

## Supplemental Information

### SEARCH STRATEGIES

#### Database: Ovid MEDLINE(R) In-Process and Other Nonindexed Citations and Ovid MEDLINE(R), 1946 to Present

1. exp Analgesics, Opioid/
2. (opiod\* or opiate\*).mp.
3. (alfentanil or alphaprodine or buprenorphine or butorphanol or codeine or dezocine or dihydrocodeine or fentanyl or hydrocodone or hydromorphone or levomethadyl or levorphanol or meperidine or methadone or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or propoxyphene or remifentanil or sufentanil or tapentadol or tramadol or heroin or nalmefene or naloxone or naltrexone).mp.
4. 1 or 2 or 3
5. exp Pregnancy/or exp Pregnancy Outcome/
6. exp Teratogens/
7. exp Congenital Abnormalities/
8. (defect or cleft or heart defect or gastroschisis or cryptorchidism or atresia or congenital or clubfoot or renal or craniosynostosis or hypospadias or malformation or spina bifida or neural tube defect).mp.
9. 5 or 6 or 7 or 8
10. 4 and 9
11. Limit 10 to (English language and humans)

#### Database: Ovid Embase, 1988–2016, Week 7

1. exp opiate/
2. (opiod\* or opiate\*).mp.
3. (alfentanil or alphaprodine or buprenorphine or butorphanol or codeine or dezocine or dihydrocodeine or fentanyl or hydrocodone or hydromorphone or levomethadyl or levorphanol or meperidine or methadone or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or propoxyphene

or remifentanil or sufentanil or tapentadol or tramadol or heroin or nalmefene or naloxone or naltrexone).mp.

4. 1 or 2 or 3
  5. exp pregnancy/or exp pregnancy outcome/
  6. exp teratogenic agent/
  7. exp congenital disorder/
  8. (defect or cleft or heart defect or gastroschisis or cryptorchidism or atresia or congenital or clubfoot or renal or craniosynostosis or hypospadias or malformation or spina bifida or neural tube defect).mp.
  9. 5 or 6 or 7 or 8
  10. 4 and 9
  11. Limit 10 to (human and English language and (article or book or book series or conference paper or conference proceeding or “conference review” or editorial or erratum or journal or letter or note or report or “review” or short survey or trade journal))<sup>a</sup>
- <sup>a</sup> Excluded conference abstracts.

Study Design	Source	External Validity					Internal Validity						
		Generalizability	Sampling Method	Sampling Frame	Selection Bias	Response Rate	Outcome Measurement	Exposure Measurement	Exp. Intensity/Dose	Information Bias	Differential Collection	Differential Measure	Confounding
Case-control (n = 13)	Bracken and Holford <sup>39</sup> (1981)	●	● Consecutive	● Hospital	●	●	● RMRR	● Self-report	●	●	●	●	●
	Bracken <sup>40</sup> (1986)	●	● Random	●	●	●	●	● Self-report	●	●	●	●	●
	Broussard et al <sup>44</sup> (2011)	●	● Random	● Registry	●	●	● Epi eval	● Self-report	●	●	●	●	●
	Daud et al <sup>43</sup> (2015)	●	● Consecutive	● Registry	●	●	● Exam	● RMRR	●	●	●	●	●
	Rothman et al <sup>69</sup> (1979)	●	● Random	● Registry	●	●	● Epi eval	● Self-report	●	●	●	●	●
	Saxen <sup>70</sup> (1975)	●	●	● Registry	●	●	● Epi eval	● Self-report	●	●	●	●	●
	Saxen <sup>71</sup> (1975)	●	● Consecutive	● Registry	●	●	● Epi eval	● RMRR	●	●	●	●	●
	Shaw et al <sup>72</sup> (1992)	●	● Random	● Registry	●	●	● Epi eval	● Self-report	●	●	●	●	●
	Shaw et al <sup>73</sup> (1998)	●	● Random	● Registry	●	●	● Epi eval	● Self-report	●	●	●	●	●
	van Gelder et al <sup>79</sup> (2009)	●	● Random	● Registry	●	●	● Epi eval	● Self-report	●	●	●	●	●
	Werler et al <sup>83</sup> (2014)	●	● Random	● Registry	●	●	● Epi eval	● Self-report	●	●	●	●	●
	Yazdy et al <sup>85</sup> (2013)	●	● Random	● Registry	●	●	● Epi eval	● Self-report	●	●	●	●	●
	Zierler and Rothman <sup>89</sup> (1985)	●	● Random	● Registry	●	●	● Epi eval	● Self-report	●	●	●	●	●
Cohort (n = 33)	Brown et al <sup>24</sup> (1998)	●	●	● Hospital	●	●	●	● Urine	●	●	●	●	●
	Chasnoff et al <sup>41</sup> (1982)	●	● Convenience	● Hospital	●	●	● Exam	● Urine	●	●	●	●	●
	Cleary et al <sup>15</sup> (2011)	●	● Convenience	● Hospital	●	●	● RMRR	● RMRR	●	●	●	●	●
	Ellwood et al <sup>45</sup> (1987)	●	● Random	● Hospital	●	●	● RMRR	● Urine	●	●	●	●	●
	Saleh Gargari et al <sup>16</sup> (2012)	●	● Random	● Hospital	●	●	● RMRR	● Self-report	●	●	●	●	●
	Gillogley et al <sup>17</sup> (1990)	●	● Convenience	● Hospital	●	●	● RMRR	● Urine	●	●	●	●	●
	Greig et al <sup>17</sup> (2012)	●	● Convenience	● Hospital	●	●	● RMRR	● Urine	●	●	●	●	●

**SUPPLEMENTAL FIGURE 3-1**

Quality assessment of studies with an unexposed comparison group in a systematic review of prenatal opioid exposure and congenital malformations ( $n = 46$ ). Green indicates criteria met; red indicates criteria not met; and yellow indicates unspecified. Epi eval, obtained from registries (collected for epidemiologic evaluation independent of health care); Exp., exposure; RMRR, retrospective medical records review (mining of data collected for health care purposes).

Study Design	Source	External Validity					Internal Validity						
		Generalizability	Sampling Method	Sampling Frame	Selection Bias	Response Rate	Outcome Measurement	Exposure Measurement	Exp. Intensity/Dose	Information Bias	Differential Collection	Differential Measure	Confounding
Cohort (n = 33)	Jick et al <sup>31</sup> (1981)	●	● Consecutive	● Hospital	●	●	● RMRR	● RMRR	●	●	●	●	●
	Kahila et al <sup>26</sup> (2007)	●	● Consecutive	● Hospital	●	●	● Exam	● Urine	●	●	●	●	●
	Kallen <sup>13</sup> (2013)	●	● Consecutive	● Registry	●	●	● Epi eval	● Self-report	●	●	●	●	●
	Kallen and Reis <sup>52</sup> (2015)	●	● Consecutive	● Registry	●	●	● Exam	● Self-report	●	●	●	●	●
	Kandall et al <sup>53</sup> (1977)	●	● Consecutive	● Hospital	●	●	●	● Self-report	●	●	●	●	●
	Lam et al <sup>56</sup> (1992)	●	●	● Registry	●	●	● RMRR	● RMRR	●	●	●	●	●
	Lendoiro et al <sup>37</sup> (2013)	●	● Consecutive	● Hospital	●	●	●	● Hair	●	●	●	●	●
	Little et al <sup>18</sup> (1990)	●	● Consecutive	● Hospital	●	●	● RMRR	● RMRR	●	●	●	●	●
	Ludlow et al <sup>13</sup> (2004)	●	● Consecutive	● Hospital	●	●	● RMRR	● RMRR	●	●	●	●	●
	Naeye et al <sup>63</sup> (1973)	●	● Consecutive	● Hospital	●	●	●	● Self-report	●	●	●	●	●
	Nezvalova-Henriksen et al <sup>65</sup> (2011)	●	● Consecutive	● Registry	●	●	●	● RMRR	●	●	●	●	●
	Norgaard et al <sup>66</sup> (2015)	●	● Consecutive	● Registry	●	●	● Exam	● RMRR	●	●	●	●	●
Ostrea and Chavez <sup>21</sup> (1979)	●	● Random	● Hospital	●	●	● RMRR	●	●	●	●	●	●	

**SUPPLEMENTAL FIGURE 3-2**

Quality assessment of studies with an unexposed comparison group in a systematic review of prenatal opioid exposure and congenital malformations, continued (n = 46). Green indicates criteria met; red indicates criteria not met; and yellow indicates unspecified. Epi eval, obtained from registries (collected for epidemiologic evaluation independent of health care); Exp., exposure; RMRR, retrospective medical records review (mining of data collected for health care purposes).

Rosen and Johnson <sup>25</sup> (1982)	●	● Convenience	● Hospital	●	●	● Exam	● Urine	●	●	●	●	●	●
Stimmel and Adamsons <sup>74</sup> (1976)	●	●	● Hospital	●	●	● RMRR	● Urine	●	●	●	●	●	●
Thornton et al <sup>76</sup> (1990)	●	● Consecutive	● Hospital	●	●	● RMRR	● RMRR	●	●	●	●	●	●
Uebel et al <sup>77</sup> (2015)	●	● Consecutive	● Registry	●	●	● Exam	● RMRR	●	●	●	●	●	●
van Baar et al <sup>78</sup> (1989)	●	● Consecutive	● Hospital	●	●	●	● Urine	●	●	●	●	●	●
Vucinovic et al <sup>19</sup> (2008)	●	● Consecutive	● Hospital	●	●	●	● RMRR	●	●	●	●	●	●
Walhovd et al <sup>80</sup> (2007)	●	● Referral	● State	●	●	● Exam	● Self-report	●	●	●	●	●	●
Walhovd et al <sup>81</sup> (2010)	●	● Referral	● State	●	●	● Exam	● Self-report	●	●	●	●	●	●
White et al <sup>84</sup> (2006)	●	● Consecutive	● Hospital	●	●	● RMRR	● RMRR	●	●	●	●	●	●
Wilson et al <sup>85</sup> (1981)	●	●	● Hospital	●	●	● Exam	● Urine	●	●	●	●	●	●
Wilson <sup>86</sup> (1989)	●	●	● Hospital	●	●	●	● Urine	●	●	●	●	●	●
Wouldes and Woodward <sup>87</sup> (2010)	●	● Consecutive	● Hospital	●	●	●	● Urine	●	●	●	●	●	●
Zelson et al <sup>88</sup> (1971)	●	● Consecutive	● Hospital	●	●	● Exam	● Self-report	●	●	●	●	●	●

**SUPPLEMENTAL FIGURE 3-3**

Quality assessment of studies with an unexposed comparison group in a systematic review of prenatal opioid exposure and congenital malformations, continued ( $n = 46$ ). Green indicates criteria met; red indicates criteria not met; and yellow indicates unspecified. Epi eval, obtained from registries (collected for epidemiologic evaluation independent of health care); Exp., exposure; RMRR, retrospective medical records review (mining of data collected for health care purposes).

Study Design	Source	External Validity					Internal Validity						
		Generalizability	Sampling Method	Sampling Frame	Selection Bias	Response Rate	Outcome Measurement	Exposure Measurement	Exp. Intensity/Dose	Information Bias	Differential Collection	Differential Measure	Confounding
Cohort (n = 14)	Blinick <sup>36</sup> (1971)	●	●	● Hospital	●	●	●	● Treatment	●	●	●	●	●
	Cleary et al <sup>82</sup> (2012)	●	●	● Hospital	●	●	● RMRR	● Urine	●	●	●	●	●
	Fajemirokun-Oduyei et al <sup>46</sup> (2006)	●	●	● Hospital	●	●	● RMRR	● RMRR	●	●	●	●	●
	Green et al <sup>88</sup> (1988)	●	● Random	● Hospital	●	●	●	● Urine	●	●	●	●	●
	Iosub et al <sup>50</sup> (1985)	●	● Convenience	● Hospital	●	●	● Exam	● RMRR	●	●	●	●	●
	Lacroix et al <sup>55</sup> (2011)	●	● Consecutive	● Hospital	●	●	● Exam	● Urine	●	●	●	●	●
	Lund et al <sup>58</sup> (2013)	●	● Consecutive	● Registry	●	●	● Epi eval	● RMRR	●	●	●	●	●
	Maas et al <sup>59</sup> (1990)	●	● Consecutive	● Hospital	●	●	● RMRR	● Urine	●	●	●	●	●
	Metz et al <sup>60</sup> (2015)	●	● Consecutive	● Hospital	●	●	● Exam	● Urine	●	●	●	●	●
	Meyer et al <sup>61</sup> (2015)	●	● Consecutive	●	●	●	● Exam	● Urine	●	●	●	●	●
	Ramer and Lodge <sup>67</sup> (1975)	●	●	● Hospital	●	●	● Exam	● Treatment	●	●	●	●	●
	Reddy et al <sup>68</sup> (1971)	●	● Consecutive	● Hospital	●	●	● RMRR	● Self-report	●	●	●	●	●
	Thaithumyanon et al <sup>75</sup> (2005)	●	●	● Hospital	●	●	● Exam	● RMRR	●	●	●	●	●
	Welle-Strand et al <sup>82</sup> (2013)	●	● Consecutive	● Registry	●	●	● Exam	● Urine	●	●	●	●	●
Cross-sectional (n = 1)	Olofsson et al <sup>4</sup> (1983)	●	● Consecutive	● Hospital	●	●	●	● Urine	●	●	●	●	●

**SUPPLEMENTAL FIGURE 4**

Quality assessment of studies with an exposed comparison group in a systematic review of prenatal opioid exposure and congenital malformations (n = 15). Green indicates criteria met; red indicates criteria not met; and yellow indicates unspecified. Epi eval, obtained from registries (collected for epidemiologic evaluation independent of health care); Exp., exposure; RMRR, retrospective medical records review (mining of data collected for health care purposes).

Source	External Validity					Internal Validity					
	Generalizability	Sampling Method	Sampling Frame	Selection Bias	Response Rate	Outcome Measurement	Exposure Measurement	Exp. Intensity/Dose	Information Bias	Differential Collection	Differential Measure
Blinick et al <sup>16</sup> (1973)	●	● Consecutive	● Hospital	●	●	●	● Treatment	●	●	●	●
Blumenthal et al <sup>38</sup> (1973)	●	●	● Hospital	●	●	● RMRR	● RMRR	●	●	●	●
Davis and Chappel <sup>44</sup> (1973)	●	● Convenience	● Hospital	●	●	●	●	●	●	●	●
Harper et al <sup>49</sup> (1974)	●	● Convenience	● Hospital	●	●	● Exam	● Urine	●	●	●	●
Kivisto et al <sup>54</sup> (2015)	●	● Consecutive	● Hospital	●	●	● Exam	● Urine	●	●	●	●
Miles et al <sup>62</sup> (2007)	●	● Convenience	● Hospital	●	●	● Exam	● Urine	●	●	●	●
Newman <sup>64</sup> (1973)	●	● Consecutive	● Hospital	●	●	● RMRR	● Treatment	●	●	●	●

### SUPPLEMENTAL FIGURE 5

Quality assessment of descriptive studies in a systematic review of prenatal opioid exposure and congenital malformations ( $n = 7$ ). Green indicates criteria met; red indicates criteria not met; and yellow indicates unspecified. Epi eval, obtained from registries (collected for epidemiologic evaluation independent of health care); Exp., exposure; RMRR, retrospective medical records review (mining of data collected for health care purposes).

**SUPPLEMENTAL TABLE 6** Number of Studies Reporting Significant Positive Associations Between Prenatal Opioid Exposure and Congenital Malformations: by Exposure

Exposure	Case-Control ( $n = 10$ ) <sup>a</sup>	Cohort ( $n = 7$ ) <sup>a</sup>
	<i>n</i> (Reference)	
Buprenorphine		1 (66)
Codeine	4 (39, 40, 69, 89)	1 (52)
Methadone		3 (15, 66, 87)
Morphine	1 (43)	
Opioid exposure (noncodeine)	1 (35)	
Opioid exposure (synthetic) <sup>b</sup>		1 (52)
Tramadol		2 (12, 52)
Unspecified opioid exposure	6 (34, 35, 39, 70, 71, 83)	4 (12, 19, 21, 66)

<sup>a</sup> Some studies evaluated multiple opioid exposures.

<sup>b</sup> Excluding tramadol and dextropropoxyphene.

**SUPPLEMENTAL TABLE 7** Number of Studies Reporting Significant Positive Associations Between Early Prenatal Opioid Exposure and Congenital Malformations: by Malformation

Malformation	Case-Control ( <i>n</i> = 10) <sup>a</sup>	Cohort ( <i>n</i> = 7) <sup>a</sup>
	<i>n</i> (Reference)	
Congenital malformations overall	1 (39)	6 (15, 19, 21, 52, 66, 87)
Relatively severe malformations <sup>b</sup>		1 (52)
Heart malformations		
Atrioventricular septal defects	1 (34)	
Double-outlet right ventricle defects	1 (89)	
Heart malformations overall	4 (34, 40, 69, 89)	1 (52)
Hypoplastic left heart syndrome	1 (34)	
Isolated cardiac septum defect		1 (52)
Other heart and circulatory defects	1 (39)	
Pulmonary valve stenosis	1 (34)	
Right ventricular outflow tract obstruction defects	1 (34)	
Tetralogy of Fallot	1 (34)	
VSD/ASD	3 (34, 39, 89)	
Non-heart malformations		
Clubfoot	1 (83)	2 (12, 52)
Dislocated hip/musculoskeletal defects	1 (39)	
Inguinal hernia with/without obstruction	1 (39)	
Neural tube defects	1 (35)	
Oral clefts	3 (39, 70, 71)	
Respiratory malformations	1 (43)	
Spina bifida	2 (34, 35)	

<sup>a</sup> Some studies reported multiple malformations.

<sup>b</sup> Study authors excluded preauricular appendix, tongue tie, patent ductus arteriosus in preterm infants, single umbilical artery, undescended testicle, unstable hip or hip (sub)luxation, and nevus.