 95% confidence intervals (CIs) of any retinal disease, retinal detachment, primary retinopathy, and retinal vascular complications between ASD and control groups. Furthermore, Cox-regression analyses were used to examine the association of atypical antipsychotics with risks of those retinal diseases among patients with ASD. Finally, sensitivity analyses after excluding those with any ophthalmological disease were performed to validate our results. Statistical significance was set at a 2-tailed $P \leq 0.05$. Data processing and statistical analyses were performed with SAS (version 9.1; SAS Institute, Cary, NC, USA).

## Results

A total of 207 614 subjects (18 874 patients with ASD and 188 740 controls) were included in the study. Table 1 summarizes the baseline demographics, clinical characteristics, and follow-up data on the incidence of retinal diseases. The mean age at enrollment was 9.16 years (SD = 6.09) for the ASD group and 9.19 years (SD = 6.14) for the control group. Both the ASD and control groups showed a male predominance with approximately a 4:1 male-to-female ratio. There was no between-group difference in age at enrollment, sex, medical

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**Table 1.** Demographic Data and Incidence of Any Retinal Disease Among Patients with ASD and Control Groups

| | | Study 1 | Study 2 | |
|---|---|---|---|---|
| | Patients with ASD (n = 18 874) | 1:10 matched controls (n = 188 740) | 1:1 matched controls (n = 18 874) | *P*-value |
| Age at enrollment (yr, SD) | 9.16 (6.09) | 9.19 (6.14) | 9.17 (6.09) | .473/.859 |
| Sex (n, %) | | | | >.999/>.999 |
| Male | 15 322 (81.2) | 153 220 (81.2) | 15 322 (81.2) | |
| Female | 3552 (18.8) | 35 520 (18.8) | 3552 (18.8) | |
| Atypical antipsychotics (n, %) | | | | <.001/<.001 |
| <30 cDDD | 15 262 (80.9) | 188 459 (99.9) | 18 846 (99.9) | |
| 30 ~ 364 cDDD | 1916 (10.1) | 251 (0.1) | 25 (0.1) | |
| ≧365 cDDD | 1696 (9.0) | 30 (0.0) | 3 (0.0) | |
| Medical and ophthalmological comorbidities (n, %) | | | | |
| Glaucoma | 125 (0.7) | 1250 (0.7) | 125 (0.7) | .995/>.999 |
| Uveitis | 2 (0.0) | 20 (0.0) | 2 (0.0) | >.999/>.999 |
| Hypertension | 47 (0.2) | 470 (0.2) | 47 (0.2) | .992/>.999 |
| Dyslipidemia | 77 (0.4) | 770 (0.4) | 77 (0.4) | .994/>.999 |
| Diabetes mellitus | 27 (0.1) | 270 (0.1) | 27 (0.1) | .989/>.999 |
| Obesity | 193 (1.0) | 1930 (1.0) | 193 (1.0) | .996/>.999 |
| Smoking | 39 (0.2) | 390 (0.2) | 39 (0.2) | .991/>.999 |
| Chronic kidney disease | 12 (0.1) | 120 (0.1) | 12 (0.1) | >.999/>.999 |
| Cerebrovascular diseases | 28 (0.1) | 280 (0.1) | 28 (0.1) | .989/>.999 |
| Intellectual disability (n, %) | 6449 (34.2) | 1611 (0.9) | 169 (0.9) | <.001/<.001 |
| Level of urbanization (n, %) | | | | >.999/>.999 |
| 1 (most urbanized) | 3037 (16.1) | 30 370 (16.1) | 3037 (16.1) | |
| 2 | 5789 (30.7) | 57 890 (30.7) | 5789 (30.7) | |
| 3 | 1540 (8.2) | 15 400 (8.2) | 1540 (8.2) | |
| 4 | 1477 (7.8) | 14 770 (7.8) | 1477 (7.8) | |
| 5 (most rural) | 7031 (37.2) | 70 310 (37.2) | 7031 (37.2) | |
| Incidence of any retinal disease (n, ‰) | 28 (1.48) | 138 (0.73) | 16 (0.85) | .001/.097 |
| Retinal detachment | 19 (1.01) | 19 (0.10) | 5 (0.26) | <.001/.007 |
| Primary retinopathy | 10 (0.53) | 108 (0.57) | 10 (0.53) | >.999/>.999 |
| Retinal vascular occlusion | 0 (0.00) | 19 (0.10) | 1 (0.05) | .410/>.999 |
| Age at diagnosis of any retinal disease (yr, SD) | 17.18 (8.53) | 18.66 (8.78) | 19.70 (9.30) | .416/.368 |
| Duration between enrollment and any retinal disease (yr, SD) | 3.73 (2.43) | 6.28 (2.51) | 6.43 (2.15) | <.001/<.001 |

*Abbreviations:* ASD, autism spectrum disorder; cDDD, cumulative defined daily dose; NTD, new Taiwan dollar; SD, standard deviation.

and ophthalmological comorbidities, and the level of urbanization. There was a significantly greater proportion of subjects with intellectual disability in the ASD group (34.2% vs 0.9%, $P < .001$).

Overall, the incidence of developing any retinal diseases was significantly higher in the ASD group (1.48‰ vs 0.73‰, $P = .001$). Specifically, the between-group difference in incidence was only significant for retinal detachment (1.01% vs 0.1%, $P < .001$), but not for primary retinopathy or retinal vascular occlusion. No subjects developed retinal vascular occlusion in the ASD group. There was no difference in the age of diagnosis of retinal diseases between the ASD and control groups. However, the mean duration of developing retinal disease since the time of enrollment was significantly shorter in the ASD group (3.73 vs 6.28 years, $P < .001$).

### *Risks of developing retinal diseases*

When compared with subjects in the control group, subjects with ASD had a significantly greater risk of developing retinal diseases (HR: 1.75; 95% CI: 1.04-2.94), and the risk was most pronounced for retinal detachment (HR: 7.84; 95% CI: 3.51-17.47). However, the risks of developing primary retinopathy or retinal vascular

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**Table 2.** Risk of Developing Any Retinal Disease Among Patients with ASD and Controls

| | Risk of any retinal disease (HR, 95% CI)[a] | | | |
|---|---|---|---|---|
| | Retinal detachment | Primary retinopathy | Retinal vascular occlusion | Total |
| | Study 1:1:10 matched cases and controls | | | |
| ASD | | | | |
| Presence | **7.84 (3.51-17.47)** | 0.84 (0.38-1.87) | n.a. | **1.75 (1.04-2.94)** |
| Absence | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | Study 2:1:1 matched cases and controls | | | |
| ASD | | | | |
| Presence | 2.84 (0.94-8.62)* | 0.91 (0.28-2.93) | n.a. | 1.56 (0.77-3.18) |
| Absence | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |

*Note:* Bold type indicates the statistical significance.
*Abbreviations:* ASD, autism spectrum disorder; CI, confidence interval; HR, hazard ratio; n.a., not available.
[a]Cox-regression model with adjustment for demographic characteristics, medical and ophthalmological comorbidities, and intellectual disability.
*$P = .066$.

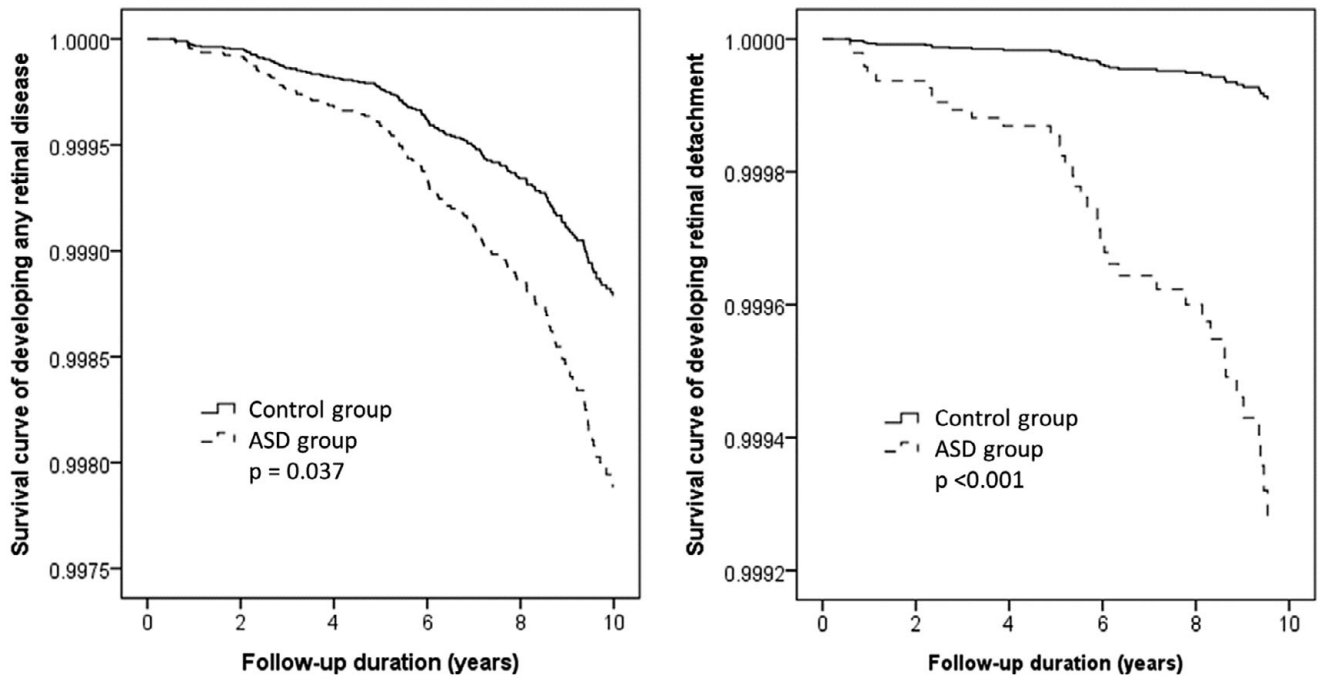


**Figure 1.** Survival curve of developing any retinal disease among patients with ASD and 1:10 matched control groups.
*Abbreviation:* ASD, autism spectrum disorder.

occlusion did not differ significantly between the ASD and control groups (Table 2).

The survival curves in Figure 1 illustrate that individuals with ASD were more likely to develop any retinal disease ($P = .037$) and retinal detachment ($P < .001$) over the 10-year follow-up period.

### Effects of atypical antipsychotics

Unsurprisingly, the cumulative dosage of atypical antipsychotics ($P < .001$) was greater in the ASD group than in the control group. Table 3 shows the cumulative exposure to antipsychotics in subjects with ASD, and the use of atypical antipsychotics was not associated with the development of any retinal diseases.

### Sensitivity analysis

The greater risk of developing retinal detachment in the ASD group remained statistically significant (HR: 8.20; 95% CI: 3.46-19.42) after excluding ophthalmological comorbidities and adjusting for demographic characteristics, medical comorbidities, and intellectual disability. However, the risk of developing any retinal disease was no longer statistically significant in the sensitivity analysis (Table 4).

### Study 2

Finally, based on a 1:1 case-control cohort sample, patients with ASD had a higher incidence of subsequent retinal detachment ($P = .007$) than non-ASD controls (Table 1). However, the

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**Table 3.** Atypical Antipsychotics and Risk of Retinal Diseases Among Patients with ASD.[a]

| | Retinal detachment | | Primary retinopathy | | Retinal vascular occlusion | | Total | |
|---|---|---|---|---|---|---|---|---|
| | N (‰) | HR (95% CI) | N (‰) | HR (95% CI) | N (‰) | HR (95% CI) | N (‰) | HR (95% CI) |
| Atypical antipsychotics (n, ‰) | | | | | | | | |
| <30 cDDD | 10 (0.66) | 1 (reference) | 8 (0.52) | 1 (reference) | 0 (0.00) | 1 (reference) | 17 (1.11) | 1 (reference) |
| 30 ~ 364 cDDD | 4 (2.09) | 2.12 (0.64-7.08) | 1 (0.52) | 0.62 (0.07-5.28) | 0 (0.00) | n.a. | 5 (2.61) | 1.60 (0.57-4.50) |
| ≧365 cDDD | 5 (2.95) | 2.10 (0.64-6.89) | 1 (0.59) | 0.37 (0.04-3.47) | 0 (0.00) | n.a. | 6 (3.54) | 1.42 (0.50-4.00) |

*Note:* Bold type indicates the statistical significance.
*Abbreviations:* ASD, autism spectrum disorder; cDDD, cumulative defined daily dose; CI, confidence interval; HR, hazard ratio; n.a., not available.
[a]Cox-regression model with adjustment for demographic characteristics, medical and ophthalmological comorbidities, and intellectual disability.

**Table 4.** Sensitivity Analyses of Developing Any Retinal Disease and Retinal Detachment Among Patients with ASD and Controls[a]

| | Exclusion of ophthalmological comorbidities | |
|---|---|---|
| | Any retinal disease HR (95% CI) | Retinal detachment HR (95% CI) |
| Study 1:1:10 matched cases and controls | | |
| ASD | | |
| Presence | 1.57 (0.89-2.76) | **8.20 (3.46-19.42)** |
| Absence | 1 (reference) | 1 (reference) |
| Study 2:1:1 matched cases and controls | | |
| ASD | | |
| Presence | 1.45 (0.68-3.07) | 3.39 (1.00-11.52)* |
| Absence | 1 (reference) | 1 (reference) |

*Note:* Bold type indicates the statistical significance.
*Abbreviations:* ASD, autism spectrum disorder; CI, confidence interval; HR, hazard ratio.
[a]Cox-regression model with adjustment for demographic characteristics, medical comorbidities, and intellectual disability.
*$P = .051$.

significance of the retinal detachment risk (HR: 2.84; 95% CI: 0.94-8.62) in ASD disappeared ($P = .066$) after adjusting for selected confounders (Table 2). Sensitivity analysis of exclusion of those with ophthalmological comorbidities showed a consistent finding that only a trend significance (HR: 3.39; 95% CI: 1.00-11.52; $P = .051$) was noted for the risk of retinal detachment in patients with ASD compared with the controls (Table 4).

## Discussion

Using a large, nationwide sample, our study demonstrated that individuals with ASD had a greater risk of developing retinal detachment than matched controls after adjusting for demographic characteristics, medical and ophthalmological comorbidities, and intellectual disability. Individuals with ASD were diagnosed with retinal diseases earlier than the matched controls. Notably, the risk of developing primary retinopathy or retinal vascular occlusion did not differ significantly between individuals with ASD and matched controls. Lastly, there was not a significant association between the cumulative dose of atypical antipsychotics and the risk of developing retinal diseases in individuals with ASD.

It has been established that the prevalence of metabolic syndromes is higher in individuals with ASD, including type 2 DM,[16] hyperlipidemia,[20] and obesity.[21] In Taiwan, adolescents with ASD have a nearly 3-fold risk of developing type 2 DM.[16] Those who are treated with atypical antipsychotics are further predisposed to developing type 2 DM,[16] which could exacerbate existing or accelerate the progression of retinal diseases. Therefore, we excluded diabetes retinopathy and hypertensive retinopathy from the analysis yet still observed a higher incidence of developing retinal diseases in individuals with ASD.

The pathophysiology underlying the association between ASD and retinal detachment remains unclear. One possible mechanism may be mediated by the abnormal retinal cytoarchitecture that predates functional damage. However, the RNFL thickness measured in ASD individuals reported in previous studies had mixed findings.[13,14] On the one hand, the thinning of RNFL indicates a loss of retinal ganglion cell axons and serves as a marker of neurodegeneration.[22] On the other hand, García-Medina et al suggested that a thickened RNFL may reflect the neuroanatomical abnormalities or neuroinflammatory processes in individuals with ASD.[14] Another possible mechanism underlying the increased risks of retinal diseases may involve retinal vascular abnormalities in individuals with ASD. In a recent study, García-Medina et al observed a trend of increased vascular density and perfusion in the macula of 14 individuals with young, high-functioning ASD when compared with neurotypical controls. However, it should be noted that we did not observe an increased risk of retinal vascular occlusion in individuals with ASD.[23]

There were limitations in our study. First, the accuracy of clinical diagnoses could not be verified as the diagnoses were based solely on the ICD-9-CM codes because ICD-10-CM codes were not available in NHIRD before 2016. Although we recognize the high prevalence of astigmatism and refractive errors in individuals with ASD,[8] we did not determine the presence of other ophthalmological conditions besides glaucoma and uveitis. We also could not assess dietary and lifestyle factors as well as the degree of blood pressure and blood sugar control, all of which could alter the risks of developing retinal diseases. Moreover, many patients with retinal diseases remain largely asymptomatic until they progress to more advanced stages. Therefore, our reported incidence of retinal diseases may be underestimated by the exclusion of diabetic and hypertensive retinopathies and by the exclusion of asymptomatic patients in the NHIRD data. Finally, the elevated likelihoods of retinal disease and retinal detachment in patients with ASD were only noted in a 1:10 case-control cohort sample, but not in a 1:1 case-control cohort sample. Additional clinical studies would be required to further elucidate the association between ASD and retinal diseases, particularly retinal detachment.

## Conclusion

After adjusting for medical and ophthalmological comorbidities, our study showed inconsistent findings on the risks of retinal

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diseases and retinal detachment in patients with ASD based on a 1:10 matching sample and 1:1 matching sample, respectively. However, our study still found that patients with ASD had a higher incidence of retinal detachment during the follow-up than the control group in both 1:10 and 1:1 matching samples. Our results may inspire clinicians and scientists to further clarify the association between ASD and retinal diseases, particularly retinal detachment.

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**Author contributions.** M.-H.C. and T.-J.W. designed the study and wrote the protocol. J.E.-H.W. and M.-H.C. drafted the manuscript. M.-H.C. performed the statistical analyses. T.-J.W., T.-J.C., and S.-J.T. reviewed the draft and revision, and assisted with the preparation and proofreading of the manuscript.

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**Data availability statement.** The NHIRD was released and audited by the Department of Health and Bureau of the NHI Program for scientific research (https://nhird.nhri.org.tw/). NHIRD can be obtained through the formal application that is regulated by the Department of Health and Bureau of the NHI Program.

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