# Evolving patterns of horizontal strabismus in a tertiary care population: a 10-year retrospective study

## Evolução dos padrões de estrabismo horizontal em população de Atenção Terciária: estudo retrospectivo de 10 anos

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## ABSTRACT

**Objective:** Strabismus is a common cause of pediatric ophthalmology consultations, yet its etiology remains incompletely understood. This study aimed to describe the clinical and epidemiological characteristics of patients with horizontal strabismus, treated at a tertiary ophthalmic center in São Paulo, Brazil, over a 10-year period.

**Methods:** A retrospective cross-sectional review of medical records was conducted for patients with horizontal strabismus between 2012 and 2022. Mechanical, sensory, paralytic, or consecutive deviations were excluded.

**Results:** A total of 3,165 individuals were included (52.1% female; mean age, 13.94 years). Esotropia accounted for 56.8% of cases overall; exotropia showed a significant increasing trend in the proportion of cases over the years. Esotropia was more frequently associated with a family history of strabismus or amblyopia, current amblyopia or ongoing treatment, prematurity, twinning, and hyperopia. Exotropia occurred more frequently among females, younger patients at the time of diagnosis, and those with emmetropia or myopia. It was also more commonly associated with an autism spectrum disorder diagnosis.

**Conclusion:** The increasing proportion of exodeviation in a predominantly Western population, may represent a changing global landscape of horizontal strabismus.

## RESUMO

**Objetivo:** O estrabismo é uma causa comum de consultas em oftalmologia pediátrica; no entanto, sua etiologia ainda não é totalmente compreendida. Este estudo teve como objetivo descrever as características clínicas e epidemiológicas de pacientes com estrabismo horizontal tratados em um centro oftalmológico terciário em São Paulo, ao longo de um período de 10 anos.

**Métodos:** Estudo retrospectivo e transversal realizado a partir de prontuários médicos de pacientes com estrabismo horizontal entre 2012 e 2022. Desvios de causa mecânica, sensorial, paralítica ou consecutiva foram excluídos.

**Resultados:** Foram incluídos 3.165 indivíduos (52,1% do sexo feminino; idade média de 13,94 anos). A esotropia representou 56,8% dos casos no geral; a exotropia apresentou aumento de casos estatisticamente significativos ao longo dos anos. A esotropia foi mais frequentemente associada a histórico familiar de estrabismo ou ambliopia, ambliopia atual ou em tratamento, prematuridade, gestação gemelar e hipermetropia. A exotropia ocorreu com mais frequência em mulheres, pacientes com menor média de idade, entre emétropes ou míopes e associada ao transtorno do espectro autista.

**Conclusão:** A crescente proporção de exotropia em uma população predominantemente ocidental pode representar uma mudança no panorama do estrabismo horizontal de forma global.

## INTRODUCTION

Strabismus is a misalignment of the eyes relative to a fixation point; the visual axes fail to intersect precisely on the fovea because of defective ocular alignment.[1] When it occurs early – during the critical period of binocular development, typically before 7 years old – it may lead to abnormal sensory adaptation, including deprivation of visual stimulation and the development of amblyopia.[1] If misalignment persists beyond this period, patients are at risk of image confusion and diplopia.[1,2]

A variety of factors have been implicated in the onset of strabismus, including refractive errors, a family history of strabismus or amblyopia, maternal exposures such as alcohol use or smoking during pregnancy, and perinatal conditions such as intrauterine growth restriction, prematurity, and low birth weight.[2] Race and ethnicity also appear to influence both the prevalence and the underlying etiology of strabismus.[1,2]

Exotropia accounts for approximately one-quarter of horizontal ocular deviations, although prevalence varies across populations.[3] The most common subtype, intermittent exotropia, generally preserves binocular sensory function and is less frequently associated with amblyopia.[3] In contrast, permanent or manifest exotropia is associated with loss of stereopsis and sensory impairment.[4-6]

Esotropia remains the most frequent form of strabismus seen in both general and pediatric ophthalmology clinics. Esotropic deviations may be congenital or acquired, cyclic or constant, and accommodative or non-accommodative.[7] The most common subtype is congenital (infantile) esotropia (ET), which manifests between 4 and 6 months of age. Accommodative ET typically appears between 2 and 5 years of age, when increased accommodative demand drives excessive convergence; it is defined as refractive accommodative when the deviation is completely corrected with full hyperopic optical correction, and as partially accommodative when the deviation improves but residual ET persists despite full correction, which, when fully corrected, usually allows normal stereopsis.[8,9] Microesotropia describes a small-angle esodeviation with disturbed stereoacuity due to anomalous retinal correspondence.[9]

Convergent deviations are more common among individuals of European descent,[2,10] whereas divergent deviations are reported more frequently in populations of Asian ancestry.[11,12] More recent data from non-Asian cohorts, however, suggest a trend toward a more balanced distribution of horizontal deviations.[13] This apparent epidemiological shift underscores the need for updated population-based studies to inform diagnosis, clinical evaluation, and therapeutic strategies for horizontal strabismus. So, this study aimed to describe the clinical and epidemiological characteristics of patients with horizontal strabismus.

## METHODS

This retrospective, cross-sectional study reviewed 3,165 medical records of patients with primary horizontal strabismus whose deviation began in childhood or adolescence and who were evaluated at a tertiary ophthalmology hospital in São Paulo, Brazil, between 2012 and 2022.

The 3,165 individuals included in the study far exceeds the sample size needed to detect differences of similar magnitude compared to those described in the literature between ET and exotropia.

Eligible records documented a diagnosis of strabismus established by ophthalmologists specializing in ocular motility. All included patients had undergone a comprehensive ophthalmic examination, including assessment of extraocular muscle motility and version testing; measurement of deviation using the alternate cover test, corneal light reflex test (Hirschberg), or Krimsky test.

Records were excluded if data were incomplete or if the deviation was mechanical, paralytic, sensory, consecutive in origin, or associated with retinopathy of prematurity. Only primary horizontal deviations were considered. The type of strabismus was classified according to findings prior to any treatment, and each chart was reviewed from the earliest available report – whether from another service or at initial evaluation in the study center – to ensure diagnostic accuracy.

Patients were classified as presenting convergent (ET) or divergent (exotropia) deviations. Esotropic cases were further subdivided into non-accommodative infantile ET, accommodative esotropia (ETa), and microesotropia (MET). Exotropic cases were categorized as intermittent exotropia (IXT) or permanent/manifest exotropia (XT). Intermittent exotropia was further classified according to the Burian system as: basic type, when the distance deviation was within 10 prism diopters of the near deviation; divergence excess, when the distance deviation exceeded the near deviation by at least 10 prism diopters; or convergence insufficiency, when the near deviation exceeded the distance deviation by at least 10 prism diopters.[14]

Cycloplegic refraction was recorded and expressed as spherical equivalent (SE). Refractive status was classified as myopia (less than or equal to -1,00 D), emmetropia (between -1,00 and +2,00 D), or hyperopia (greater than or

equal to +2,00 D). Additional variables collected included sex, age at presentation to the tertiary center, medical history (including pregnancy and current comorbidities), family history of strabismus or amblyopia, and presence or ongoing treatment of amblyopia.

Descriptive statistics included absolute and relative frequencies, means, medians, standard deviations, interquartile ranges, and 95% confidence intervals (CI) for means and proportions. Associations between categorical variables were assessed with the chi-square or Fisher exact test (for 2x2 tables when expected cell counts were < 5). For continuous variables, Student's *t* test or the Mann-Whitney U test was applied, as appropriate. The strength of these associations was quantified by univariate and multivariate logistic regression, with calculation of odds ratio (OR) and 95% CI, considering $p < 0.05$ as significant.

Data were analyzed using Microsoft Excel (2016), Epi Info version 7.2.1.0 (2017), and StatSoft Statistica version 7.0 (2004). The study was approved by the local Research Ethics Committee (protocol number 6.544.020).

## RESULTS

Of the 3,165 patients, 1,648 (52.1%) were female. The mean age at admission was 13.94 years. Overall, ET was more frequent than exotropia (56.8% *versus* 43.2%; Table 1). The most common comorbidities were asthma (2.56%), delayed neuropsychomotor development (1.74%), Autism Spectrum Disorder (ASD, 0.95%), epilepsy (0.92%), hypothyroidism (0.85%), and Attention Deficit/Hyperactivity Disorder (ADHD, 0.32%; Figure 1).

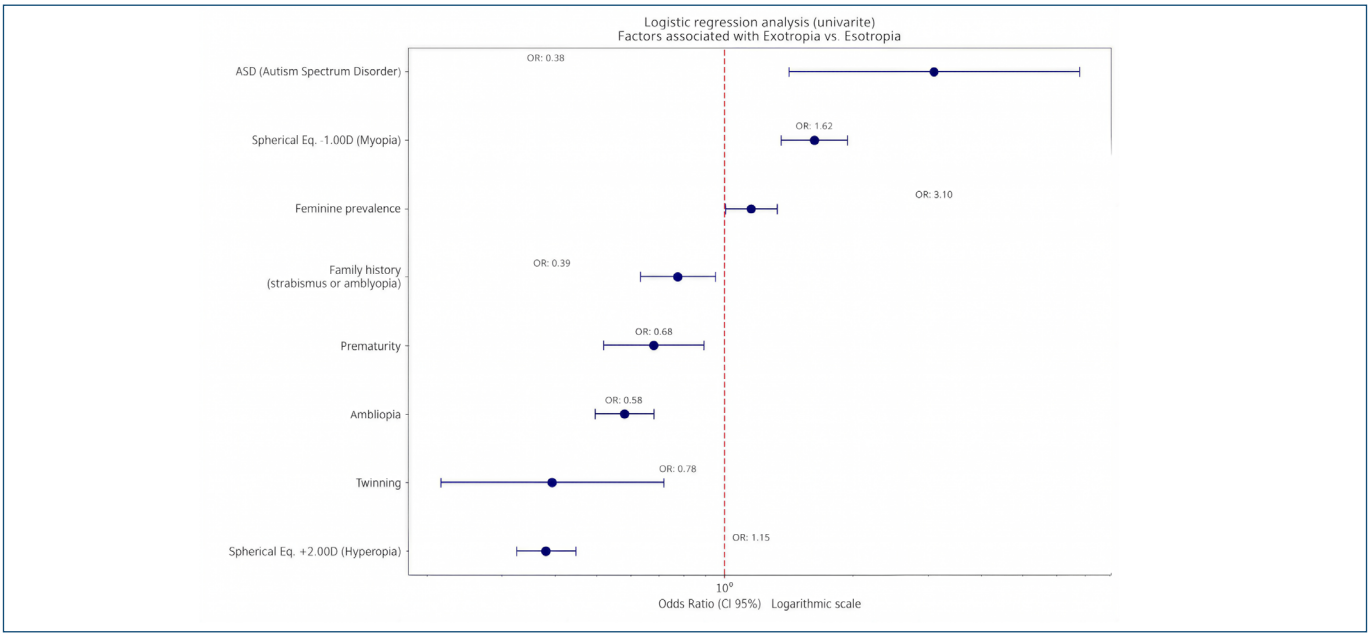
Year-by-year analysis demonstrated a gradual increase in mean age, particularly in the last 5 years. A concurrent refractive shift was also noted: myopia increased and hyperopia decreased, reaching nearly equal proportions in 2021 in both groups. Although esodeviations predominated in most years, exodeviations showed a significant increasing trend in the proportion of cases over the years analyzed (OR 1.10; 95%CI 1.07 - 1.13), indicating that each year, the chance of a newly admitted case being exotropia increases by 10%. From 2019 onward, intermittent exotropia became more prevalent than other subtypes (Figure 2). The ratio between the two most prevalent subtypes – non-accommodative infantile ET and intermittent exotropia (IXT) - decreased from 2.29 in 2012 to 1.2 in 2018-2019 and subsequently fell below 1 after 2019.

Among divergent deviations, manifest exotropia occurred more often in males and in older individuals and was significantly associated with epilepsy, as well as amblyopia or its treatment. Manifest exotropia also showed a higher prevalence of myopia, whereas intermittent

**Table 1.** Comparison between convergent and divergent deviations from 2012 to 2022

| Characteristics | Horizontal deviations | | Total (n = 3,165) | p-value | OR (95%CI) |
|---|---|---|---|---|---|
| | Esotropia (n = 1,797) | Exotropia (n = 1,368) | | | |
| Female prevalence | 908 (50.5) | 740 (54.1) | 1,648 (52.1) | 0.0467 | 1.15 (1.00-1.33) |
| Male prevalence | 889 (49.5) | 628 (45.9) | 1,517 (47.9) | 0.5234 | 0.88 (0.76-1.01) |
| Age at admission, years | | | | | |
| Mean ± SD | (13.57 ± 12.92) | (14.41 ± 14.22) | (13.94 ± 13.5) | 0.08761 | 1.00 (0.99-1.01) |
| Median ± IQR | (8 ± 9.5) | (8 ± 10) | (8 ± 9.5) | | |
| Family history (strabismus or amblyopia) | 284 (15.8) | 174 (12.7) | 458 (14.5) | 0.0167 | 0.78 (0.63-0.95) |
| Defined amblyopia or treatment for amblyopia | 626 (34.8) | 324 (23.7) | 950 (30) | 0.00001 | 0.60 (0.51-0.70) |
| Prematurity | 161 (8.9) | 86 (6.3) | 247 (7.8) | 0.0055 | 0.68 (0.52-0.89) |
| Twinning | 46 (2.5) | 14 (1) | 60 (1.9) | 0.0017 | 0.39 (0.22-0.72) |
| Comorbidities | | | | | |
| ASD | 9 (0.5) | 21 (1.5) | 30 (0.9) | 0.0029 | 3.10 (1.41-6.78) |
| Asthma | 54 (3) | 27 (1.9) | 81 (2.6) | 0.0687 | |
| Delayed Neuropshycomotor Development | 35 (1.9) | 20 (1.4) | 55 (1.7) | 0.3002 | |
| ADHD | 6 (0.3) | 4 (0.3) | 10 (0.3) | 0.8367 | |
| Hypothyroidism | 18 (1) | 8 (0.6) | 26 (0.8) | 0.1980 | |
| Epilepsy | 13 (0.7) | 16 (1.1) | 29 (0.9) | 0.1918 | |
| Spherical Equivalent | | | | | |
| Less than or equal to -1,00D | 279 (15.5) | 314 (23) | 593 (18.7) | < 0.001 | 1.62 (1.35-1.94) |
| Between -1,00 and +2,00D | 778 (43.3) | 766 (56) | 1,544 (48.8) | | |
| Greater than or equal to +2,00D | 740 (41.2) | 288 (21.1) | 1,028 (32.5) | < 0.001 | 0.40 (0.33-0.47) |
| Deviation type | | | | | |
| Infantile non-accommodative esotropia | 1178 (65.5) | - | 1178 (37.2) | < 0.0001 | |
| Accommodative esotropia | 544 (30.3) | - | 544 (17.2) | | |
| Microesotropia | 69 (3.8) | - | 69 (2.2) | | |
| Intermittent exotropia | - | 1060 (77.5) | 1060 (33.5) | | |
| Manifest exotropia | - | 308 (22.5) | 308 (9.7) | | |

Results are expressed as n (%) unless not otherwise specified.
OR: odds ratio; 95%CI: 95% of confidence interval; SD: standard deviation; IQR: interquartile range; ASD: Autism Spectrum Disorder; ADHD: Attention Deficit Hyperactivity Disorder.




OR: odds ratio; 95%CI: 95% of confidence interval.

**Figure 1.** Logistic regression analysis (univariate) of factors associated with exotropia and esotropia from 2012 to 2022.

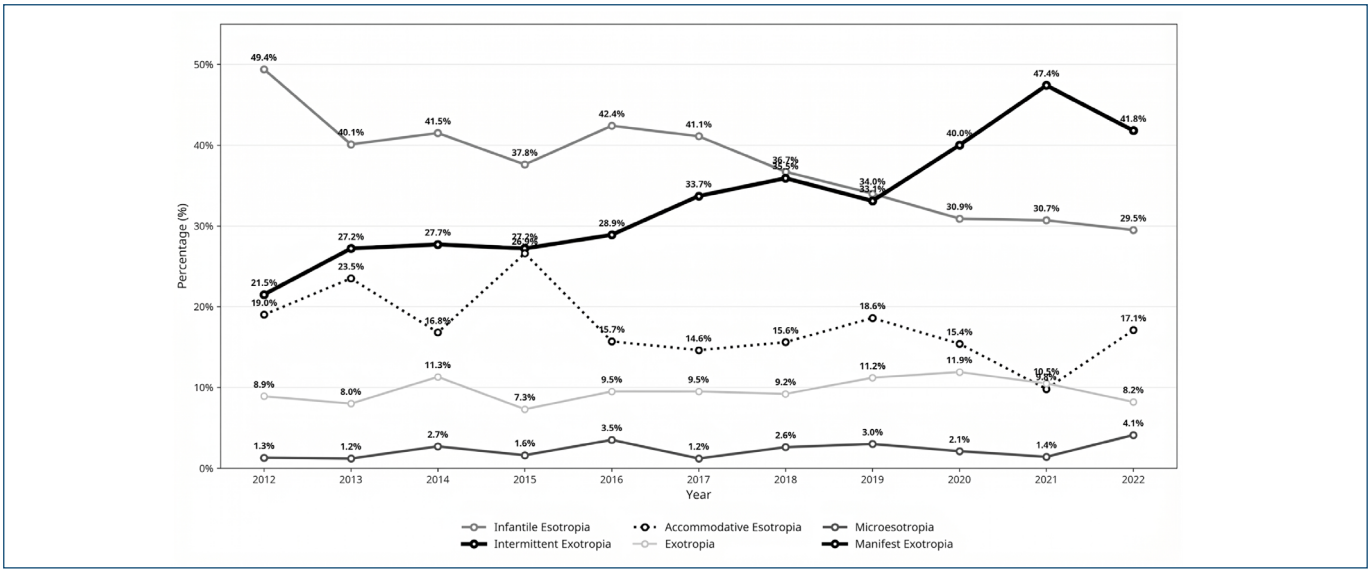



**Figure 2.** Year-by-year analysis of each subtype of horizontal strabismus from 2012 to 2022.

exotropia was more commonly associated with emmetropia. Prematurity, twinning, and ASD were likewise more frequent in intermittent exotropia. The basic type accounted for 88% of intermittent cases. On version testing, a V pattern was more prevalent in the manifest exotropia group (5.5%; Table 2).

Convergent deviations remained the largest group overall. Microesotropia and accommodative ET were more frequent in females. Non-accommodative ET presented at a younger mean age and showed a higher prevalence of diagnosis or treatment for amblyopia. Regarding refractive error, non-accommodative infantile ET was more often associated with emmetropia, whereas accommodative ET predominated among hyperopes. Infantile ET showed higher frequencies across most evaluated variables ($p < 0.05$), except for superior oblique overaction and diplopia, the latter being more common in MET cases (13%). Among the 544 cases of accommodative ET (30.4% of all convergent deviations), 325 (59.7%) were classified as refractive accommodative and 219 (40.3%) as partially accommodative (Table 3).

When ET and exotropia were compared, all variables except age differed significantly. Esotropia was associated with higher frequencies of family history of strabismus

**Table 2.** Characteristics of divergent deviations from 2012 to 2022

| Characteristics | Exotropia | | Total (n = 1,368) | p-value |
|---|---|---|---|---|
| | Manifest (n = 308) | Intermittent (n = 1060) | | |
| Female prevalence | 150 (48.7) | 590 (55.7) | 740 (54.1) | 0.0310 |
| Age at admission, years | | | | |
| Mean ± SD | 24.34 ± 16.27 | 11.53 ± 12.13 | 14.41 ± 14,22 | 0.00001 |
| Median ± IQR | 25 ± 12,63 | 6 ± 6 | 8 ± 10 | |
| Family history (strabismus or amblyopia) | 31 (10.1) | 143 (13.5) | 174 (12.7) | 0.1122 |
| Defined amblyopia or treatment for amblyopia | 93 (30.2) | 231 (21.8) | 324 (23.7) | 0.0023 |
| Spherical equivalent | | | | |
| Less than or equal to -1,00 D | 94 (30.5) | 220 (20.8) | 314 (23) | 0.0006 |
| Between -1,00 and +2,00 D | 147 (47.7) | 619 (58.4) | 766 (56) | |
| Greater than or equal to +2,00 D | 67 (21.8) | 221 (20.8) | 288 (21.1) | |
| Version exam | | | | |
| Lateral rectus pseudoelasticity | 68 (22.1) | 280 (26.1) | 348 (25.4) | 0.143 |
| Inferior oblique overaction | 16 (5.2) | 32 (3.1) | 48 (3.3) | 0.099 |
| V pattern | 17 (5.5) | 21 (2) | 38 (2.8) | 0.00175 |
| A pattern | 3 (0.9) | 5 (0.5) | 8 (0.6) | 0.553 |
| Classification of intermittent exotropia | | | | |
| Basic | - | 931 (88) | - | < 0.005 |
| Convergence insufficiency | - | 66 (6.2) | - | |
| Divergence excess | - | 63 (5.9) | - | |

Results are expressed as n (%) unless otherwise specified.
SD: standard deviation; IQR: interquartile range.

**Table 3.** Characteristics of convergent deviations from 2012 to 2022

| Characteristics | Esotropia | | | Total (n = 1797) | p-value |
|---|---|---|---|---|---|
| | Microesotropia (n = 69) | Accommodative (n = 544) | Infantile (n = 1178) | | |
| Female prevalence | 36 (52.2) | 300 (55.1) | 569 (48.3) | 905 (50.5) | 0.0294 |
| Age at admission, years | | | | | |
| Mean ± SD | 25.62 ± 16.91 | 17.46 ± 15.58 | 12.86 ± 12.81 | 14.75 ± 14.19 | 0.0001 |
| Median ± IQR | 26 ± 13.5 | 11 ± 12.5 | 7 ± 8.5 | 8 ± 10.5 | |
| Family history (strabismus or amblyopia) | 4 (5.8) | 84 (15.4) | 196 (16.6) | 284 (15.9) | 0.0539 |
| Defined amblyopia or treatment for amblyopia | 16 (23.2) | 154 (28.3) | 453 (38.5) | 623 (34.8) | 0.00001 |
| Spherical equivalent | | | | | |
| Lesser than or equal to -1,00D | 7 (10.1) | 62 (11.4) | 208 (17.7) | 277 (15.5) | 0.00001 |
| Between -1,00 and +2,00D | 34 (49.3) | 196 (36) | 548 (46.5) | 778 (43.4) | |
| Greater than or equal to +2,00D | 28 (40.6) | 286 (52.6) | 422 (35.8) | 736 (41.1) | |
| Version exam | | | | | |
| Diplopia | 9 (13) | 7 (1.3) | 75 (6.4) | 91 (5.1) | < 0.0001 |
| Nystagmus | 0 | 1 (0.2) | 41 (3.5) | 42 (2.3) | < 0.0001 |
| Inferior oblique overaction | 0 | 4 (0.7) | 58 (4.9) | 62 (3.5) | < 0.0001 |
| Superior oblique overaction | 0 | 1 (0.2) | 6 (0.5) | 7 (0.4) | 0.523 |
| DVD | 1 (1.4) | 2 (0.4) | 57 (4.8) | 60 (3.3) | < 0.0001 |
| V pattern | 0 | 6 (1.1) | 73 (6.2) | 79 (4.4) | < 0.0001 |
| A pattern | 0 | 0 | 14 (1.2) | 14 (0.8) | 0.025 |
| Classification of accommodative esotropia | | | | | |
| Refractive accommodative | - | 325 (59.7) | - | - | > 0.05 |
| Partially accommodative | - | 219 (40.3) | - | - | |

Results are expressed as n (%)unless otherwise specified.
SD: standard deviation; IQR: interquartile range; DVD: dissociated vertical deviation.

or amblyopia, diagnosis or treatment for amblyopia, prematurity, twinning and hyperopia. Exotropia, in contrast, was more frequent in females and more commonly associated with ASD, myopia, or emmetropia.

## DISCUSSION

In a multicenter study of children with strabismus aged 1-6 years, ET was more frequent among non-Hispanic white participants, particularly infantile ET (32.7%), whereas Asian children showed higher rates of exotropia, especially intermittent exotropia (37%).[15] In a population-based Australian cohort of more than 1,700 children, Robaei et al. reported that in their sample of 48 individuals with strabismus, 27% had intermittent exotropia, 20.8% had non-accommodative infantile ET, 12.5% accommodative ET, and 2% had MET.[16] Consistent with our findings, non-accommodative infantile ET and intermittent exotropia were the most frequent subtypes. Although their individual prevalence remained stable, our data demonstrate a distinct epidemiological shift in recent years, with intermittent exotropia emerging as the predominant horizontal deviation. The present study is

based on data from a tertiary care center and therefore reflects a hospital-based population, in contrast to most studies conducted in school settings.

In East Asian populations, the predominance of exotropia is well-established. Yu et al., in a 10-year retrospective study from Hong Kong with a mean patient age similar to our cohort (14 years), documented a progressive rise in the ratio of exotropia to ET, driven mainly by intermittent exotropia. By 2000, intermittent exotropia accounted for roughly 60% of all horizontal deviations, suggesting that this trend has been evolving since the 1990s.[12]

Lambert has proposed that the increasing exotropia-ET ratio may not necessarily reflect a true increase in exotropia; rather, it could be driven by declining rates of hyperopia, which is strongly associated with ET. In this view, the apparent increase in exotropia represents a relative decrease in ET rather than a surge in exotropia itself.[17] Our Brazilian data parallel this interpretation: the shift has occurred more recently – within the past 5 to 10 years – and appears to result chiefly from a fall in ET prevalence. A 2007 Brazilian study reported an overall ET-exotropia proportion of 2.84,[11] whereas in our analysis, the ratio approached 1, with an inversion of prevalence after 2019.

Several studies from other regions echo the demographic patterns we observed. In Turkey, a series of strabismic patients under 18 years without associated risk factors showed a mean age of 8 years and an almost even gender distribution (51% female, 49% male).[18] In Brazil, Kac et al. reported a slight female predominance (54%) among 935 patients, with more than half younger than 15 years.[11] Wu et al., examining 3-16-year-olds in Shanghai, found a female prevalence of 56.7%, with most patients aged 5-10 years (64%).[19] Likewise, a population-based Danish study of 3,785 adults found that 55.5% were female, although most were older than 20 years.[20] In Japan, Matsuo and Matsuo, reviewing over 80,000 schoolchildren, documented a high frequency of divergent deviations, most between 8 and 10 years of age.[21] Our findings are consistent with these data: 52.1% of our patients were female and the mean age was 13.9 years. Despite this consistency, the higher average age at admission is likely due to the fact that, as a tertiary hospital, patients often arrive after prior referral through primary and secondary levels of the healthcare system.

The coronavirus disease 2019 (Covid-19) pandemic may have influenced the apparent increase in mean age, as in-person consultations declined in the last 2 to 3 years – probably due to parental concerns about exposing young children to hospital settings. When stratified by deviation type, divergent deviations showed a higher female prevalence (54.1% *versus* 50.5%) and a higher mean age (14.4 *versus* 13.6 years) than convergent deviations.

Amblyopia and family history of strabismus also varied across studies. In an Ethiopian pediatric cohort, Agaje et al. reported amblyopia in 9.5% of children aged 0-10 years and a family history of amblyopia or strabismus in 3.6%.[22] In Turkey, Çakır et al. found amblyopia in 15.8% and a family history in 34%.[18] In our study, amblyopia was present in 30% of patients, and 14.5% reported a family history of amblyopia or strabismus. Both features were more frequent in convergent deviations.

The worldwide rise in myopia, driven partially by early and sustained use of digital screens, has altered refractive profiles. In Nanjing, China, a study of 5,831 children aged 3-6 years found that ET was strongly linked to high hyperopia, whereas exotropia displayed a more heterogeneous distribution: 52% had mild hyperopia, 31% were emmetropic, and 17% were myopic.[23] In Shanghai, Wu et al. reported no significant difference between strabismic and non-strabismic children (42% hyperopic, 36% emmetropic, and 22% myopic).[19] In South Korea, 65% of children overall – and 74% of those with exotropia – were myopic.[24] By contrast, a Minnesota study of children aged 5 to 7 years with intermittent exotropia found that 62.2% were hyperopic, 28.9% myopic, and 8.9% emmetropic; however, after a 10-year follow up, the refractive status shifted, with nearly 70% becoming myopic.[25] In Singapore, among 682 children with strabismus, 43% of those with exotropia were myopic, compared with 22% of those with ET.[26] Despite differences in refractive thresholds, our cohort showed that 48.8% of patients were emmetropic, particularly in the exotropia group (56% versus 43.3%). Hyperopia, in contrast, was more frequent in ET (41.2% versus 21.1% in exotropia). Notably, from 2018 onwards, we observed a clear decline in hyperopia.

This study is limited by its retrospective design and reliance on medical records not originally created for research purposes, leading to inevitable gaps in documentation. It is also important to highlight that the referral patterns and access to specialized care may limit the representativeness of the study population. Another limitation is the lack of subgroup analysis by patient ethnicity, which could enhance the applicability of the findings to Brazil's diverse population.

Despite these limitations, the present decade-long analysis of more than 3,000 individuals treated in a multicultural metropolis of a developing country provides a robust and representative overview of the epidemiological trends in horizontal strabismus.

## CONCLUSION

The long-standing predominance of esodeviations – once the principal focus of epidemiological and clinical research – appears to be declining worldwide. While earlier reports questioned whether this pattern might be transient, contemporary data, including the present analysis, point to a sustained shift in the relative frequencies of horizontal strabismus subtypes.

Although the drivers of this change remain uncertain, evolving refractive profiles and associated comorbidities are likely to contribute to the rising proportion of divergent deviations and the parallel decline in convergent deviations. Recognition of this trend should inform the refinement of screening strategies, diagnostic criteria, and management guidelines for a condition with substantial implications for visual development and quality of life.

## AUTHORS' CONTRIBUTION

Conception and design: Bernardo Przysiezny, Fabio Pimenta de Moraes, Graciella Miyuki Kato Sakamiti, and Marcia Ferrari Perez; analysis and interpretation of results: Bernardo Przysiezny and Fabio Pimenta de Moraes; drafting and critical revision of the manuscript content: Bernardo Przysiezny and Fabio Pimenta de Moraes. All authors approved the final version of the manuscript and are responsible for all aspects thereof, including ensuring its accuracy and integrity.

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