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ORIGINAL ARTICLE

Visual function in Norwegian children aged 5–13 years with prenatal exposure to opioid maintenance therapy: A case–control study

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Abstract

Purpose: To assess various aspects of visual function in school children prenatally exposed to opioid maintenance therapy (OMT) and to explore possible outcome differences between prenatal methadone and buprenorphine exposure.

Methods: In a cross-sectional case–control study, 63 children aged 5–13 years with prenatal OMT exposure were compared with 63 age- and gender-matched, non-exposed controls regarding important visual parameters, such as visual acuity, orthoptic status, refractive state, colour vision, and visual field.

Results: The OMT-exposed children had significantly poorer visual acuity, both for the best eye, the worst eye and binocularly. Two children had mild visual impairment. Manifest strabismus was more frequent in the OMT group, 30%, vs. 4.8% in the control group. The most frequent types of strabismus were accommodative esotropia and intermittent exotropia. Manifest nystagmus was present in 10 (16%) of the exposed children compared to one among the non-exposed children. The accommodative amplitude was decreased in the OMT group compared to the controls. After adjusting for polydrug exposure and SGA (small-for-gestational-age), the between-group differences in visual acuity, strabismus, and nystagmus remained. The methadone-exposed children had poorer visual acuity, increased frequency of strabismus and a higher percentage of nystagmus, hypermetropia and astigmatism compared to the buprenorphine-exposed children.

Conclusions: School-age children exposed to methadone or buprenorphine in utero had a higher prevalence of strabismus and nystagmus, and a lower visual acuity and accommodation amplitude. Buprenorphine exposure was associated with more favourable results than methadone exposure on most visual outcome measures and should be the preferred substance in OMT.

KEYWORDS
buprenorphine, methadone, nystagmus, opioid maintenance therapy, strabismus, visual acuity

1 | INTRODUCTION

Opioid maintenance therapy (OMT) is the internationally recommended treatment to opioid-addicted patients (World Health Organization (WHO), 2014). It combines pharmacological treatment—buprenorphine (Subutex) or methadone—with a comprehensive psychosocial support. Among the 8200 patients in OMT in Norway, there are approximately 1400 women in childbearing age (Waal et al., 2019), and on average, 30 children are born to women in OMT each year (Odsbu et al., 2021). Based on WHO's recommendations, a Norwegian treatment guideline for pregnant women in OMT and a follow-up programme

for their children to school age was published in 2011 (Bakstad & Welle-Strand, 2011) and revised in 2019 (Helsedirektoratet, 2019). According to WHO, the recommendation is based on "very low quality of evidence" (World Health Organization, 2014) and hence rises a need for evaluation. In contrast to WHO, which recommends methadone as the drug of choice, the revised Norwegian guideline advices that buprenorphine should be preferred over methadone to pregnant women (Helsedirektoratet, 2019).

There is no doubt that OMT has advantages by ensuring a more secure obstetric outcome and improving general health and quality of life, reducing risk-taking behaviour and over-dose deaths (Bakstad & Welle-Strand, 2011; Lambert & Peeler, 2019; Suarez et al., 2022). However, there is an ongoing debate about the possible harm of OMT on foetal health, in particular on the developing brain.

The opioids freely cross the placenta and the foetal blood–brain barrier (Nanovskaya et al., 2002; Nekhayeva et al., 2005), and present knowledge suggests that exogenous opioids have an impact on prenatal neuronal growth and maturation (Boardman et al., 2022; Lambert & Peeler, 2019; Mactier & Hamilton, 2020). In a clinical setting, prenatal opioid exposure is associated with premature birth, impaired foetal growth, and reduced head circumference (Boardman et al., 2022; Mactier & Hamilton, 2020; Yen & Davis, 2022). Magnetic resonance imaging (MRI) findings in exposed infants and in older children 10–14 years have shown reduced neuroanatomical volumes and delayed white matter myelination (Andersen et al., 2020; Mactier & Hamilton, 2020; Sirnes et al., 2017) supporting the hypothesis of an adverse effect of opioid—exposure upon foetal brain development.

A major question arises: Do these findings relate to functional outcome?

The high incidence (40%–90%) of Neonatal Abstinence Syndrome (NAS) is the most undesirable *neonatal* adverse outcome, bringing the newborn baby into a serious neuro-withdrawal condition which may in turn affect further brain development (McGlone & Mactier, 2015; Midtlyng & Høiseth, 2016) and disrupt the early mother–child attachment (Lambert & Peeler, 2019; Welle-Strand et al., 2013; Yen & Davis, 2022).

Visual evoked potential (VEP) studies on OMT- and illicit drug-exposed infants have shown abnormal patterns, suggesting an adverse impact on the visual system of opioid exposure (Boardman et al., 2022; Hamilton et al., 2010; Lambert & Peeler, 2019; Mactier & Hamilton, 2020; McGlone et al., 2013, 2014; Whitham et al., 2010). While abnormal VEPs in the neonate reflect neuronal maturation and not necessarily predict long-term visual outcome (Whitham et al., 2010), current research data report decreased visual acuity, increased rate of strabismus, nystagmus, and refractive errors in toddlers and preschool children prenatally exposed to illicit substances and OMT (Auger et al., 2020; Cornish et al., 2013; Lambert & Peeler, 2019; Mactier & Hamilton, 2020; McGlone et al., 2014; Monnelly et al., 2019; O'Connor et al., 2021; Yen & Davis, 2022).

Studies in this field have methodological limitations such as small sample size, selection bias, lack of sufficient adjustment for known confounders, as well as loss to follow up in longitudinal studies (Lambert & Peeler, 2019; Monnelly et al., 2019; O'Connor et al., 2021). The majority of studies on visual outcome have been conducted in the United States, Australia and Great Britain on *methadone*-maintained pregnancies (Cornish et al., 2013; Gill et al., 2003; Hamilton et al., 2010; McGlone et al., 2014; Mulvihill et al., 2007; Nelson et al., 1987), but studies on children exposed in utero to buprenorphine are emerging (Kivistö et al., 2015; O'Connor et al., 2021).

In the Scandinavian countries, all pregnant women in OMT are enrolled in a public-based follow-up programme with a holistic approach to ensure the best possible obstetric outcome (Handal et al., 2020). This includes close monitoring to prevent illicit/polydrug use. Hence, the OMT care programme facilitates studies on *cohorts* of in utero OMT-exposed children with a limited exposure to illicit drugs.

Three recent review articles (Boardman et al., 2022; Hemmati et al., 2022; Lambert & Peeler, 2019) address the need for more long-term follow-up studies on visual outcome in a larger scale, including studies comparing exposure to methadone vs. buprenorphine (Kornør et al., 2019; McGlone et al., 2013; Suarez et al., 2022).

Our aims in this study were (1) to examine the long-term effects of prenatal exposure to OMT on various aspects of visual function in a relatively large group of children in a Norwegian setting and (2) to assess possible outcome differences between methadone and buprenorphine exposure. In addition, we wanted to learn how the follow-up programme and the general screening system at the mother-and-child health care centres were able to pick up treatable visual conditions like amblyopia in the OMT-exposed children.

2 | MATERIALS AND METHODS

We conducted a case–control study to assess visual function in prenatally OMT-exposed children aged 5–13 years ($n=63$) compared to age-matched controls ($n=63$).

The children were recruited from two Norwegian centres, Haukeland University Hospital and Sørlandet Hospital, during the period January 2018 to June 2021.

A multidisciplinary team consisting of an ophthalmologist, an optometrist, and an orthoptist did the visual function assessments at Sørlandet Hospital, while at Haukeland University Hospital these examinations were performed by an experienced paediatric ophthalmologist and an ophthalmic nurse (who did the visual field examinations). The examiners were blinded to the child's group adherence and previous medical history.

2.1 | Participants

2.1.1 | The OMT-exposed group

Sixty-three children (31 from Haukeland University Hospital and 32 from Sørlandet Hospital) were

recruited in three different ways by searching for; (1) Children with the diagnosis of Neonatal abstinence syndrome (NAS) or "observation for NAS" as keywords in medical records or in the Norwegian patient registry (NPR), (2) Women in childbearing age diagnosed with Opioid use dependency (OUD) and child deliveries, and (3) Children in the National follow-up programme for children at risk of deviant development due to prenatal exposure to OMT.

Only children exposed to opioids as part of the mothers' OMT were included.

One mother in the OMT discontinued medication during the first trimester. Her child was included in the OMT-exposed group.

All caregivers received a written invitation to participate in the study resulting in an acceptance rate of 74% and 95% for the participants from Haukeland University Hospital and Sørlandet Hospital, respectively. The children received a written age-appropriate information about the project.

The following background data were collected from medical records, questionnaires, and personal interviews:

a. Prenatal exposure: OMT medication (buprenorphine/methadone), alcohol, tobacco, prescribed drugs, and illicit drugs (polydrug use).
b. Neonatal data: gestational age (GA), birth weight (BW), head circumference (HC), presence of Neonatal Abstinence Syndrome (NAS), medication, and congenital disorders.
c. Child: age, sex, care base/home placement.
d. Mother: level of education.

2.1.2 | The control group

The children in the control group were recruited from the same two study sites, Haukeland University Hospital ($n=10$) and Sørlandet Hospital ($n=53$). We invited gender-matched children born at the same or nearby date as the participants in the OMT-group. Similar to the study group, the following data were collected from medical records and from a questionnaire: prenatal drug exposure, any alcohol, tobacco, prescription or illicit drug use during pregnancy, and neonatal health data, age, sex and mother's level of education.

2.2 | Clinical assessment—outcome measures

All participants underwent a thorough eye examination and visual assessment. To ensure a uniform practice for the eye examinations at the two centres, we used a detailed examination protocol, and the involved examiners from both centres did the assessments of the first recruited patients together.

Medical history: Previous eye-related history (any glass prescription, use of patching, eye surgery) was noted.

Visual acuity: LH or ETDRS chart was used, depending on the child's age. Visual acuity was noted as logMAR values, both for distance (best eye, worst eye, and binocularly) and near (40 cm, binocularly).

Orthoptic status: Strabismus was assessed with prism and cover test for near and distance. Manifest strabismus was noted dichotomously (yes/no) as well as recording the clinical type of strabismus. Both manifest and latent strabismus were noted according to direction (eso-, exo-, vertical) and size (in prism dioptres). Data on clinically observed nystagmus, either in primary position or gaze-induced, were included. Binocular function was noted in terms of stereoacuity (TNO-test, Stereo Fly Test or Lang stereotest no. 1). Accommodation and near point of convergence were both tested with a RAF-ruler and recorded as the mean value of three measurements.

Refractive state: Autorefraction (Nidek ARK-530A) was done before and after cycloplegia. Retinoscopy in cycloplegia was performed 30 min after instillation of cyclopentolate 1% twice in each eye. Refractive state was recorded as the spherical equivalent of retinoscopy in cycloplegia. Astigmatism (amount and axis) was recorded from the autorefraction measurements in cycloplegia.

Eye dominance: Eye dominance was tested for distance and near, using the hole-in-card method (Dolman).

Colour vision: At both the participating centres, the HRR test (Richmond Products, Inc., USA) was applied to test colour vision.

Visual field: Peripheral visual field boundaries were assessed for each eye with Goldmann kinetic perimetry (Haag-Streit AG, Köniz, Switzerland), using object V4e. The four oblique meridians (45, 135, 225, and 315 degrees) were tested three times, and the mean value was noted.

Anterior segment: The anterior segment of the eye was examined with a slit lamp, especially with regard to congenital anomalies, corneal or lens opacities, and pupil reactions.

Posterior segment: The fundus was examined with indirect ophthalmoscopy, either using head-mounted indirect ophthalmoscope and 20 D lens or slit lamp and 90 D lens. In addition, colour fundus photo and optical coherence tomography (OCT) of the macula and optic disc was performed.

The results of the posterior segment examinations will be reported in a separate publication.

2.3 | Statistics

We used the SPSS statistical package version 28. We assumed normal distribution of the means, and numerical outcomes (as visual acuity) were compared using Student's *t*-test. The same applied to subgroups as long as $n>30$. Categorical outcomes (as strabismus and nystagmus) were compared using chi-squared test, or Fisher's exact test when there were cells with less than five observations. We have stated the *p*-values explicitly for all tests, assuming a significance level of 5%. Regression analysis was used to estimate odds ratios and the potential confounding effect of polydrug exposure (for strabismus and visual acuity).

2.4 | Ethics

The study protocol was approved by the South East Norwegian Committee for Medical Research Ethics (2017/712) and met the ethical requirements stated in the Declaration of Helsinki. Written informed consent was obtained from the caregivers.

3 | RESULTS

3.1 | Demographic characteristics

A total of 126 children were included in the study; 63 born to mothers in OMT and 63 children in the control group. Table 1 summarizes the demographic characteristics of the two groups.

The OMT-exposed children had significantly lower mean birth weight, head circumference at birth, and a higher number were born small-for-gestational-age (SGA), i.e. birth weight below the 10th centile adjusted for gender, parity and gestational age at birth.

Fifty-nine of the 63 (94%) OMT children had a history of Neonatal Abstinence Syndrome (NAS), and 44 were in need of medical treatment for this condition. Mothers' education level was significantly lower in the OMT group compared with controls.

Thirty-two children in the OMT group were in foster care and 31 lived with biologic parents (4 with the father alone). Mean age at foster care placement was 39 months (range 1–144). Twice as many children in the OMT group were exposed to buprenorphine (68%) as to methadone (32%).

Concerning possible alcohol exposure during pregnancy, we spent effort on getting as reliable data as possible, from medical records, questionnaires to the mothers, as well as personal interviews. In this way, we found that five children in the OMT group had been exposed to alcohol. Fifty-five mothers in the OMT group smoked during pregnancy, compared to two in the control group.

3.2 | Visual findings in OMT-exposed children vs. controls

We found statistically significant differences in visual acuity, manifest strabismus, nystagmus, and accommodation between the OMT-exposed children and the

TABLE 1 Demographic characteristics of the study groups.

	OMT-exposed ($n=63$)	Controls ($n=63$)	p-Value
Neonatal data			
Sex, n (%)			
Boys	31 (49.2)	30 (47.6)	
Girls	32 (50.8)	33 (52.4)	
Gestational age (weeks), mean (SD)	39.3 (1.8)	39.2 (1.6)	0.71
Birthweight (g), mean (SD)	3172 (558)	3567 (536)	<0.001
SGA, n (%)[a]	14/62 (22.6)	3/58 (5.2)	0.006
Head circumference (cm), mean (SD)	34.2 (1.8)	35.0 (1.6)	0.016
Neonatal abstinence syndrome (NAS), n (%)	59/63 (93.7)		
Medicamental treatment for NAS	44 (75% of NAS)		
Child data			
Age at the time of examination (years), mean (SD)[b]	8.2 (2.3)	8.8 (2.1)	0.126
Maternal data			
OMT medication			
Methadone, n (%)	20 (31.7)		
Mean dose, mg (range)	98 (8–150)		
Buprenorphine (Subutex), n (%)	43 (68.3)		
Mean dose, mg (range)	16 (4–34)		
Other drugs during pregnancy, n (%)[c]			
Only one drug	12 (19.0)		
Two or more drugs	14 (22.2)		
Only prescribed psychopharmaca	3 (4.8)	1	
Other			
Alcohol, n	5/61	0	
Nicotine, n	55/58	2/60	
Education level, mean (SD)[d]	2.2 (1.0)	3.9 (0.7)	<0.001

[a]SGA, small-for-gestational-age (birth weight < 10th percentile).

[b]Age in months = year × 12 + decimal × 1.2.

[c]Cannabis only ($n=4$), benzodiazepines only ($n=6$), cannabis + benzodiazepines ($n=2$), multidrugs ($n=12$), stimulantia only ($n=1$), other opioids only ($n=1$).

[d]1 = lower secondary school; 2 = upper secondary school (not specified); 3 = upper secondary school (vocational studies); 4 = university college (3–4 years); 5 = university (5–6 years).

controls. In addition, there was a tendency towards more astigmatism and hypermetropia in the OMT-exposed group. The results are presented in Table 2.

3.3 | History of glass prescription, patching and amblyopia

At the eye examination, 12 (19%) of the OMT children and seven (11%) of the controls wore a habitual glass correction. All the corrections were due to hypermetropia, either alone or in combination with astigmatism. According to the definition of amblyopia (interocular difference of two lines or more on a logMAR chart), there were three amblyopic children in both the OMT group and the control group. All the amblyopia children in the OMT group had strabismus, two with an accommodative esotropia and one with a constant exotropia. They had all been followed with regular eye examinations from infancy. The esotropia children had been treated with glass correction and patching, while the exotropia child was emmetropic and for various reasons had not been patched. Four children in the OMT group and one in the control group had been operated for strabismus.

Additionally, there were two children in the OMT group with bilaterally reduced visual acuity. One had been examined by an ophthalmologist at 7 months of age, with normal results and no further appointment. This girl was not examined again until six years of age due to the onset of esotropia, showing a high hypermetropia of 7–8 D in both eyes. She got glasses, but still her best corrected visual acuity is logMAR 0.4, probably due to a bilateral amblyopia. The other child with bilaterally reduced visual acuity had insignificant hypermetropia, but congenital nystagmus. This child had been followed with eye examinations from early infancy, showing reduced, but stable visual function. At the examination in our study, she had a visual acuity of logMAR 0.5 in both eyes, but improved to 0.4 binocularly, and 0.2 at near acuity.

3.4 | Eye dominance

Eye dominance could be tested for near and distance in the majority of children, both in the study group and the control group. When fixating at distance, 29/51 (56.9%) in the OMT-exposed group showed right eye dominance, 21/51 (41.2%) showed left eye dominance, while one had

TABLE 2 Visual outcomes: OMT-exposed vs. controls.

Variable	Study group ($n=63$)	Control group ($n=63$)	p-Value
Visual acuity, distance (logMAR), mean (SD)			
Best eye	0.05 (0.12)	−0.02 (0.07)	<0.001
Worst eye	0.10 (0.15)	0.03 (0.12)	0.004
Binocular	0.03 (0.13)	−0.05 (0.08)	<0.001
Visual acuity, near (binocular), mean (SD)	0.09 (0.11)	−0.01 (0.11)	<0.001
Amblyopia[a], *n* (%)	3/61 (4.9)	3/63 (4.8)	
Spherical equivalent RE (D), mean (SD)	+1.46 (1.91)	+1.02 (1.09)	0.12
Spherical equivalent LE (D), mean (SD)	+1.50 (1.92)	+1.10 (1.20)	0.18
Hypermetropia ≥ +2.0 D, *n* (%)	12/61 (19.7)	6/63 (9.5)	0.11
Hypermetropia ≥ +5.0 D, *n* (%)	5/61 (8.2)	1/63 (1.6)	0.11
Astigmatism RE (D), mean (SD)	−0.43 (0.65)	−0.26 (0.22)	0.06
Astigmatism LE (D), mean (SD)	−0.47 (0.67)	−0.29 (0.23)	0.04
Manifest strabismus, *n* (%)			
Distance	15/63 (23.8)	3/63 (4.8)	0.004
Near	14/63 (22.2)	1/63 (1.6)	<0.001
Distance and/or near	19/63 (30.2)	3/63 (4.8)	<0.001
Type of manifest strabismus, *n*			
Accommodative esotropia	7	0	
Intermittent exotropia	7	3	
Other exotropia	3	0	
Non-accommodative esotropia	2	0	
Stereo (+) among manifest strabismus, *n* (%)	9 (47)	3 (100)	
Latent strabismus, *n* (%)			
Distance	13/59 (22.0)	9/63 (14.3)	0.27
Near	22/54 (40.7)	31/63 (49.2)	0.36
Nystagmus, *n* (%)	10/63 (15.9)	1/63 (1.6)	0.01
Accommodation amplitude (D), mean (SD)	12.85 (2.87)	14.24 (2.69)	0.009
Near point of convergence (cm), mean (SD)	5.9 (2.4)	5.9 (2.4)	0.93

Abbreviations: D, dioptres; LE, left eye; RE, right eye; SD, standard deviation.

[a]Defined as difference in logMAR visual acuity of ≥0.2 (2 lines) between the right and left eye.

variable dominance. In the control group, 42/61 (68.9%) had right eye dominance and the rest (19/61) had left eye dominance ($p=0.27$). At near fixation, the results were very similar, showing no significant differences between the OMT-exposed group and the control group. Five children in the OMT group and two children in the control group had right–left disparity (opposite side) for fixation at distance and near ($p=0.24$).

3.5 | Colour vision

In the OMT group, 60 children could be tested for colour vision. Among these, ten (five girls, five boys) showed a mild protanomaly, one boy had a moderate protanomaly, and two had results indicating poor cooperation. In the control group, there was one female with a mild protanomaly.

3.6 | Visual field

When analysing the visual field data, we found that the children examined at centre A (Sørlandet Hospital) had slightly better (but statistically significant) results than the children examined at centre B (Haukeland University Hospital), in terms of more peripheral outer boundaries, in spite of identical instruments (Goldmann perimeter) used at both centres. This difference persisted also after excluding the results of first three children tested at centre B, as the instructions from the examining nurse clearly were misunderstood. As the visual fields were tested by an orthoptist at centre A, who was more familiar with testing children than the ophthalmic nurse who did the testing at centre B, we have concluded that this is the most probable explanation of the difference. Thus, we have chosen to divide the table of the visual field data between the two centres (Table 3), showing no significant differences in visual field extensions, except for the lower temporal quadrant in the right eye at centre A.

3.7 | Anterior segment

Minor lens opacities in two OMT-exposed children (both unilateral) and three controls (two unilateral and one bilateral) were noted. There were no other anterior segment changes in these eyes, and all six eyes had visual acuity of ≤logMAR 0.0. Apart from this, all the other OMT-exposed children and the controls had a completely normal anterior segment on slit lamp examination.

3.8 | Visual findings in children exposed to buprenorphine vs. methadone

The children in the methadone-exposed group had poorer visual acuity, increased frequency of strabismus for distance fixation (both manifest and latent), and a higher percentage of nystagmus, hypermetropia, and astigmatism compared with the buprenorphine group (Table 4).

No significant differences in demographics were found between the methadone and the buprenorphine

TABLE 3 Visual field measurements; Goldmann perimetry.

Visual field outer borders (degrees), Mean (SD); eye and meridian	OMT-exposed group	Control group	*p*-Value
Centre A			
Right eye			
45° (upper temporal)	60.5 (8.2)	61.7 (8.7)	0.54
135° (upper nasal)	49.5 (7.2)	50.4 (6.0)	0.54
225° (lower nasal)	51.8 (10.9)	47.7 (8.2)	0.06
315° (lower temporal)	68.1 (12.0)	73.2 (10.7)	0.05
Left eye			
45° (upper nasal)	51.5 (7.1)	51.9 (7.2)	0.81
135° (upper temporal)	58.6 (9.3)	60.6 (9.4)	0.35
225° (lower temporal)	69.3 (10.3)	70.0 (9.6)	0.76
315° (lower nasal)	49.1 (11.9)	47.4 (7.1)	0.43
Centre B			
Right eye			
45° (upper temporal)	50.7 (16.9)	56.8 (18.5)	0.30
135° (upper nasal)	45.1 (13.6)	48.1 (13.8)	0.55
225° (lower nasal)	45.6 (18.1)	46.1 (10.9)	0.94
315° (lower temporal)	55.0 (19.9)	67.0 (23.8)	0.13
Left eye			
45° (upper nasal)	44.6 (14.6)	51.0 (14.6)	0.24
135° (upper temporal)	50.1 (15.7)	53.5 (20.1)	0.59
225° (lower temporal)	59.5 (19.5)	68.6 (24.8)	0.25
315° (lower nasal)	45.9 (16.3)	45.0 (11.1)	0.87

TABLE 4 Visual outcomes: methadone vs. buprenorphine group.

	Buprenorphine group ($n=43$)	Methadone group ($n=20$)	p-Value
Visual acuity (logMAR), mean (SD)			
Best eye	0.02 (0.10)	0.12 (0.13)	0.002
Worst eye	0.07 (0.13)	0.19 (0.17)	0.003
Binocular	0.01 (0.13)	0.08 (0.12)	0.058
Visual acuity near, binocular, mean (SD)	0.07 (0.10)	0.14 (0.11)	0.015
Visual impairment, *n*			
Mild[a]	1/43	1/20	
Amblyopia[b], *n* (%)	1/43 (2.3)	2/18 (11.1)	0.21
Spherical equivalent RE (D), mean (SD)	+1.18 (1.75)	+2.06 (2.15)	0.12
Spherical equivalent LE (D), mean (SD)	+1.08 (1.47)	+2.38 (2.45)	0.02
Hypermetropia ≥ +2.0 D, *n* (%)	6/42 (14.3)	6/19 (31.6)	0.12
Hypermetropia ≥ +5.0 D, *n* (%)	2/42 (4.8)	3/19 (15.8)	0.31
Astigmatism RE (D), mean (SD)	−0.40 (0.53)	−0.84 (1.03)	0.08
Astigmatism LE (D), mean (SD)	−0.36 (0.33)	−1.11 (1.16)	0.002
Manifest strabismus, *n* (%)			
Distance	7/43 (16.3)	8/20 (40.0)	0.04
Near	7/43 (16.3)	7/20 (35.0)	0.10
Distance and/or near	8/43 (18.6)	11/20 (55.0)	0.003
Type of manifest strabismus, *n*			
Accommodative esotropia	3	4	
Intermittent exotropia	3	4	
Other exotropia	1	2	
Non-accommodative esotropia	1	1	
Latent strabismus, *n* (%)			
Distance	6/42 (14.3)	7/17 (41.2)	0.02
Near	13/39 (33.3)	9/15 (60.0)	0.07
Nystagmus, *n* (%)	4/43 (9.3)	6/20 (30.0)	0.06
Accommodation amplitude (D), mean (SD)	13.05 (2.48)	12.36 (3.70)	0.42
Near point of convergence (cm), mean (SD)	5.7 (1.9)	6.2 (3.3)	0.44

Abbreviations: D, dioptres; LE; left eye; RE, right eye; SD, standard deviation.
[a]ICD-11: mild visual impairment: Snellen <6/12–6/18.
[b]Defined as difference in logMAR visual acuity of ≥0.2 (2 lines) between the right and left eye.

groups, apart from head circumference at birth (33.4 ± 2.0 vs. 34.6 ± 1.5 cm, respectively).

3.9 | Impact of polydrug exposure and SGA on visual findings

To explore the possible impact of polydrug exposure on visual findings, we compared important visual outcomes (manifest strabismus, nystagmus, and visual acuity) for those with and without polydrug exposure in the OMT group. Significant visual outcome differences in manifest strabismus, nystagmus, and visual acuity between the OMT group and the control group persisted when looking at those without polydrug exposure vs. controls. Strabismus was more common among polydrug (39%) than non-polydrug (24%)-exposed children; however, this difference did not reach statistical significance (Table 5).

The possible impact of OMT exposure, polydrug exposure, and being SGA on strabismus and visual acuity were also explored with regression analyses, as shown in Table 6. The odds ratio (OR) for developing strabismus in the OMT group (regression 1) was 8.6 (CI: 2.4–31.0; $p<0{,}001$). When adjusting for polydrug exposure (regression 2), OR fell to 6.4 (CI: 1.6–25.6; $p=0.008$). SGA did not have a significant impact on the OR for strabismus (regression 3). Also, the group difference in visual acuity still reached significance ($p<0{,}001$) when adjusting for polydrug exposure (regression 4 and 5).

4 | DISCUSSION

In this case–control study, which includes a relatively large group of OMT-exposed children and a comparison group, we found a significant negative impact on several aspects of visual function in the OMT group. This impact was most clearly demonstrated in terms of a higher prevalence of strabismus (30% vs. 4.8%) and nystagmus (15.6% vs. 1.6%), and a lower mean visual acuity both for near and distance (Table 2). There was also a higher percentage of severe hypermetropia in the OMT group, although this did not reach statistical significance. After adjustment for polydrug exposure, these differences persisted.

4.1 | Visual acuity

Visual acuity (mean values of visual acuity both for the best eye, the worst eye, binocularly and for near acuity) was significantly poorer in the OMT group compared to the controls. This persisted after adjusting for polydrug exposure. Two children in the OMT group had mild visual impairment according to WHO's recent criteria (World Health Organization, 2022).

We have not found any other studies on prenatally OMT-exposed children where visual acuity has been tested in school-age children compared to non-exposed age-matched controls. A case series of 20 OMT-exposed children (methadone) referred to an ophthalmological examination due to concern about the visual function (Hamilton et al., 2010) found that 60% had visual acuity in the best eye of ≥logMAR 0.3. There was, however, an obvious selection in this group. Cornish and co-workers examined 5-year-old OMT-exposed children and found that 28.2% had a visual acuity of ≥logMAR 0.3 in the worst eye (no information about the best eye) (Cornish et al., 2013).

TABLE 5 Visual outcomes with or without polydrug exposure.

Variable	OMT-exposed ($n=63$)	Controls ($n=63$)	p-Value
Manifest strabismus, distance and/or near, n (%)			
Total	19/63 (30.2)	3/63 (4.8)	<0.001
Polydrug exposure[a]	10/26 (38.5)		
No polydrug exposure	9/37 (24.3)	3/63 (4.8)	0.008
(Polydrug vs. no polydrug exposure: $p=0.14$)			
Nystagmus, n (%)			
Total	10/63 (15.9)	1/63 (1.6)	0.01
Polydrug exposure	5/26 (19.2)		
No polydrug exposure	5/37 (13.5)	1/63 (1.6)	0.025
(Polydrug vs. no polydrug exposure: $p=0.31$)			
Visual acuity, near (logMAR), mean (SD)			
Total	0.09 (0.11)	−0.01 (0.11)	<0.001
Polydrug exposure	0.10 (0.11)		
No polydrug exposure	0.08 (0.11)	−0.01 (0.11)	<0.001
(Polydrug vs. no polydrug exposure: $p=0.37$)			

[a]Polydrug exposure = one or more side drugs during pregnancy.

4.2 | Strabismus

Our findings confirm the increased prevalence of manifest strabismus reported in previous studies on prenatally OMT-exposed children, both regarding methadone (Cornish et al., 2013; Gill et al., 2003; McGlone et al., 2014; Nelson et al., 1987; Yoo et al., 2017) and buprenorphine (Kivistö et al., 2015; O'Connor et al., 2021). These studies differ however considerably in terms of age group (from infants to 5- to 10-year-old children), and design (retrospective hospital-record data vs. planned study examinations, control group vs. no control group), which makes it difficult to compare the results directly.

To our knowledge, studies assessing long-term visual outcome in OMT-exposed children are rare; see review by Hemmati et al. (2022). However, one follow-up study by Cornish et al. (2013) found strabismus in 14.5% of methadone and illicit drug-exposed 5-year-old children, with an odds ratio of 5.7 for strabismus compared to controls. This is lower than our findings of 30% strabismus in the OMT group and an OR of 8.6 (6.4 when adjusted for polydrug exposure). Preliminary data from another follow-up study (Hamilton et al. 2020) on 8–10-year-old children ($n=22$) born to opioid-dependent, methadone-maintained mothers, demonstrated impaired visual function with some combination of strabismus (50%), nystagmus (23%), poor acuity (41%) and impaired binocular vision (36%); see review by Mactier & Hamilton (2020).

It is interesting that Cornish et al. (2013) only found one patient with infantile esotropia, while the majority of the strabismus patients either had acquired esotropia or intermittent exotropia. These findings are in accordance with our own results. Both accommodative esotropia (which is the most common acquired esotropia) and intermittent exotropia, the two most frequent strabismus types in our OMT group, are conditions that have a potential for normal binocular function. Thus, we found stereopsis in

TABLE 6 Unadjusted and adjusted odds ratio for manifest strabismus and visual acuity.

	Strabismus ($n=22/126$) Logistic regression[a]			Visual acuity ($n=126$) Linear regression[b]	
Regressor	Regression 1	Regression 2	Regression 3	Regression 4	Regression 5
OMT controls	8.6 (2.4–31.0); $p<0.001$	6.4 (1.6–25.6); $p=0.008$	6.2 (1.5–25.6); $p=0.012$	0.09 (0.05–0.13); $p<0.001$	0.08 (0.035–0.13); $p<0.001$
Polydrug use[c]		1.9 (0.65–5.8); $p=0.23$	1.9 (0.61–5.7); $p=0.28$		0.022 (−0.036–0.08) $p=0.45$
SGA (small-for-gestational-age)			0.97 (0.26–3.7) $p=0.97$		
Nagelkerke R^2	19%	21%	20%		
Adjusted R^2				14%	13%

[a]OR (95% CI).

[b]B-coefficient (95% CI).

[c]Polydrug use = one or more side drugs during pregnancy.

3 of 7 (43%) of the accommodative esotropias and in 6 of 7 (86%) of the intermittent exotropias. In contrast to this, with infantile esotropia, which is by far the most common type of strabismus in cerebral palsy (Erkkilä et al., 1996), the potential for binocular function is very poor.

The prevalence of strabismus in the general population is variably reported, from 2.3% in 7-year-olds in a study from 2008 (Williams et al., 2008) to 5.3% in 6-year-old children (Cornish et al., 2013). This is quite similar to our control group (4.8%), but clearly lower than in the OMT group (30%).

4.3 | Nystagmus

Nystagmus is rare in the general population, but has been reported in several studies of children exposed in utero to opioids and/or benzodiazepines (Cornish et al., 2013; McGlone et al., 2014; Mulvihill et al., 2007). The study by Cornish and co-workers on 5-year-old children found a prevalence of nystagmus in the control group of 0.04% ($n=7887$), and 3.3% in the methadone-exposed group (Cornish et al., 2013). A case–control study (McGlone et al., 2014) reported a prevalence in 81 opioid-exposed infants of 11%. However, in this study, 73% of the children in the study group were exposed to more than one drug and only eight of the infants were exposed to methadone alone. In our study, three (4.8%) of the 63 OMT-exposed children had nystagmus in primary position, while additional seven had gaze-induced nystagmus. Nystagmus was more frequent in the methadone group compared to the buprenorphine group, almost reaching statistical significance ($p=0.06$).

4.4 | Visual fields

The difference in visual field between the OMT group and the control group in one quadrant in the right eye at only one of the testing centres (centre A) is regarded a random finding, although within statistical significance.

4.5 | Nicotine as a possible confounder

In the present study, 91% of the OMT women smoked during pregnancy, compared to only 3% in the control group. It is known that prenatal nicotine exposure is a risk factor for strabismus (Fernandes et al., 2015; Hakim & Tielsch 1992; Stone et al., 2006; Torp-Pedersen et al., 2010; Williams et al., 2008). A recent meta-analysis (Yang et al., 2019) including 4883 patients up to 17 years referred for visual assessment reported an association between maternal smoking during pregnancy and strabismus, with a pooled OR of 1.46 (CI: 1.32–1.60). Most of the studies in this review had adjusted for gestational age, birth weight and socio-economic status but other confounders, such as alcohol and drugs, were mostly not reported on.

The odds ratio for strabismus in our study (8.6, adjusted 6.4) is considerably higher, suggesting a strong relationship between prenatal OMT exposure and strabismus, although some of the effect may be attributed to nicotine. However, in the review above some of the studies lacked a clear definition of strabismus, and comparing the odds ratio in our study with the pooled odds ratio in the review may not be completely justified.

A systematic review from China and UK (Fernandes et al., 2015) has reported conflicting results on visual acuity and refractive errors following prenatal nicotine exposure. We cannot disregard smoking as a confounder on strabismus, visual acuity, and severe hypermetropia among the OMT- and nicotine-exposed children in our study.

4.6 | Impact of small-for-gestational-age (SGA)

The OMT-exposed group had a significantly higher prevalence of SGA than the controls. When adjusting for this, the OR for strabismus was nearly unchanged, and thus, SGA does not seem to have any separate effect on strabismus. Previous studies have conflicting results regarding the association between SGA and strabismus. In a Norwegian study by Lindqvist et al. (2008) on 58 adolescents born SGA at term, the authors found no increased prevalence of strabismus. The study by Williams et al. (2008) mentioned above reported SGA as a risk factor for divergent strabismus. However, there was a high overlap between SGA and nicotine exposure in this study, which leaves it uncertain if SGA is a separate risk factor for strabismus.

4.7 | The screening programme

Except for the child with bilateral amblyopia due to excessive hypermetropia, we were content to find that the national screening programme at the mother-and-child health care centres had discovered and referred all the OMT children with amblyopia. As far as we can ascertain, these children were adequately examined and treated, with glass correction and patching according to accepted practice.

4.8 | OMT with methadone or buprenorphine?

Importantly, we found highly significant differences between the methadone- ($n=20$) and buprenorphine-exposed ($n=43$) children. The methadone group had poorer visual acuity, a marked increased frequency of manifest strabismus (distance or near strabismus 55.0% vs. 18.6%), and a higher percentage of severe hypermetropia and nystagmus. The methadone-exposed children had significantly smaller head circumference at birth than the buprenorphine exposed; otherwise, the two OMT groups were comparable with respect to demographics and exposure to polydrug use, alcohol and tobacco. We are not aware of other studies comparing *long-term* visual outcome of the two drugs used in OMT.

One recent systematic review and two cohort studies compared the prevalence of neonatal abstinence

syndrome (NAS) and foetal growth outcomes in neonates exposed to methadone vs. buprenorphine and found that buprenorphine was associated with a more favourable outcome regarding both NAS, preterm birth, head circumference, and birth weight (Christianson et al., 2021; Suarez et al., 2022; Welle-Strand et al., 2013). In line with these data, our methadone-exposed children had smaller head circumference at birth and the results show that buprenorphine is associated with a clearly improved outcome than methadone also when it comes to long-term visual parameters.

4.9 | Strengths and limitations

Major strengths of our study are a relatively large sample size, a high attendance rate in a geographically based population of OMT-exposed children, and an age- and gender-matched control group.

Previous studies in this field have raised doubt about a possible causal relationship between prenatal OMT exposure and adverse visual outcome, due to the high prevalence of polydrug use in OMT pregnant women (Hemmati et al., 2022; Midtlyng & Høiseth, 2016). The majority of the OMT women in this study were closely monitored during pregnancy (including regular urine analyses), in line with the national follow-up programme.

As opposed to other countries, Norway has a law that protects the foetus; if any illicit drug use is considered to harm foetal health; the mother will be treated in an inpatient clinic, either voluntarily or under duress. Of additional importance is that most OMT women in Norway (85%–90%) are already in OMT before they become pregnant (Odsbu et al., 2021). Taken together, this may explain the lower prevalence of polydrug use (21%) and alcohol (8%) in this study compared to previous studies. At the same time, we are aware of the limitations related to retrospective data collection on polysubstance use.

An additional strength in our study is that the ophthalmologists and optometrists, doing all the visual assessments, were blinded to which group the children belonged to, thus minimizing any interpretation bias of outcomes.

Three different optometrists did the examinations. This may represent a weakness related to interpersonal differences in the assessments. However, we had a detailed, common examination protocol at both study locations and held regular meetings during the patient inclusion period to minimize these problems.

The control group in our study did not match on maternal smoking and mother's education level. The prevalence of smoking during pregnancy in Norway is low (2.8%–12%) (Nordeng & Jettestad, 2019), making it difficult to obtain a representative control group of smoking mothers.

4.10 | Clinical implications

To our knowledge, this is the first study to assess long-term visual function in a relatively large group of children prenatally exposed to OMT (methadone or buprenorphine) with limited exposure to other drugs and alcohol.

Of particular clinical importance is the high prevalence of strabismus and/or nystagmus in the OMT-exposed children in this study. It is likely that impaired oculomotor function has an impact on school performance, motor, and social skills (Fernandes et al., 2015; Feuillade et al., 2023; Read, 2015), which may add to the burden of neurocognitive challenges often found in these children.

Our results point clearly to a favourable visual outcome in the buprenorphine-exposed group compared to the methadone-exposed group. This is a major finding of this study and in our opinion of clinical importance. It supports the recommendation in the Norwegian guidelines that buprenorphine should be the drug of choice in OMT treatment in pregnancy.

Our study emphasizes the importance of informing women in OMT about the risk of visual impairments in the offspring when exposed to OMT medication and the additive risk related to polydrug exposure, alcohol, and nicotine. When planning for pregnancy, we suggest a stronger advice towards buprenorphine than given in the existing Norwegian guidelines, even if it involves a shift in medication. To minimize the drug exposure burden to the foetus, we suggest a supportive attitude towards women's desire to attend residential opioid tapering therapy.

Finally, our findings emphasize the need for comprehensive follow-up of these children, in particular regular and thorough visual assessment from infancy through school age. If visual impairment or any other significant visual problems are encountered, referral to a special education professional, in addition to the ophthalmologist, should be considered, to achieve the best possible educational and social outcome.

5 | CONCLUSION

The findings in our study suggest a direct opioid-related adverse effect on the foetal developing visual system, causing a high risk of long-term abnormal visual outcomes. The in utero OMT-exposed children had a significantly higher prevalence of strabismus and nystagmus, as well as lower visual acuity and accommodation amplitude than the controls. Tobacco exposure is a likely confounder, at least for the increased risk of strabismus. Buprenorphine exposure was clearly associated with more favourable results than methadone exposure on most visual outcome measures.

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