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Ophthalmic Outcomes in Children Exposed to Opioid Maintenance Treatment in Utero: A Systematic Review and Meta-Analysis

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Abstract:	Opioid use disorder is a significant global issue. As the rates of opioid use in women of childbearing age and pregnant women increase, it is crucial that the adverse neonatal outcomes of prenatal exposure are investigated. Whilst general health, cognitive, and neurodevelopmental outcomes have been studied in this population, prospective, controlled, longitudinal research into the ophthalmic outcomes of in utero opioid exposure is lacking. The research done provides reasons to believe that there is an association between prenatal exposure and future risk of abnormalities in visual functioning. This systematic review and meta-analysis analysed studies that measured eye abnormalities in infants or children exposed to opioid maintenance therapy in utero and compared them to non-opioid exposed controls. After considering the clinical findings, limitations of the studies, confounding factors, and quantitative analysis, a causal relationship between in utero opioid exposure and future eye abnormalities could not be confirmed. The implications of the findings and their clinical relevance, in addition to identified gaps for future research are also discussed in this paper.
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Title: Ophthalmic Outcomes in Children Exposed to Opioid Maintenance Treatment in Utero: A Systematic Review and Meta-Analysis

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Highlights

- The association between prenatal opioid maintenance therapy exposure and ophthalmic outcomes is unclear

- Some evidence suggests the presence of visual abnormalities in children prenatally exposed to OMT compared to non-exposed controls

- Current data is not enough to conclude a causal relationship

- Longitudinal research is needed to investigate the link between opioid maintenance therapy in utero and ophthalmic outcomes

Abstract

Opioid use disorder is a significant global issue. As the rates of opioid use in women of childbearing age and pregnant women increase, it is crucial that the adverse neonatal outcomes of prenatal exposure are investigated. Whilst general health, cognitive, and neurodevelopmental outcomes have been studied in this population, prospective, controlled, longitudinal research into the ophthalmic outcomes of in utero opioid exposure is lacking. The research done provides reasons to believe that there is an association between prenatal exposure and future risk of abnormalities in visual functioning.

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1. Introduction

Opioids refer to the opiate morphine, which is the natural derivative of the opium poppy *Papaver somniferum*, semi-synthetic agents such as buprenorphine and diamorphine or heroin, and synthetic derivatives such as fentanyl and methadone. They act mainly on mu, delta and kappa G-protein coupled receptors found throughout the central nervous system and the peripheries. Opioids remain the most significant drugs for analgesia, but they also have euphoric and consciousness altering effects that make them subject to abuse (Pathan and Williams, 2012).

Opioid use disorder is the problematic pattern of opioid use with a psychological and physical inability to cease its consumption regardless of the harm induced (Mactier and Hamilton, 2020). Its diagnostic criteria are outlined in the DSM-5 based on 11 key symptoms, which characterise opioid use disorder by an excessive desire for and amount of time spent using and obtaining opioids, signs of tolerance or withdrawal, and changes in behaviour and social activities (American Psychiatric Association, 2013). It is a significant global issue, with 66% of deaths being attributed to opioid use in 2017, and reports of its use in 57.8 million people in 2017-2018 (UNODC, 2020). Opioid use disorder is particularly concerning in pregnant women and women of childbearing age, and it was reported that of the 5.4% of pregnant women in the US who misused drugs in 2018, 0.9% misused opioids (Mactier and Hamilton, 2020). In the UK, approximately 30% of opioid users are women, and 55% of drug misusing pregnant mothers were thought to misuse opioids in Scotland in 2010 (Baldacchino et al., 2014). Uncontrolled substance use in pregnancy has biopsychosocial adverse outcomes: increased risk of intrauterine growth restriction, preterm labour, neonatal death, and maternal depression, in addition to higher involvement in high-risk behaviours, imprisonment, and guardianship conflicts (American Society of Addiction Medicine, 2017). Untreated opioid use increases

obstetric risks such as septicaemia, bleeding in the last trimester, and foetal distress by 6 times (Minozzi et al., 2020).

Unfortunately, there are many factors that could discourage pregnant women from seeking treatment for substance use disorder such as fear of losing parental control or a relationship, lack of familial support, inability to access treatment, or a lack of trust in the efficacy of treatment (UNODC, 2016).

A holistic prenatal care approach for pregnant women is critical – screening for substance use, reduction in using opioids for analgesia, more STI and ultrasound testing, and the involvement of relevant services including family and addiction therapy (American Society of Addiction Medicine, 2017). In terms of the pharmacological approach to treating opioid dependence in pregnancy, the regimen must balance the risk of withdrawal from prescription medicine with the risk of relapse to illicit drug use (NICE, 2007). The current guidelines for the pharmacological treatment are to undergo opioid maintenance therapy (OMT) with the long-acting opioids methadone or buprenorphine (World Health Organization, 2014). The ultimate objective is to 'progress from maintenance to detoxification and then abstinence' (NICE, 2007). Methadone hydrochloride is a synthetic full opioid agonist usually given as a 1 mg/mL oral solution daily, with a recommended starting dose of 10-40 mg/day, titrated up to 60-120 mg/day in OMT (NICE, 2007). The dosage is adjusted clinically based on withdrawal symptoms such as cramps, sleeplessness, and nervousness, and the risk of prolonging the QTc interval (American Society of Addiction Medicine, 2017). Buprenorphine is a semi-synthetic partial opioid agonist, available sublingually and as prolonged-release injections, with a recommended starting dose of 4 mg/day, titrated up to 12-24 mg/day for maintenance (NICE, 2007). It is preferred as a mono-product rather than combined with naloxone in pregnancy to prevent in utero naloxone exposure and subsequent withdrawal. Compared to methadone, it has a higher risk of misuse in pregnancy, and is associated with a lower risk of overdose due

to its partial action on the mu receptor (American Society of Addiction Medicine, 2017). It is also important to note that a transition to buprenorphine should not be made for a pregnant woman already undergoing methadone maintenance due to a high risk of sudden withdrawal (American Society of Addiction Medicine, 2017). In terms of the benefits of OMT, it is established that both maternal and neonatal outcomes are improved in opioid-dependent pregnant women who enrol in methadone therapy compared to those who do not (NICE, 2007). For the mother, methadone therapy facilitates access to antenatal care and lowers the risk of premature delivery, and for the foetus, it promotes growth and lowers the risk of death in utero (Boardman, Mactier, and Devlin, 2021). Additionally, enrolling in methadone maintenance treatment allows greater parental control and chances for more stability in childcare (Wilson, Desmond, and Wait, 1981). Buprenorphine maintenance therapy has also proven to be more advantageous compared to placebo or no therapy (NICE, 2007). When comparing methadone and buprenorphine for maintenance treatment, some studies have suggested differences between their therapeutic outcomes, but a recent Cochrane review by Minozzi et al. (2020) concluded that they do not significantly differ in their efficacy and safety for use in pregnant women.

Despite the benefits of opioid maintenance treatment, both methadone and buprenorphine cross the placenta, and the adverse effects of prenatal exposure on the foetus need to be considered. Nekhayeva et al. (2005) demonstrated that methadone passively diffuses across the placenta and suggested that its disposition and metabolism in utero impact the opioid concentration in foetal circulation, thus affecting the severity of neonatal abstinence syndrome. Neonatal abstinence syndrome (NAS) or neonatal opioid withdrawal syndrome (NOWS) is the most imminent opioid-induced outcome in infants and occurs due to the abrupt cessation of prenatal opioid exposure at birth (Kaltenbach and Jones, 2016). It is identified by signs of excessive CNS irritability such as hypertonia and insomnia, digestive system abnormalities, and

autonomic reactions such as sweating, and tends to present in the first 2 to 3 days after birth (Kaltenbach and Jones, 2016). NAS is reported in about 50% of the infants exposed to methadone in utero (Baldacchino et al., 2014), and is currently treated by oral morphine and methadone, with buprenorphine also being under investigation (Kaltenbach and Jones, 2016). Despite the risks of NAS, it is advisable that pregnant women undergo opioid maintenance therapy rather than opioid detoxification, as the risks of relapse and harm with detoxification have been highly detrimental compared to OMT (World Health Organization, 2014). The other outcomes associated with prenatal opioid exposure include increased general health problems and hospitalisation rates, neurodevelopmental deficits, educational deficits, and visual abnormalities. In a retrospective study of children with OMT exposure, Kelty and Hulse (2017) reported that the mortality rate in methadone-exposed children was 1.6 compared to 0.2 in non-exposed children per thousand person years. A study by Skurtveit et al. (2019) reported a higher chance of hospitalisation for children exposed to maintenance therapy by the age of 3, especially for diseases of infectious, digestive, skin or subcutaneous tissue origin. In terms of neurodevelopment, a meta-analysis conducted by Monnelly et al. (2018) revealed that 6 months old infants with prenatal methadone exposure had lower mental (MDI) and psychomotor (PDI) development indices. They also suggested that there may be long-term implications for these children, as most of the behavioural and cognitive outcomes seemed to persist at 2 years. Yeoh et al.'s (2019) meta-analysis also concluded a negative impact of prenatal opioid exposure on children's cognitive functioning, which persisted through school age and showed a significant discrepancy compared to their peers. In an older age group, Nygaard et al. (2017) demonstrated that drug exposed youths aged 17-22 have much worse cognitive and motor abilities compared to non-drug exposed controls. In terms of educational outcomes, Lee et al.'s longitudinal study revealed that methadone exposed children had lower readiness for school entry at 4.5 years old (2019a) and were behind in all academic measures besides physical education at 9.5 years

compared to their non-exposed peers (2019b). The observation that neurodevelopmental impairments related to prenatal opioid exposure persist over time has been made in various studies and the long-term consequences need to be investigated further.

Among these outcomes, the ophthalmic consequences have been investigated least. Ghetau, Bloor, and Firth (2009) have attributed this to the lack of research exploring ocular abnormalities in this population to the low interest and attendance of drug-using mothers for the visual assessments, and their anxiety in revisiting addiction services, especially if they have chosen to withhold their drug use history from a new partner, for example. Additionally, it is challenging to make associations between observed visual abnormalities and prenatal opioid exposure due to the extensive poly-drug use present in this population and social stigmas that make underreporting more likely (Mulvihill et al., 2007). However, there are reasons to believe that the visual functioning in opioid exposed children could be compromised. The majority of studies conducted have measured visual evoked potentials (VEPs) in this population, which are an effective measure of afferent visual integrity and maturity. A normal VEP response relies on an unimpaired path from the retina via the optic chiasm to the visual cortex (McGlone, Hamilton, and Weaver, 2009). Some case studies in opioid exposed children have reported delayed, absent, or abnormal VEPs (McGlone et al., 2008; Hamilton et al., 2010). Other studies have clinically assessed these children or retrospectively reviewed their case notes, and have reported finding nystagmus, strabismus, and/or reduced visual acuities (Dominguez et al., 1991; Rosen and Johnson, 1982; Gill et al., 2003; Mulvihill et al., 2007; Gupta et al., 2012; Tinelli et al., 2013; Mactier and Hamilton, 2020). However, there remains a lack of prospective, longitudinal research for ophthalmic abnormalities in these children with comparisons to non-exposed children. Without long-term observance of these children, it is uncertain whether the visual abnormalities recorded are transient or the consequence of a teratogenic effect (McGlone et al., 2008). Additionally, more research is needed to explain the findings that have been

reported, and the pathways by which opioids could impair visual pathways, but some hypotheses have been made. Animal studies have shown that methadone can bind to both brain and ocular tissue, and its prenatal exposure can lead to reductions in acetylcholine, dopamine, noradrenaline, and serotonin levels in the brain (McGlone et al., 2013a). Mactier and Hamilton (2020) have suggested that the pattern of ophthalmic findings alludes to a teratogenic impact on the primary visual area (V1), which in turn hinders the process of binocular fusion and can present as nystagmus or strabismus, for example. Depending on how long and how intense the visual deprivation is, early impairments in binocular vision result in varying severities of exotropia, esotropia, and amblyopia (Hamilton et al., 2010). Rottach et al. (2002) have suggested three possible areas of the brain that could be impacted by opioids to result in visual or oculomotor disturbances. Firstly, the cerebellum, because of the presence of mu opioid receptors, and the types of eye movements generated there, such as the vestibulo-ocular reflex and smooth pursuit (Rottach et al., 2002). In line with this, Mulvihill et al. (2007) have hypothesised that nystagmus following prenatal drug exposure is a teratogenic effect that could be explained by impaired mu receptor binding in the cerebellum. Secondly, opioid-induced brainstem dysfunctions that can lead to slower saccadic movements and ocular flutter. Thirdly, and less likely, the medial vestibular nuclei, which could be impacted by opioids to cause downbeat nystagmus (Rottach et al., 2002). Opioids such as methadone would activate the mu opioid receptors on the vestibular nuclei, and this receptor activation would in turn impede neuronal differentiation during the infant's development (Hamilton et al., 2010). For electrophysiological findings, McGlone et al. (2013) have suggested that the impairments seen in visual evoked responses in prenatally drug exposed children are due to a teratogenic effect, rather than a result of reduced acuity.

Overall, there is a need to expand research and understanding on the consequences of opioid abuse in pregnancy, and the infants' developing visual functions (McGlone, Mactier, and

Weaver, 2009). Investigating this association is significant because it would allow more clarity in clinical practice for early detection, management, and potential treatments of visual abnormalities in this exposed, at-risk population (Cornish et al., 2013). Moreover, visual abnormalities in children are highly prevalent, but prenatal drug exposure is not normally assessed in studies as a possible aetiology (Auger et al., 2020). Ophthalmic surveillance is necessary in the exposed children to observe for later presentations of eye abnormalities and tend to their healthcare needs (Gupta et al., 2012). Building on this, the primary aim of this systematic review is to qualitatively collate, synthesise, and analyse the studies that have measured ophthalmic outcomes in infants or children who were exposed to opioid maintenance therapy in utero, and compared them to non-exposed infants or children. Thus, this review aims to determine whether there is a causal relationship between prenatal opioid exposure and an increased risk of future visual abnormalities.

2. Methods

2.1 Study Identification and Selection

This review was conducted according to the meta-analysis of observational studies in epidemiology (MOOSE) (Stroup et al., 2008), and the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines (Liberati et al., 2009). The following databases were searched until 19/03/2021: Web of Science (1900-2021), PubMed (1978-2021), Ovid (AMED (1985-2021), Embase (1974-2021), ERIC (1965-2021), HMIC (1979-2021), Medline (1946-2021), MIDIRS, APA PsycInfo (1967-2021)), Scopus (1973-2021), APA PsycNet (2011-2021), and the search engine Google Scholar. In order to determine the search terms, the PICO was outlined: infants or children aged 0-18 years old (population), exposure to opioids in utero (intervention), comparison to non-opioid exposed infants or children (comparison), and ophthalmic abnormalities (outcome). Search terms and synonyms related to children and ophthalmic abnormalities were combined with opioids using Boolean operators, and the following search entry was performed in each database: (infant OR bab* OR newborn* OR toddler* OR child* OR teen* OR youth* OR adolescen*) AND opioid* AND (prenatal* OR antenatal* OR antepartum* OR pregnan* OR utero* OR foetal* OR fetal*) AND (eye* OR visual* OR vision* OR ocular* OR ophthalm* OR optic* OR nystagmus* OR strabismus* OR acuity* OR potential* OR VEP* OR sensorimotor* OR stereovision* OR hypermetropia* OR hypotropia* OR squint* OR esotropia* OR exotropia* OR blind* OR amblyopia* OR refractive* OR glaucoma* OR cataract* OR macula*). The inclusion of comparison groups in the search entry was refrained from to ensure that all relevant studies appeared in the search results, and they were then manually checked for the presence of control groups. No limitations were set on the language, country, or dates of publication. There were no limitations on the

study type either, such that prospective and retrospective trials and case studies were all examined for eligibility.

In order to ensure completeness of the results, the following non-Western databases were also searched: African Index Medicus, Chinese Medical Journal (17 results), and the Latin American and Caribbean Health Sciences Literature (9 results), but none of the publications were relevant to the PICO. The Indian medical database could not be accessed via any browser or server location. Besides extensive database searching, all other efforts were made to gather relevant publications to be considered. Researchers in the field of addiction medicine were contacted via e-mail to retrieve all possible literature on the topic and gain contact with other active researchers. Additionally, a backward search technique was employed to look for studies done by the same authors, and a snowballing technique was conducted to find more publications from the relevant studies' references.

The PRISMA chart depicted in Figure 1 outlines how the search results were screened, and the number of records that were eligible for inclusion. The search results from Web of Science, PubMed, Ovid, Scopus, and APA PsycNet were all imported into the reference management software EndNote. The software's 'find duplicates' feature was used to detect multiple copies of the same reference, and a manual check for duplicates was also conducted afterwards as the feature is not 100% sensitive. Following that, the titles and abstracts of the results were screened and checked for relevance to the research question. The remaining records were then examined in line with the eligibility criteria, and meta-analyses, systematic reviews, and studies with no control groups were excluded. One study by O'Connor et al. (2021) did match the eligibility criteria, and efforts were made to contact the researchers via e-mail and ResearchGate, but access to the full text was not possible. The Google Scholar search engine was also searched for publications, leading to the inclusion of 2 new articles.

2.2 Eligibility Criteria

The inclusion criteria were set according to the PICO: studies of infants or children aged 0-18 years old, with prenatal exposure to opioids, presence of non-opioid exposed control groups, and measurements of ophthalmic outcomes. The exclusion criteria were studies without human subjects, literature reviews, systematic reviews, meta-analyses, studies without opioids as the primary prenatal exposure measure, studies with no control groups, and studies without ophthalmic consequences as the main outcomes. Ophthalmic outcomes include any diseases pertaining to the eyes, by anatomical site or known infantile or childhood pathologies, visual disturbances, oculomotor disturbances, visual evoked potentials, latencies and visual pathway disturbances.

2.3 Quantitative Analysis

Meta-analytic calculations were employed to assess the impact of prenatal opioid exposure (methadone, buprenorphine) on ophthalmic outcomes in infants. It was possible to extract means (M) and standard deviations (SD) of scores on ophthalmic outcome measures (VEP latencies and visual attention) from five studies included in the current review (Whitham et al., 2010, 2015; Melinder et al., 2013; Konijinberg & Melinder, 2012; Konijinberg & Melinder, 2015). These were inserted in the Comprehensive Meta-analysis version III software (Borenstein, 2013). Sample sizes of prenatally exposed infants and control groups were also extracted. A standardised mean difference (SMD) effect size was computed as the pooled studies utilised different instruments to test ophthalmic outcome measures (Higgins & Green, 2011). An effect size of 0.8 would have implied a large effect size, an effect size of 0.5 would have implied a medium effect size, and an effect size of 0.2 would have implied a small effect

size according to Cohen's benchmark criteria (Cohen, 1988). Statistical significance was set at $p<0.05$ (Cohen, 1988). Heterogeneity was assessed by I2 and Q statistics. A random effect model was preferred over a fixed effect model to address heterogeneity between the pooled studies. Sizes of checkerboard patterns (48' and 69' of retinal arc) were also extracted and utilised to conduct subgroup analyses for studies investigating VEP latencies in offspring exposed prenatally to opioids (Whitham et al., 2010, 2015). The sample tested by Whitham et al. (2015) consists of a subsample of the participant cohort tested by Whitham et al. (2010). However, participants were tested at different time points (4 and 36 months). Thus, age (in months) at the time of measurement was extracted from each study and inserted in the CMA software as a moderator variable. Subgroup analyses were therefore conducted by computing effect sizes (SMD) for each time point level.

2.4 Publication Bias

Publication bias for the studies pooled for the meta-analysis was assessed by visually inspecting funnel plots (see supplementary figures 1, 2, 3, 4) and by computing Egger's test results (Egger et al., 1997). This was done in order to minimize subjectivity related to the visual inspection of funnel plots. A statistically significant ($p<0.05$) Egger's test result would have indicated the presence of publication bias.

2.5 Qualitative analysis

A narrative-synthesis methodology (Dixon-Woods et al., 2005) was utilized to summarize and describe the results of studies investigating ophthalmic outcome measure that were not pooled for the meta-analysis due to the lack of available statistical data.

2.6 Quality Assessment

Quality assessment of the included articles was performed using the Scottish Intercollegiate Guidelines Network (SIGN) cohort study methodology checklist (Sleith, 2012), and the answers to each question are outlined in Table 3. Question 2.4 is for comments or additional notes for each study, and the answers to these are described throughout the discussion section of this review and not included within the table. The papers were assessed as high quality (++), acceptable (+), or unacceptable (0), and the risks of bias were evaluated. A high-quality study has little or no risk of bias with results that are unlikely to change with future research, an acceptable study has some flaws and is susceptible to change, and an unacceptable study is significantly flawed and to be rejected (Sleith, 2012). It is important to note that the quality score for Hamilton et al.'s (2020) study remains inconclusive because the majority of the required information was not available. The authors were contacted, and it was revealed that the long-term follow-up data for this cohort is yet to be published, and the measurements are undergoing analysis. Nevertheless, their publication was included in this review because it is in line with the PICO.

3. Results

The database and Google Scholar searches resulted in 2,777 findings, which were screened for duplicates to yield 2,014 references to be screened for relevance. After checking the titles and abstracts, 1,983 results were excluded for the following reasons: not studies of human subjects, not of infants or children, not opioid related, not related to exposure in utero, no control groups, and/or no measures of ophthalmic outcomes. This led to 13 articles that were examined for eligibility and cross-checked with each other for duplicates, resulting in a total of 9 articles to be included in this review. Not included in Figure 1, the Chinese Medical Journal and Latin American and Caribbean Health Sciences Literature searches yielded 17 and 9 results, respectively, but as mentioned previously, none were in line with the PICO.

3.1 Characteristics of Included Studies

A total of 9 cohort studies with varying designs were included in this review: 2 open-label non-randomised flexible-dosing longitudinal studies, 1 mixed factorial design experiment, 1 between-subject factorial design experiment, 3 prospective cohort studies, and 2 longitudinal cohort studies. They were conducted in Australia, Canada, Norway, or Scotland, with the earliest dating 2009 and the latest in 2020. In terms of cohort selection, the two McGlone et al. (2013a,b) and consequently Hamilton et al.'s (2020) papers studied the same samples. The two Konijnenberg and Melinder (2012, 2015) and Melinder, Konijnenberg, and Sarfi (2013) studies derived their drug exposed samples from a study by Bakstad et al. (2009). Additionally, Whitham et al. (2015) conducted a longitudinal study on their previously studied cohort (Whitham et al., 2010). Taking into account the sample numbers and considering them only

once by the highest group number from each related study, a total of 1,995 prenatally exposed children were compared to 782,042 non-exposed children for ophthalmic outcomes. The age group of the subjects ranged from 13 weeks to 10 years old. The demographic and sample characteristics of the studies are outlined in Table 1.

3.2 Quantitative Analysis

VEP Latencies – Methadone Exposed Infants vs Controls

Results of I2 and Q tests revealed substantial heterogeneity between the pooled studies (Q=9.47, p=0.02, I2=68.33), therefore justifying the choice of a random effect model over a fixed effect model. Visual inspection of the funnel plot (supplementary Figure 1) revealed the presence of publication bias. This was confirmed by a statistically significant ($p<0.05$) Egger's test result. A non-significant effect size (SMD) of 0.253 was detected in favor of non-exposed controls compared to methadone exposed infants (p=0.40, z= 0.83) (see Figure 2).

Subgroup analyses did not reveal any effect of the checkerboard patterns' size on VEPs. For 48' checks, a non-significant effect size (SMD) of 0.285 was identified in favor of non-exposed controls compared to methadone-exposed infants (p=0.60, z=0.51). For 69' checks, a non-significant effect size (SMD) of 0.175 was identified in favor of non-exposed controls compared to methadone-exposed infants (p= 0.73, z=0.33) (see Figure 3).

A significant effect was instead detected for time point levels on VEPs. Specifically, methadone exposed infants who were tested at 4 months displayed significant prolonged VEP latencies compared to non-exposed controls in response to both 48' and 69' checkerboard

patterns (SMD=0.728, p<0.0001, z=3.62). On the other hand, no differences in VEP latencies were identified between methadone exposed infants who were tested at 36 months and non-exposed controls (SMD=-0.351, p=0.22, z=-1.20) (see Figure 4).

VEP Latencies – Buprenorphine Exposed Infants vs Controls

Results of I2 and Q tests did not reveal the presence of heterogeneity between the pooled studies (Q=1.54, p=0.67, I2=0.00). Therefore, sensitivity analyses were conducted by employing both fixed and random effect models. No results differences were detected between the two models. Visual inspection of the funnel plot (supplementary Figure 2) did not reveal the presence of publication bias. This was confirmed by a non-significant (p=0.13) Egger's test result. A non-significant effect size (SMD) of -0.037 was detected in favor of buprenorphine exposed infants compared to non-exposed controls (p=0.80, z= -0.24) (see Figure 5).

Subgroup analyses did not reveal any effect of the checkerboard patterns' size on VEPs. For 48' checks, a non-significant effect size (SMD) of -0.101 was identified in favor of buprenorphine exposed infants compared to non-exposed controls (p=0.63, z=-0.47). For 69' checks, a non-significant effect size (SMD) of 0.027 was identified in favor of non-exposed controls compared to buprenorphine exposed infants (p=0.89, z=0.12) (see Figure 6).

No time point effect was detected on VEPs. Specifically, a non-significant effect size (SMD) of -0.291 was detected in favor of buprenorphine exposed infants compared to non-exposed controls tested at 36 months (z=-1.03, p=0.30). Furthermore, a non-significant effect size (SMD) of 0.065 was detected in favor of non-exposed controls compared to buprenorphine exposed infants tested at 4 months (z=0.36, p=0.71) (see Figure 7).

VEP Latencies – Buprenorphine Exposed Infants vs Methadone Exposed Infants

Results of I2 and Q tests revealed small heterogeneity between the pooled studies (Q=3.82, p=0.28, I2=21.47). Visual inspection of the funnel plot (supplementary Figure 3) did not reveal the presence of significant publication bias. This was confirmed by a non-significant (p=0.06) Egger's test result. Methadone exposed infants displayed significant prolonged VEP latencies compared to buprenorphine exposed infants (SMD= 0.392, z=2.00, p<0.05) (see Figure 8).

Subgroup analyses revealed an effect of the checkerboard patterns' size on VEPs. Specifically, methadone exposed infants displayed prolonged VEP latencies to checks of 48' compared to buprenorphine exposed infants (SMD=0.510, z= 2.11, p<0.05). However, no VEP differences between methadone exposed infants and buprenorphine exposed infants were detected in response to 69' checks (SMD=0.22, z=0.54, p=0.58) (see Figure 9).

Additionally, methadone exposed infants displayed prolonged VEP latencies to both 48' and 69' checkerboard patterns in comparison to buprenorphine exposed infants when tested at 4 months (SMD=0.622, z=3.06, p<0.005). However, no differences in VEP latencies were detected between methadone exposed infants and buprenorphine exposed infants when tested at 36 months (SMD=-0.055, z=-0.17, p=0.85) (see Figure 10).

Visual Attention – OMT Exposed Infants vs Non-Exposed Controls

Results of I2 and Q tests did not reveal the presence of heterogeneity between the pooled studies (Q=0.69, p=0.70, I2=0.00). Therefore, sensitivity analyses were conducted by employing both fixed and random effect models. No results differences were detected between the two models. Visual inspection of the funnel plot did not reveal the presence of publication bias (Supplementary Figure 4). This was confirmed by a non-significant (p=0.09) Egger's test result. A non-significant effect size (SMD) of -0.30 was detected in favor of OMT (methadone and buprenorphine) exposed infants compared to non-exposed controls (p=0.08, z= -0.30) (see Figure 11).

3.3 Qualitative Analysis

The ophthalmic and visual functions measured across the studies include visual evoked potentials (binocular, flash, pattern onset), eye movements in response to stimuli, visual selective attention, comprehensive clinical visual assessments derived from the Atkinson battery, Cardiff cards and retinoscopy, and eye hospitalisation records. Some neuropsychological subtests related to vision were also included: visual attention from NEPSY, perception from Bender Gestalt II, and the attention problems subscale from the Child Behaviour Checklist (CBCL). Konijnenberg and Melinder (2012) tested the mirror neurone system by measuring gaze arrival at the area of interest using a human versus mechanistic design. They reported that the opioid exposed cohort took a longer time to shift gaze in the human condition compared to the controls and found no differences in the mechanistic condition. The opioid group's gaze shifting was reactive, with a mean timing score of -37.73, SD = 208.56, whilst the control group's gaze shifting was predictive, with a mean timing score of 181.47, SD = 228.65. Then, Melinder, Konijnenberg, and Sarfi (2013), also measured gaze data to link smooth pursuit and visuomotor functioning. They found no significant difference between the opioid and control groups in the slow-moving condition, but a significant difference was reported in the fast-moving object condition. This difference disappeared when controlling for maternal education and the child's birth weight (Melinder, Konijnenberg, and Sarfi, 2013). McGlone et al. (2013a) measured visual evoked potentials in methadone exposed infants and reported smaller ((27 μV (interquartile range 17–42) vs 39 μV (interquartile range 28–67)), and less typical VEPs, in addition to a lower likelihood of presenting the P1 (21% vs 48%, X2=11.6, p = .001) and N2 (odds ratio = 0.27, CI 0.09 – 0.84) components of the response

compared to the controls. In their other study, with a retention rate of 52%, McGlone et al. (2013b) demonstrated that 40% of their methadone exposed group failed the visual assessment criteria compared to 8% of the controls, with the ophthalmic abnormalities including nystagmus, strabismus, reduced visual acuity and maturity. The relative risk of an impaired visual assessment in the methadone exposed infants was reported as 5.1 (CI 1.3 – 20, p = 0.02) (McGlone et al., 2013b). Assessing the same cohort at the ages of 8-10, Hamilton et al. (2020) reported failed visual criteria in 56% of the methadone exposed sample compared to 18% of the controls, with the same types of ophthalmic abnormalities mentioned previously. Finally, Auger et al. (2020) observed drug-exposed infants and their hospitalisation rates for eye disorders and reported that prenatal opioid exposure increases the risk of any eye disorder by 1.48 times, and of ocular muscle disorders by 3.15 times. Descriptive information about the aims, methodology, and results of each study are summarised in Table 2.

4. Discussion

4.1 Findings of the Studies

The findings of the studies and the main confounding variables are discussed categorised by ophthalmic abnormalities detected clinically or anatomically, electrophysiological findings via visual evoked potentials, and neurodevelopmental findings related to visual functioning.

Starting with Auger et al. (2020), generally, they established that in utero drug exposure posed a 1.50 (CI 1.18-1.90) risk of eye disorders, whilst pre-pregnancy exposure posed a 1.09 risk (CI 0.86 – 1.38). Amongst cocaine, cannabis, and other substances, opioid exposure in utero (including NAS) was most highly associated with the risk of hospitalisation for eye disorders in childhood. A 1.48 times risk was reported for disorders on any site, including the eyelid, conjunctiva, cornea, lens, retina and the vitreous body, and a 3.15 times risk for ocular muscle disorders. They only collected information on eye abnormalities severe enough for hospitalisation, and in all parts of the eye, they found that opioid exposure was most associated with strabismus (Auger et al., 2020). These findings are consistent with Uebel et al.'s (2015), who reported that children with NAS have higher hospitalisation rates compared to those without and showed 12 times increase in the likelihood of attendance for strabismus and nystagmus. McGlone et al.'s (2013b) clinical evaluation of their cohort also revealed that of the 32 drug-exposed infants who failed the visual assessment, 63% had strabismus, 28% horizontal nystagmus, 56% reduced visual acuity, and 6% delayed visual maturity. They stated a relative risk of 5.1 for an impaired visual assessment and suggested a causal relationship between prenatal drug exposure and ophthalmic abnormalities in children, such that 80% of visual impairments could be diminished if in utero exposure was avoided (McGlone et al., 2013b). Moreover, in the follow-up of this cohort, Hamilton et al. (2020) demonstrated that of the 50 drug-exposed children who failed the visual criteria, 94% had strabismus, 60% poor distance acuity, 28% poor stereovision and 6% poor near vision. These ophthalmic abnormalities have been reported previously in other opioid exposed samples. 29% of Gill et

al.'s (2003) opioid exposed sample either presented with or had a history of intermittent strabismus. In a case review study of 14 prenatally drug exposed children by Mulvihill et al. (2007), of which 12 had opioid exposure, 100% had horizontal nystagmus, 50% strabismus, 21% astigmatism, and 14% bilateral optic nerve hypoplasia. Additionally, at least 50% were reported to have delayed visual maturity, and the mean visual acuity was 20/80. A larger case review by Gupta et al. (2012) of 25 opioid exposed children revealed 100% nystagmus, 64% strabismus, 56% bilateral farsightedness, >36% delayed visual maturation, and 8% bilateral optic nerve hypoplasia. Moreover, in Hamilton et al.'s (2010) retrospective case study of 20 infants with prenatal methadone exposure, the most reported visual abnormalities were 95% reduced acuity, 70% nystagmus, 50% delayed visual maturation, which resolved by 6 months, 35% strabismus, 30% refractive errors, and 10% abnormal fundal exams. Studies that have investigated the long-term visual impacts of prenatal opioid exposure are rare. Cornish et al. (2013) reported that at the age of 5 years, their drug exposed group had a 14% prevalence of strabismus compared to 2.8% in the controls, and a 3.3% prevalence for nystagmus compared to 0.004% in the controls. Eye abnormalities in opioid-exposed children are also reported in some studies that did not primarily measure ophthalmic abnormalities. Rosen and Johnson (1982) followed up children of methadone-maintained mothers until 1.5 years old, and reported nystagmus and strabismus amongst their neurobehavioral findings. Nelson et al. (1987) suggested an increased risk of strabismus in children prenatally exposed to drugs. 24% of the 29 infants that underwent ophthalmological examinations had strabismus; and apparently their mean dose of methadone exposure was higher than those without (Nelson et al., 1987). Kivistö, Tupola, and Kivitie-Kallio's (2015) prospective study of 102 buprenorphine exposed children reported nystagmus, optic atrophy, and strabismus in 11%. Additionally, Kelty and Hulse's study (2017) reported the rate of hospital visit for eye causes was 0.9 for methadone, 0.2 for buprenorphine, and 1.0 for naltrexone, compared to 0.4 for their control group. It seems that

nystagmus and strabismus are among the most reported findings in the opioid exposed cohorts. The pathways for drug-induced infantile nystagmus or strabismus are not extensively understood, but there are possible explanations. One suggestion is that infantile nystagmus results from visual deprivation, such that the sensory component is delayed compared to oculomotor development (Papageorgiou, McLean, and Gottlob, 2014). Another proposal is that prenatal opioid exposure hinders cell maturation and promotes abnormal mu opioid receptor binding in the medial vestibular nucleus, which is one of the main components of stabilising horizontal gaze (Hamilton et al., 2010). Mulvihill et al. (2007) hypothesized that the nystagmus after prenatal drug exposure is due to abnormal binding in the developing cerebellum. Moreover, McGlone et al.'s (2013b) study suggested that the high rate of strabismus in addition to latent nystagmus may signify compromised development of binocular fusion in the infants.

In terms of visual electrophysiological findings, they are helpful as they give insight into the integrity of the visual pathway and neural maturity (Whitham et al., 2010), and are more easily obtained than visual acuity measures in young children to test afferent visual functioning (Whitham et al., 2015). VEP latencies quantify how fast information from a visual stimulus is processed and leads to the peak depolarisation of visual cortex neurones (Whitham et al., 2015). As shown by the meta-analytic findings reported in section 3.2, Whitham et al.'s study (2010) revealed longer P1 latencies for 4 months old methadone exposed infants compared to the buprenorphine and control groups, which persisted for checks of 48 minutes of retinal arc but not for 69 minutes after adjusting for covariates. They corrected for many confounding variables through multiple regression analyses, listed in Table 2, to determine which contributed to the P1 latencies in both 48' and 69' checks. The biggest contributors for both check sizes were older corrected age (age at testing + gestational age – 40 weeks) and maternal reported marijuana use, and poorer family income for checks of 48' only. Equipment was also included as a covariate because the original measurement apparatus was not available after a

certain point in the study. The main associations made in their study were: a) prenatal methadone and marijuana exposure may lead to delayed visual maturity supported by prolonged P1 latencies and b) buprenorphine may be better than methadone at the age of 4 months as shown by the VEP outcomes, which could be explained by their differing pharmacology or varying concentrations in foetal circulation (Whitham et al., 2010). In their follow-up study at 36 months, Whitham et al. (2015) did not find any significant differences in the P100 latencies across the methadone, buprenorphine, and control groups. The significant predictor found at analysis was head circumference for checks of 69', and the previously reported marijuana significance was not present anymore. They were unable to attribute visual outcomes to methadone or buprenorphine exposure alone, primarily due to the 58% loss to follow-up (Whitham et al., 2015). Upon comparing children who participated and those lost to follow-up, they reported that those assessed at 36 months had significantly longer P100 latencies at 4 months and inferred that they have delayed visual maturity compared to those lost to follow-up (Whitham et al., 2015). McGlone et al. (2013a) measured flash evoked potentials in 3-days-old infants and found less P1 (21% vs 48%) and N2 (38% vs 60%) components in the methadone exposed group compared to the controls. Moreover, they had smaller VEP amplitudes (27 μV vs 39 μV) and more immature responses. These differences remained after correcting for variables including illicit poly-drug use, and no dose-effect relationship between methadone dose and the latency or morphology of visual evoked responses was found. They stated that their data strongly shows a link between impaired visual development and prenatal methadone exposure, rather than concurrent illicit drug use. These findings are consistent with McGlone et al.'s pilot study (2008) of 21 methadone exposed 4-days-old infants, in which 5 VEPs were undetectable, and other exposed infants had low VEP amplitudes and atypical response waveforms; the latter became more typical after a week

(McGlone et al., 2008). In Hamilton et al.'s (2010) exposed cohort mentioned previously, 60% had abnormal visual electrophysiology results.

The 3 other studies included in this review investigated visual functioning from a neurodevelopmental perspective.

Konijnenberg and Melinder (2012) studied the mirror neurone system through tracking eye movements in 4-years-old prenatally opioid exposed children using a mixed factorial design. In line with their first hypothesis, they found that the opioid exposed group took longer to shift their gaze to the goal area of interest, and this persisted after controlling for maternal education. They categorised gazes with positive values as predictive, meaning the child looked at the area of interest before the object had reached, and negative values as reactive, meaning the child looked at the area only after the object had reached. The opioid group's gaze shifting was reactive, with a mean timing score of -37.73, SD = 208.56, whilst the control group's was predictive, with a mean timing score of 181.47, SD = 228.65 ($t(1,14) = 3.07$, $P = 0.008$, $d = 1.64$). Therefore, they confirmed reduced 'proactive goal-directed eye movements' in the opioid maintenance exposed group, but a causal relationship was not established due to the many confounding and possible alternative factors, such as social environment, nutrition and poly-drug exposure in the children (Konijnenberg and Melinder, 2012). For their secondary hypotheses, they also found impaired fine motor skills in the opioid exposed group, but unlike the gaze shifting score, these differences were not significant after correcting for maternal education (Konijnenberg and Melinder, 2012). In the next study, Melinder, Konijnenberg, and Sarfi (2013) explored whether visuomotor functioning relies on smooth pursuit rather than proactive goal-directed eye movements. The middle temporal visual cortex receives signals from the primary visual cortex and the processing of the information here is key to smooth pursuit (Melinder, Konijnenberg, and Sarfi, 2013). Eye movements were recorded in response to slow-moving and fast–moving object motion, and smooth pursuit was measured. There were

no differences between the exposed and non-exposed groups in response to the slow-moving presentation, but a significant difference was seen in the fast-moving condition. This difference persisted after controlling for maternal employment but diminished after controlling for maternal education and birth weight. Based on these results, they suggested that deviant smooth pursuit is linked to prenatal methadone or buprenorphine exposure, possibly due to reduced dopamine levels. Their hypothesis for the association between smooth pursuit and visuomotor abilities was supported, and a saccadic aetiology for impaired goal-directed eye movements was rejected. Additionally, they found a link between impaired attention and buprenorphine dosage (n = 8, r = -0.77, p = 0.02) (Melinder, Konijnenberg, and Sarfi, 2013). Finally, Konijnenberg and Melinder (2015) investigated whether the impairments in goal-directed eye movements and smooth pursuit can be explained by problems in visual attention in prenatally opioid exposed children. Visual selective attention was tested through spatial negative priming and eye movements were tracked. In terms of saccade latency, no significant differences were found between groups, but for the spatial negative priming effect, only 45% of the opioid exposed group showed it compared to 60% in the control group ($p > 0.05$), and this finding persisted after controlling for covariates. They suggested that opioid exposed children may find it more difficult to ignore unnecessary visual information, which can make it harder for them to have focused goal-directed eye movements (Konijnenberg and Melinder, 2015). Overall, as supported by the meta-analytic findings (section 3.2), visual attention may not be significantly impaired by prenatal opioid exposure.

4.2 Strengths and Limitations of the Systematic Review and Meta-Analysis

This systematic review and meta-analysis present several strengths. An extensive search was implemented with stringent inclusion and exclusion criteria and search terms. Significant efforts were made to contact the relevant researchers to obtain missing/unavailable data. Standardised quality and bias checks were also conducted using the SIGN guidelines, and the strengths and limitations of each study were evaluated and discussed. In terms of the meta-analysis, publication bias was only identified for methadone vs controls VEP analyses. Furthermore, high heterogeneity between the pooled studies was only identified for methadone vs control VEP analyses.

One of the main limitations of the current review is that the systematic search, study selection, and quality checks were not done in duplicate. This would have minimised the risk of selection bias and substantiated data collection and interpretation. Additionally, it was possible to pool just a few studies for the meta-analysis, and only two outcome measures, VEP and visual attention, were able to be tested. Furthermore, VEP results may present issues of generalizability as the study conducted by Whitham et al. (2015) was conducted on a subsample of participants recruited for their previous study (Whitham et al., 2010).

4.3 Clinical Relevance and Future Research

The associations depicted between prenatal opioid exposure and reduced visual functioning or an increased presentation of ophthalmic disorders, regardless of the lack of support for a causal relationship, call for the consideration of these findings in clinical practice. It would be advisable to provide prenatally drug exposed infants with visual assessments and follow-ups early in their development, and to monitor them for the incidence of long-term effects (McGlone et al., 2013; Whitham et al., 2015). Findings including strabismus or nystagmus can

be observed for via regular ophthalmic check-ups, and VEPs can be used to test visual maturity. In utero drug exposure needs to be one of the differential diagnoses in children presenting with ophthalmic disorders and delayed visual maturity (Mulvihill et al., 2007). Moreover, the neurodevelopmental findings reported in association with visual functioning are valuable. Poor functioning of the motor neurone system in children could impact their ability to learn and interact (Konijnenberg and Melinder, 2012), and problems with smooth pursuit risk impaired executive functioning as children develop and have increased visual attentional demands (Melinder, Konijnenberg, and Sarfi, 2013). Therefore, prenatally drug-exposed children also need to be monitored and trained for cognitive development.

In terms of future research, much work needs to be done to understand the link between in utero opioid exposure and ophthalmic abnormalities, through research designs that are less prone to biases discussed in this review. Firstly, more prospective, long-term studies with strategies to maximise retention of participants are needed to explore the duration of visual abnormalities. Secondly, research needs to be conducted across different regions of the world as opioid use in pregnancy is a global issue, and the studies presented in this review were limited in their demographic diversity. Thirdly, larger sample sizes are necessary to raise the statistical power of the studies and aim for a sample that is truly representative of the exposed children. Fourth, more consistency is needed in the control of the various confounding variables, especially for poly-drug exposure. Where minimising exposure and covariates is not possible, much more detailed information on them need to be collected, reported, and included in data analyses, in order to distinguish the true effect of in utero opioid maintenance exposure on the eyes. Fifth, more research is needed to explore the pathophysiology of opioid-induced visual outcomes, and the pathways by which opioids impact ocular tissue and receptors. These future suggestions are also in line with the World Health Organisation's priority to increase awareness of the consequences of prenatal opioid dependence and the options for maintenance

therapy (WHO, 2014). The importance of this is underscored in light of the current COVID-19 pandemic and how it could impact opioid use and the services available to pregnant women (Boardman, Mactier, and Devlin, 2021). Thus, overall, more research is critical to better supporting mothers in maintenance treatment and informing them of the potential ophthalmic risks associated with methadone or buprenorphine, and to predicting and managing already exposed children more efficiently.

5. Conclusion

In conclusion, this paper identified studies that measured the ophthalmic outcomes of children exposed to opioids in utero, via clinical, electrophysiological, neurodevelopmental tests, and hospitalisation rates. After considering meta-analytic results and qualitative synthesis, a causal relationship between the exposure to opioid maintenance therapy in utero and future ophthalmic abnormalities could not be confirmed. The existing lack of research in this population of children and the gaps that need to be covered by future research were also highlighted.

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Figures Captions

Figure 1. PRISMA Flow Diagram of Study Selection of Clinical Studies

Figure 2. VEP-methadone exposed infants vs non-exposed controls forest plot. (std diff= standard difference; Z value=one sample z statistics; p value= probability that Z statistics is significantly different than 0; Lower limit= lower limit of the 95% confidence interval for the effect size; Upper limit= upper limit of the 95% confidence interval for the effect size).

Figure 3. Subgroup analysis (checkerboard size) forest plot for VEP Methadone exposed infants vs non-exposed controls. (std diff= standard difference; Z value=one sample z statistics; p value= probability that Z statistics is significantly different than 0; Lower limit= lower limit of the 95% confidence interval for the effect size; Upper limit= upper limit of the 95% confidence interval for the effect size).

Figure 4. Subgroup analysis (time point) forest plot for VEP Methadone exposed infants vs non-exposed controls. (std diff= standard difference; Z value=one sample z statistics; p value= probability that Z statistics is significantly different than 0; Lower limit= lower limit of the 95% confidence interval for the effect size; Upper limit= upper limit of the 95% confidence interval for the effect size).

Figure 5. VEP-buprenorphine exposed infants vs non-exposed controls forest plot. (std diff= standard difference; Z value=one sample z statistics; p value= probability that Z statistics is significantly different than 0; Lower limit= lower limit of the 95% confidence interval for the effect size; Upper limit= upper limit of the 95% confidence interval for the effect size).

Figure 6. Subgroup analysis (checkerboard size) forest plot for VEP-buprenorphine exposed infants vs non-exposed controls. (std diff= standard difference; Z value=one sample z statistics;

p value= probability that Z statistics is significantly different than 0; Lower limit= lower limit of the 95% confidence interval for the effect size; Upper limit= upper limit of the 95% confidence interval for the effect size).

Figure 7. Subgroup analysis (time point) forest plot for VEP-buprenorphine exposed infants vs non-exposed controls. (std diff= standard difference; Z value=one sample z statistics; p value= probability that Z statistics is significantly different than 0; Lower limit= lower limit of the 95% confidence interval for the effect size; Upper limit= upper limit of the 95% confidence interval for the effect size).

Figure 8. VEP-methadone exposed infants vs buprenorphine exposed infants forest plot. (std diff= standard difference; Z value=one sample z statistics; p value= probability that Z statistics is significantly different than 0; Lower limit= lower limit of the 95% confidence interval for the effect size; Upper limit= upper limit of the 95% confidence interval for the effect size).

Figure 9. Subgroup analysis (checkerboard size) forest plot for VEP-methadone exposed infants vs buprenorphine exposed infants. (std diff= standard difference; Z value=one sample z statistics; p value= probability that Z statistics is significantly different than 0; Lower limit= lower limit of the 95% confidence interval for the effect size; Upper limit= upper limit of the 95% confidence interval for the effect size).

Figure 10. Subgroup analysis (time point) forest plot for VEP-methadone exposed infants vs buprenorphine exposed infants. (std diff= standard difference; Z value=one sample z statistics; p value= probability that Z statistics is significantly different than 0; Lower limit=

lower limit of the 95% confidence interval for the effect size; Upper limit= upper limit of the 95% confidence interval for the effect size).

Figure 11. Visual attention-OMT exposed infants vs non-exposed controls. (std diff= standard difference; Z value=one sample z statistics; p value= probability that Z statistics is significantly different than 0; Lower limit= lower limit of the 95% confidence interval for the effect size; Upper limit= upper limit of the 95% confidence interval for the effect size).

Table 1: Demographic and Sample Characteristics of the Included Clinical Studies

Study and Design	Aim	Year	Country	Opioid Exposed Group				Non-opioid exposed group			Matching
				n	Age at testing	Gender % male	Dose (mg)	n	Age at testing	Gender % male	
Whitham et al. The Effects of Prenatal Exposure to Buprenorphine or Methadone on Infant Visual Evoked Potentials Open-label non-randomised flexible-dosing longitudinal study	Assess the neurophysiologic development of infants prenatally exposed to OMT, and whether the visual maturity of infants prenatally exposed to buprenorphine differs from infants exposed to methadone, or from a control group	2010	Australia	30 BM 22 MM	BM 4.15 ± 0.79 months MM 3.88 ± 0.45 months	BM 47 MM 45	BM 7.33 ± 4.29 (range 0.4-20) MM 45.41 ± 20.21 (range 15-100)	33	3.86 ± 0.28 months	52	Maternal age, parity, gravida, tobacco and alcohol use
Konijnenberg and Melinder Neurodevelopmental Investigation of the Mirror Neurone System in Children of Women Receiving Opioid Maintenance	Examine the mirror neurone system in prenatally opioid exposed children in relation to eye movements, visual attention and goal understanding	2012	Norway	15 BM + MM	51.61 months	47	BM 10 (2) MM 85 (54.7)	15	51.98 months	47	Child's age, maternal age, gender

Therapy During Pregnancy Mixed factorial experiment											
McGlone et al. Neonatal Visual Evoked Potentials in Infants Born to Mothers Prescribed Methadone Prospective cohort study	Examine how maternal methadone use impacts neonatal flash VEPs, and explore a link between visual electrophysiology and NAS	2013	Scotland	100 MM	3 days old	46	Not reported	50	3 days old	44	Birth weight, completed gestation, Carstairs score
McGlone et al. Visual Outcome in Infants Born to Drug-Misusing Mothers Prescribed Methadone in Pregnancy Prospective cohort study	Investigate visual outcomes and VEPs in 6 months old prenatally methadone exposed infants	2013	Scotland	81 MM	6.21 (5.98 - 6.90) months	Not reported	Not reported	26	6.21 (5.98 - 6.90) months	Not reported	Birth weight, completed week of gestation, DEPCAT score

Melinder, Konijnenberg, and Sarfi Deviant Smooth Pursuit in Preschool Children Exposed Prenatally to Methadone or Buprenorphine and Tobacco Affects Integrative Visuomotor Capabilities Between-subject factorial experiment	Measure smooth pursuit and saccadic eye movements in prenatally opioid and tobacco exposed children	2013	Norway	26 BM + MM + tobacco	52.42 months	50	Not reported	23	51.65 months	44	Age and gender
Konijnenberg and Melinder Visual Selective Attention is Impaired in Children Prenatally Exposed to Opioid Agonist Medication Prospective cohort study	Examine visual selective attention in children prenatally exposed to methadone or buprenorphine via spatial negative priming	2015	Norway	9 BM 22 MM	BM 52.41 months MM 52.17 months	BM 33 MM 64	BM 12 (6.5) MM 86.19 (61.1)	25	51.44 months	44	None

Whitham et al. Visual Evoked Potential Latencies of Three-Year-Old Children Prenatally Exposed to Buprenorphine or Methadone Compared with Non-Opioid Exposed Children: The Results of a Longitudinal Study Open-label non-randomised flexible-dosing longitudinal study	Describe P100 latencies at 36 months of age, and document any long-term effects of exposure to buprenorphine or methadone on visual maturity	2015	Australia	11 BM 10 MM	36 months	BM 36 MM 50	Not reported	15	36 months	33	Maternal age, parity, gravida, alcohol and tobacco use
Auger et al. Impact of Prenatal Exposure to Opioids, Cocaine, and Cannabis on Eye Disorders in Children Longitudinal cohort study	Investigate the link between prenatal substance exposure and risk of hospital admission for eye disorders	2020	Canada	1,791	Not reported	Not reported	Not reported	781, 919	Not reported	Not reported	None

Hamilton et al. Long-Term Visual Outcomes of Children Born to Opioid-Dependent, Methadone-Maintained Mothers Suggest a Foetal Opioid Syndrome Longitudinal cohort study	Present the long term visual findings in a previously studied cohort of prenatally methadone exposed children	2020	Scotland	89 MM	8-10 years	Not reported	Not reported	44	8-10 years	Not reported	Not reported

BM: buprenorphine maintained, MM: methadone maintained, OMT: opioid maintenance therapy, VEP: visual evoked potential, NAS: neonatal abstinence syndrome

Table 2: Summary of the Aims, Criteria, Findings, and Analyses of the Included Clinical Studies

Study	Presence of Polysubstance Use	Data Collection Period and/or Method	Inclusion Criteria	Exclusion Criteria	Ophthalmic Measures	Results	Statistical Analyses	Adjustments
Whitham et al. (2010)	Tobacco, alcohol, opioids, cannabis, benzodiazepines, amphetamines and antidepressants used in all groups, in addition to heroin in the OMT groups	Recruited between September 2002 and December 2006	Women ≤ 28 weeks of gestation and aged 16-40	Concurrent medication that interacts with OMT, excess alcohol consumption, multiple pregnancy, congenital foetal malformations, participation in another research project	Binocular pattern reversal VEPs using Enfant 4010 for the first 69 infants and Nicolet Bravo Evoked Potential system for the final 16	Prenatal methadone exposure remained a significant predictor of prolonged P1 latency for checks of 69' but not for checks of 48'	One-way ANOVA to compare P1 latencies between groups, Bonferroni procedure to identify significance of differences between pairs of groups, Chi square analyses and Fisher's exact tests for differences among the 3 groups for categorical variables, Pearson product-moment correlations for dose and latency, Reciprocal square transformation to	Corrected for age, family income, VEP equipment, and marijuana use in pregnancy

							check significance of P1 latencies	
Konijnenberg and Melinder (2012)	All women in OMT reported smoking tobacco, 7 used opiates, benzodiazepines, cannabinoids, amphetamines and/or alcohol during pregnancy, control group reported no cigarette or drug use during pregnancy	Structured interview for drug use	Not reported	Not reported	Eye movements recorded using Tobii 1750 eye tracker while watching stimuli movies, Visual attention subtest from NEPSY, Perception subtest from Bender Gestalt II	OMT group was slower at gaze shifting in the human condition only No differences on the visual perception tests	Data analysed using PASW version 18 statistics software, t-tests and ANOVA comparisons, tested with Levene's test of equality of variances, MANOVA for gaze timing scores, one-sample tests and Bonferroni's corrected paired-samples t-tests	Maternal education
McGlone et al. (2013a)	OMT group: 95% smoking, 74% opiates, 66% benzodiazepines, 62% cannabis, 26/61 infants had elevated FAEEs, and 14 mothers used antipsychotics/	Infants born between October 2008 – April 2010 Drug and alcohol history by interview, maternal and infant urine samples analysed by immunoassay and meconium	Not reported	Birth < 36 weeks' gestation, congenital ocular abnormalities, significant neonatal illness	Flash VEPs recorded within the first 72 hours of life via Esoion evoked potential system	Methadone exposed group had less P1 and N2 components of the VEP, VEPs with smaller total amplitude, and more immature responses No link between early VEPs and	VEPs tested for normality by Anderson-darling tests, Mann-Whitney tests, Kruskal-Wallis tests for comparing between groups, X^2 tests for VEP morphology, linear and	Corrected for occipitofrontal head circumference, maternal cigarette smoking, and excess alcohol exposure in utero

	antidepressants Control group: 60% smoking and 5/21 infants had elevated FAEEs	samples by immunoabsorbent assays, FAEEs to identify excess alcohol exposure by a cut-off value of >10,000 ng/g				NAS development	logistic regression models for confounders	
McGlone et al. (2013b)	OMT group: 75% opioids, 67% benzodiazepines, 64% cannabis, 26% stimulants, and 20/46 infants had elevated FAEE levels Control group: 3/18 infants had elevated FAEEs and 2 tested positive for cannabis No diagnosis of foetal alcohol syndrome	Infants born between October 2008 – April 2010 Data collected at enrolment and NAS by case notes Drug history by interview, maternal urine samples at 12-16 weeks' gestation, infant urine and meconium, urine samples analysed by immunoassay techniques, meconium samples by ELISA screening	Infants born to drug-misusing mothers prescribed substitute methadone in pregnancy	Birth < 36 weeks, congenital ocular abnormalities, significant neonatal illness	Clinical visual assessment and pattern onset VEPs at 6 months Fail criteria: strabismus, nystagmus, reduced visual acuity, refractive error > 3 dioptres Normal limits of visual acuity (0.5-0.9 logMAR) and VEPs based on the controls	32/81 of methadone exposed group failed the visual assessment: 9 horizontal nystagmus, 12 exotropia, 8 esotropia, 18 reduced visual acuity, 2 delayed visual maturity 2/26 controls failed the visual assessment: 1 intermittent esotropia and 1 refractive error 9/81 drug-exposed scored borderline on visual assessment: 2 refractive errors	X^2 or Fisher's tests for categorical outcomes, Mann-Whitney tests for comparison between groups, Kruskall-Wallis tests between subgroups, Dunnet's post hoc test comparisons	Corrected for excess in utero alcohol exposure by logistic regression models

						not assessed, 3 moderate refractive errors without glasses, 2 exophoria, 1 anisocoria, 1 absent blink response Methadone group had slower and lower amplitude VEPs		
Melinder, Konijnenberg, and Sarfi (2013)	OMT group: 100% cigarette smoking	Not reported	Not reported	Not reported	Eye movements recorded using Tobii 1750 eye tracker while watching stimuli movies, Visual attention subtest from NEPSY, Attention scores from the CBCL	Looking time and saccades per second did not differ significantly between groups CBCL revealed OMT group has more attention problems, and a significant difference was found for fast smooth pursuit between OMT and control groups	t-scores for the CBCL subscore, gaze data analysed in Matlab, all data analysed using PASW statistics software version 18, Fisher's exact test for demographics analysis, ANOVA to compare scores on Bender and gaze data, Shapiro-Wilk's and Levene's tests	Controlled for maternal employment, maternal education and children's birth weight for fast smooth pursuit

Konijnenberg and Melinder (2015)	OMT group: tobacco, alcohol, marijuana, amphetamines, benzodiazepines, opioids and other illicit substances by needle	Not reported	Not reported	Not reported	Visual selective attention by spatial negative priming Attention problems subscale of the CBCL Eye movements recorded using Tobii 1750 Eye Tracker	Reduced SNP and saccade latency scores in exposed group A total of 60% demonstrated the SNP effect in the comparison group, compared to 45% in the exposed group No significant effect of group on reported attention problems Multivariate regression revealed NAS and prenatal marijuana exposure as significant predictors of saccade latency	IBM SPSS version 20 software, Shapiro-Wilk's and Levene's tests for normality and homogeneity, Pearson's correlation for multicollinearity, two-tailed probabilities, and significance at alpha = 0.05, ANCOVA for saccade latency and CBCL outcomes, multivariate regression	ANCOVA analyses controlled for birth weight, gestational age, and maternal education and employment
Whitham et al. (2015)	Cannabis use in 73% of the buprenorphine exposed, 70% of the methadone exposed, and 29% of the controls	Enrolled between September 2002 and December 2006	Women ≤ 28 weeks of gestation and aged 16-40	Concurrent medication that interacts with maintenance treatment, excess alcohol consumption, multiple	Binocular pattern reversal VEPs recorded using Nicolet Bravo Evoked	No significant difference found in P100 latencies in response to checks of 48' or 69' between the three groups	ANOVA for differences between latencies of P100 response, Kruskal-Wallis equality of populations rank tests, Mann-	Age and marijuana use

	Benzodiazepine use in 27% of the buprenorphine exposed, 50% of the methadone exposed, and 13% of controls			pregnancy, congenital foetal malformations, participation in another research project	Potential system		Whitney U tests, Fisher's exact tests, standard multiple regression analyses, analyses using Stata/IC 10.0 and alpha level 0.05	
Auger et al. (2020)	Not reported for opioid exposed cohort specifically	2006 – 2016 Cohort tracked until 2018 by health insurance Study of Hospital Clientele registry, information from pre-pregnancy hospitalisations, used diagnostic codes to capture substance use, information from the obstetric dossier	Opioid, cocaine, cannabinoid, sedative, hypnotic, hallucinogen, or volatile solvent use before or during pregnancy	Missing health insurance numbers, preterm infants with retinopathy of prematurity, neonatal death	Any ophthalmic diagnosis or procedures in childhood, by anatomical site and common childhood pathologies Death during follow-up was a competing outcome	Prenatal opioid exposure is associated with 1.48 times the risk of any eye disorder, and 3.15 times the risk of ocular muscle disorders	Cox proportional hazards regression, inverse probability weighting, logistic regression models for propensity scores, robust sandwich estimators for infants born to the same woman, sensitivity analyses and excluded preterm infants, data analysis using SAS version 9.4	Maternal age at delivery, parity, multiple birth, tobacco & alcohol abuse, maternal comorbidity, infant's sex, preterm birth, low birth weight, infant morbidity, socioeconomic deprivation, place of residence, time period

Hamilton et al (2020)	Not reported	Same cohort was studied at 6 months old Visual assessment or case note reviews, maternal history & urinalysis, infant urine and meconium	Not reported	Not reported	Near & distance acuity, stereovision, binocular fusion, strabismus, eye movements, VEPs Fail criteria: acuity < 0.2 logMAR, strabismus, nystagmus, poor stereovision	50/89 failed visual criteria: 47 strabismus, 30 poor distance acuity, 14/50 poor stereovision, 3/50 poor near vision vs 8/44 controls: 6/8 strabismus, 6/8 poor distance acuity, 3/8 poor near vision	Not reported	Not reported

OMT: opioid maintenance therapy, VEP: visual evoked potential, NAS: neonatal abstinence syndrome, SNP: spatial negative priming, FAEE: fatty acid ethyl esters, CBCL: child behaviour checklist

Table 3: Quality Assessment of the Included Clinical Studies Using the SIGN* Cohort Study Checklist

Study	Q1.1	Q1.2	Q1.3	Q1.4	Q1.5**	Q1.6	Q1.7	Q1.8	Q1.9	Q1.10	Q1.11	Q1.12	Q1.13	Q1.14	Q2.1	Q2.2	Q2.3
Whitham et al. (2010)	Yes	Yes	Yes	No	23% BM, 27% MM, 6% controls	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	No	(+)	No	Yes
Konijnenberg and Melinder (2012)	Yes	Yes	No	No	NR	Can't say	Yes	Yes	NA	Yes	No	No	Yes	No	(+)	No	Yes
McGlone et al. (2013a)	Yes	Yes	No	Yes	NR	Can't say	Yes	Yes (1/2)	No	Yes	Yes	Yes	Yes	Yes	(+)	Can't say	Yes
McGlone et al. (2013b)	Yes	Yes	Yes	Yes	21% MM 48% controls	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	(+)	No	Yes
Melinder, Konijnenberg and Sarfi (2013)	Yes	Yes	No	No	NR	Can't say	Yes	Can't say	Can't say	Yes	No	No	Yes	No	(+)	No	No
Konijnenberg and Melinder (2015)	Yes	No	Yes	No	34% OMT 31% comparison	No	Yes	Can't say	Can't say	Yes	Yes	Can't say	Yes	No	(+)	No	Yes
Whitham et al. (2015)	Yes	Yes	Yes	Yes	21% BM, 19% MM, 17% controls	No	Yes	Can't say	Can't say	Yes	Yes	Can't say	Yes	No	(+)	No	Yes

Auger et al. (2020)	Yes	No	NA	No	NA	NA	Yes	No	NA	Yes	No	NA	Yes	Yes	(+)	Yes	No
Hamilton et al. (2020)	Yes	Yes	No	No	13% methadone 12% controls	Can't say	Yes	Can't say	Can't say	Yes	No	Can't say	Can't say	No	Undecided	Can't say	Yes

High quality (++), Acceptable (+), Low quality (-)

NA: not applicable, NR: not reported

* (Sleith, 2012)

** Rate of participant dropout

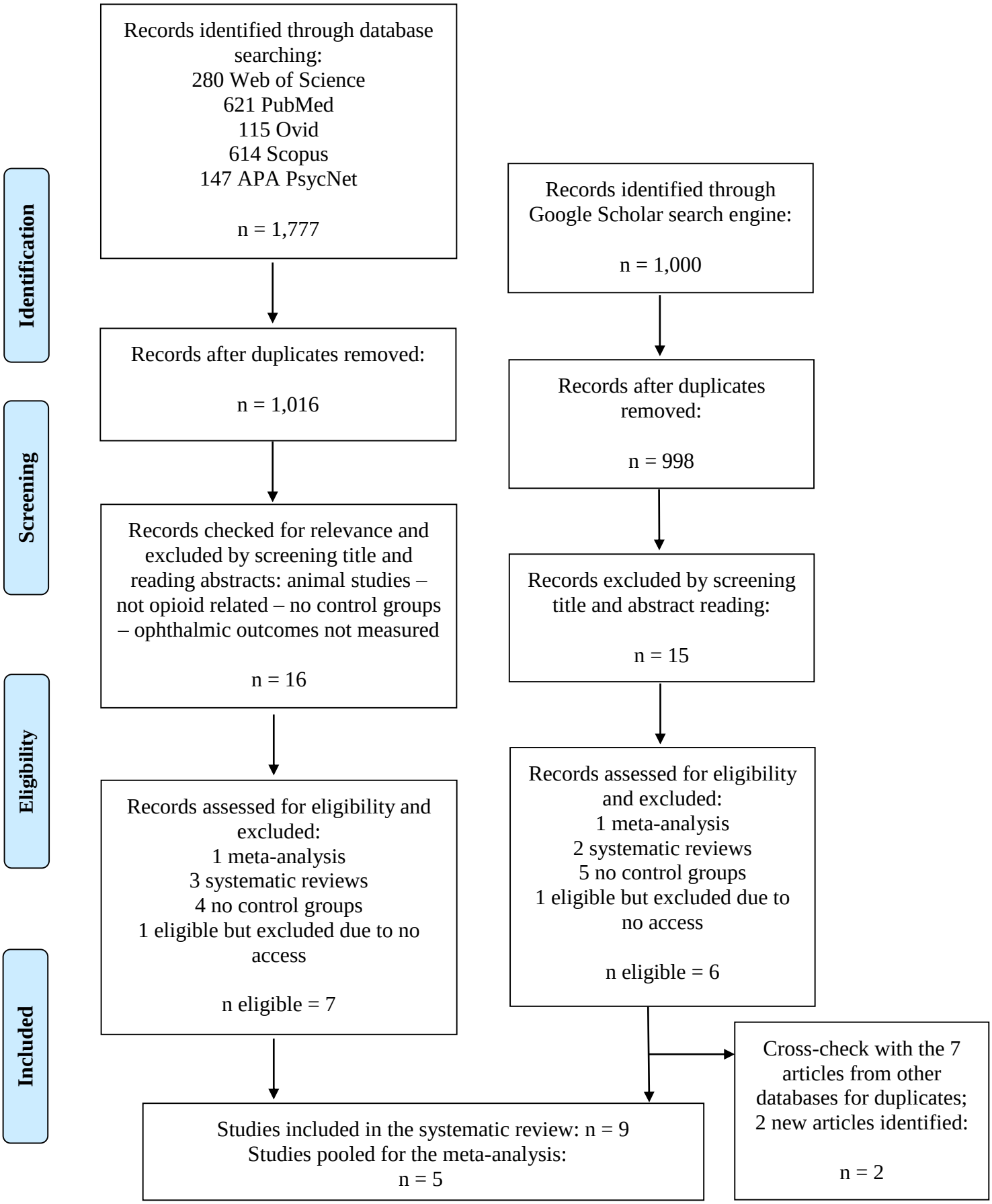


Figure 1

Study name	Subgroup within study	Outcome	Time point	Statistics for each study						
				Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Whitham et al (2010)	48' retinal arc	VEP-Enfant 4010 system	4.000	0.802	0.286	0.082	0.242	1.361	2.806	0.005
Whitham et al (2010)	69' retinal arc	VEP-Enfant 4010 system	4.000	0.657	0.282	0.080	0.103	1.210	2.326	0.020
Whitham et al (2015)	48' retinal arc	VEP-Nikolet bravo system	36.000	-0.310	0.411	0.169	-1.115	0.494	-0.756	0.450
Whitham et al (2015)	69' retinal arc	VEP-Nikolet bravo system	36.000	-0.392	0.412	0.170	-1.199	0.416	-0.951	0.342
				0.253	0.302	0.091	-0.339	0.846	0.838	0.402

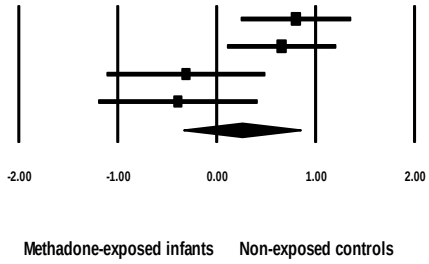


Figure 2

Group by Subgroup within study	Study name	Subgroup within study	Outcome	Time point	Statistics for each study						
					Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
48' retinal arc	Whitham et al (2010)	48' retinal arc	VEP-Enfant 4010 system	4.000	0.802	0.286	0.082	0.242	1.361	2.806	0.005
48' retinal arc	Whitham et al (2015)	48' retinal arc	VEP-Nikolet bravo system	36.000	-0.310	0.411	0.169	-1.115	0.494	-0.756	0.450
48' retinal arc					0.285	0.555	0.308	-0.802	1.372	0.513	0.608
69' retinal arc	Whitham et al (2010)	69' retinal arc	VEP-Enfant 4010 system	4.000	0.657	0.282	0.080	0.103	1.210	2.326	0.020
69' retinal arc	Whitham et al (2015)	69' retinal arc	VEP-Nikolet bravo system	36.000	-0.392	0.412	0.170	-1.199	0.416	-0.951	0.342
69' retinal arc					0.175	0.522	0.273	-0.848	1.199	0.336	0.737

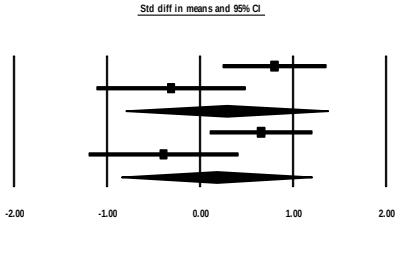


Figure 3

Group by Time point	Study name	Subgroup within study	Outcome	Time point	Statistics for each study						
					Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
36.00	Whitham et al (2015)	48' retinal arc	VEP-Nikolet bravo system	36.000	-0.310	0.411	0.169	-1.115	0.494	-0.756	0.450
36.00	Whitham et al (2015)	69' retinal arc	VEP-Nikolet bravo system	36.000	-0.392	0.412	0.170	-1.199	0.416	-0.951	0.342
36.00					-0.351	0.291	0.085	-0.921	0.219	-1.207	0.228
4.00	Whitham et al (2010)	48' retinal arc	VEP-Enfant 4010 system	4.000	0.802	0.286	0.082	0.242	1.361	2.806	0.005
4.00	Whitham et al (2010)	69' retinal arc	VEP-Enfant 4010 system	4.000	0.657	0.282	0.080	0.103	1.210	2.326	0.020
4.00					0.728	0.201	0.040	0.335	1.122	3.627	0.000

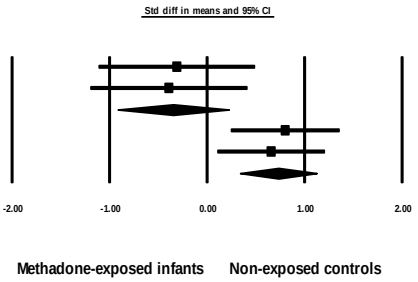


Figure 4

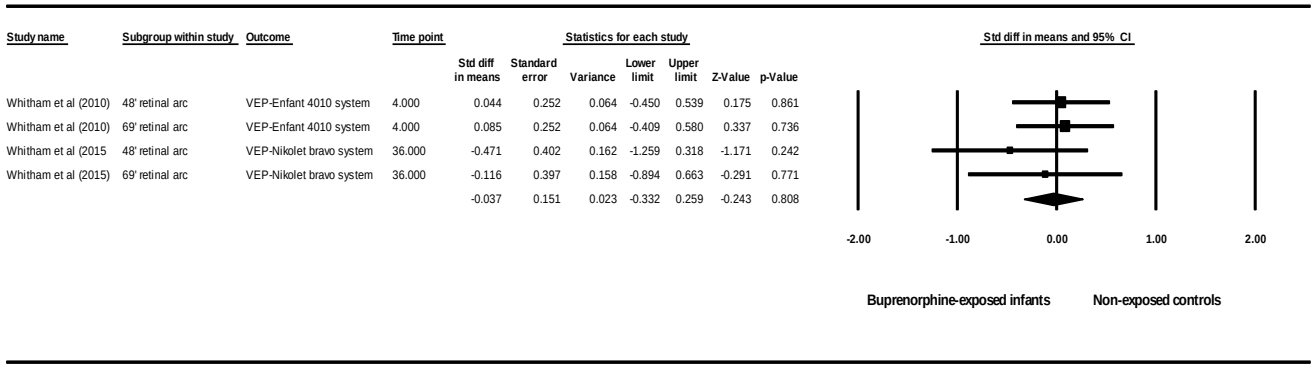


Figure 5

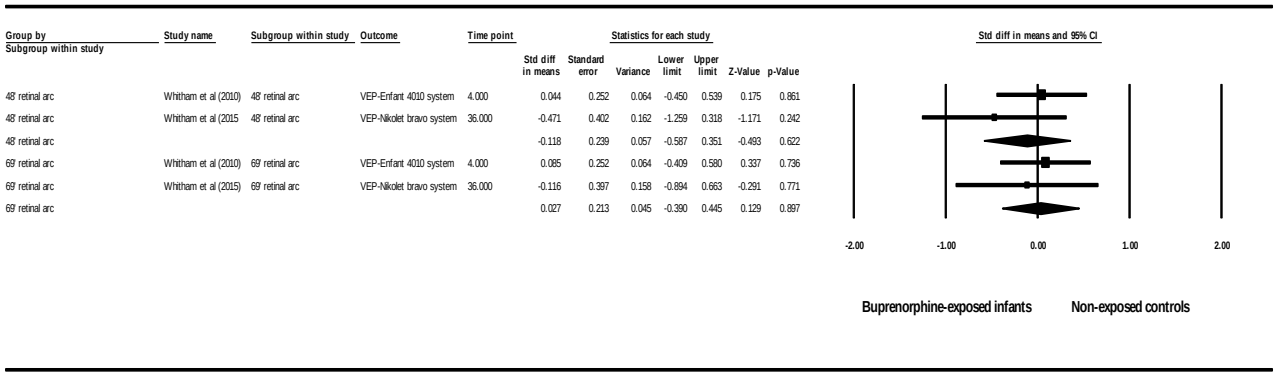


Figure 6

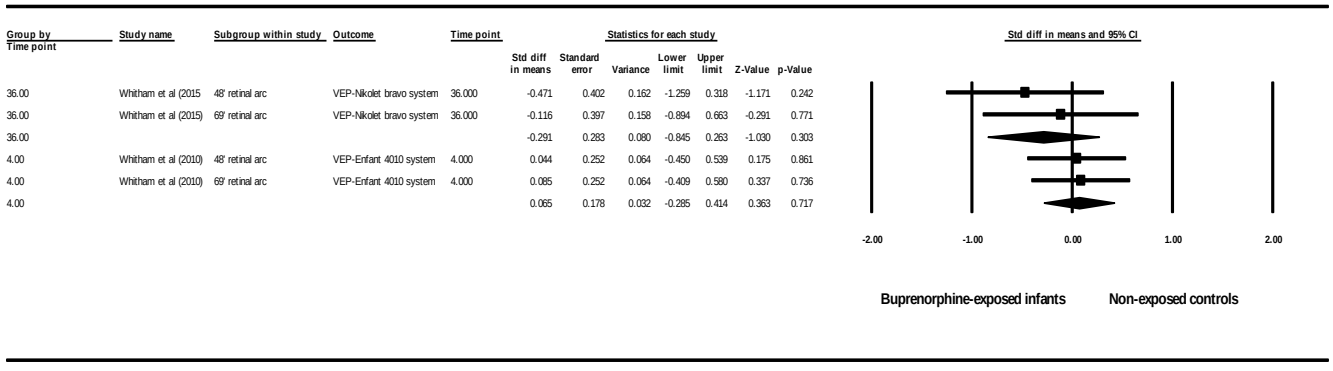


Figure 7

Study name	Subgroup within study	Outcome	Time point	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Whitham et al (2010)	48' retinal arc	VEP-Enfant 4010 system	4.000	0.667	0.288	0.083	0.102	1.231	2.313	0.021
Whitham et al (2010)	69' retinal arc	VEP-Enfant 4010 system	4.000	0.577	0.286	0.082	0.016	1.139	2.016	0.044
Whitham et al (2015)	48' retinal arc	VEP-Nikolet bravo system	36.000	0.149	0.438	0.191	-0.708	1.007	0.341	0.733
Whitham et al (2015)	69' retinal arc	VEP-Nikolet bravo system	36.000	-0.260	0.439	0.193	-1.120	0.600	-0.593	0.553
				0.392	0.196	0.038	0.009	0.775	2.004	0.045

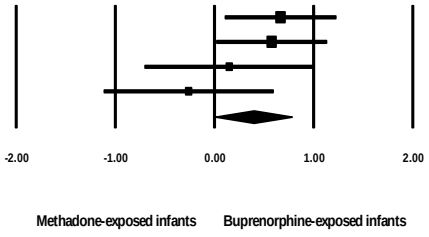


Figure 8

Group by Subgroup within study	Study name	Subgroup within study	Outcome	Time point	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
48' retinal arc	Whitham et al (2010)	48' retinal arc	VEP-Enfant 4010 system	4.000	0.667	0.288	0.083	0.102	1.231	2.313	0.021
48' retinal arc	Whitham et al (2015)	48' retinal arc	VEP-Nikolet bravo system	36.000	0.149	0.438	0.191	-0.708	1.007	0.341	0.733
48' retinal arc					0.510	0.241	0.058	0.038	0.982	2.119	0.034
69' retinal arc	Whitham et al (2010)	69' retinal arc	VEP-Enfant 4010 system	4.000	0.577	0.286	0.082	0.016	1.139	2.016	0.044
69' retinal arc	Whitham et al (2015)	69' retinal arc	VEP-Nikolet bravo system	36.000	-0.260	0.439	0.193	-1.120	0.600	-0.593	0.553
69' retinal arc					0.225	0.414	0.171	-0.586	1.035	0.543	0.587

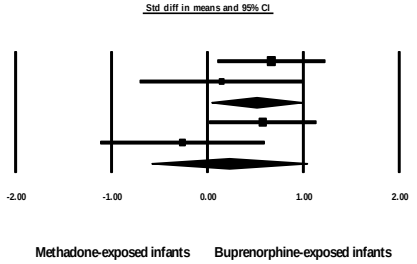


Figure 9

Group by Time point	Study name	Subgroup within study	Outcome	Time point	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
36.00	Whitham et al (2015)	48' retinal arc	VEP-Nikolet bravo system	36.000	0.149	0.438	0.191	-0.708	1.007	0.341	0.733
36.00	Whitham et al (2015)	69' retinal arc	VEP-Nikolet bravo system	36.000	-0.260	0.439	0.193	-1.120	0.600	-0.593	0.553
36.00					-0.055	0.310	0.096	-0.662	0.552	-0.177	0.859
4.00	Whitham et al (2010)	48' retinal arc	VEP-Enfant 4010 system	4.000	0.667	0.288	0.083	0.102	1.231	2.313	0.021
4.00	Whitham et al (2010)	69' retinal arc	VEP-Enfant 4010 system	4.000	0.577	0.286	0.082	0.016	1.139	2.016	0.044
4.00					0.622	0.203	0.041	0.224	1.020	3.060	0.002

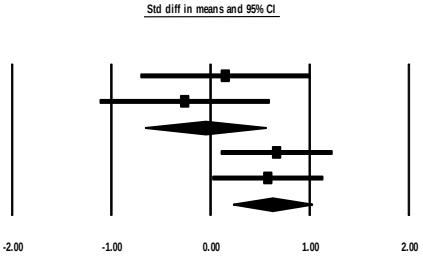


Figure 10

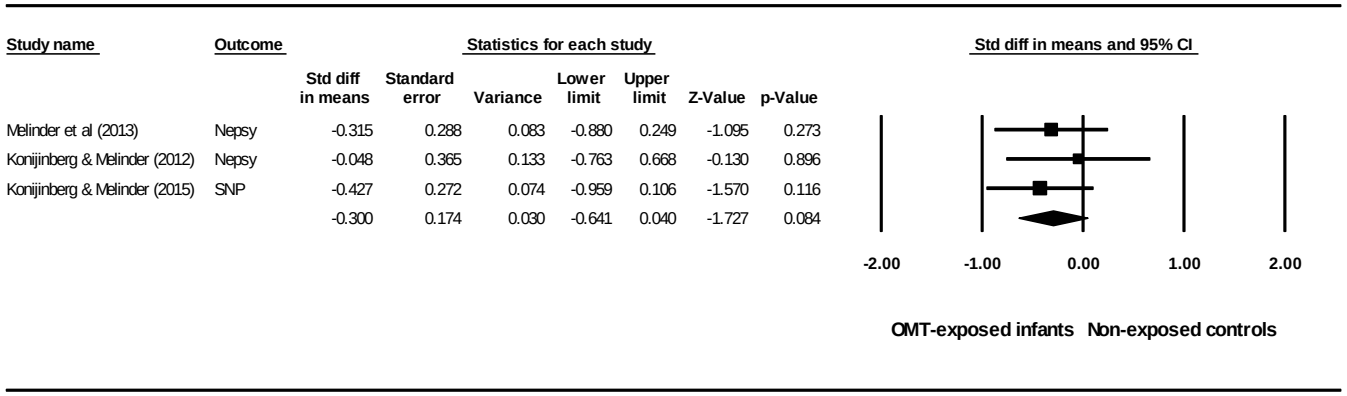
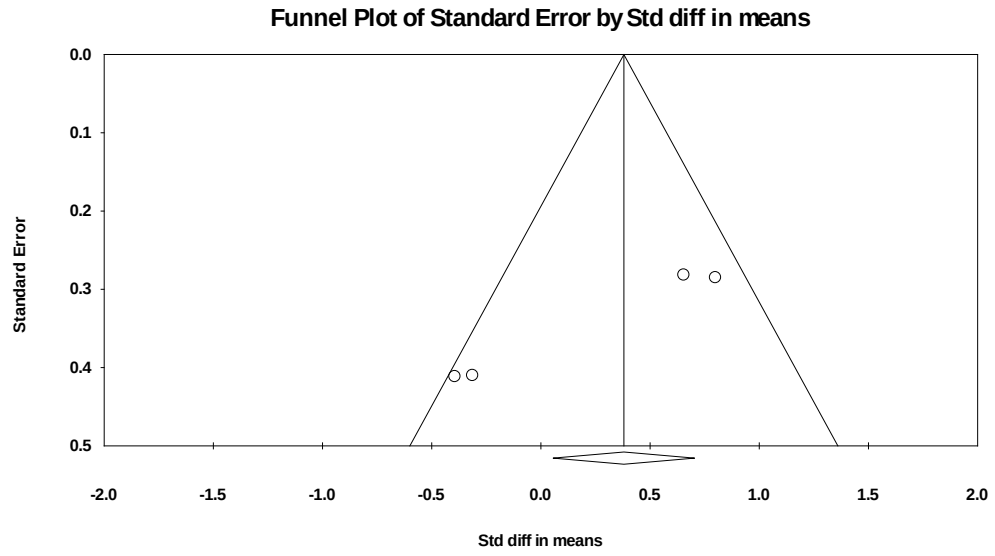
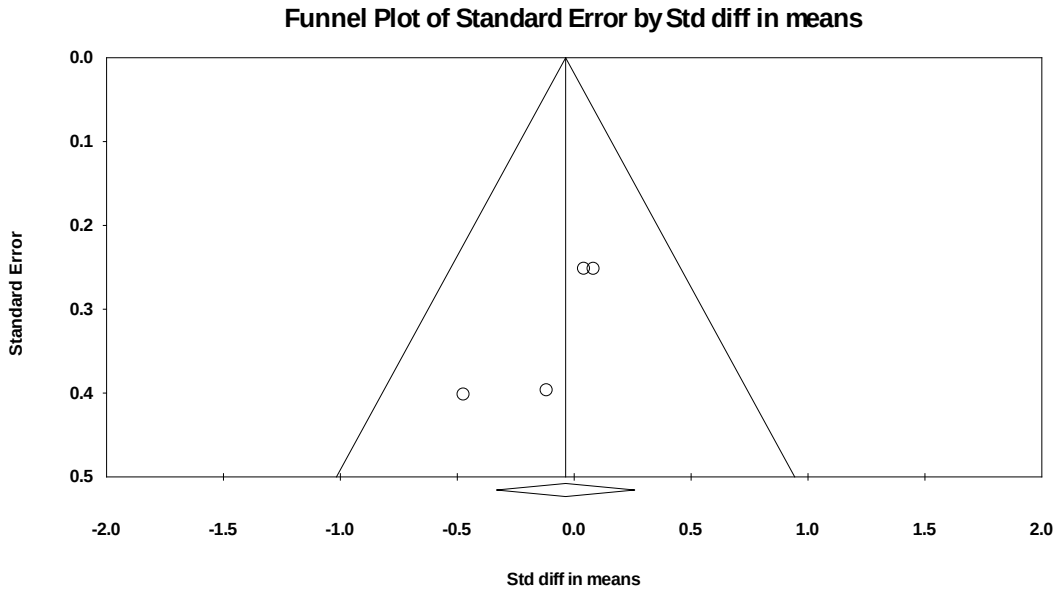

Study name
Outcome
Statistics for each study
Std diff in means and 95% CI
Std diff in means
Standard error
Variance
Lower limit
Upper limit
Z-Value
p-Value
Melinder et al (2013) Nepsy -0.315 0.288 0.083 -0.880 0.249 -1.095 0.273
Konijinberg & Melinder (2012) Nepsy -0.048 0.365 0.133 -0.763 0.668 -0.130 0.896
Konijinberg & Melinder (2015) SNP -0.427 0.272 0.074 -0.959 0.106 -1.570 0.116
-0.300 0.174 0.030 -0.641 0.040 -1.727 0.084
-2.00
-1.00
0.00
1.00
2.00
OMT-exposed infants
Non-exposed controls

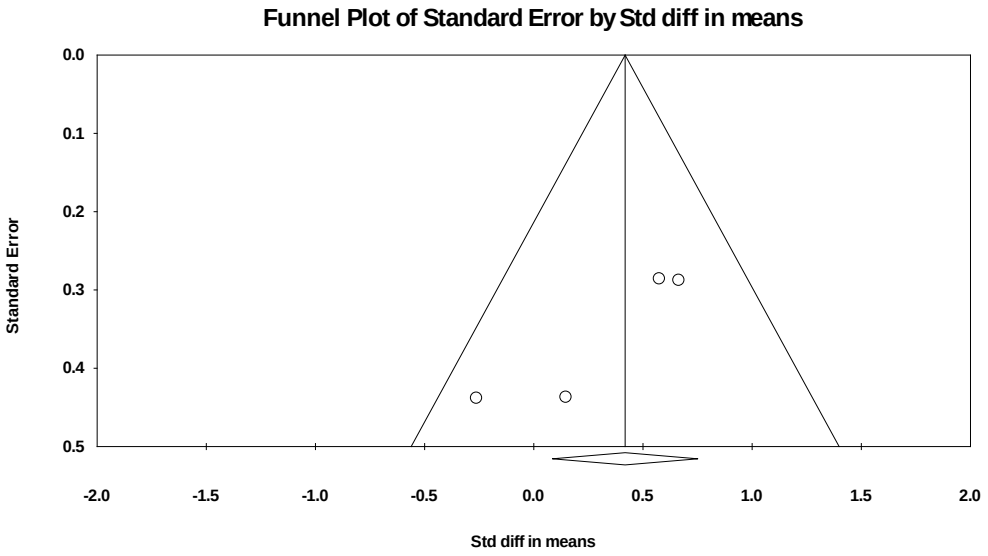
Figure 11



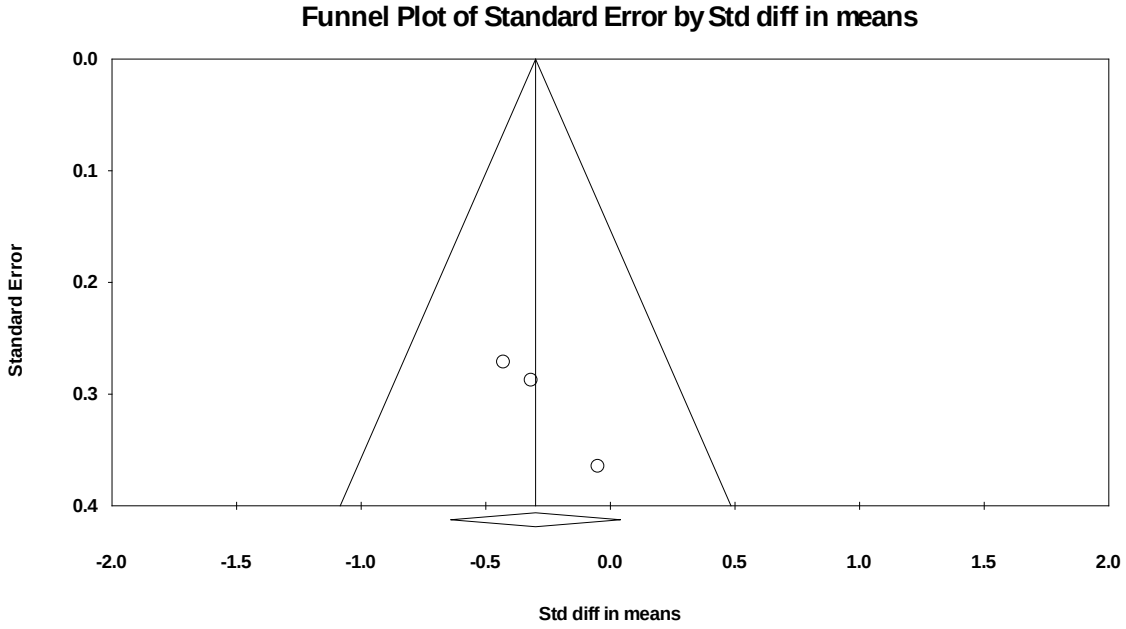
Supplementary Figure 1. VEP Latencies – Methadone Exposed Infants vs Non-Exposed Controls, funnel plot.



Supplementary Figure 2. VEP Latencies – Buprenorphine Exposed Infants vs Non-Exposed Controls, funnel plot.



Supplementary Figure 3. VEP Latencies – Methadone Exposed Infants vs Buprenorphine Exposed Infants, funnel plot.



Supplementary Figure 4. Visual Attention - OMT Exposed Infants vs Non-Exposed Controls, funnel plot.