Prevalence and types of strabismus in cerebral palsy: A global and historical perspective based on a systematic review and meta-analysis

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Abstract

Purpose. Strabismus is more frequent in cerebral palsy (CP) than in the normal population, but reports differ how much it is increased. We here examined the global prevalence and types of strabismus in CP, whether esotropia or exotropia is more frequent, and whether the prevalence differs between ethnicities and/or country income levels, and between generations.

Methods. We compiled in a systematic review and meta-analysis the results of 147 CP studies that report the prevalence of strabismus or the ratio of esotropia to exotropia, and we conducted subgroup analyses for region (income level) and ethnicity. We performed a pooled analysis for the CP strabismus prevalence, and estimated the global number of CP cases with strabismus.

Results. The pooled prevalence of strabismus in CP is 49.8% in high-income countries and 39.8% in lower-income countries. We estimate the global number of strabismus cases in CP as 12.2 million, with 7.6 million males and 4.6 million females, based on current estimates of 29.6 million global CP cases. Esotropia is more frequent than exotropia in Caucasians, while exotropia is more frequent than esotropia in Hispanic and in some Asian and African populations. The strabismus prevalence in CP increases with increasing country income levels.

Conclusion. Generational changes in strabismus prevalence appear to reflect a transition of CP types and an increase in prevalence as countries attain higher income and more effective maternal health care. The distribution of esotropia and exotropia in CP patients largely reflects the horizontal strabismus type that is predominant in the subject's ethnicity.

250/250 words

Key words: strabismus, cerebral palsy, esotropia, exotropia, global, ethnicity, geographic mapping

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Introduction

Strabismus is one of the most frequent co-morbidities of cerebral palsy (CP).[1–6] While there is a consensus that strabismus is much more frequent in CP than in the normal, non-CP population (where it is estimated at 2-3%),[7,8] reports of the prevalence of CP-associated strabismus differ considerably, ranging from 15% or less[9–13] to over 90%.[14–16] The prevalence of strabismus in CP differs not only between studies, but may differ between geographic regions or ethnicities. The only previous systematic review of strabismus in CP[6] estimated the prevalence of strabismus at 48%, but Caucasians in high-income countries were over-represented, while Africans and Asians in lower-income countries were under-represented.

It is not known how many cases of CP with strabismus exist worldwide. Some of this uncertainty is due to controversies about the global prevalence of CP. CP is well-studied in Caucasian populations, in high-income countries, where the prevalence is about 2 per 1,000,[17–20] but the CP prevalence in lower-income countries (which is the large majority of the world population) is uncertain, with estimates ranging between 2 and 10 per 1,000.[5,16,18,20–32] Since CP types differ between developing and high-income countries,[26,33–35] and most authors conclude that the type of CP associates with strabismus prevalence,[5,6,10,11,28,33,35–47] it needs to be explored whether socioeconomic factors and/or ethnicity are significant variables for the strabismus prevalence among CP patients.

Another issue of contention is whether esotropia (ET) or exotropia (XT) is more frequent in CP. Initial studies, most of them examining populations of European ancestry, report more ET than XT, although some studies noted a lower ET/XT ratio in CP than in the general population.[15,48–53] Several of the more recent studies, many of them from East Asia and the South of the Indian subcontinent, reported more XT than ET in CP patients.[54–59] It has not been established whether the type of horizontal strabismus in CP is associated with the type of the underlying brain lesion, or whether it rather reflects the type of horizontal strabismus generally seen within the same ethnicity. We sought to answer the following questions:

1. What is the global prevalence of strabismus in people with CP? How much more frequent is it compared to the non-CP population? Can the global number of CP cases with strabismus be estimated?
2. Is the prevalence of strabismus in CP the same in Caucasians as in other ethnicities or regions (lower- vs high-income countries)?
3. Is the ET/XT ratio in CP significantly different between ethnicities?
4. Does the type of brain lesion in CP influence the type of horizontal strabismus (ET or XT), or does the direction of deviation reflect the type of horizontal strabismus that is predominant in the same ethnic population?
5. Are there longitudinal trends of strabismus prevalence in CP over generations?

To resolve these issues, we performed a systematic review and meta-analysis of strabismus in CP that was initially posted as a preprint.[60] Our review provides a comprehensive compilation of relevant studies, and we map their geographic distribution. We offer a global and historical perspective by exploring the role of ethnicity and socioeconomic factors.

Materials and Methods

Search Strategy

For our systematic review of the literature, we adhered to the PRISMA guidelines.[61] Reports of studies were identified through a search of three databases: Google Scholar, PubMed, and CNKI (China National Knowledge Infrastructure), with unrestricted years. We used the keywords “cerebral palsy”, “strabismus”, “esotropia” and “exotropia” in Google Scholar, and “cerebral palsy” and “strabismus”, as well as “cerebral palsy” and “squint” in PubMed. Only English terms were used for the search strategy of the first two databases. We searched the CNKI database using the Chinese words for "cerebral palsy" and "strabismus" as key words. Reference lists from eligible articles were examined to find additional relevant studies. Studies were also identified by searching papers that cited relevant sources. All titles were screened, and when potentially relevant, the abstract was evaluated to decide whether the paper should be obtained for full-text reading to verify eligibility (Fig. 1). We failed to obtain an abstract and full text in two cases (2/708).

Inclusion/Exclusion Criteria

To be eligible for the systematic review, studies had to report the numerical prevalence of strabismus in humans with cerebral palsy (CP) and/or provide the ratio of esotropia vs exotropia in a CP cohort. CP was defined as a “disorder of movement and posture due to a defect or lesion of the immature brain”, a definition that was subsequently refined and expanded.[62,63] We excluded studies that reported on children with various other causes of visual impairment, unless they reported specific data for a CP cohort. We excluded disability conditions that can be similar to CP, such as premature birth, hydrocephalus, microcephalus, meningitis, developmental delay, Down syndrome, epilepsy, or autism spectrum disorders. We also excluded reviews only, case studies, abstracts at meetings when later published as a peer-reviewed paper, and papers focused on surgical outcomes. We included 54 studies on Caucasians (most of them in Europe, North America and Australia),[9,10,14,36–42,44,48–53,64–101] 11 studies from the Middle East,[5,16,23,102–109] 9 on Hispanics (most of them from Latin America),[15,110–117] 41 from East Asia,[12,13,43,46,56,58,118–152] 23 from South Asia,[33,35,45,47,54,57,153–169] and 5 from Africa[11,170–174] (Supplemental Table 1).

Data Extraction and Analyses

Data were extracted by using pre-designed tables, including date of publication, first author name, country, geographic region, cohort size, number of cases of strabismus, and, when available, age range and the type of strabismus: horizontal vs. vertical, and among the horizontal strabismus, how many cases of esotropia, and how many cases of exotropia. We compiled information about gender distribution in the cohort and in strabismus cases when such data was reported. The percentage of strabismus cases was calculated from the number of cases per cohort. We conducted subgroup analyses between ethnicities, as well as between high-income and lower-income countries. Income levels were defined by the GDP as per the World Bank Report (1987 to 2022).[175] Because of ethnic differences between populations, the prevalence for each major ethnicity (European ancestry, African, Middle East, East Asian, South Asian, Latino/Hispanic) was estimated separately and weighted by population size to generate an overall estimate of the current global strabismus prevalence in CP. This was also necessary to prevent bias: the largest fraction of available studies examined people with European ancestry (in high-income countries). There were sufficient data for Caucasians, South Asians, and East Asians to assess generational (longitudinal) trends.

Statistical Analyses

The primary purpose of our meta-analysis was to generate a more precise and reliable estimate of the prevalence of strabismus among people with CP and to predict the global number of CP cases with strabismus. Pooled analyses were performed for strabismus prevalence in CP and the ET/XT ratio. The heterogeneity among studies was evaluated by Cochran's Q test and the I^2 index.[176,177] The random-effect models were used to conservatively diminish the heterogeneity between studies.[177] The study weights were obtained based on the DerSimonian-Laird method.[177] A continuity correction of 0.5 was applied to studies with zero cases.[176] Subgroup pooled analyses were conducted by region/ethnicity, separately for prevalence and for the ET/XT ratio, to assess differences between Caucasians and other ethnicities. Meta-regression analyses were performed to test associations between risk factors and study outcomes. The risk of publication bias was evaluated using funnel plots and Egger's test.[178] The significance level was set to 0.05. All meta-analyses were performed using the Stata SE 16.0 software (StataCorp, TX, USA).

Results

Our analyses are based on 147 studies, with 136 of them reporting the prevalence of strabismus in CP (total cohort number: 21,449), 102 partially overlapping studies reporting the esotropia/exotropia (ET/XT) ratio in CP cases (total cohort number: 13,613), and 90 partially overlapping studies reporting the gender distribution in the CP cohorts (total cohort number: 15,728). Altogether, these studies examined 21,753 CP cases in cohorts from 29 countries on five continents.

Global prevalence of CP and estimate of the total number of CP cases worldwide

While the prevalence of CP in developed (high-income) countries is well-established at about 2/1,000,[2,19,20,24,26,44,49,64,71,179] there is less information about the prevalence of CP in lower-income countries.[17,25,27–31] Initially, it was assumed that the CP prevalence was similar between developed and developing countries.[17–19,24] Recent studies have revealed a much higher prevalence of CP in many lower-income countries.[20,25,26,30,31] For example, the prevalence of CP per 1,000 in India was reported as 2.8,[180] in rural Uganda it is 3,[27] in Bangladesh 3.4,[28] in Egypt 3.6,[181] in Mexico 4.4,[32] in Turkey between 4.4 and 5.6,[22,182] and in rural South Africa as 10.[21,25] These prevalences are thought to be underestimates.[20,28] Some authors noted that the prevalence of CP in lower-income countries is twofold larger than in high-income countries.[20,26,28] Very recent studies, based on new data and statistical modeling, estimated the prevalence and total number of global CP cases significantly greater, at about 6 per 1,000,[20,27,28,30] equivalent to about 50 million global cases.[29,31] However, the statistical modeling appears to include cases with motor dysfunction similar to CP, but not strictly with a CP diagnosis.[29] The much higher CP prevalence in lower-income countries has important implications for the estimates of the global prevalence of CP.

In our approach to estimate global CP numbers, we applied a prevalence of 2/1,000 for high-income countries, and 4/1,000 for lower-income countries (distinction according to The World Bank).[175] We estimate the CP cases in high-income countries (population of about 1.2 billion) to be 2.4 million (1.2 billion x 0.2%), and in lower-income countries (population of about 6.8 billion) to be 27.2 million (6.8 billion x 0.4%), which combines for a global total of 29.6 million CP cases. This estimate is intermediate between the previous, too low notion of 18 million global CP cases,[183] and the likely too high 50 million global cases.[29]

Global prevalence of strabismus in CP: estimate of total numbers of CP cases with strabismus

The geographic distribution of studies reporting the prevalence of strabismus in CP is shown in Fig. 2A, with the prevalence indicated by a color gradient and the size of the cohort reflected by the size of the circles. The prevalence of strabismus in CP seems lower in some regions (Africa, for example) when compared with other regions. We therefore performed subgroup analyses to determine whether socioeconomic conditions or ethnicity are significant factors. Subgroup analyses for the major ethnicities were not significantly different, except for Caucasians vs. East Asians ($p=0.001$, Fig. 3A). Subgroup analysis by country income level showed a significantly higher strabismus prevalence for high income (49.8%, 95% confidence interval CI=44.3–55.2%) than for lower income (39.8%, CI=34.4–45.1%, $p=0.004$). The global strabismus prevalence was 41.3% when adjusted for the population size of high-income countries (1.2 billion) and lower-income countries (6.8 billion, Table 1A). When the differences in CP cases between regions as well as the differences between prevalence of strabismus in CP cases are taken into account, we can use the above estimate of the global number of CP cases (29.6 million) to calculate the total number of CP cases with strabismus worldwide – as 12.2 million (29.6 x 41.3%).

Frequencies, numbers and ratios of esotropia and exotropia cases in CP

The large majority of strabismus cases in CP are horizontal deviations, either esotropia (ET) or exotropia (XT), with a much smaller percentage of strabismus cases that have an exclusive vertical deviation (1.8%, CI=1.2–2.4%), based on 5,092 CP cases with information on hypertropia, Supplemental Table 1). The predominance of horizontal over vertical deviations is similar in non-CP and in CP populations. In the rest of our review, we will focus on horizontal strabismus. Most studies (74.5%) report more ET than XT in cases of CP (Fig. 2B; Supplemental Table 1). Populations with more ET than XT include Caucasians in Europe and North America, and most of the populations in the Middle East, South Asia, and East Africa. Populations with more XT than ET include parts of East Asia, the South of the Indian subcontinent, West Africa, and Hispanics in Central America (Figs. 2B; 4). Differences in the ET/XT ratio reached significance in Caucasians vs Hispanics (p=0.036) and was borderline for South Asians (South) vs Caucasians (p=0.062). Based on the estimate of the global prevalence of CP (see section above), we calculated the total number of CP cases with ET or with XT. Weighted by population size, the total global number of CP cases with ET is 7.0 million, and the total global number of CP cases with XT is 5.0 million (Table 1B).

Gender distribution of strabismus in CP

Among our eligible CP studies, 89 report the gender distribution in the cohort, but only two of these studies also report the gender of the cases with strabismus.[166,167] In CP cohorts, males nearly always exceed females, overall by a factor of about 1.5 to 1.[184] The same is true for “our” CP cohorts – the ones that have been examined for strabismus (n=15,728), with 9,808 males and 5,920 females), which is a male/female ratio of 1.66 to 1 (7.6 million males and 4.6 million females). Two of these studies disclosed gender among strabismus cases (total cohort of 484)[166,167]; they indicate that there is no gender difference – males and females appear to contribute equally to the strabismus cases in the CP cohort, with the male and female prevalence of strabismus not being significantly different (p=0.440). In other words, there are more males with CP-associated strabismus than females, but only because more males than females have CP.

Longitudinal analysis: strabismus prevalence in CP has increased over decades

To determine whether the prevalence of CP-associated strabismus has changed between generations, we examined the prevalence data in three ethnicities: Caucasians, East Asians, and South Asians (Supplemental Table 1). There was a significant trend in Caucasians from about 35% to 55% prevalence of strabismus in CP between 1950 and 1995, and the trendline slightly decreased from about 55% to 50% between 1995 and 2022 (Fig. 5A). The data for East Asians also showed an increasing trendline (Fig. 5B), from about 28% to 37%, but a nearly flat trendline for South Asians (Fig. 5C). These trends are consistent with the notion that strabismus prevalence in CP is associated with socioeconomic factors (see Discussion).

Discussion

An association between CP and strabismus was first noted in the middle of the 19th century; for a review of the early literature, see Smith.[1] In the second half of the 20th century, a series of more detailed studies from Europe and North America reported on the prevalence of strabismus in CP (Supplemental Table 1). Until the year 2000, most studies (39/49=79.6%) were carried out on Caucasian populations, thereby creating a Eurocentric bias. More recent studies examined populations from other regions of the world, notably in South Asia, East Asia and the Middle East (Table 1A; Supplemental Table 1), allowing to gain a better global perspective.

Global prevalence of strabismus in CP

We estimate the total number of CP cases worldwide at 29.6 million (Table 1A). Given the incomplete ascertainment of CP cases as well as survival bias in developing countries, our estimate of 29.6 million CP cases globally may be an underestimate.[20,25,27,28,34] How many of these CP patients have strabismus? The only previous systematic review estimated a 48% strabismus prevalence in CP which was based on 17 studies, with a combined cohort of 1,734.[6] We find a lower global prevalence, of 41.3%. Our estimate is based on a much larger number of CP cases (21,449 cases), nearly 13-fold larger than the cohort size in the previous estimate. The higher prevalence estimates[3–6,185] are likely due to bias towards Caucasian populations in high-income countries.

The CP prevalence is known to increase with lower socioeconomic status.[18,25,28,34,186–188] The recent studies from Africa and from South and East Asia are consistent with this notion. We show that lower-income countries (LICs) have a lower prevalence of CP-associated strabismus than high-income countries (HICs) (Fig. 3B). The key to understanding this surprising finding likely is that the timing of the brain insult and the mechanism of CP (and possibly strabismus) differ between LICs and HICs (Supplemental Fig. 2B). In LICs, the majority of CP cases are caused by peri- and postnatal events: asphyxia during delivery, or post-partum infection, while in HICs, the majority of CP cases are due to preterm births – when the immature brain is more vulnerable to lesions of the visual pathways.[26,28,33,34,185,189,190] Additional factors complicate this basic pattern, in that very preterm babies rarely survive in LICs, but are more likely to survive in HICs, and that severe cases of CP are also more likely to survive in HICs, while in LICs, many may die prior to the age of CP diagnosis.[24,27,28,34] This explanation is consistent with the observed data of a lower CP prevalence in HICs, but a higher prevalence of strabismus in CP cases in HICs than in LICs.

The trendlines of strabismus prevalence in CP (Fig. 5) are consistent with the prediction that developing countries will undergo similar shifts in CP types as developed countries did several decades ago – when more effective maternal health care systems were implemented. With an increasing number of studies from Asian, African and Hispanic populations, it now is possible to estimate the global prevalence of CP-associated strabismus and the global number of such cases. Accordingly, we estimate about 12.2 million such cases worldwide. This allows us to calculate how many cases of strabismus, due to CP, need to be added to the number of strabismus cases in the normal (non-CP) population. The normal (non-CP) population is thought to have a strabismus prevalence of 2-3%.[7,8] Since most of the epidemiological studies rely on surveys of normal schools,[8,191] many of the CP-associated strabismus cases (the ones with more severe CP) would have been missed. The ~12.2 million CP strabismus cases comprise 6% of the total global number of strabismus cases (2-3% of a population of 8 billion people translates to 160-240 million cases).[7,8]

Variation between studies

There is considerable variability in the prevalence of CP-associated strabismus between studies, ranging from less than 15% to over 90%, I^2=97.9 (Table 1A; Fig. 3A,B; Supplemental Table 1). Multiple factors, not mutually exclusive, may contribute to this variability. First, the severity of CP differs between cohorts, and severity of CP is associated with strabismus prevalence. When cohorts primarily comprise mild cases of CP, they tend to have a lower prevalence of strabismus, while cohorts with severe cases have a higher prevalence of strabismus[9,37,192]. Second, the types of brain lesions differ between studies and between populations, due to differences in maternal health care as mentioned above. Third, ethnicity may be a significant variable, due to differences between populations in CP prevalence.[193,194] Whether socioeconomic factors can fully account for such ethnic differences is controversial.[193,195] Ethnicity may affect the type of strabismus (ET vs XT, see below), as well as the overall prevalence of strabismus.[142] Fourth, methodological issues likely play a role, especially the criteria used to identify and diagnose CP cases which varies between countries and studies.[19,29,34,188] Finally, there likely is natural variation between populations and also between risk factors for both CP and strabismus that may change over time – e.g., maternal smoking is a major risk factor for strabismus,[196,197] regardless whether the offspring has CP or not. All of these factors likely contribute to the observed variation between studies.

Is strabismus prevalence associated with CP types?

Strabismus prevalence is associated with the severity of CP, visual impairment, and also with the extent of intellectual capacity.[3,5,37,38,45,46,48,58,70,115,153,159,198–202] Relatively few authors disagree with this conclusion.[39,74,101] Some authors noted that strabismus is most frequent in spastic tetraplegia (or triplegia) and somewhat less in diplegia, still less in hemiplegia, and rare in athetoid or ataxic CP,[5,11,36,39,40,45,47,64,70,101,105,149,163] while others disagree with this notion.[15,41–43,52,56,67,78,100,111,203] Authors concur that there is no association between the *type* of strabismus (esotropia, exotropia, hypertropia) and the *type* of CP.[15,46,51,52,67,100,114]

The esotropia/exotropia (ET/XT) ratio in CP

Our work has revealed differences between populations in how prevalent ET and XT are in CP (Figs. 2B, 4). Why do Caucasians, North Indians and people in the Middle East have more ET than XT, while populations in West Africa, Hispanics in Central America, and South Indians have more XT than ET? CP increases the likelihood of strabismus, but whether the strabismus will be ET or XT depends largely on the ethnicity, presumably due to differences in orbital anatomy, as first proposed by Holm[204] and Waardenburg.[205] The ET/XT ratio appears to be changed in CP (closer to 1), as has been noted by several authors for Caucasians[15,48,50–53] and for East Asians.[56] It seems that CP “tempers” the extremes and makes the ET/XT ratio more balanced than it is in the non-CP population (of the same ethnicity).

Gender distribution

In the CP cohorts examined for gender, males dominate over females by a ratio of 1.66:1. This ratio is similar to the known male dominance in CP (about 1.5 to 1).[184] Among CP cases, the strabismus prevalence appears to be the same between males and females (although this is based on sparse data). Because of the male dominance in CP, there are more males with CP-associated strabismus than females. In the normal (non-CP) population, the prevalence of strabismus is the same between males and females.[206] Our data suggest that there is a male predominance of CP-associated strabismus (7.6 million males vs 4.6 million females), which would indicate a 3 million male/female difference in the global cases of all strabismus, when CP-associated strabismus cases are included in the count.

Pathogenesis of strabismus in CP

It is currently controversial what causes strabismus in CP; three different explanations have been proposed: (1) spasticity of extraocular muscle, (2) lesion of cortical or subcortical motor circuits, and (3) lesion of cortical or subcortical visual circuits. We will discuss these scenarios in sequence and evaluate their merits.

Extraocular muscle spasticity (similar to the limb spasticity seen in CP) as a mechanism for strabismus was discussed by Smith,[1,70] and proposed by Sandfield-Nielsen et al.[200] This notion was essentially refuted by Smith[1,70] and Kalbe et al.[51] It was pointed out that extraocular muscles are not spastic in CP, and there is no reason why any such “spasticity” should selectively affect certain extraocular muscles and spare others. While strabismic extraocular muscles do exhibit abnormal extracellular matrix gene and protein expression,[207] which resembles abnormalities in CP limb skeletal muscle,[26] such dysregulation may be a general response of muscle tissue to abnormal functional demands, and does not necessarily imply similarity in pathogenesis.

Some authors state that subcortical motor lesions (midbrain, brainstem) may cause strabismus in CP.[1,45,54,94,155,167] Lesions of basal ganglia and cerebellum (dyskinetic and ataxic CP) less often associate with strabismus.[10,36,37,47,105,189]

Other authors implicate lesions of cortical or subcortical visual pathways as the primary cause of strabismus in CP.[1,46,56,56,189,208,209] The significance of impaired visual pathways (optic radiations and/or cortical areas involved in visual motion processing) for strabismus in CP is supported by imaging studies (CT, MRI).[189,208,210–214]. Disturbance of motor pathways appears to play a lesser role in the pathogenesis of strabismus in CP than compromised visual pathways. It was noted that the lesion of subcortical visual pathways – more frequent in preterm births due to the immaturity of the pathways – appears to cause more esotropia, while lesions of visual cortex more often cause exotropia[189,214,215] – but some authors disagree.[209] Such differences in the direction of horizontal misalignment are consistent with prenatal lesions being more frequent in high-income countries, and perinatal lesions being more frequent in lower-income countries. Overall, the direction of horizontal strabismus in CP appears to be determined primarily by ethnic/genetic factors rather than socioeconomic factors or timing of lesions (prenatal vs perinatal). Regions with a lower ET/XT ratio (South India) utilize maternal health care more frequently than regions with a higher ET/XT ratio (North of India),[216] so a shift to more prenatal insults than perinatal insults cannot explain the lower ET/XT ratio in South India (Fig. 2B).

Conclusion

Differences in maternal health care between lower-income and high-income countries are important to understand global and regional differences in CP and to predict trends in CP prevalence as well as the prevalence of strabismus in CP.

3,999 words

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TABLES

Table 1. Prevalence of strabismus in cerebral palsy (CP): Data and estimates of numbers (**A**). Esotropia (ET) and exotropia (XT) in CP: Data and estimates of numbers (**B**).

A.

Ethnicity/ Region	**Population**	**Studies**	**Cohort**	**CP with Strabismus in cohort**	**Cohort: CP Strabismus Prevalence**	**CP with Strabismus, Cases in population (estimate)**	**CP Cases in population (estimate)**
	billion	number	number	number	percent	million	million
Caucasian	1.2	53	6,329	2,711	48.8	1.17	2.4
Middle East	0.5	9	584	300	48.6	0.97	2.0
Hispanic	0.7	6	1,016	677	60.8	1.70	2.8
African	1.3	5	736	263	31.5	1.64	5.2
East Asian	2.4	40	7,182	2,287	35.7	3.43	9.6
South Asian	1.9	23	5,602	1,990	43.0	3.27	6.0
Global (Total)	**8.0**	**136**	**21,449**	**8,228**	**41.3**	**12.2**	**29.6**

B.

Ethnicity/ Region	**Population**	**Studies**	**Cohort**	**Cohort CP cases with ET**	**Cohort CP cases with XT**	**ET/XT ratio in Cohort**	**CP with ET, entire population (estimate)**	**CP with XT, entire population (estimate)**
	billion	number	number	number	number		million	million
Caucasian	1.2	42	5,167	2,747	1,481	1.76	0.733	0.417
Middle East	0.5	9	590	235	135	1.56	0.579	0.371
Hispanic	0.7	9	1,098	303	331	0.94	0.809	0.861
African	1.3	4	587	84	155	0.85	0.739	0.871
East Asian	2.4	22	3,281	590	451	1.40	1.966	1.404
South Asian (North)	1.5	6 7	1,800	496	120	2.99	1.754	0.586
South Asian (South)	0.4	9	1,090	228	267	0.94	0.417	0.443
Global (Total)	**8.0**	**102**	**13,613**	**4,683**	**2,940**		**6.997**	**4.953**

Footnote: The number of studies differs between prevalence and ET/XT ratio, because not all studies reported overall prevalence and ET/XT ratios, although most studies reported both. The estimates for global numbers of ET and XT cases in CP do not include the estimated number of pure vertical deviations which are about 0.2 million cases. We distinguish between South Asians in the North and South for the ET/XT ratio, because of the significant difference between these populations as discussed in the text and illustrated in Fig. 2B.

FIGURES

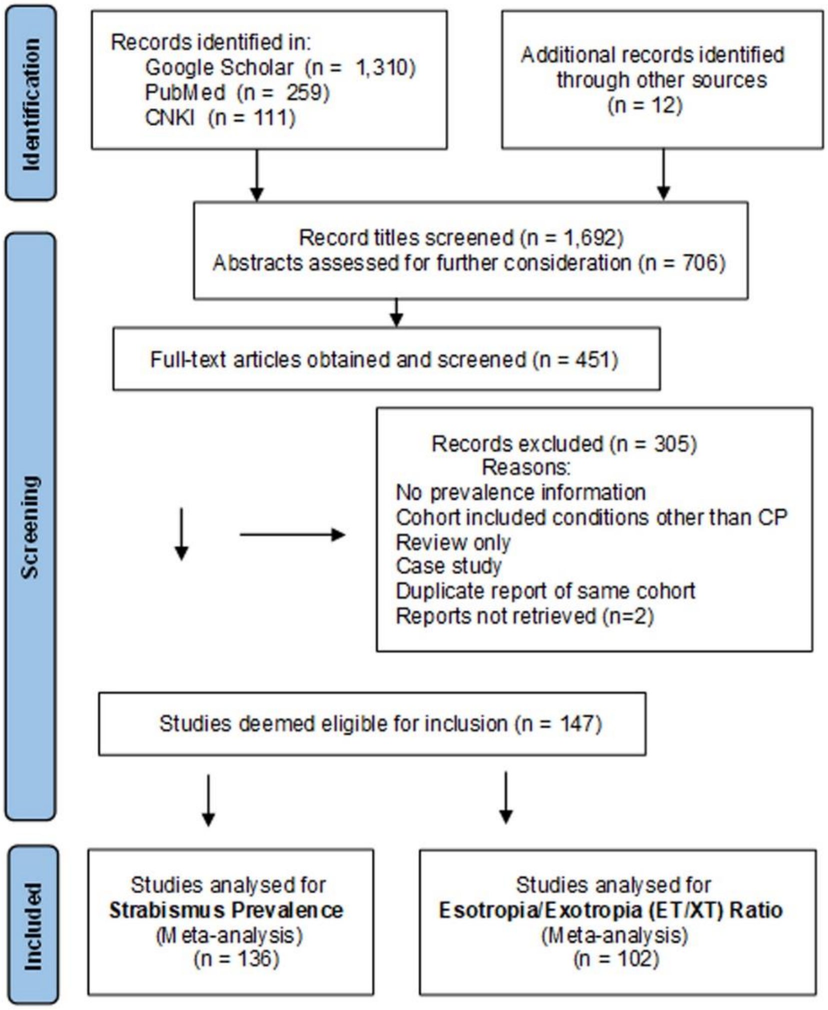


Fig. 1. Flowchart of the Literature Search and Screening Strategy.

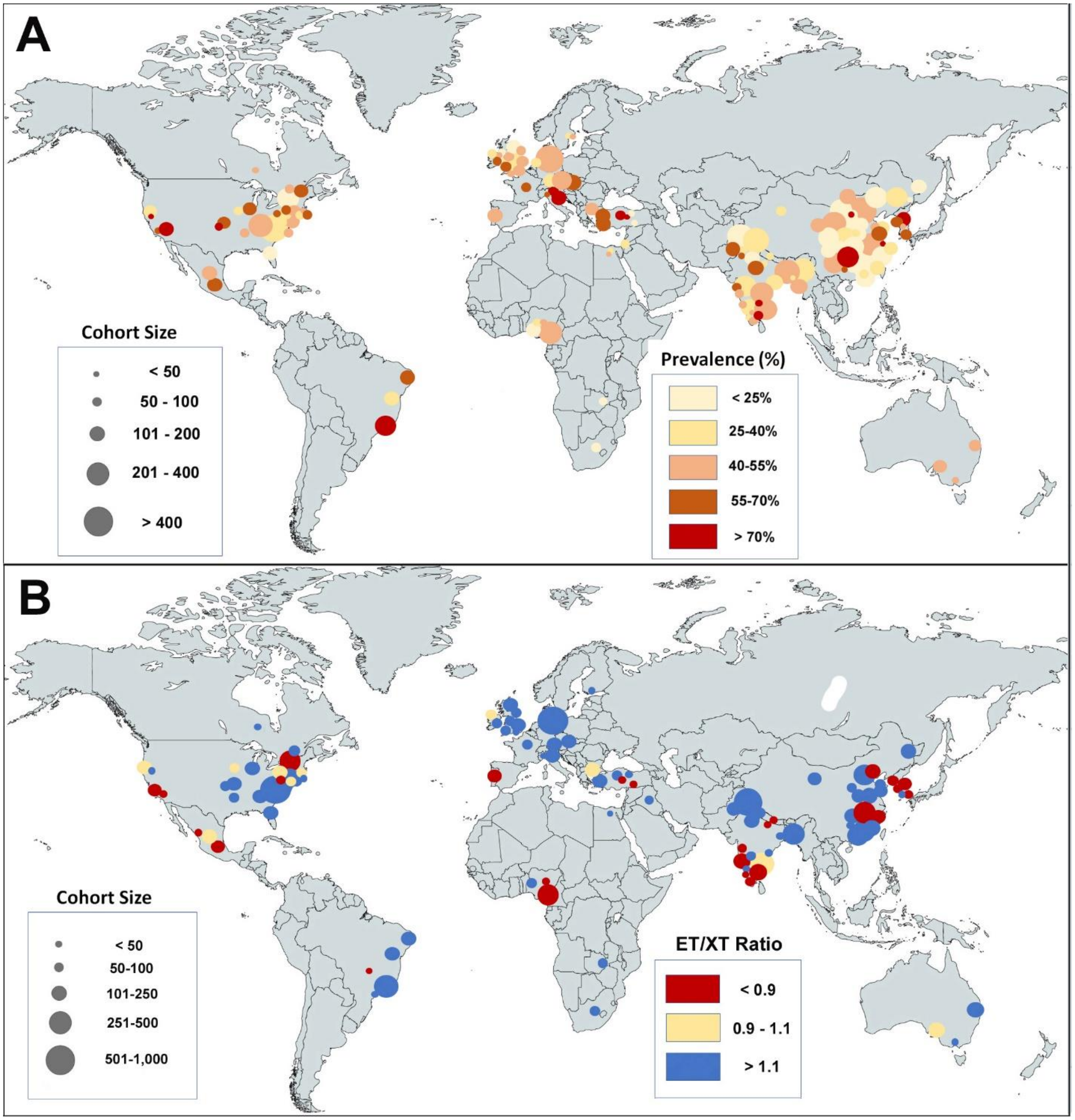


Fig. 2A, B. World maps showing the distribution of studies reporting the prevalence of strabismus in cerebral palsy (**A**) and the esotropia/exotropia (ET/XT) ratio in cerebral palsy (**B**). The cohort size is indicated by the circle size and the prevalence or ratio is indicated by the color gradient. In **A**, note that lower-income countries (Africa and India) have a somewhat lower prevalence than high-income countries. In **B**, the ET/XT ratio below 0.9 is indicated in red, a nearly equal distribution (0.9 to 1.1) is indicated in tan, and a ratio above 1.1 is indicated in blue. Note that regions with Caucasian populations mostly have a high ET/XT ratio, while some populations in Africa, East Asia, Southern India and some Hispanic populations have a low ET/XT ratio.

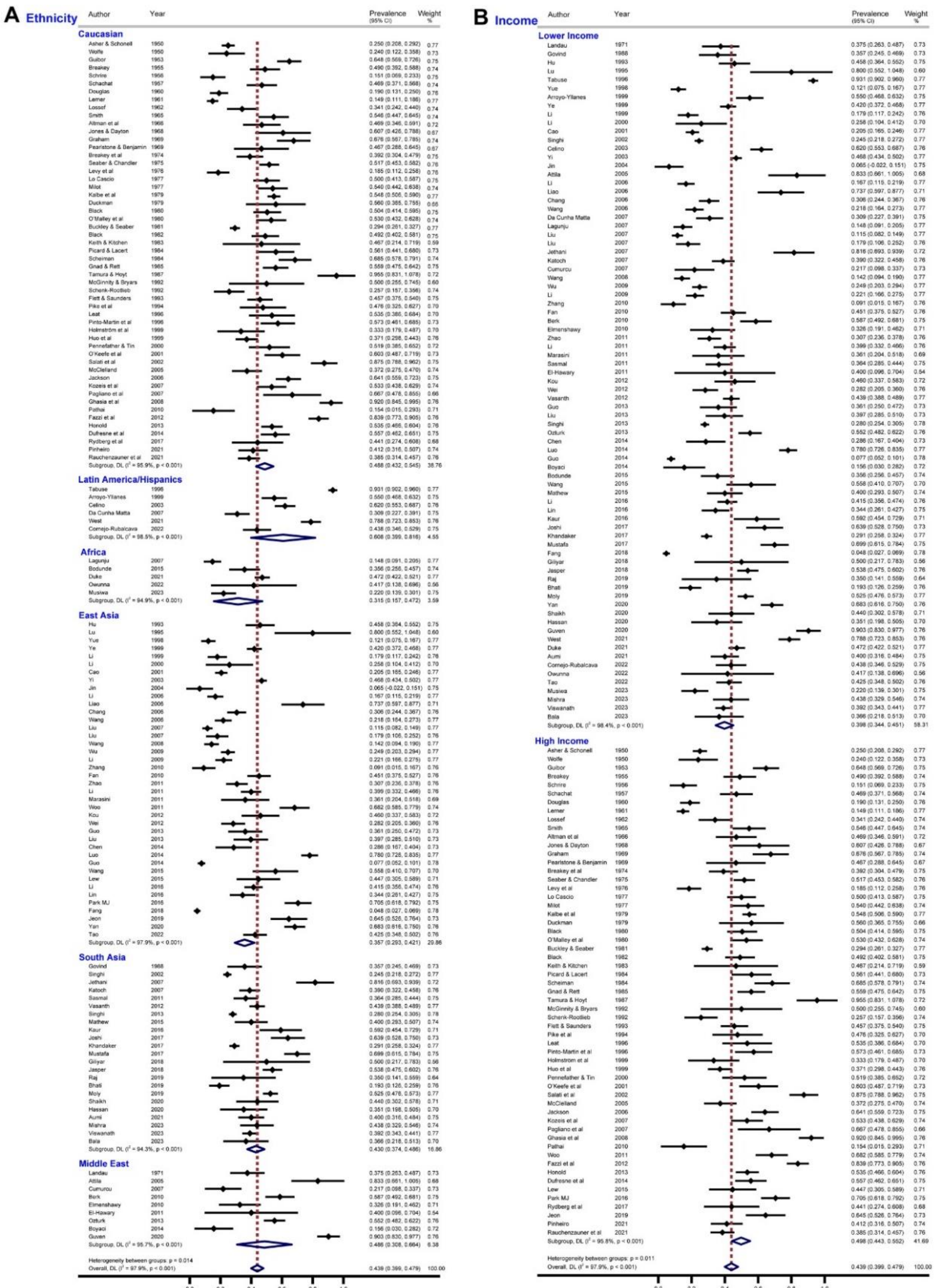


Fig. 3A, B: Forest Plots of the Prevalence of Strabismus in Cerebral Palsy. **A.** Sorted by ethnicity. **B.** Sorted by lower-income countries vs high-income countries – a statistically significant difference (p=0.004, see Supplemental Fig. 2A). Note the shift in high-income countries towards a higher prevalence of strabismus. The diamonds show the pooled prevalence for the listed studies.

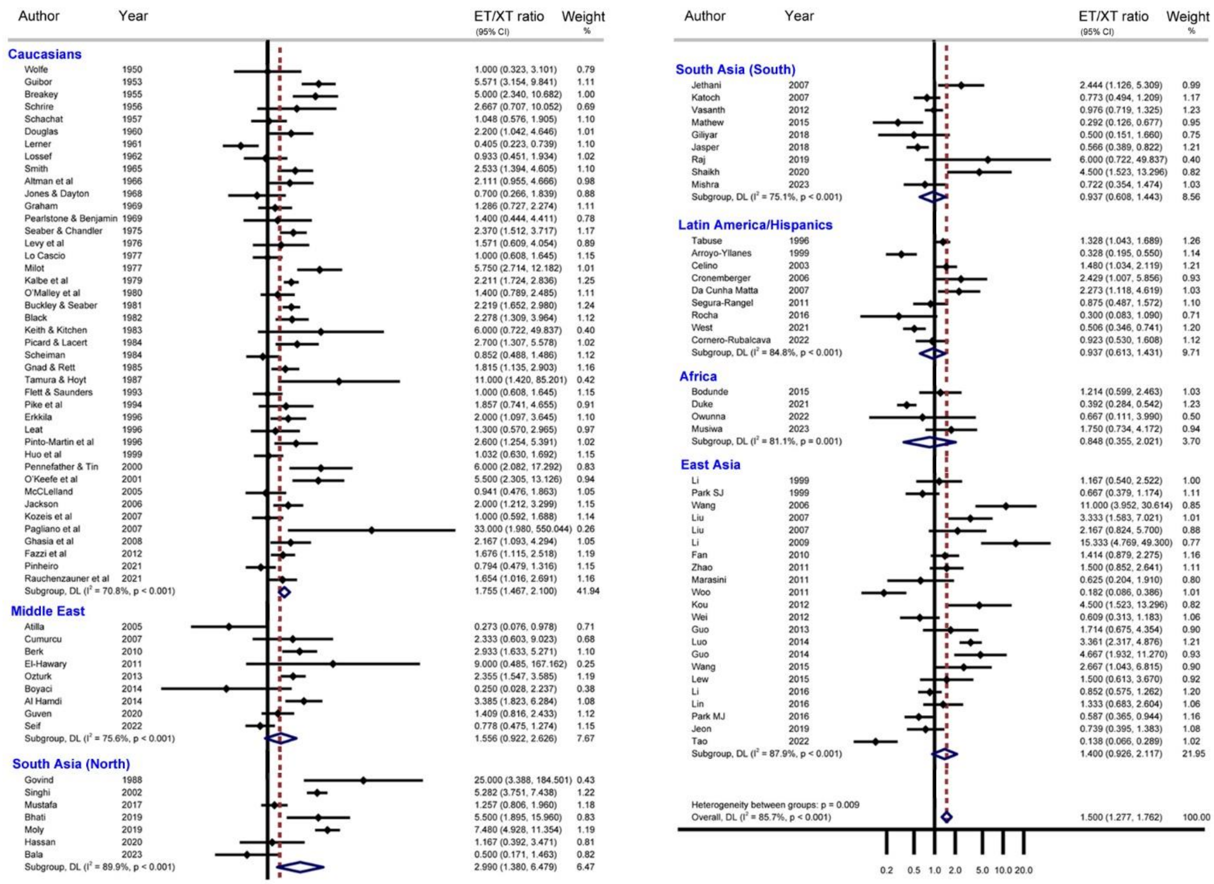


Fig. 4: Forest Plot of Esotropia/Exotropia (ET/XT) Ratios in Cerebral Palsy sorted by Ethnicity. Ethnicities with higher ET/XT ratios (higher than 1.5) are compiled on the left side, ethnicities with lower ET/XT ratios (below 1.5, several below 1.0) are compiled on the right side of the forest plot. The diamonds show the pooled ratios for the listed studies.

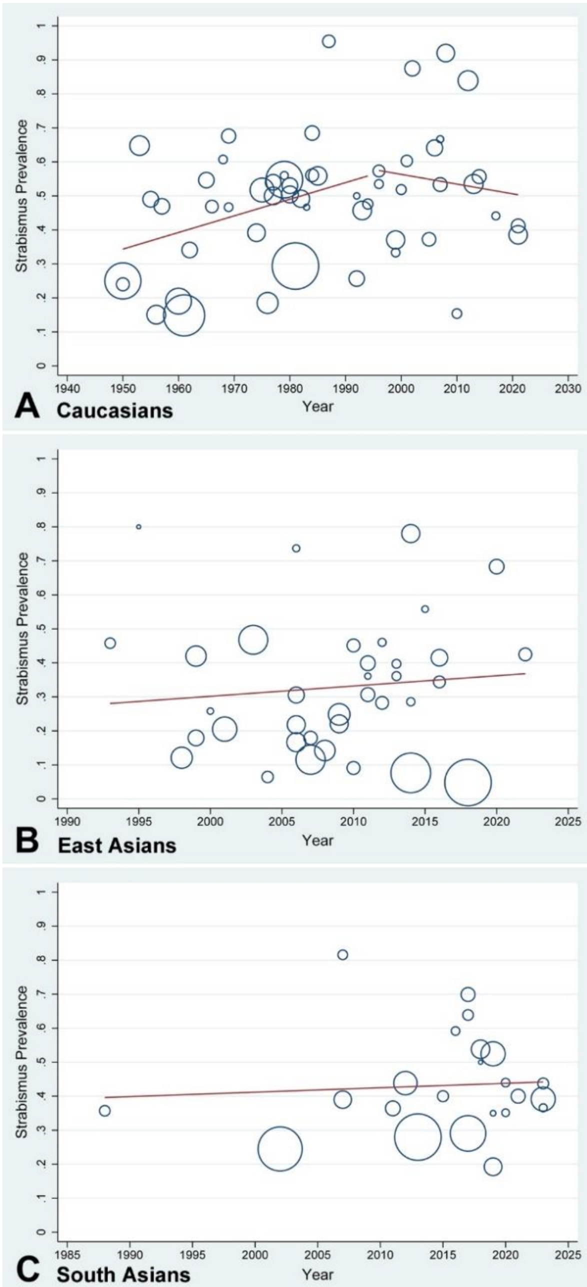


Fig. 5A-C. Trends over decades in the prevalence of strabismus in cerebral palsy (CP) in Caucasians (**A**), East Asians (**B**), and South Asians (**C**). Note the increasing trend from about 35% to 55% (significant with p=0.039) in Caucasians from 1950 to 1995, and a near stable trend thereafter (**A**). East Asians show a more gradual increase from 1995 to 2022 (**B**), while the trendline for South Asians is nearly flat (**C**). These data are consistent with the notion that with more effective maternal health care, the prevalence of strabismus in CP increases, likely due to fewer cases of CP with perinatal etiology and increased numbers of surviving premature babies, and then reaches a plateau.

SUPPLEMENTAL FILES

Supplementary Table 1. Prevalence of strabismus, esotropia (ET), exotropia (XT), vertical deviation (Vert.) and all strabismus (All Strab.) in cohort studies of cerebral palsy. Ref., Reference. The Table is organized by region/ethnicity as well as chronological within those regions. Explanations: ?, data are uncertain or inconsistent in the report; ~, approximate numbers; +, a few subjects in the cohort exceeded the value; blank, no information was given. We list only one study in cases where multiple papers report on the same cohort.

First Author	Ref. #	Year	Region	Age (years)	Cohort size	ET %	XT %	ET+XT %	Vert. %	All Strab.
EUROPE										
Asher	64	1950	Birmingham, UK	children	400					25%
Douglas	48	1960	Dundee, UK	?	168	13.1	6.0	19.1		19.1%
Smith	70	1965	Manchester, UK	children	97	39.2	15.5	54.6		54.6%
Graham	49	1969	Cardiff, UK	5-16	71	38	29.6	67.6		67.6%
Kalbe	51	1979	Lübeck, Germany	children	544	36.6	16.5	53.1		54.8%
Black	78	1980	Cambridge, UK	6-16	117					50.5%
Black	37	1982	Cambridge, UK	6-16	120	34.2	15	49.2		49.2%
Picard	82	1984	Garches, France	6-19	66	40.9	15.2	56.1		56.1%
Gnad	52	1985	Vienna, Austria	1-24	136	36	19.9	56		56%
McGinnity	84	1992	Belfast, UK	9	16			50		50%
Schenk-Rootlieb	85	1992	Netherlands	0-19	74					25.7%
Pike	87	1994	Oxford, UK	2-9	42	31	16.7	47.6		47.6
Erkkila	53	1996	Helsinki, Finland	1-13	48	ET/XT ratio 2:1				
Holmström	89	1999	Stockholm, Sweden	3.5	36					25.7%
Pennefather	9	2000	Newcastle, UK	2	54	44.4	7.4	51.9		51.9%
O'Keefe	92	2001	Dublin, Ireland	0.5-12	68	48.5	8.8	57.4	2.9	60.3%
Salati	93	2002	Milan, Italy	2-16	56			87.5	?	87.5%
McClelland	39	2005	Northern Ireland	4-15	94	17	18.1	35.1	2.1	35.1%
Kozeis	40	2007	Thessaloniki, Greece	6-15	105	26.7	27.6	54.3		54.3%
Pagliano	96	2007	Milan, Italy	2-6	24	66.7	0	66.7		66.7%
Pathai	97	2010	UK	1-3	26					15.4%
Fazzi	42	2012	Brescia, Italy	0-15	118	52.5	31.4	83.9		83.9%
Honold	98	2013	Innsbruck, Austria	2-17	200	32.1				53.5%
Rydberg	99	2017	Stockholm, Sweden	7-17	34			44.1		44.1%
Pinheiro	100	2021	Coimbra, Portugal	1-40	102	26.1	33.3	59.4?		41.1%
Rauchenzauner	101	2021	Innsbruck, Austria	2-17	179	24	14.5	38.5		38.5%
NORTH AMERICA, AUSTRALIA, SOUTH AFRICA (mostly Caucasians)										
Wolfe	65	1950	Iowa, USA	5-20	50	12	12	24		26%
Guibor	66	1953	Chicago, USA	0-9	142	54.9	9.8	64.8		64.8%
Breakey	67	1955	New York, USA	children	100	40	8	48	1	49%
Schrire	9	1956	Kimberley, South Africa	5-20+	73	11	4.1	15.1		15.1%

Schachat	68	1957	New York, USA	4-10	98	22.4	21.4	43.0		46.9%
Lerner	10	1961	Rochester, USA	children	350	4.3	10.6	15		15%
Lossef	69	1962	New York City	5-20	88	15.9	17	32.9		34.1%
Altman	71	1966	Memphis, USA	0.5-12	64	29.7	14.1	43.8	3.1	46.9%
Jones	72	1967	Los Angeles, USA	adults	28	24.3	35.7	60		60%
Pearlstone	73	1969	Fairfax, USA	2-23	30	23.3	16.7	40	6.7	46.7%
Breakey	74	1974	New York, USA	7-21	120					39.2%
Seaber	50	1976	Duke, USA	children	232	27.6	11.6	50.9	0.8	51.7%
Levy	75	1976	Gainesville, USA	4	108	10.2	6.2	16.4	3.7	18.6%
Lo Cascio	36	1977	New York, USA	1-58	128	24.2	24.2	48.4	1.6	50%
Milot	76	1977	Montreal, Canada	0.3-15	100	46	8	54		54%
Duckman	77	1979	New York, USA	children	25					56%
O'Malley	79	1981	Brisbane, Australia	3-16	100	28	20	48	18	53
Buckley	80	1981	North Carolina, USA	children	732	19.4	8.7	28.1	1.1	29.4
Keith	81	1983	Melbourne, Australia	2	15	43.3	0	43.3	3.3	46.7%
Scheiman	83	1984	Philadelphia, USA	6-18?	73	31.5	37	68.5		68.5%
Tamura	14	1987	San Francisco, USA	~1-3	11	100	0	100		100%
Flett	86	1993	Adelaide, Australia	2-19	140	~22	~22			45.7%
Leat	88	1996	Ontario, Canada	3-35	43	30	23	53		53%
Pinto-Martin	38	1996	New Jersey, USA	2	75	34.7	13.3	48	10?	58%
Huo	90	1999	San Francisco, USA	~3	170	18.8	18.2	37		37%
Jackson	94,95	2006	St Louis, USA	children	131	35.1	17.6	52.7	0.8	64%
Ghasia	41	2008	St Louis, USA	2-19	50	52	24	76	16	92%
Dufresne	44	2014	Montreal, Canada	2-13	106					55.7%

First Author	Ref. #	Year	Region	Age (years)	Cohort size	ET %	XT %	ET+XT %	Vert. %	All Strab.
MIDDLE EAST										
Landau	102	1971	Jerusalem, Israel	8-16	72					37.5%
Atilla	103	2003	Ankara, Turkey	0.9-19	18	16.3	61.1	77.4		83.3%
Cumurcu	104	2007	Tokat, Turkey	5-15	46	15.2	6.5	21.7		21.7%
Berk	105	2010	Izmir, Turkey	0.5-18	104	42.3	14.4	56.7	1.9	58.7%
Elmenshawy	106	2010	Cairo, Egypt	children	46	32.8?				32.8%
El-Hawar	107	2011	Cairo, Egypt	2-13	10	40	0	40		40%
Ozturk	5	2013	Izmir, Turkey	0.5-18	194	37.6	12.5	53.6	1.6	55.2%
Al-Hamdi	108	2014	Baghdad, Iraq	<12	60	40	0	40		40%
Boyaci	23	2014	Sanliurfa, Turkey	4.2-14.3	32	3.1	12.5	15.6		15.6%
Guven	16	2021	Ankara, Turkey	0.3-14	62	50	35.5	85.5	4.8	90.1%
Seif	109	2022	Beirut, Lebanon	children	64	ET/XT ratio: 0.79				

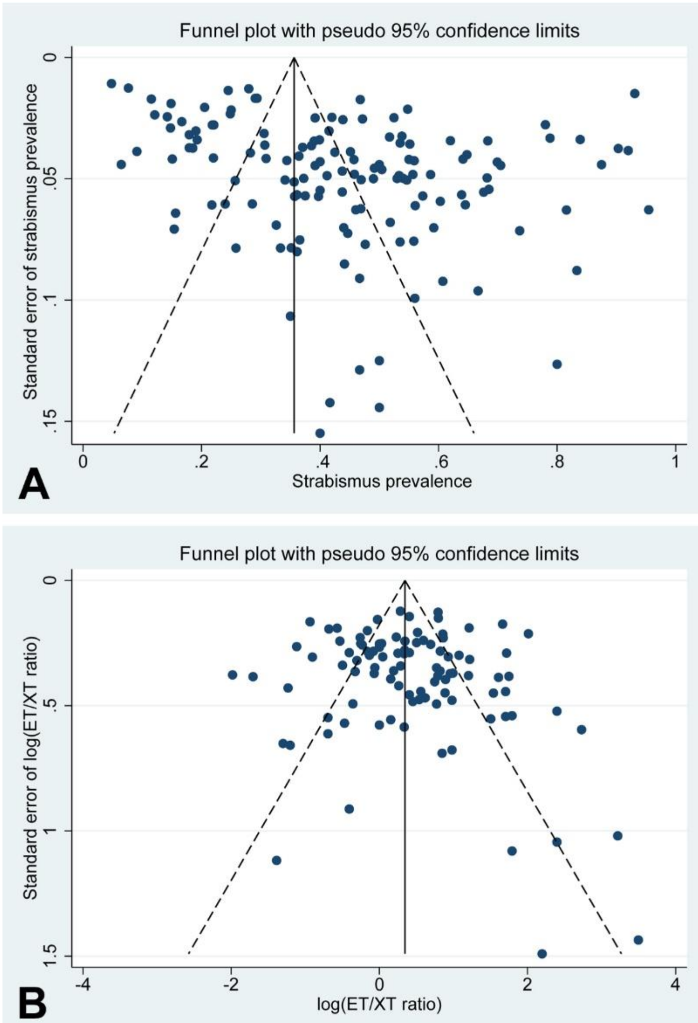
HISPANICS (most in Latin America)										
Tabuse	15	1996	Sao Paulo, Brazil	2-14	290	53	40	93		93%
Arroyo-Yllanes	111	1999	Mexico City, Mexico	children	140	13.6	41.4	55		55%
Celino	112	2003	Recife, Brazil	children	200	"more ET than XT"				62%
Cronemberger	113	2006	Sao Paulo, Brazil	0.5-13	24	ET/XT ratio 2.43:1				
Da Cunha Matta	114	2008	Rio de Janeiro, Sao Paulo, Brazil	4-12	123	20.3	8.9	30.9		30.9%
Segura-Rangel	115	2011	Occidente de Mexico, Mexico	1-178	45	ET/XT ratio 0.875				
Rocha	116	2016	Goiania, Brazil	1-41	13	ET/XT ratio 0.3				
West	110	2021	Los Angeles, USA	0.2-18	151	26.5	52.3	78.8		78.8%
Cornejo-Rubalcava	117	2022	Aguascalientes, Mexico	children	112	21	23	44		44%

First Author	Ref. #	Year	Region	Age (years)	Cohort size	ET %	XT %	ET+XT %	Vert. %	All Strab.
EAST ASIA										
Hu Y	118	1993	Beijing, China	children	107					45.79%
Lu Y	119	1995	Zhejiang, China	4.5-17	10					80%
Yue W	120	1998	Chongqing, China	0-13	190					12.11%
Ye Y	121	1999	Anhui, China	0-12	400					42%
Li H	122	1999	Heilongjiang, China	5-7	145	9.66	8.28	17.93		17.93%
Park SJ	123	1999	Seoul, Korea	children	50	ET/XT ratio 4:6				
Li F	124	2000	Shanxi, China	4-20	31					25.81%
Cao J	125	2001	Shanxi, China	0.5-14	385					20.52%
Yi B	126	2003	Beijing, China	2.5-27	825					46.79%
Jin C	127	2004	Jilin, China	0-9	31					25.81%
Chang F	128	2006	Shanxi, China	5-20	216					30.56%
Li F	129	2006	Shanxi, China	4-20	198					16.67%
Liao B	130	2006	Beijing	1-11	38					73.68%
Wang X	131	2006	Beijing, Hebei, China	2-14	220	20	1.82	21.82		21.82%
Liu Y	132	2007	Guangdong, China	0-8	347	8.65	2.59	11.24	0.29	11.53%
Liu YP	133	2007	Henan, China	0-4	106	12.26	5.66	17.92		17.92%
Wang S	134	2008	Beijing, China	3-28	204					14.22%
Li M	135	2009	Henan, China	2-14	222	20.72	1.35	22,07		22.07%
Wu H	136	2009	Jiangxi, China	4-19	346					24.86%
Fan Z	137	2010	Gansu, China	0.5-6	164	25	17.68	42.68	2.44	45.12%
Zhang X	138	2010	Henan, China	0-8	55					9.09%
Li Y	139	2011	Jilin, China	0-6	208					39.90%

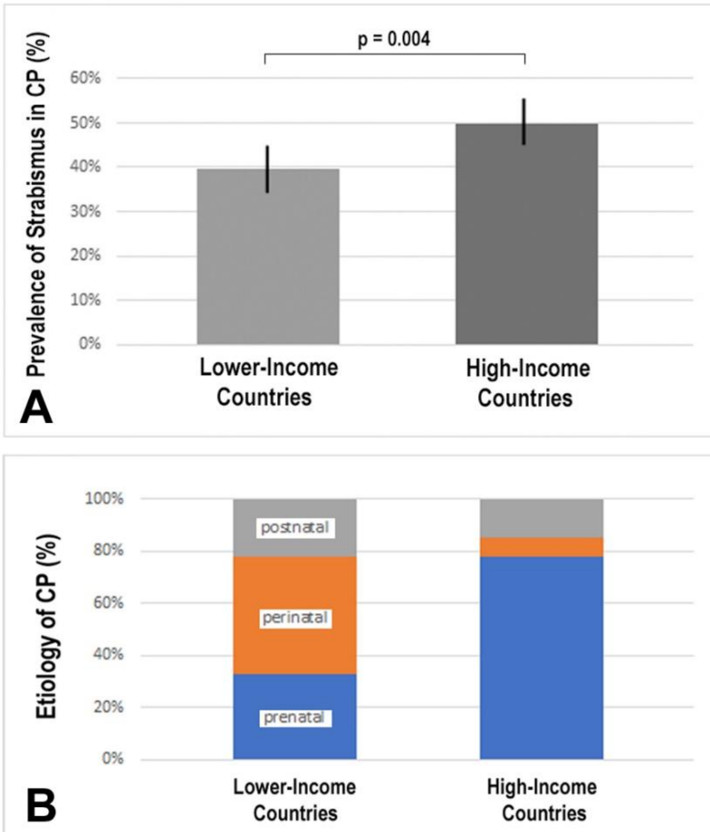
Marasini S	140	2011	Kathmandu, Nepal	children	36	14	22	36		36%
Zhao J	141	2011	Shandong, China	0.3-9	163	18.4	12.27	30.67		30.67%
Woo SJ	142	2011	Seoul, Korea	5-39	88	9	50	59	9.10	68.10%
Kou X	43	2012	Shandong, China	3-13	63	28.57	6.35	34.92	11.11	46.03%
Wei H	143	2012	Zhejiang, China		131	10.69	17.56	28.24		28.24%
Guo Y	144	2013	Shaanxi, China	2.5-12	72	16.67	9.72	26.39	9.72	36.11%
Liu B	145	2013	Xinjiang, China	3-12	73					39.73%
Chen Y	146	2014	Guangdong, China	children	56					28.20%
Guo J	12	2014	Guangdong	children	444	6.31	1.35	7.66	0	7.66%
Luo Y	147	2014	Hunan, China	0.5-9	223	54.26	16.14	70.40	7.62	78.03%
Lew H	148	2015	Bundang, Korea	1-7	47	25.50	17.00	42.60		44.70%
Wang P	149	2015	Hunan, China	3-5	43	37.21	13.95	51.16	4.65	55.81%
Li X	150	2016	Hunan, China	0-13	265	17.36	20.38	37.74	3.77	41.51%
Lin B	151	2016	Fujian, China	0-9	125	16	12	28	6.4	34.40%
Park MJ	56	2016	Seoul, Korea	2-22	105	25.7	43.8	69.5	1.0	70.5%
Fang T	13	2018	Beijing, China	3-14	395					4.81%
Jeon H	46	2019	Busan, Korea	0.9-15	62	27.40	37.10	64.50		64.50%
Yan Y	152	2020	Shandong, China	children	183					68.31%
Tao J	58	2022	Beijing, China	6-18	160	5.00	36.50	41.30	1.25	42.50%

First Author	**Ref. #**	**Year**	**Region**	**Age (years)**	**Cohort size**	**ET %**	**XT %**	**ET+XT %**	**Vert. %**	**All Strab.**
SOUTH ASIA (NORTH)										
Govind	153	1988	Chandigarh, India	0.5-5	70	35.7	0	35.7		35.7%
Singhi	33	2002	Chandigarh, India	<18	1000	20.6	3.9			24.5%
Sasmal	155	2011	Kolkata, India	0.5-16	140		36.4			36.4%
Singhi	35	2013	Chandigarh, India	<18	1212					28%
Kaur	157	2016	Punjab, India	3-16	49					59.2%
Joshi	158	2017	Mumbai, India	2-12	72					63.9%
Khandaker	159	2017	Bangladesh	0.5-16	726		29.1			29.1%
Mustafa	160	2017	Lahore, Pakistan	1-15	113	38.9	31.1	69.9		69.9%
Bhati	163	2019	New Delhi, India	2-15	135	16.3	3	19.3		19.3%
Hassan	165	2020	Bangladesh	0.5-16	37	18.9	16.2	35.1		35.1%
Aumi	47	2021	Bangladesh	1-~6	130					40%
Moly	166	2022	Bangladesh	0.5-16	404	46.3	6.2	52.5		52.5%
Bala	169	2023	Tanda, India	1-18	41	12.2	24.4	36.6		37%
SOUTH ASIA (SOUTH)										
Jethani	154	2007	Tamil Nadu, India	children	38	57.9	23.7?	81.6		81.6%
Katoch	54	2007	Karnataka, India	0.7-21	200	17	22	39		39%
Vasanth	156	2014	Chennai, India	children	374	21.7	22.2	43.9		43.9%

Mathew	45	2015	Kerala, India	1-14	80	8.8	30	38.8	1.3	40%
Giliyar	161	2018	Bangalore, India	0-6	12	33.3?	67.7?	50		50%
Jasper	57	2018	Tamil Nadu, India	0.3-17	236	18.2	32.2	50.4	3.4	53.8%
Raj	162	2019	Karnataka, India	1.5-18	20	30	5	35		35%
Shaikh	164	2020	Karnataka, India	0.5-18	50	36	8	44		44%
Mishra	167	2023	Pune, India	1-15	80	16.2	22.5	38.7		44.3%
Viswanath	168	2023	Pune, India	2-18	383					39.2%
AFRICA										
Lagunju	11	2007	Ibadan, Nigeria	0.5-13	149		14.7			14.7%
Bodunde	170	2015	Ilorin, Nigeria	0.5-14	87	19	16.1	35.1		35.1%
Duke	171,172	2021	Calabar, Nigeria	4-15	388	13.1	33.5	46.6	0.5	47.2%
Owunna	173	2022	Ima, Nigeria	5-19	12	16.7	25	41.7		41.7%
Musiwa	174	2023	Lusaka, Zambia	0.5-16	100	14	7.5	21.5		21.5%



Supplemental Fig. 1A, B. Funnel Plot for Prevalence Studies (**A**). Note that the asymmetry (p<0.001) arises because the central location of the funnel plot is at ~35%. For studies with prevalence rates between 70% and 100% not to appear as outliers, the Funnel Plot would have to include prevalence data in a range of less than 0 to -30%, which is impossible for a prevalence. Esotropia/Exotropia (ET/XT) Ratio (**B**). There is no significant asymmetry in this Funnel Plot (p=0.381).



Supplemental Fig. 2A, B. Graph illustrates the difference in strabismus prevalence in cerebral palsy (CP) between lower-income countries (LICs) and high-income countries (HICs) (**A**). Bars indicate the 95% confidence intervals; the difference is significant with p=0.004.

Graph illustrates the differences in the etiology of CP between LICs and HICs: prenatal, perinatal and postnatal (**B**). The perinatal causes include mostly asphyxia, but also jaundice, seizures and infections. Prenatal causes include preterm births and low birthweight. CP etiology is represented in LICs according to Singhi et al.,[33] and in HICs according to Reddihough and Collins.[217]