**Supplementary table 6: Prevalence of eye abnormalities (Chapter XVII of ICD-10: Congenital malformations, deformations and chromosomal abnormalities) reported in children with FASD/PAE**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **ICD-10 code** | **Reported abnormality** | **Reported prevalence in children with FAS/FASD** | **Reported prevalence in children with PAE or FASD+PAE** | **Estimated prevalence or pooled prevalence, OR or mean difference (95%CI)** |
| Q10.0 Congenital ptosis | Ptosis | *Hanson 1976:*  FAS: 4.9% to 12.2% (2-5/41)  *Steinhausen 1982:*  FAS: 14.1%  *Strömland 1985:*  FAS: 20.0% or 23.3% (inconsistent reports)  *Carones 1992:*  FAS: 12.5%  *Spohr 1993:*  FAS: 18.0%  *Kvigne 2004:*  FAS: 9.3%  *Viljoen 2005:*  FAS: 6.3%; Control: 0 (*p*=0.013)  *Ervalahti 2007:*  FASD: 14.6%  *May 2007:*  FAS: 18.2%; PFAS: 5.6%; Controls: 2.1% (*p*<0.001)  *Landgren 2010:*  FAS: 4.8%  *May 2011:*  FASD: FAS: 0; PFAS: 8.3%; Control: 0 (*p*=0.005)  *Strömland 2015:*  FASD: 6.3% | *Majewski 1981†:*  PAE: 38.3%  *Flanigan 2008†:*  PAE: 2.3%; Control: 1.8% (*p*=0.97) | *FASD:*  OR: 11.56 (4.10 to 32.56); *p*<0.0001) (I2=0.0; Q=0.68; *p*=0.878)  Pooled prevalence: 12.7 (9.7 to 16.5)%  *PAE:*  OR: 7.65 (0.33 to 177.72); *p*=0.205) (I2=50.59; Q=2.02; *p*=0.155)  Pooled prevalence: 12.4 (0.6 to 77.3)% |
|  | Blepharoptosis | *Strömland 1996:*  FAS: 24.0%  *Ribeiro 2007:*  FAS: 18.8% | - | *FAS:*  Pooled prevalence: 21.2 (12.4 to 33.7)% |
| *Q10.1 Congenital ectropion* | Lateral ectropion | - | *Flanigan 2008:*  PAE: 2.3% (1/43) children  Control: 0  (*p*=0.79) | *PAE:*  Prevalence: 2.3 (0.3 to 14.7)% |
| Q10.3 Other congenital malformations of eyelid | Downward palpebral slant | - | *Majewski 1981:*  PAE (alcohol embryopathy): 37.1% (39/105) children | *PAE:*  Prevalence: 37.1 (28.5 to 46.7)% |
|  | Blepharophimosis | *Steinhausen 1982:*  FAS: 49.3%; Control: nr  *Strömland 1985:*  FAS: 4.5%; Control 1 (some with PAE): 0; Control 2 (intrauterine growth retardation): 0  *Steinhausen 2003:*  FASD: 26.3%; Control: nr  *Ribeiro 2007:*  FAS: 18.8% children (15.6% eyes); Control: nr | *Majewski 1981:*  PAE (alcohol embryopathy): 11.3% | *FASD:*  Pooled prevalence: 18.1 (5.6 to 45.1)%  *PAE (alcohol embryopathy):*  Prevalence: 11.3 (5.7 to 20.9)% |
|  | Epicanthus or epicanthal folds | *Hanson 1976:*  FAS: 49.0%  *Steinhausen 1982:*  FAS: 67.6%; Control: nr  *Beattie 1983:*  FAS: 100%  *Church 1988:*  FAS: 23.1%  *Spohr 1993:*  FAS: 44.0%  *Strömland 1996:*  FAS: 100%  *Kvigne 2004:*  FAS: 14.0%; Control: 1.2% (OR: 12.0 (1.4 to 99.7))  *Viljoen 2005:*  FAS: 53.1%; Control: 31.1% (*p*=0.003)  *May 2006:*  FASD: 40.9%; Control: 14.9 (*p*=0.01)  *Ervalahti 2007:*  FASD: 70.8%  *May 2007:*  FAS: 61.8%; PFAS: 55.6%; Control: 48.7% (*p*=0.299)  *Ribeiro 2007:*  FAS: 27.0% eyes; Control: nr | *Majewski 1981:*  PAE (alcohol embryopathy): 65.7%  *Flanigan 2008:*  PAE: 20.9%; Control: 10.9% (*p*=0.33) | *FAS/FASD:*  OR: 2.57 (95%CI: 1.45 to 4.52; *p*=0.001) (I2=14.98; Q=5.24; *p*=0.155)  Pooled prevalence: 53.5 (40.6 to 66.0)%  *PAE:*  Pooled prevalence: 42.2 (9.5 to 83.6)% |
|  | Telecanthus | *Carones 1992:*  FAS [n=8]: 62.5%  *Ribeiro 2007:*  FAS: 13.0% | - | *FAS:*  Pooled prevalence: 31.7 (4.0 to 83.7)% |
|  | Short or small PFL | *Hanson 1976:*  Chouke 1929 reference:  FAS: 92.0%  *Church 1988:*  FAS: 53.8%  *Carones 1992:* [n=8]  FAS: 100%  *Spohr 1993:*  FAS: 41.7%  *Strömland 1996:*  FAS: 100%  *Egeland 1998:*  FAS: 66%  *Kvigne 2004:*  FAS: 32.6%; Control: 0 (*p*=0.001)  *Ervalahti 2007:*  ≤ 10%:  FASD: 85.4%  *Ribeiro 2007:*  Hall 1989 charts:  FAS: 81.0%  *Elliott 2008:*  FASD: 60.9%  *Landgren 2010:*  < -2 SD:  FAS: 47.6%  *Strömland 2015:*  ≤ 10th percentile:  FASD: 62.5%; Control: nr | *Flanigan 2008:*  ≤ -2 SD:  PAE: 14.0%; Control: 18.2% (*p*=0.66)  *Suttie 2013:*  ≤10th percentile:  FAS: 81.8%; PFAS: 69.2%; HE: 12.0%; Control: 11.6% (*p*<0.001)  *Astley 2010:*  ≤ -2 SD:  FAS/PFAS: 93.5%; SE/AE: 66.0; ND/AE: 57.9%; PAE (normal CNS): 45.4% (*p*=0.00) | *FAS/FASD:*  Pooled prevalence: 66.1 (57.9 to 73.5)%  *PAE:*  Pooled prevalence: 21.5 (6.7 to 51.0)% |
|  | PFL | *Viljoen 2005:*  FAS: 2.3±0.13 cm; Control: 2.6±0.14 cm (*p*<0.001)  *May 2007:*  FAS: 2.3±0.11 cm; PFAS: 2.3±0.09 cm; Control: 2.5±0.12 cm (*p*<0.001)  *Moore 2007:*  FAS (mm): NAC: 24.3±2.5; AA: 24.2±0.6; FC: 23.6±2.0; CC: 23.7±1.8  Control (mm): NAC: 26.5±1.7; AA: 26.1±0.7; FC: 25.7±1.8; CC: 24.6±1.8  *Andersson Grönlund 2010:*  Median – right eye (mm):  FAS: 25 (21 to 26); Control: 26 (23 to 31)  Median – left eye (mm):  FAS: 25 (21 to 27); Control: 26 (24 to 31)  (*p*=0.001)  *Astley 2010:*  Mean Z-score:  FAS/PFAS: -3.2±1.2; SE/AE: -2.6±1.6; ND/AE: -2.3±1.4; PAE (normal CNS): -1.9±1.5 (differences seen across 4 groups, *p*=0.00)  *May 2011:*  FAS: 2.4±0.1 cm; PFAS: 2.4±0.1 cm; Control: 2.5±0.1cm (*p*<0.001)  *Blanck-Lubarsch 2019:*  Mean – right eye (mm):  FAS: 21.7±2.33; Control: 24.0±1.6  Mean – left eye (mm):  FAS: 21.6±2.0; Control: 23.9±1.6  Median – right eye (mm):  FAS: 21.9 (19.2 to 24.9); Control: 24.1 (21.6 to 2.8)  Median – left eye (mm):  FAS: 21.8 (18.4 to 25.7); Control: 23.9 (21.6 to 27.7)  (*p*<0.001) *Values also presented separately for males/females, nr here* |  | *FAS/FASD:*  Mean difference: -1.9mm (95%CI: -2.6 to -1.2mm; *p*<0.0001) (I2: 91.12; Q=56.34; *p*<0.0001)  *FAS:*  Mean difference: -2.2mm (95%CI: -3.0 to -1.5mm; *p*<0.0001) (I2=85.10; Q=20.14; *p*<0.0001)  *FASD:*  Mean difference: -1.5mm (95%CI: -2.5 to -0.5mm; *p*=0.003) (I2=94.20; Q=17.25; *p*<0.0001) |
| *Q10.7 Congenital malformation of orbit* | “Other severe ocular abnormality” | *Ribeiro 2007:*  FAS: 0 | - |  |
| Q11.2 Microphthalmos | Microphthalmos or microphthalmia | *Hanson 1976:*  Moderate to severe:  FAS: 4.9 to 12.2% (2-5/41)  *Church 1988:*  FAS: 7.7%  *Strömland 1996:*  FAS: 4.0%  *Hellström 1997a:*  FAS: 12.5%; Control: 0  *Kvigne 2004:*  FAS: 9.3%; Control: 0 (*p*=0.02)  *Ribeiro 2007:*  FAS: 0 | - | *FAS:*  OR: 24.79 (95%CI: 2.94 to 208.82); *p*=0.003) (I2=0.0; Q=0.05; *p*=0.825)  Pooled prevalence: 7.2 (4.0 to 12.7)% |
| *Q13.0 Coloboma of iris* | Coloboma of the iris and uvea | *Strömland 1996:*  FAS: 4.0% (1/25) children | - | *FAS:*  Prevalence: 4.0 (0.6 to 23.5)% |
| Q13.3 Congenital corneal opacity | Corneal opacities | *Ribeiro 2007:*  FAS: 0 | *Flanigan 2008:*  PAE: 0; Control: 0 |  |
|  | Clouded corneae | *Church 1988:*  FAS: 7.7% | - | *FAS:*  Prevalence: 7.7 (1.1 to 39.1)% |
| Q13.4 Other congenital corneal malformations | Mean corneal endothelial cell density (cells/mm2) | *Carones 1992:*  Total cohort:  FAS [n=8]: 3411±188; Control [n=80]: 3599±333 (*p*=0.032)  5 to 9yo:  FAS [n=5]: 3534±89; Control [n=40]: 3690±326 (*p*=0.026)  10 to 14yo:  FAS [n=3]: 3206±87; Control [n=40]: 3508±319 (*p*=0.003) | - |  |
|  | Polymegathism (coefficient of area variation, %) | *Carones 1992:*  Total cohort:  FAS [n=8]: 22.66±2.45; Control [n=80]: 17.75±2.73 (*p*=0.000)  5 to 9yo:  FAS [n=5]: 21.20±1.42; Control [n=40]: 16.87±2.91 (*p*=0.000)  10 to 14yo:  FAS [n=3]: 25.10±1.66; Control [n=40]: 18.63±2.23 (*p*=0.024) | - |  |
|  | Pleomorphism (% hexagonal cells) | *Carones 1992:*  Total cohort:  FAS [n=8]: 89.31±3.55; Control [n=80]: 93.25±3.41 (*p*=0.000)  5 to 9yo:  FAS [n=5]: 89.15±4.33; Control [n=40]: 94.62±2.98 (*p*=0.000)  10 to 14yo:  FAS [n=3]: 89.57±2.0; Control [n=40]: 91.88±3.29 (*p*=0.102) | - |  |
|  | Microcornea | *Carones 1992:*  FAS: 0  *Strömland 1996:*  FAS: 4.0% | *Flanigan 2008:*  PAE: 0; Control: 0 | *FAS:*  Pooled prevalence: 4.5 (0.9 to 19.4)% |
|  | Peters anomaly | *Ribeiro 2007:*  FAS: 0 | *Flanigan 2008:*  PAE: 0; Control: 0 |  |
|  | Posterior embryotoxon | *Ribeiro 2007:*  FAS: 0 |  |  |
| Q13.8 Other congenital malformations of anterior eye segment | Axenfeld-Rieger syndrome | *Ribeiro 2007:*  FAS: 0 | *Flanigan 2008:*  PAE: 0; Control: 0 |  |
| Q13.9 Congenital malformation of anterior segment of eye, unspecified | Anterior segment abnormalities (including microcornea, shallow anterior chamber & congenital glaucoma, cataract, & persistent hyaloid) | *Ribeiro 2007:*  FAS: 1.6% eyes | - | *FAS:*  Prevalence: 1.6 (0.2 to 10.3)% eyes |
|  | Mesenchymal dysgenesis | *Carones 1992:*  FAS: 0 | - |  |
|  | Shallow anterior chamber | *Ribeiro 2007:*  (assessed for within “anterior segment abnormalities”, but not specified if present in the cases reported) | *Flanigan 2008:*  PAE: 0; Control: 0 |  |
| *Q14.0 Congenital malformation of vitreous humour* | Persistent hyperplasic primary vitreous | *Strömland 1996:*  FAS: 4.0% (1/25) children. This child also had partial cataract and a completely malformed retina with only light perception in the same eye | - | *FAS:*  Prevalence: 4.0 (0.6 to 23.5)% |
| Q14.2 Congenital malformation of optic disc | Double ring sign | *Strömland 1985:*  Funduscopic signs of hypoplasia incl. double ring sign & sharply defined borders of the optic disc:  FAS: 73.3% eyes (25% eyes also had normal discs, 48.3% eyes also had optic nerve hypoplasia); Control 1 (some with PAE): 0; Control 2 (intrauterine growth retardation): 0  *Ribeiro 2007:*  FAS: 15.0% (3/20 from Table IV of original article, which did not match article text [12.5%]) | - | *FAS:*  Prevalence: 15.0 (4.9 to 37.6)% |
|  | Optic disc area (mm2) | *Strömland 1985:*  FAS: 1.99±0.60; Control 1 (some with PAE): 2.6±0.53; Control 2 (intrauterine growth retardation): 2.52±0.32 (*p*=0.016)  *Hellström 1997b:*  FAS: 2.10±0.49; Control: 2.8±0.42 (*p*<0.01)  *Hellström 1999:*  FAS (median): 2.18 (*p*=0.02 compared to reference data)  *Andersson Grönlund 2010:*  FAS (median): 2.13 (1.45 to 2.8); Control: 2.48 (1.09 to 4.43) (*p*=0.02) | - | *FAS:*  Mean difference: -0.582 (95%CI: -0.78 to -0.38; *p*<0.0001) (I2=0.0; Q=1.53; *p*=0.676) |
|  | Small optic discs | *Strömland 1982:*  FAS: 16.7%  *Strömland 1985:*  ≤ 1 SD:  FAS: nr; Control 1 (some with PAE): 15.9% eyes; Control 2 (intrauterine growth retardation): 13.6% eyes  *Ribeiro 2007:*  DM/DD ratio > mean control group value +1SD:  FAS: 40.0% | - | *FAS:*  Pooled prevalence: 27.0 (10.2 to 54.6)% |
|  | DM/DD ratio (the ratio of the distance from the centre of the disc to the fovea, to the disc diameter) | *Ribeiro 2007:*  FAS: 2.9±0.3; Control: 2.7±0.2 (*p*=0.001) | - |  |
|  | Optic nerve hypoplasia, Optic disc hypoplasia or Optic nerve head hypoplasia (≤ 2.07 mm2) | *Strömland 1982:*  FAS: 30.0%  *Beattie 1983:*  FAS: 5.0%  *Strömland 1985:*  Optic nerve head hypoplasia:  FAS: 48.3% eyes; Control 1 (some with PAE): 0; Control 2 (intrauterine growth retardation): 0  Optic disc hypoplasia (bilateral):  FAS: 18.3%  Optic disc hypoplasia (unilateral):  FAS: 11.7%  *Carones 1992:*  FAS: Absent (57.1%); Present (28.6%); Severe (28.6%); More severe (0)  *Strömland 1996:*  FAS: 76.0%  *Ribeiro 2007:*  FAS: 35.0% children (27.5% eyes)  *Landgren 2010:*  FAS: 19% bilateral  *Strömland 2015:*  FASD: 6.3% bilateral | *Flanigan 2008:*  PAE: 0; Control: 0 (*p*=1.0) | *FAS:*  Pooled prevalence: 30.2 (16.2 to 49.4)% children  Pooled prevalence: 38.1 (20.3 to 59.8)% eyes |
|  | Optic nerve atrophy | *Strömland 1982:*  FAS: 13.3% | - | *FAS:*  Prevalence: 13.3 (5.1 to 30.6)% |
|  | Tilted optic disc | - | *Flanigan 2008:*  PAE: 0; Control: 1.8% (*p*=0.79) |  |
| Q14.8 Other congenital malformations of posterior segment of eye | Malformations of the total fundus | *Strömland 1982:*  FAS: 3.3% | - | *FAS:*  Prevalence: 3.3 (0.5 to 20.2)% |
|  | Persistent hyaloids | *Ribeiro 2007:*  (assessed for within “anterior segment abnormalities”, but not specified if present in the cases reported) | *Flanigan 2008:*  PAE: 0; Control: 0 |  |
| Q14.9 Congenital malformation of posterior segment of eye, unspecified | Abnormal tortuosity | *Strömland 1985:*  FAS: 63.0%; Control 1 (some with PAE): 19.0%; Control 2 (intrauterine growth retardation): 32.0%  *Carones 1992:*  Retinal:  FAS: Absent (12.5%); Present (37.5%); Severe (25.0%); More severe (25.0%)  *Strömland 1996:*  Artery:  FAS: 36.0%  *Ribeiro 2007:*  Retinal:  FAS: 30.0% | *Flanigan 2008:*  Artery:  PAE: 16.3%; Control: 14.5% (*p*=0.88) | *FAS:*  Pooled prevalence: 50.5 (28.7 to 72.1)%  *PAE:*  Prevalence: 16.3 (8.0 to 30.4)% |
|  | Tortuosity | *Hellström 1999:*  Retinal artery:  FAS (median): 1.13 (*p*=0.04 compared to reference data)  Retinal vein:  FAS (median): 1.13 (*p*=0.002 compared to reference data) |  |  |
|  | Tortuosity index | *Strömland 1985:*  Artery (≥1.44):  FAS: 49.0% eyes; Control 1 (some with PAE): 19.4% eyes; Control 2 (intrauterine growth retardation): 27.3% eyes  Artery:  FAS: 1.52±0.36; Control 1 (some with PAE): 1.24±0.2; Control 2 (intrauterine growth retardation): 1.25±0.21 (*p*=0.011)  Vein:  FAS: 1.5±0.6; Control 1 (some with PAE): 1.37±0.18; Control 2 (intrauterine growth retardation): 1.42±0.29 (*p*=0.66)  *Hellström 1997b:*  Artery:  FAS: 1.16±0.08; Control: 1.10±0.03 (*p*<0.01)  Vein:  FAS: 1.14±0.09; Control: 1.08±0.02 (*p*<0.01) | - | *FAS:*  Artery:  Mean difference: 0.168 (95%CI: -0.003 to 0.340; *p*=0.054) (I2=65.09; Q=5.73; *p*=0.057)  Vein:  Mean difference: 0.062 (95%CI: 0.017 to 0.106; *p*=0.007) (I2=0.000; Q=0.19; *p*=0.908) |
|  | Other vascular abnormalities | *Strömland 1982:*  Retinal vessel abnormality:  FAS: 3.3%  *Strömland 1985:*  Abnormal width & course of retinal vessels:  FAS: 15.4% eyes  *Hellström 1997b:*  Mean N branching points:  FAS: 19.6±3.95; Control: 22.6±3.25 (*p*<0.05)  *Hellström 1999:*  N branching points:  FAS (median): 20 (*p*=0.04 compared to reference data) | - | *FAS: Retinal vessel abnormality:*  Prevalence: 3.3 (0.5 to 20.2)% |
|  | Combined abnormalities including vascular anomalies | *Strömland 1985:*  Malformation of optic nerve + retina + retinal vessels:  FAS: 7 eyes [denominator nr]; Control 1 (some with PAE): 0; Control 2 (intrauterine growth retardation): 0  Retinal artery tortuosity + optic nerve hypoplasia:  FAS: 25.6% eyes  *Strömland 2015:*  Vascular anomalies + dysmorphic optic nerve:  FASD: 12.5%; Control (orphans): 1.3% | - |  |
|  | Other: Cataract or pronounced fundus lesions | *Strömland 1985:*  FAS: 8.8% eyes | - | *FAS:*  Prevalence: 8.8 (3.7 to 19.4)% eyes |
|  | Other: bilateral hypoplastic optic discs and other intraocular anomalies (leading to blindness) | *Elgen 2007:*  FAS: 1; FASD: 0 | - | *FAS:*  Prevalence: 2.1 (0.3 to 13.4)% |
|  | Other: macular ectopia | *Ribeiro 2007:*  FAS: 0 | - |  |
|  | Other: malformation of anterior and posterior segments of the eye | *Strömland 1982:*  FAS: 3.3% | - | *FAS:*  Prevalence: 3.3 (0.5 to 20.2)% |
| Q15.0 Congenital glaucoma | Glaucoma | *Church 1988:*  FAS: 7.7%  *Carones 1992:*  FAS: 0 | *Flanigan 2008:*  PAE: 0; Control: 0 | *FAS:*  Pooled prevalence: 6.9 (1.4 to 28.0)% |
|  | Buphthalmus (often a symptom of childhood glaucoma) | *Strömland 1996:*  FAS: 4.0%  *Hellström 1997a:*  FAS: 6.3%; Control: 0 | - | *FAS:*  Pooled prevalence: 5.0 (1.3 to 17.9)% |
| Q75.2 Hypertelorism [& other orbital measures] | Hypertelorism | *Church 1988:*  FAS: 15.4% | - | *FAS:*  Prevalence: 15.4 (3.9 to 45.1)% |
|  | Short inner canthal distance (≤ 25%) | *May 2011:*  FAS: 25.0%; PFAS: 19.4%; Control: 6.0% (*p*=0.022) | - | *FAS/PFAS:*  Prevalence: 20.5 (11.0 to 34.9)% |
|  | Inner canthal width | *Moore 2007:*  FAS: NAC: 33.9±2.8; AA: 34.5±0.6; FC: 33.2±3.3; CC: 30.2±2.4  Control: NAC: 34.4±3.1; AA: 32.7±0.7; FC: 34.2±2.4; CC: 32.2±2.5 | - |  |
|  | Outer canthal width | *Moore 2007:*  FAS: NAC: 79.9±4.9; AA: 80.0±1.7; FC: 78.6±4.4; CC: 74.9±4.2  Control: NAC: 84.8±4.1; AA: 82.4±1.4; FC: 84.4±3.8; CC: 79.0±4.5 | - |  |

95%CI = 95% confidence interval; AA = African American; CC = Cape Coloured; CNS = central nervous system; FAS = fetal alcohol syndrome; FASD = fetal alcohol spectrum disorder; FC = Finnish Caucasian; HE = healthy-exposed; ICD-10 = 10th revision of the International Statistical Classification of Diseases and Related Health Problems; NAC = North American Caucasian; ND/AE = neurodevelopmental disorder/alcohol exposed; nr = not reported; OR = odds ratio; PAE = prenatal alcohol exposure; PFAS = partial fetal alcohol syndrome; PFL = palpebral fissure length; SD = standard deviation; SE/AE = static encephalopathy/alcohol exposed.

*Italicised* codes indicate those which were reported in one study (N=4 codes).

Studies including rates (%) were included in pooled prevalence values. Pooled prevalence was not calculated where no cases were reported (n=0). All values relate to % children unless specified as % eyes. Child and eye data were not combined for pooled values.