Supplementary file 2:

Detailed summary of eye abnormalities by ICD-10 reported in articles included in this review

**Chapter VII: Diseases of the eye and adnexa**

*H26.0 Infantile, juvenile & presenile cataract*

In children with FAS, cataract was reported in three (out of 57; 5.3%) children.1,2 The single case of cataract reported by Ribeiro and colleagues did not affect the child’s vision.2

No significant difference was observed between individuals with high-risk (≥1 oz AA/d or ≥ 48g/d) PAE (without FAS; 0/43) and controls (2/55; *p*=0.65).3

*H40.9 Glaucoma, unspecified*

Two small, older FAS studies assessed children for glaucoma, although one of these (reporting zero glaucoma cases in eight children with FAS) may have included glaucoma as an exclusion criterion for the study.4 However, this was unclear: the text suggests that children with anterior segment anomalies were excluded, yet some anterior segment anomalies are included in a data table within the paper.4 Another study of 13 children with FAS born to alcohol-dependent mothers found one case of glaucoma (7.7%).5

*H44.5 Degenerated conditions of the globe – Phthisis*

Two Swedish studies reported one case each of phthisis in children with FAS (4% to 6.3%). The cohort in the earlier study were born to mothers with documented history of alcohol abuse during pregnancy.1 In the second study, the child presented with phthisis of the right eye, and his left eye later also became phthitic after having an anterior chamber haemorrhage and buphthalmos.6 Pthisis is an acquired, end-stage ocular response to either chronic disease or trauma. Other than this case of phthisis reported as secondary to the buphthalmos, no other reports indicated potential causes of the phthisis cases. Level of alcohol exposure was not reported. No control group children (non-exposed and without a history of ocular disorders or malformations) had phthisis.6

*H50.0 Convergent concomitant strabismus – Esotropia*

Rates of esotropia in FASD ranged from 0 to 57.1%.1,2,7-9 In Ribeiro et al’s study of FAS, four cases (9.4%) of esotropia were reported: three with small and variable angle, and one with a preference fixation pattern and amblyopia. All four children also had strabismus.2 Esotropia rates in comparison groups, which included children with intrauterine growth retardation of unknown cause,9 and children living in an orphanage, many of whom were exposed to PAE, trauma, parental alcohol abuse or drug abuse problems7 were 9.1% (N=1/11 children) and 6.4% (5/78 children) respectively. Zero to one (1/21 [4.8%]) cases were observed in typically developing, non-exposed controls, where the single case observed was small-angle unilateral esotropia.8,9 Pooled OR for esotropia was 3.95 (95%CI: 0.45 to 34.84; *p*=0.216) (I2=62.08; Q=7.91; *p*=0.048).7-9

*H50.1 Divergent concomitant strabismus – Exotropia & H51.1 Convergence insufficiency & excess*

The five studies which reported on esotropia above also reported on exotropia and/or exophoria. Rates of unspecified exotropia were 0 to 8% (2/25) in FAS1,9 and 0 in FASD.7 Intermittent exotropia with strabismus was reported in 4/32 (12.5%) children with FAS,2 and small angle exotropia in 1/21 child (4.8%) with FASD.8 One child with FAS had exophoria (3.1%).2

No cases of exotropia or exophoria were reported in healthy non-exposed controls,2,8 or in healthy controls who may have had some sporadic PAE during special occasions.9 In other comparison groups without FASD, exophoria rates were 1.3% (1/78) in orphans (with high rates of trauma, PAE or drug exposure)7 and 27.3% (3/11) in children with intrauterine growth retardation.9 Pooled OR for exotropia was 1.31 (95%CI: 0.23 to 7.51; *p*=0.766) (I2=15.47; Q=3.55; *p*=0.314) in FAS/FASD versus comparison groups.7-9

*H50.9 Strabismus, unspecified*

In fifteen studies, strabismus was observed in 3.1% to 43.0% of children with FAS,1,2,4,5,9-19 and 0 to 5.6% in those with PFAS.16,17

Four of six FASD studies included control groups and reported strabismus rates. Strabismus was observed in 0 to 1.7% of non-FASD controls,9,15-17 and 36.4% of children with intrauterine growth retardation (4/11).9 Pooled OR for strabismus in FASD was significant (3.78 (95%CI: 1.32 to 10.82; *p*=0.013) (I2=0; Q=4.19; *p*=0.523)), but could be explained by the effect of FAS (4.21 (95%CI: 1.23 to 14.47; *p*=0.022) (I2=25.32; Q=4.02; *p*=0.26))9,16,17 rather than PFAS (2.83 (95%CI: 0.38 to 21.17; *p*=0.311) (I2=0; Q=0.07; *p*=0.79))16,17 (Figure 3).

One PAE study reported positive kappa angle in 2.3% (1/43) children with high-risk PAE (≥48g alcohol/day), with no cases in non-exposed healthy controls.3 Kappa angle is defined as the angle between the visual axis (line connecting the fixation point with the fovea) and the pupillary axis. The normal kappa angle is slightly positive because the fovea lies slightly temporal to the point at which the pupillary axis intersects with the posterior pole of the globe. The cut-off value used in this PAE study was not specified.

*H50.0 Hypermetropia*

Hypermetropia (or hyperopia) was reported in 3.4% to 7.7% children with FAS,5,20 and 3.2% eyes of children with FAS.2 No control group rates were reported.2,20 Mean spherical refractive error (hyperopia) was not significantly different between children with FAS or PFAS (1.6 dioptres) compared to non-exposed, typically developing controls (1.4 dioptres).21

The difference in hypermetropia rate in children with (21.1%) and without PAE was not statistically significant (7.8%; *p*=0.29).22

*H52.1 Myopia*

Severe myopia (not defined) was reported in 5.3% to 16% children with FAS,20,23 and 4.54% with FASD.23 Myopia >-5.0 dioptres was reported in 9.6% eyes of children with FAS.2 No control data was available.

In children with high-risk PAE, 2.6% had myopia with nil cases in non-exposed controls.22

*H52.2 Astigmatism*

Astigmatism was reported in 15.4% children5 and 37.5% eyes.2 In a FASD group primarily consisting of children with PFAS (N=19) rather than FAS (N=2), mean cylindrical refractive error was within normal limits with no significant difference between children with and without FASD (0.5 dioptres for both groups).21

No significant differences in rates of astigmatism were observed in those with (2.6%) and without PAE (2.0%; *p*=1.0).22

*H52.7 Disorder of refraction, unspecified*

Refraction was reported in nine FASD and one PAE studies. The overall range of refraction values was -23.0 to +6.5D in FASD, which corresponds to extreme pathological myopia to moderate hypermetropia.24 In controls, refraction ranged from -2.5 to +4.0D corresponding to mild myopia to mild hyperopia. The single PAE study reported mean refraction of 1.05±1.77D in PAE and 1.06±0.64D in controls, reflecting mild myopia to mild astigmatism (Appendix 4: CHAPTER VII TABLE). No between-group comparisons were undertaken, and while refraction ranges were most often reported (demonstrating wide ranges), we were unable to determine proportions with refractory errors from the data available. While Hellström et al (1997b and 1999) reported refraction of -2 to +4D in FASD, they excluded children with refraction >+4D or <-4D to minimise the impact on ocular fundus structures so the upper limit of hyperopia is not known for that cohort.

Where reported, mean or median values were close to normal range in FASD and PAE, and 83.8% to 84.2% of eyes of children with FAS had refraction range of -2.0 to +3.5D. Emmetropia was reported in 21.1% FAS eyes, 50% control eyes, and 32% comparison eyes of children with intrauterine growth retardation (Appendix 4). Although many eyes were emmetropic, there was a group with refractive error in the mild to medium group and a few outliers with pathological myopia.

Other refraction variables reported were: “refractive error” (undefined) in 7.6% children with FAS;25 spherical and cylinder values, and refraction axis of the cylinder in 4 to 12 eyes only (Appendix 4).4

*H53.8 Other visual disturbances*

Amblyopia, stereoacuity, and contrast sensitivity were classified here.

In one FAS cohort study, 15.4% (2/13) children had amblyopia.5 Amblyopia rate in children with heavy PAE (2.3%) and controls (0%) were similar (*p*=0.79).22

Mean stereoacuity was significantly higher (poorer) in children with FAS/PFAS (150 arcsec) than non-exposed controls (45 arcsec; *p*<0.005), resulting in higher referral rates to paediatric eye care specialists in FAS/PFAS (*p*<0.001).21 It was noted that the data were skewed, with most FAS/PFAS children (66.7%) having normal stereoacuity (between 40 – 60 arcsec), and 33.3% having very poor stereoacuity (>200 arcsec). The FAS/PFAS group was predominantly PFAS (N=19 versus N=2 FAS).21 In a study of FAS, the rate of subnormal (>60 arcsec) stereoacuity was significantly greater in FAS adoptees (73.3%) than non-FAS adoptees (34.5%; *p*=0.009).26

Contrast sensitivity was assessed in one FAS/PFAS study, and although group means were not reported, children with FAS/PFAS had lower contrast sensitivity than typically developing controls (mean difference: 0.3 log units; *p*=0.01).21

*H54.1-54.3 No, mild, moderate or severe visual impairment, binocular*

Visual acuity was reported in 13 papers, with an additional two reporting “vision problems/impairment”25,27 and another reporting resolution acuity28 (Figure 4; Table 3; Appendix 4). Where reported, visual acuity tests used were appropriate for age and intellect, including Snellen’s E chart and letter chart,1,3,7,9,29 HOTV chart,1,9,26,29 simpler tests (e.g., light fixation, picking up small cake decorating sweets from a black blanket, small object identification),1,2,9 linear KM-Boks chart,26 Patti Pics linear optotype chart,8 and/or Teller acuity cards.7,28 Due to inconsistent reporting and classification of impaired visual acuity across the 13 papers, we applied the ranges of vision loss categories recommended in the Visual Standards report from the International Council of Ophthalmology 2002 (ICO-2002; http://www.icoph.org/downloads/visualstandardsreport.pdf [accessed: 2 June 2020]), to standardise the data. Use of this classification method revealed a lack of detail about prevalence of more severe vision loss (e.g., visual acuity <0.13). Here, we have summarised the visual acuity data according to ICO-2002 classifications after converting reported values into decimal values for consistency (Figure 4). Where visual acuity data were presented for both eyes and best eye (or best-corrected), only the data for the best eye (or best-corrected value) was recorded.

Of the five FAS studies of visual acuity which included comparison/control groups, only one undertook between-group analysis. In this study, a statistically significant difference in best-corrected visual acuity was observed between adoptees with FAS (median (range): 0.65 (0.2 to 0.65)) compared to adoptees without FASD (median (range): 0.80 (0.2 to 1.25); *p*=0.0029).26 In FAS, mean visual acuity values were 0.47 to 0.83 (‘mild vision loss’ to ‘normal’),2,4 median values were 0.5 to 0.8 (‘mild vision loss’ to ‘normal’), and ranges reported spanned 0 (‘total vision loss/blindness’) to 1.0 (‘normal’). Data from two FAS studies were pooled (combining data from Hellström et al papers as they had overlapping participants), showing a mean difference in visual acuity of -0.25 (95%CI: -0.40 to -0.10; *p*=0.001) (I2=52.20; Q=2.09; *p*=0.148) in FAS versus controls.6,26,29,30

In five FAS papers, visual acuity was presented in categories. Although the categories were not standardised across the papers, the more severe categories defined were mostly within the ICO-2002 “moderate vision loss” range [to more severe vision loss] at either ≤2.01,2,9 or <3.031 (Figure 4). One study reported frequency of subnormal acuity, which included all values below normal range (<0.8).19 Figure 4 visually shows the visual acuity data according to ICO-2002 categories. Although the data reported generally did not correspond with ICO-2002 categories, the figure shows that children with FAS most often had subnormal visual acuity, while comparison groups (some with sporadic PAE at special occasions but without FAS; and intrauterine growth retardation) had values more often in the Normal range.

In FASD, 6.7% orphans with FASD compared to 9.1% orphans without FASD had visual acuity ≤0.33 (‘mild vision loss’; significance level not reported).7 A Canadian study reported significantly poorer visual acuity in a clinic-recruited FASD group (mean: 0.59, range: 0.31 to 1.0) than typically-developing controls (mean: 0.77, range: 0.5 to 1.25; *p*=0.03).8 Children with FAS/PFAS were more frequently referred to paediatric eye care specialists due to poor visual acuity than controls (*p*<0.002).8

In the study of heavy PAE, best-corrected visual acuity was assessed with no significant differences observed in rates of ‘severe vision loss’ (0.1 - <0.5: 2.6% vs 2.2%; *p*=1.00), ‘mild vision loss’ (0.5–0.7: 2.6% vs 2.2%; *p*=1.00), or ‘normal vision’ (>0.7-1.0: 94.7% vs 95.6%; *p*=0.95) in heavy PAE compared to non-exposed controls respectively.3

Using the Teller acuity card test for resolution acuity, Carter et al found that a significantly higher proportion of 6.5 month-old infants with FAS (27.3%) were below the fifth percentile compared to non-FAS controls (9.3%; *p*<0.005).28 Acuity scores were ≤3.2 cycles/degree in infants performing within the bottom fifth percentile. In this study, acuity was associated with absolute alcohol consumed per day at conception (r=0.21, *p*<0.01) and during pregnancy (r=-0.23, *p*<0.01), number of drinking days per week at conception (r=-0.23, *p*<0.01) and during pregnancy (r=-0.26, *p*<0.01), and with a diagnosis of FAS (r=-0.38, *p*<0.001).28

*H54.9 Unspecified visual impairment (binocular)*

Two large studies from Australia and USA reported prevalence of undefined visual impairment. The Australian Paediatric Surveillance Unit study collected data over four years from paediatricians, on <15 year-old children who were diagnosed with FAS, reporting visual impairment in 4.3%.25 The USA clinic-based study included data over a 13y period of all Washington State residents (all ages) who underwent a FASD diagnostic evaluation in one of seven Washington State FASD and Prevention Network clinics.27 Vision problems were documented in FAS/PFAS (37.5%), static encephalopathy/alcohol exposed (33.2%), neurodevelopmental disorder/alcohol exposed (25.2%), and PAE (no central nervous system abnormalities; 18.5%) (*p*=0.00)27 (Table 3).

*H55 Nystagmus & other irregular eye movements*

Nystagmus was documented in five FAS and one FASD study, with no control group data reported. In orphans with FASD, 6.3% had nystagmus.7 Rates of nystagmus in FAS ranged from 2.2% to 8.0%.1,2,5,25,32

Impaired fixation ability was reported in 33.3% (2/6) children with FAS, with no mention of control rates.9

**Chapter XVII: Congenital malformations, deformations and chromosomal abnormalities**

*Q10.0 Congenital ptosis*

Ptosis (or blepharoptosis) was documented in 16 studies. In 12 FAS/PFAS studies,1,2,4,9,11,13,15-17,19,33,34, 0% to 24% children with FAS had ptosis, compared to 0 to 2.1% controls (reported in four studies, all with *p*<0.05).15-17,34 Ptosis rates were 5.6% to 8.3% in PFAS16,17 and 6.3% to 14.6% in FASD.7,18 Pooled data showed significantly greater odds of ptosis in children with FAS/PFAS compared to controls (OR: 11.56 (95%CI: 4.10 to 32.56); *p*<0.0001) (I2=0.0; Q=0.68; *p*=0.878).15-17,34

Rates of ptosis were similar in children with high level PAE (2.3%) compared to controls (1.8%; *p*=0.97), which was much lower than the rate observed in children with alcohol embryopathy (38.3%).35 Pooled data, sharing the control group data from Flanigan et al between the two studies36, indicated the OR was not significantly greater in alcohol-exposed children compared to controls in a random effects model (OR: 7.65 (95%CI: 0.33 to 177.72); *p*=0.205) (I2=50.59; Q=2.02; *p*=0.155).3,35

*Q10.3: Other congenital malformations of eyelid - Blepharophimosis*

Blepharophimosis was reported in 0 to 49.3% children with FAS in three studies,2,11,31 compared to 0 in comparison groups containing some children with sporadic PAE on special occasions, or with intrauterine growth retardation.9 Rates reported in FASD (mild FAS/fetal alcohol effects and moderate-to-severe FAS)10 and PAE studies35 were 26.3% and 11.3% respectively. Control data was not available.

*Q10.3: Other congenital malformations of eyelid – Epicanthus*

In children with FAS, 14% to 100% had epicanthus,1,2,5,11,13,15,32-34 compared to 1.2% to 31.1% controls (*p*=0.003,15 or OR: 12.0 (1.4-99.7)34). In cohorts with FASD, 40.9% to 70.8% had epicanthus.16,18,37 In children from the Lazio region (Italy), epicanthus was more prevalent in children with FASD (40.9%) compared to controls (14.9%; *p*=0.01).37 In contrast, no significant difference was found in epicanthus rates between children with FAS (61.8%), PFAS (55.6%) or controls (48.7%) from the Western Cape Province of South Africa (*p*=0.299).16 Pooling data from four FAS and FASD studies which included control group data15,16,34,37 indicated greater odds of epicanthus in FAS/FASD than controls (OR: 2.57 (95%CI: 1.45 to 4.52; *p*=0.001) (I2=14.98; Q=5.24; *p*=0.155).15,16,34,37

In children with PAE or alcohol embryopathy, 20.9% to 65.7% had epicanthus3,35 with no significant difference observed between those with PAE and controls (10.9%; *p*=0.33).3

*Q10.3: Other congenital malformations of eyelid – Telecanthus*

Two FAS studies reported telecanthus in 13% (4/32) to 62.5% (5/8) children from Portugal and Italy respectively.2,4 No control data were available. Hall normative charts were referred to for the Portuguese measures,2 while no description of telecanthus assessment method was provided for the Italian study.4

*Q10.3: Other congenital malformations of eyelid - PFL*

FAS studies (N=13): PFL measures were obtained from several countries including USA, South Africa, Finland, Germany, and Sweden. PFL in children with FAS ranged from 1.8 to 2.7cm and was significantly shorter than in Controls (range: 2.2 to 3.1cm)15,26,38,39 (Table 4).

Most studies reported proportions (%) of children with short PFL, although almost half did not specify the criteria used.4,5,14 Surprisingly, not all children with FAS had short PFL, with proportions ranging from 32.6% to 100% (Appendix 5). One study reported no cases of short PFL in controls (*p*=0.001).34

FASD studies (N=5): Two studies reported mean PFL in FAS (range: 2.3 to 2.4cm), PFAS (range: 2.3 to 2.4cm), and controls (range: 2.5 to 2.5cm).16,17 Significant differences were reported between those with FASD and Controls (some of whom had PAE but without detectable associated anomalies), and between those with FAS and PFAS.16,17 Overall pooled mean difference in PFL between FAS/FASD and Control groups was -1.9mm (95%CI: -2.6 to -1.2mm; *p*<0.0001) (I2: 91.12; Q=56.34; *p*<0.0001).15-17,26,38,39 Pooling data separately for FAS and FASD studies also yielded significant mean differences compared to controls: FAS: -2.2mm (95%CI: -3.0 to -1.5mm; *p*<0.0001) (I2=85.10; Q=20.14; *p*<0.0001);15,26,38,39 FASD: -1.5mm (95%CI: -2.5 to -0.5mm; *p*=0.003) (I2=94.20; Q=17.25; *p*<0.0001).16,17,37

Rates of “short PFL” (defined as ≤10th percentile) ranging from 60.9% to 85.4% were reported in two cohorts consisting of children with FAS, PFAS, alcohol-related neurodevelopmental disorder (ARND),7,18 and/or suspected FAS.25 PFL was also explored as a percentage of inner-canthal distance, with no significant differences observed between FAS/PFAS and Control groups (*p*=0.139).17

PAE studies (N=1): Flanigan et al defined “short PFL” as ≤ 2SD below the mean using Hall charts.3 Rates of short PFL were not significantly different between those with (14%) and without PAE (18%; *p*=0.66).

*Q11.2 Microphthalmos*

Microphthalmia/microphthalmos was reported in six FAS studies with rates of 0 to 12.5% in FAS1,2,5,6,13,34 and no cases in non-FAS comparison groups, including some with PAE and FAS features (*p*=0.022),34 patients requiring minor surgery with no history of ocular disorders or malformations, and healthy controls.6 Data could be pooled for two studies, and showed higher odds of microphthalmos in FAS compared to controls (OR: 24.79 (95%CI: 2.94 to 208.82); *p*=0.003) (I2=0.0; Q=0.05; *p*=0.825).

*Q13.3 Congenital corneal opacity*

In FAS studies, corneal opacities or clouded corneae were observed in 0 to 1 (7.7%) child respectively.2,5 22 No corneal opacities were observed in children with heavy PAE or controls.3

*Q13.4 Other congenital corneal malformations*

Mean corneal endothelial cell density: was lower in children with FAS (3411±188 cells/mm2) compared to healthy controls (3599±333 cells/mm2; *p*=0.032), regardless of age with significant differences between groups at age 5 to 9 years (*p*=0.026) and 10 to 14 years (*p*=0.003).4

Polymegathism: was estimated by calculating the coefficient of area variation using the formula: (SD of mean cell area ÷ mean cell area) x 100.4 The mean coefficient of area variation was higher in children with FAS (22.66±2.45) than controls (17.75±2.73; *p*=0.000), with consistent findings at age 5 to 9y (*p*=0.000) and 10 to 14y (*p*=0.024).4

Pleomorphism: was defined as the percentage of hexagonal cells in the corneal endothelium.4 Percentage of hexagonal cells was lower in children with FAS (89.31±3.55) versus controls (93.25±3.41; *p*=0.000). The difference between FAS and control groups was significant at age 5 to 9y (*p*=0.000) but not at age 10 to 14y (89.57±2.0 vs. 91.88±3.29; *p*=0.102).4

Microcornea: was mentioned in three FAS papers1,2,4 but specifically reported in two,1,4 affecting up to 4% (1 child) in FAS. The third FAS study reported one case of “anterior segment abnormalities” encompassing microcornea, shallow anterior chamber and congenital glaucoma, cataract, and persistent hyaloid, although it was not clear if all the abnormalities were present in that child.2 No cases were observed in children with heavy PAE or controls in one PAE study.3

Peters anomaly: No cases were observed in FAS,2 or heavy PAE and control groups.3 Only two studies reported on this anomaly.

Posterior embryotoxon: No cases were observed in the single FAS study reporting on this condition.2

*Q13.8 Other congenital malformations of anterior eye segment*

Axenfeld-Rieger syndrome was reported in two papers (one FAS, one PAE). No cases were reported in FAS,2 heavy PAE or controls.3

*Q13.9 Congenital malformation of anterior segment of eye, unspecified*

In FAS, there was one case (1.6%) of anterior segment abnormalities (including microcornea, shallow ant. chamber & congenital glaucoma, cataract, & persistent hyaloid),2 and no cases of mesenchymal dysgenesis.4 No cases of shallow anterior chamber were observed in PAE or controls.3

*Q14.2 Congenital malformation of optic disc*

Double ring sign: was observed in two FAS studies. One reported a rate of 12.5% in their text, but 15% (3/20 children) in their table.2 The other reported on the funduscopic signs of hypoplasia which included double ring sign and sharply defined borders of the optic disc, and reported the anomaly in 25% (15/60) eyes with normal discs, and in 48.3% (29/60) eyes with optic nerve hypoplasia (i.e., in a total of 73.3% eyes).9 No double ring signs were observed in comparison groups.9

Optic disc area: was measured in six FAS studies. Mean and median optic disc area values were significantly smaller in FAS than controls with a mean of 2.05±0.55mm2 in FAS versus 2.7±0.48mm2 in controls and 2.52±0.32mm2 in comparison children with intrauterine growth retardation (*p*<0.02).9,29 Median values were similar in two Swedish FAS studies (2.13mm2 and 2.18mm2)26,30 with range 1.45mm2 to 2.80mm2.26 These values were significantly smaller than reference data (*p*=0.002)30 and in non-FASD adoptees from Eastern Europe (median: 2.48 (range: 1.09 to 4.43)mm2; *p*=0.02).26 Pooled mean difference between FAS and No FAS groups was -0.582 (95%CI: -0.78 to -0.38; *p*<0.0001) (I2=0.0; Q=1.53; *p*=0.676). 9,26,29

Small optic discs was reported in 16.7% to 40% children with FAS;2,31 and in 15.9% eyes of controls (some of whom may have had sporadic PAE at special occasions) and 13.6% eyes of children with intrauterine growth retardation of unknown aetiology.9 When defined, small optic discs were defined as values ≤1SD9 or as a DM/DD ratio (distance from the disc centre to the fovea: disc diameter) greater than the mean control group value +1SD.2

Optic nerve hypoplasia: (also termed optic disc hypoplasia and optic nerve head hypoplasia: ≤2.07mm2)9 was found in 5% to 76% children,1,4,7,19,31,32 and 48.3% eyes with FAS:2,9 bilaterally in 18.3% and unilaterally in 11.7% children.9

Carones et al assigned arbitrary gradings of severity and of 42.9% of children with FAS who had retinal optic nerve hypoplasia, 37.5% were classified as having it “present”, 25% severe, and 25% more severe.4 Strömland reported funduscopic hypoplasia signs with normal disc in 25% eyes, which were not registered as optic nerve hypoplasia in their study.9

In one study of FASD (consisting mostly of children with PFAS [n=6] and ARND [n=6], with 3 FAS cases), 6.3% children had optic nerve hypoplasia;7 while one PAE study reported no cases in heavily exposed children and controls (*p*=1.0).3

Optic nerve atrophy: was reported in one FAS study, bilaterally in 13.3% (n=4) children.31

Tilted optic disc: In one PAE paper, one child in the control group (1.8%) had a tilted optic disc, with no cases in the PAE group (*p*=0.79).3

*Q14.8 Other congenital malformations of posterior segment of eye*

One child with FAS (3.3%) had “malformations of the total fundus”31 which were not defined further.

No persistent fetal vasculature (not specified if anterior or posterior) were found in PAE or control groups.3

*Q14.9 Congenital malformation of posterior segment of eye, unspecified*

Abnormal retinal tortuosity: In FAS, 30% to 87.5% children had abnormal tortuosity,1,2,4,9 compared to 19% in controls (some may have had sporadic PAE at special occasions) and 32% in a comparison group with intrauterine growth retardation of unknown cause (significance not reported).9 In one study of PAE, rates of increased arterial tortuosity were not significantly different between PAE (16.3%) and control groups (14.5%; *p*=0.88).3

Tortuosity in 16 Swedish children with FAS was significantly higher than in a healthy reference group, with a median value of 1.13 in both arteries (*p*=0.04) and veins (*p*=0.002; reference group values not reported).30 Mean tortuosity index was 1.39±0.28 for arteries,9,29 and 1.32±0.35 for veins.9,29 Comparison group values for artery and vein tortuosity index were 1.20±0.15 and 1.29±0.16 respectively. In the two studies comparing tortuosity between FAS and comparison groups, artery tortuosity index was significantly greater in FAS than comparison/control groups across both studies, while the difference in vein tortuosity reached statistical significance in one study (*p*<0.01)29 but not the other (*p*=0.66).9 Pooled mean difference was 0.168 (95%CI: -0.003 to 0.340; *p*=0.054) (I2=65.09; Q=5.73; *p*=0.057) for artery tortuosity, and 0.062 (95%CI: 0.017 to 0.106; *p*=0.007) (I2=0.000; Q=0.19; *p*=0.908) for vein tortuosity.9,29 Because Strömland 1985 had two comparison groups, the FAS group sample size was divided by two in the meta-analysis.36

Other vascular abnormalities: Undefined retinal vessel abnormality was found in one child with FAS (3.3%),31 and abnormal width and course of retinal vessels in 15.4% eyes.9 Number and length of arteries and veins were reported by Strömland9 but are not reported here because they were used to calculate index of tortuosity (reported above).

Two Swedish FAS papers reported number of branching points, although there may have been overlapping participants in both papers. Median (*p*=0.04) and mean (*p*<0.05) number of branching points was significantly lower in FAS (median: 20; mean: 19.6±3.95) compared to controls (median: not reported; mean: 22.6±3.25).29,30

Combined abnormalities including vascular anomalies: In Swedish children with FAS, Strömland reported combined malformation of the optic nerve, retina, and retinal vessels in seven eyes compared to zero in two comparison groups (denominator unclear; consisting of at least two of the following: i) a highly visible choroid; ii) absence of the macula; iii) a deformed optic disc; and iv) retinal vessels with increased tortuosity, abnormal width, and/or with an abnormal course over the retinal surface).9 Presence of extensive fundus anomalies of the optic nerve, retina, blood vessels (singly or in combination) were noted in 12% FAS children.9 Of the 19/39 eyes of FAS children with increased artery tortuosity, 10 (25.6%) also had optic nerve hypoplasia.9 In a cohort of Brazilian orphans, 12.5% with FASD had vascular anomalies in combination with a dysmorphic optic nerve, compared to 1.3% in orphans without FASD.7

Other anomalies: Cataract or pronounced fundus lesions was observed in 8.8% eyes in FAS.9 One case of bilateral hypoplastic optic discs and other intraocular anomalies (leading to blindness) was reported in FAS (2.1%) with no cases in FASD.23 No cases of macular ectopia were reported in FASD.2 Malformation of anterior and posterior segments of the eye were found in one child with FAS (3.3%).31

*Q15.0 Congenital glaucoma*

No cases of congenital glaucoma were observed in children with PAE or controls.3 Glaucoma was reported in up to 1 (7.7%) child with FAS,4,5 and buphthalmus (often a symptom of childhood glaucoma) was found in one child in two separate FAS studies (4% to 6.3%)1,6 with no cases in controls.6

*Q75.2 Hypertelorism [and other orbital measures]*

Hypertelorism and telecanthus were observed in 15.4%,5 and 13% to 62.5%2,4 of children with FAS respectively. Rates of short inner canthal distance (defined as ≤25%) were significantly different between children with FAS (25%), PFAS (19.4%), and controls (6%; *p*=0.022).17 Moore et al documented inner and outer canthal width (among other measures) in children of different ethnicities using 3D images, to identify a set of specific features that discriminated between FAS and controls in different ethnicities.38 Although different sets of features were discriminative of FAS according to ethnicity, mean inner canthal width ranged between 30.2mm to 34.5mm in FAS and 32.2mm to 34.4mm in controls (significance not reported). Mean outer canthal width was 74.9mm to 80.0mm in FAS and 79.0mm to 84.8mm in controls.38

*Other measures unable to be classified using ICD-10*

Unspecified intraocular defects were found in 2-5/41 (4.9% to 12.2%) children with FAS;13 and Church and Gerkin reported one child with FAS (7.7%) to have “corneal atresia”, although this condition was not described.5

Several other ophthalmic measures were assessed:

Cup area: Median cup area in FAS (0mm2) was significantly smaller than reference data from controls (*p*<0.01).30

Neuroretinal rim area: According to two studies, neuroretinal rim area was significantly smaller in FAS than controls. Reported medians in FAS were 1.77 to 2.13 (1.03 to 2.18)mm2 compared to 2.14 (0.82 to 4.43)mm2 in controls (*p*≤0.005).26,30

Keratometry (horizontal/vertical) (FAS): Mean calculated keratometry values were 46.6/47.2 in FAS and 44.6/44.8 in controls (between group comparison not reported).6

Vitreous body depth to total axial length ratio: Values were not reported although females with FAS had a significantly lower ratio than females without FAS (*p*=0.015). No significant differences were seen in males with and without FAS (*p*=0.068).6

Mean axial length: Axial length in seven females with FAS (21.6±1.3mm) was significantly shorter than four age and sex-matched controls (22.0±0.9mm; *p*=0.045). No significant difference was observed in males with (21.6±0.4mm) and without FAS (22.6±1.0mm; *p* not reported).6

Mean excavation area: was 0.38±0.29mm2 (95% CI: 0.11-0.65) in FAS, and 0.31±0.2mm2 (95% CI: 0.20-0.42) in controls with no significant difference between groups.29

Mean peripapillary crescent area: No significant difference was observed FAS (0.47±0.5mm2 (95%CI: 0.09-0.85)) or controls (0.30±0.20mm2 (95% CI: 0.17-0.43)).29

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