SUPPLEMENTARY ONLINE CONTENT

Association of First Trimester Prescription Opioid Use with Congenital Malformations in the Offspring: Population Based Cohort Study

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Supplementary Tables

eTable 1 Specific Prescription Opioids Considered and Number of Pregnancies Exposed During First Trimester. 2
eTable 2 Definition of Congenital Malformations. 3
eTable 3 Cohort Characteristics of Pregnancies With and Without Exposure to Opioids During the First Trimester (Unadjusted). 6
eTable 4 Cohort Characteristics of Pregnancies With and Without Exposure to Opioids During the First Trimester (Propensity Score Weighted). 10
eTable 5 Absolute Risk of Congenital Malformations (Primary Outcomes) Among Infants Born to Mothers With and Without Exposure to Opioids. 14
eTable 6 Risk of Congenital Malformations (Primary Outcomes) in Infants Following Exposure to Opioids During the First Trimester: Sensitivity Analyses 15
eTable 7 Risk of Congenital Malformations (Oral Cleft Subgroups) in Infants Following Exposure to Opioids During the First Trimester: Sensitivity Analyses 29
eTable 8 Absolute Risk of Congenital Malformations (Secondary Outcomes) Among Infants Born to Mothers With and Without Exposure to Opioids 34

Supplementary Figures

eFigure 1 Cohort Selection for Pregnancies in the Medicaid Analytic Extract 2000-2014. 36
eFigure 2 Cohort Selection for Pregnancies in the IBM Health MarketScan Research Database 2003-2015. . 37
eFigure 3 Opioid Dispensing Patterns Among Pregnancies With >=2 Opioid Prescriptions During the First Trimester. 38
eFigure 4 Risk of Congenital Malformations (Oral Cleft Subgroups) in Infants Following Exposure to Opioids During the First Trimester: Main Analyses (Unadjusted and Propensity Score Stratified). 39
eFigure 5 Risk of Congenital Malformations (Oral Cleft Subgroups) in Infants Following Exposure to Opioids During the First Trimester: Sensitivity Analyses (Pooled Estimates, Propensity Score Stratified). 40
eFigure 6 Risk of Congenital Malformations (Oral Cleft Subgroups) in Infants Following Exposure to Opioids During the First Trimester: Subgroup Analyses (Pooled Estimates, Propensity Score Stratified). 41
eFigure 7 Risk of Congenital Malformations (Secondary Outcomes – Cardiac Malformations) in Infants Following Exposure to Opioids During the First Trimester: Main Analyses (Unadjusted and Propensity Score Stratified). 42
eFigure 8 Risk of Congenital Malformations (Secondary Outcomes – Non-Cardiac Malformations) in Infants Following Exposure to Opioids During the First Trimester: Main Analyses (Unadjusted and Propensity Score Stratified). 43

Appendix

Appendix 1 Cohort Selection 44
Appendix 2 Validation Study Description and Results 45
Appendix 3 Quantifying the Potential Effect of Restriction to Live Births 46
Appendix 4 Sensitivity Analysis of Residual Confounding to Explain Increase in Oral Clefts 50

References

eTable 1 Specific Prescription Opioids Considered and Number of Pregnancies Exposed During First Trimester.

	MAX 2000-2014	MarketScan 2003-2015
Specific Opioid	**N Pregnancies with ≥ 1 Dispensing During First Trimester**	
Butorphanol	140	85
Codeine	22707	3657
Dihydrocodeine	264	13
Fentanyl	394	129
Hydrocodone	50605	8543
Hydromorphone	530	170
Levorphanol	<11*	1
Meperidine	377	113
Methadone	606	117
Morphine	700	147
Oxycodone	13800	2826
Oxymorphone	78	34
Pentazocine	135	18
Propoxyphene	7239	1195
Tapentadol	32	41
Tramadol	11179	1695

*Cell size <11 for MAX cohort. Numbers suppressed in accord with the CMS cell size suppression policy.
Abbreviation: N, number.

eTable 2 Definition of Congenital Malformations.

Malformation Group	Malformation Subgroup	ICD-9 Dx Code
Cardiovascular Anomalies	Conotruncal Defects	745.0x, 745.1x, 745.2x
	Single Ventricle	745.3x
	Ventricular Septal Defect	745.4x
	Secundum Atrial Septal Defect/Patent Foramen Ovale	745.5x AND no preterm
	Atrioventricular Septal Defect	745.6x
	Right Sided Defects	746.00, 746.01, 746.09, 746.1x, 746.2x, 746.83, 747.3x AND no preterm, 746.02 AND no preterm
	Left Sided Defects	747.1x, 747.2x, 746.3x, 746.5x, 746.7x, 746.81, 746.82, 746.84
	Patent Ductus Arteriosus	747.0x AND no preterm
	Persistent Pulmonary Hypertension of the Newborn	(416.0x or 747.83) AND no preterm
	Anomalous Pulmonary Venous Return	747.4x
	Other Cardiac Malformation	745.7x,745.8x, 746.8, 746.85-746.87, 746.89
	Cardiac Malformation NOS	745, 745.9, 746, 746.9x (exclude if only 746.99), 747
Central Nervous System	Overall	740.xx-742.xx
	Microcephaly	742.1x
	Hydrocephaly	742.3x
	Reduction Deformities of Brain	742.2x
	Neural tube Defects	741.xx, 756.17, 740.0x, 740.2x, 742.0x
Club Foot		754.50, 754.51, 754.59, 754.60, 754.62, 754.69, 754.70, 754.71, 754.79
Gastroschisis		756.73 if coded after 9/2009;
		756.79 AND ICD-9 Proc 54.71 if coded before 10/2009
Oral Cleft	Cleft Palate	749.0x
	Cleft Lip	749.1x
	Cleft Palate with Cleft Lip	749.2x
Eye Anomalies		743.xx (exclude if only 743.6x and 743.8x)
Ear Anomalies		744.xx (exclude if only 744.1x, 744.21, 744.29, and 744.4x-744.9x)

Malformation Group	Malformation Subgroup	ICD-9 Dx Code
Other Vascular (Non-Cardiac) Anomalies		747.6x-747.9x (exclude if only 747.83)
Respiratory Anomalies		748.xx (exclude if only 748.1x)
Gastrointestinal Anomalies		750.xx-751.xx (exclude if only 750.0x, 750.1x, 750.50, 751.0x)
Genital (Male and Female) Anomalies		752.xx (exclude if only 752.42, 752.52) (in addition, exclude 752.5x if preterm)
Urinary Anomalies		753.xx (exclude if only 753.7x)
Musculoskeletal Anomalies		754.xx and 756.xx (exclude if only 754.3x, 754.81, 754.82, 756.2x)
Limb Defects		755.xx (exclude if only 755.65)
Other Anomalies		757.xx; 759.xx (exclude if only 757.2-757.6, 759.81-759.83)

Abbreviations: Dx, diagnosis; Proc, procedure; NOS, not otherwise specified.

Consider claims in infant record between date of birth (DoB) and DoB+90 days and/or in the maternal record between delivery and delivery+30 days, using both in- and out-patient data.

Subgroups of Cardiovascular Malformations:

- If there are ≥ 2 dates with a code for a malformation within the group
  - Exception: Codes 747.3x, 746.02, 745.5x, 747.0x require ≥ 2 dates with a code for a malformation of which at least one code is documented at ≥ 6 weeks after DoB
- ≥ 1 date with a code for a malformation within the subgroup and cardiac procedure
  - Exception: Code 746.02
- ≥ 1 date with a code for a malformation within the subgroup and infant died
- If codes identified in the maternal record between LMP and LMP+105 AND there are no codes in the infant record between DoB and DoB+90 days (i.e., only maternal codes between delivery and delivery+30), the defect is considered a pre-existing maternal defect.

Cardiovascular Malformations overall:

- Any of the subgroups of cardiovascular anomalies is present
- ≥ 2 dates with a code for any of the cardiac malformations (regardless of the subgroup [1])
- ≥ 1 date with a code for any of the cardiac malformations [1] and cardiac procedure
- ≥ 1 date with a code for any of the cardiac malformations [1] and infant died
- If codes identified in the maternal record between LMP and LMP+105 AND there are no codes in the infant record between DoB and DoB+90 days (i.e., only maternal codes between delivery and delivery+30), the defect is considered a pre-existing maternal defect.

Specific Non-Cardiovascular Malformations:

- ≥ 2 dates with a code for the malformation group/subgroup

    - Exception: for gastroschisis: if code 756.79 was used (before 10/2009), require ≥ 1 date with a code AND ICD-9 Proc 54.71
- ≥ 1 date with a code for the malformation group/subgroup and malformation-specific procedure
- ≥ 1 date with a code for the malformation group/subgroup and infant died
- If codes identified in the maternal record between LMP and LMP+105 AND there are no codes in the infant record between DoB and DoB+90 days (i.e., only maternal codes between delivery and delivery+30), the defect is considered a pre-existing maternal defect.

Any Congenital Malformation:

- Any of the malformation groups/subgroups mentioned above is present.

[1] the following codes should not be considered: 745.4x, 745.5x, 747.0x, 746.4x, 746.6x, 746.99, 747.3x if preterm, 746.02 if preterm, 747.5x, 416.0x if preterm, 747.83 if preterm, 746.08, 746.105

eTable 3 Cohort Characteristics of Pregnancies With and Without Exposure to Opioids During the First Trimester (Unadjusted).

		MAX 2000-2014					***MarketScan 2003-2015***				
		Exposed		**Unexposed**			**Exposed**		**Unexposed**		
		N/Mean	**%/SD**	**N/Mean**	**%/SD**	**Stdiff**	**N/Mean**	**%/SD**	**N/Mean**	**%/SD**	**Stdiff**
Total		70,447		1,532,133			12,454		1,165,222		
Age, mean (SD)		26.03	5.46	24.27	5.98	0.31	32.00	4.85	31.97	4.60	0.01
Year of delivery, N (%)											
	2000-2002	5,234	7.43	162,483	10.61	-0.11	*	*	*	*	*
	2003-2005	15,707	22.30	372,573	24.31	-0.05	1,221	9.80	112,153	9.63	0.01
	2006-2010	30,531	43.33	617,713	40.32	0.06	5,724	45.96	485,901	41.70	0.09
	2011-2015**	18,975	26.93	379,364	24.76	0.05	5,509	44.23	567,168	48.68	-0.09
Race/Ethnicity, N (%)											
	White	45,328	64.34	543,765	35.49	0.60	*	*	*	*	*
	Black	15,045	21.36	510,311	33.31	-0.27	*	*	*	*	*
	Hispanic	5,169	7.34	267,363	17.45	-0.31	*	*	*	*	*
	Other or unknown	4,905	6.96	210,694	13.74	-0.22	*	*	*	*	*
Opioid indications, N (%)											
	Abdominal pain	27,837	39.51	235,467	15.37	0.56	3,049	24.48	68,916	5.91	0.54
	Back/neck pain	29,198	41.45	88,306	5.76	0.93	4,546	36.50	102,311	8.78	0.70
	Dental problems	11,710	16.62	22,213	1.45	0.55	221	1.77	747	0.06	0.18
	Fibromyalgia	3,385	4.81	7,978	0.52	0.27	780	6.26	11,189	0.96	0.29
	Joint pain	12,318	17.49	40,329	2.63	0.51	1,638	13.15	30,585	2.62	0.40
	Migraine/headache	16,812	23.86	77,038	5.03	0.56	2,863	22.99	38,511	3.31	0.61
	Orthopedic injury	16,459	23.36	58,530	3.82	0.59	1,943	15.60	41,969	3.60	0.42
	Surgery	6,663	9.46	19,656	1.28	0.37	1,374	11.03	7,381	0.63	0.46
	Arthritis/arthropathy, musculoskeletal pain	22,291	31.64	93,620	6.11	0.69	3,276	26.30	79,745	6.84	0.54
	Complex regional pain syndrome	86	0.12	57	0.00	0.05	29	0.23	87	0.01	0.07
	Cough	5,204	7.39	29,378	1.92	0.26	702	5.64	17,901	1.54	0.22
	Generalized pain	425	0.60	1,370	0.09	0.09	62	0.50	520	0.04	0.09
	Gout	74	0.11	242	0.02	0.04	22	0.18	248	0.02	0.05
	Infection	8,129	11.54	95,451	6.23	0.19	695	5.58	31,791	2.73	0.14

		MAX 2000-2014					*MarketScan 2003-2015*				
		Exposed		**Unexposed**			**Exposed**		**Unexposed**		
		N/Mean	**%/SD**	**N/Mean**	**%/SD**	**Stdiff**	**N/Mean**	**%/SD**	**N/Mean**	**%/SD**	**Stdiff**
	Osteoarthritis	1,494	2.12	2,188	0.14	0.19	236	1.89	2,185	0.19	0.17
	Other neuropathies	6,647	9.44	9,943	0.65	0.41	1,526	12.25	19,494	1.67	0.42
	Other pain	3,881	5.51	2,932	0.19	0.32	591	4.75	1,257	0.11	0.30
	Pain related to psychological factors	123	0.17	172	0.01	0.05	21	0.17	55	0.00	0.06
	Peripheral neuropathy	30	0.04	76	0.00	0.02	9	0.07	80	0.01	0.03
	Post herpetic neuralgia	13	0.02	18	0.00	0.02	10	0.08	26	0.00	0.04
	Rheumatoid arthritis	331	0.47	1,028	0.07	0.08	108	0.87	1,743	0.15	0.10
	Sciatica	1,611	2.29	1,820	0.12	0.20	333	2.67	3,950	0.34	0.19
	Sickle cell disease	372	0.53	941	0.06	0.09	21	0.17	153	0.01	0.05
	Trigeminal neuralgia	50	0.07	82	0.01	0.03	23	0.18	132	0.01	0.06
	Urinary calculus	2,275	3.23	3,741	0.24	0.23	495	3.97	3,252	0.28	0.26
Maternal conditions, N (%)											
	Anxiety	9,468	13.44	43,165	2.82	0.40	1,199	9.63	32,346	2.78	0.29
	Depression	10,911	15.49	76,216	4.97	0.35	1,470	11.80	41,210	3.54	0.31
	Diabetes	2,478	3.52	21,350	1.39	0.14	340	2.73	13,374	1.15	0.11
	Hypertension	4,518	6.41	27,597	1.80	0.23	835	6.70	23,801	2.04	0.23
	Alcohol abuse or dependence	978	1.39	9,101	0.59	0.08	46	0.37	776	0.07	0.06
	Amphetamine abuse or dependence	286	0.41	2,872	0.19	0.04	3	0.02	56	0.00	0.02
	Cocaine abuse or dependence	347	0.49	2,639	0.17	0.06	2	0.02	46	0.00	0.01
	Hallucinogen abuse or dependence	<11***	0.01	108	0.01	0.00	0	0.00	5	0.00	0.00
	Infertility	404	0.57	5,928	0.39	0.03	1,266	10.17	83,644	7.18	0.11
	Marijuana abuse or dependence	730	1.04	9,286	0.61	0.05	10	0.08	151	0.01	0.03
	Obesity or overweight	3,243	4.60	30,634	2.00	0.15	495	3.97	17,998	1.54	0.15
	Posttraumatic stress disorder	1,128	1.60	7,532	0.49	0.11	72	0.58	1,457	0.13	0.08
	Renal disease	207	0.29	1,268	0.08	0.05	89	0.71	1,899	0.16	0.08
	Sarcoidosis	44	0.06	159	0.01	0.03	2	0.02	153	0.01	0.00
	Sedative hypnotic use disorder	90	0.13	194	0.01	0.04	5	0.04	34	0.00	0.03
	Sleep disorder	2,273	3.23	7,528	0.49	0.20	551	4.42	8,497	0.73	0.23

		MAX 2000-2014					*MarketScan 2003-2015*				
		Exposed		**Unexposed**			**Exposed**		**Unexposed**		
		N/Mean	**%/SD**	**N/Mean**	**%/SD**	**Stdiff**	**N/Mean**	**%/SD**	**N/Mean**	**%/SD**	**Stdiff**
	Tobacco use	9,021	12.81	33,936	2.21	0.41	617	4.95	5,627	0.48	0.28
Concomitant medications, N (%)											
	Antidepressants	21,233	30.14	98,446	6.43	0.64	3,712	29.81	77,348	6.64	0.63
	Antiemetics	27,570	39.14	215,914	14.09	0.59	5,504	44.19	187,701	16.11	0.64
	Antihypertensives	6,192	8.79	32,567	2.13	0.30	1,316	10.57	30,810	2.64	0.32
	Benzodiazepines	14,600	20.72	24,985	1.63	0.64	2,971	23.86	31,726	2.72	0.66
	Anti-diabetics	1,402	1.99	11,593	0.76	0.11	558	4.48	26,712	2.29	0.12
	Insulin	1,293	1.84	11,102	0.72	0.10	265	2.13	10,382	0.89	0.10
	Psychostimulants	1,850	2.63	8,038	0.52	0.17	527	4.23	7,721	0.66	0.23
	Suspected teratogens	16,477	23.39	137,941	9.00	0.40	2,098	16.85	79,845	6.85	0.31
	Antibiotics	53,457	75.88	584,656	38.16	0.82	8,406	67.50	376,602	32.32	0.75
	Anticonvulsants	7,619	10.82	20,697	1.35	0.40	1,308	10.50	9,310	0.80	0.43
	Anxiolytics	1,442	2.05	4,009	0.26	0.17	159	1.28	2,146	0.18	0.13
	Atypical antipsychotics	217	0.31	952	0.06	0.06	16	0.13	150	0.01	0.04
	Barbiturates	3,906	5.54	10,436	0.68	0.28	1,183	9.50	9,390	0.81	0.40
	Clomiphene	13	0.02	123	0.01	0.01	384	3.08	28,456	2.44	0.04
	Corticosteroids	17,818	25.29	148,555	9.70	0.42	3,760	30.19	136,787	11.74	0.47
	Folate Supplementation	37,659	53.46	679,575	44.35	0.18	4,885	39.22	402,624	34.55	0.10
	Gonadotropin	<11***	0.00	15	0.00	0.00	569	4.57	25,009	2.15	0.13
	Mood stabilizers	3,665	5.20	14,233	0.93	0.25	684	5.49	6,800	0.58	0.29
	Other hypnotics	8,736	12.40	41,482	2.71	0.37	1,669	13.40	16,123	1.38	0.47
	Progestins	5,146	7.30	63,988	4.18	0.13	2,261	18.15	140,325	12.04	0.17
	Triptans	3,604	5.12	10,322	0.67	0.27	1,181	9.48	11,460	0.98	0.39
	Typical antipsychotics	3,267	4.64	14,921	0.97	0.22	212	1.70	1,952	0.17	0.16
General markers of comorbidity, mean (SD)											
	Obstetric comorbidity index	0.52	0.97	0.24	0.64	0.34	0.72	1.04	0.49	0.82	0.25
	N distinct non-opioid prescription drugs	3.82	3.49	1.12	1.79	0.97	3.70	3.43	1.20	1.82	0.91

		MAX 2000-2014					*MarketScan 2003-2015*				
		Exposed		**Unexposed**			**Exposed**		**Unexposed**		
		N/Mean	**%/SD**	**N/Mean**	**%/SD**	**Stdiff**	**N/Mean**	**%/SD**	**N/Mean**	**%/SD**	**Stdiff**
	N distinct diagnoses	5.55	4.81	2.08	2.62	0.90	4.28	4.07	1.87	2.35	0.72
	N emergency room visits	0.96	1.73	0.20	0.61	0.59	0.24	0.80	0.03	0.23	0.35
	N hospitalizations	0.07	0.32	0.03	0.18	0.18	0.03	0.19	0.00	0.06	0.19
	N outpatient visits	4.26	4.87	1.55	2.92	0.67	4.05	4.44	1.85	2.98	0.58
Multiple gestation, N (%)		1,142	1.62	19,645	1.28	0.03	435	3.49	22,949	1.97	0.09
Multiparity, N (%)		57,309	81.35	1,087,559	70.98	0.25	*	*	*	*	*

* Information not available for MarketScan.
** 2011-2014 for MAX.
*** Cell size <11 for MAX cohort. Numbers suppressed in accord with the CMS cell size suppression policy.
Abbreviations: N, number; SD, standard deviation; Stdiff, standardized difference.

eTable 4 Cohort Characteristics of Pregnancies With and Without Exposure to Opioids During the First Trimester (Propensity Score Weighted).

		MAX 2000-2014					***MarketScan 2003-2015***				
		Exposed		**Unexposed**			**Exposed**		**Unexposed**		
		N/Mean	**%/SD**	**N/Mean**	**%/SD**	**Stdiff**	**N/Mean**	**%/SD**	**N/Mean**	**%/SD**	**Stdiff**
Total		70,074		1,532,118			12,430		1,152,470		
Age, mean (SD)		26.02	5.47	25.90	5.59	0.02	32.00	32.08	4.85	4.92	-0.02
Year of delivery, N (%)											
	2000-2002	5,228	7.46	120,720	7.88	-0.02	*	*	*	*	*
	2003-2005	15,660	22.35	352,505	23.01	-0.02	1,221	9.82	112,208	9.74	0.00
	2006-2010	30,351	43.32	637,860	41.63	0.03	5,715	45.98	528,656	45.88	0.00
	2011-2015**	18,835	26.87	421,033	27.47	-0.01	5,494	44.19	511,606	44.40	0.00
Race/Ethnicity, N (%)											
	White	45,015	64.24	984,729	64.27	0.00	*	*	*	*	*
	Black	15,015	21.43	330,963	21.60	0.00	*	*	*	*	*
	Hispanic	5,160	7.36	111,896	7.30	0.00	*	*	*	*	*
	Other or unknown	4,884	6.96	104,530	6.82	0.01	*	*	*	*	*
Opioid indications, N (%)											
	Abdominal pain	27,543	39.31	624,298	40.75	-0.03	3,030	24.38	283,167	24.57	0.00
	Back/neck pain	28,850	41.17	629,888	41.11	0.00	4,523	36.39	434,201	37.68	-0.03
	Dental problems	11,460	16.35	253,711	16.56	-0.01	216	1.74	19,924	1.73	0.00
	Fibromyalgia	3,282	4.68	77,678	5.07	-0.02	775	6.23	78,666	6.83	-0.02
	Joint pain	12,093	17.26	270,883	17.68	-0.01	1,626	13.08	151,651	13.16	0.00
	Migraine/headache	16,556	23.63	385,438	25.16	-0.04	2,843	22.87	277,320	24.06	-0.03
	Orthopedic injury	16,196	23.11	353,848	23.10	0.00	1,925	15.49	178,014	15.45	0.00
	Surgery	6,475	9.24	134,270	8.76	0.02	1,359	10.93	117,529	10.20	0.02
	Arthritis/arthropathy, musculoskeletal pain	21,962	31.34	492,131	32.12	-0.02	3,256	26.19	306,259	26.57	-0.01
	Complex regional pain syndrome	83	0.12	688	0.04	0.03	28	0.23	3,417	0.30	-0.01
	Cough	5,105	7.29	117,633	7.68	-0.01	695	5.59	65,961	5.72	-0.01
	Generalized pain	411	0.59	8,404	0.55	0.01	60	0.48	6,076	0.53	-0.01
	Gout	74	0.11	1,970	0.13	-0.01	22	0.18	1,918	0.17	0.00
	Infection	8,046	11.48	169,850	11.09	0.01	693	5.58	63,843	5.54	0.00

		MAX 2000-2014					*MarketScan 2003-2015*				
		Exposed		**Unexposed**			**Exposed**		**Unexposed**		
		N/Mean	**%/SD**	**N/Mean**	**%/SD**	**Stdiff**	**N/Mean**	**%/SD**	**N/Mean**	**%/SD**	**Stdiff**
	Osteoarthritis	1,452	2.07	34,518	2.25	-0.01	235	1.89	20,004	1.74	0.01
	Other neuropathies	6,465	9.23	137,277	8.96	0.01	1,515	12.19	141,811	12.30	0.00
	Other pain	3,675	5.24	75,665	4.94	0.01	572	4.60	51,010	4.43	0.01
	Pain related to psychological factors	113	0.16	2,770	0.18	0.00	21	0.17	1,381	0.12	0.01
	Peripheral neuropathy	29	0.04	915	0.06	-0.01	9	0.07	823	0.07	0.00
	Post herpetic neuralgia	12	0.02	86	0.01	0.01	10	0.08	1,612	0.14	-0.02
	Rheumatoid arthritis	324	0.46	5,953	0.39	0.01	105	0.84	8,952	0.78	0.01
	Sciatica	1,549	2.21	31,840	2.08	0.01	330	2.65	29,034	2.52	0.01
	Sickle cell disease	369	0.53	7,071	0.46	0.01	20	0.16	1,875	0.16	0.00
	Trigeminal neuralgia	47	0.07	2,201	0.14	-0.02	23	0.19	2,886	0.25	-0.01
	Urinary calculus	2,196	3.13	44,039	2.87	0.02	490	3.94	40,409	3.51	0.02
Maternal conditions, N (%)											
	Anxiety	9,324	13.31	207,851	13.57	-0.01	1,188	9.56	112,635	9.77	-0.01
	Depression	10,783	15.39	253,206	16.53	-0.03	1,457	11.72	139,548	12.11	-0.01
	Diabetes	2,452	3.50	56,264	3.67	-0.01	339	2.73	31,067	2.70	0.00
	Hypertension	4,439	6.33	98,368	6.42	0.00	825	6.64	75,969	6.59	0.00
	Alcohol abuse or dependence	965	1.38	23,362	1.52	-0.01	46	0.37	3,564	0.31	0.01
	Amphetamine abuse or dependence	280	0.40	5,570	0.36	0.01	3	0.02	459	0.04	-0.01
	Cocaine abuse or dependence	343	0.49	9,220	0.60	-0.02	2	0.02	140	0.01	0.00
	Hallucinogen abuse or dependence	<11***	0.01	108	0.01	0.00	0	0.00	0	0.00	.
	Infertility	400	0.57	8,629	0.56	0.00	1,263	10.16	124,926	10.84	-0.02
	Marijuana abuse or dependence	723	1.03	17,245	1.13	-0.01	10	0.08	673	0.06	0.01
	Obesity or overweight	3,201	4.57	71,156	4.64	0.00	489	3.93	46,009	3.99	0.00
	Posttraumatic stress disorder	1,111	1.59	27,166	1.77	-0.01	70	0.56	8,455	0.73	-0.02
	Renal disease	203	0.29	4,776	0.31	0.00	87	0.70	7,970	0.69	0.00
	Sarcoidosis	43	0.06	1,283	0.08	-0.01	2	0.02	190	0.02	0.00
	Sedative hypnotic use disorder	86	0.12	1,736	0.11	0.00	5	0.04	309	0.03	0.01
	Sleep disorder	2,230	3.18	55,395	3.62	-0.02	549	4.42	50,604	4.39	0.00

		MAX 2000-2014					*MarketScan 2003-2015*				
		Exposed		**Unexposed**			**Exposed**		**Unexposed**		
		N/Mean	**%/SD**	**N/Mean**	**%/SD**	**Stdiff**	**N/Mean**	**%/SD**	**N/Mean**	**%/SD**	**Stdiff**
	Tobacco use	8,812	12.58	191,161	12.48	0.00	606	4.88	50,555	4.39	0.02
Concomitant medications, N (%)											
	Antidepressants	21,002	29.97	482,632	31.50	-0.03	3,697	29.74	342,963	29.76	0.00
	Antiemetics	27,289	38.94	593,935	38.77	0.00	5,481	44.09	513,389	44.55	-0.01
	Antihypertensives	6,108	8.72	137,786	8.99	-0.01	1,305	10.50	117,523	10.20	0.01
	Benzodiazepines	14,340	20.46	307,909	20.10	0.01	2,952	23.75	264,276	22.93	0.02
	Anti-diabetics	1,390	1.98	32,018	2.09	-0.01	556	4.47	52,196	4.53	0.00
	Insulin	1,280	1.83	29,833	1.95	-0.01	265	2.13	25,598	2.22	-0.01
	Psychostimulants	1,819	2.60	42,073	2.75	-0.01	522	4.20	44,927	3.90	0.02
	Suspected teratogens	16,309	23.27	357,238	23.32	0.00	2,094	16.85	195,552	16.97	0.00
	Antibiotics	53,099	75.78	1,173,517	76.59	-0.02	8,386	67.47	803,993	69.76	-0.05
	Anticonvulsants	7,435	10.61	172,260	11.24	-0.02	1,298	10.44	113,085	9.81	0.02
	Anxiolytics	1,410	2.01	36,562	2.39	-0.03	157	1.26	15,256	1.32	-0.01
	Atypical antipsychotics	214	0.31	5,214	0.34	-0.01	16	0.13	2,315	0.20	-0.02
	Barbiturates	3,831	5.47	81,998	5.35	0.01	1,170	9.41	106,263	9.22	0.01
	Clomiphene	13	0.02	241	0.02	0.00	383	3.08	37,266	3.23	-0.01
	Corticosteroids	17,633	25.16	396,749	25.90	-0.02	3,749	30.16	359,271	31.17	-0.02
	Folate Supplementation	37,473	53.48	828,743	54.09	-0.01	4,876	39.23	456,494	39.61	-0.01
	Gonadotropin	<11***	0.00	<11***	0.00	0.01	567	4.56	56,742	4.92	-0.02
	Mood stabilizers	3,618	5.16	79,957	5.22	0.00	680	5.47	60,262	5.23	0.01
	Other hypnotics	8,608	12.28	187,804	12.26	0.00	1,663	13.38	143,308	12.43	0.03
	Progestins	5,096	7.27	110,642	7.22	0.00	2,255	18.14	215,294	18.68	-0.01
	Triptans	3,541	5.05	87,064	5.68	-0.03	1,171	9.42	114,559	9.94	-0.02
	Typical antipsychotics	3,215	4.59	72,488	4.73	-0.01	208	1.67	18,960	1.65	0.00
General markers of comorbidity, mean (SD)											
	Obstetric comorbidity index	0.52	0.96	0.53	0.97	-0.01	0.72	0.74	1.04	1.04	-0.02
	N distinct non-opioid prescription drugs	3.79	3.46	3.64	3.24	0.04	3.69	3.59	3.42	3.14	0.03

		MAX 2000-2014					*MarketScan 2003-2015*				
		Exposed		**Unexposed**			**Exposed**		**Unexposed**		
		N/Mean	**%/SD**	**N/Mean**	**%/SD**	**Stdiff**	**N/Mean**	**%/SD**	**N/Mean**	**%/SD**	**Stdiff**
	N distinct diagnoses	5.48	4.70	5.71	4.92	-0.05	4.25	4.60	4.02	4.44	-0.08
	N emergency room visits	0.93	1.66	0.85	1.53	0.05	0.23	0.20	0.76	0.58	0.06
	N hospitalizations	0.07	0.32	0.07	0.29	0.01	0.03	0.03	0.19	0.18	0.01
	N outpatient visits	4.21	4.79	4.47	5.83	-0.05	4.03	4.53	4.42	5.21	-0.10
Multiple gestation, N (%)		1,135	1.62	22,917	1.50	0.01	435	3.50	42,343	3.67	-0.01
Multiparity, N (%)		57,007	81.35	1,233,226	80.49	0.02	*	*	*	*	*

* Information not available for MarketScan.
** 2011-2014 for MAX.
*** Cell size <11 for MAX cohort. Numbers suppressed in accord with the CMS cell size suppression policy.
Abbreviations: N, number; SD, standard deviation; Stdiff, standardized difference.

eTable 5 Absolute Risk of Congenital Malformations (Primary Outcomes) Among Infants Born to Mothers With and Without Exposure to Opioids.

	MAX 2000-2014			MarketScan 2003-2015		
	Events	Total	Risk	Events	Total	Risk
	no. of affected infants	*no. of pregnancies*	*no./1,000 infants (95 % CI)*	*no. of affected infants*	*no. of pregnancies*	*no./1,000 infants (95 % CI)*
Any Congenital Malformation						
Exposed	2,887	70,447	40.98 (39.52 - 42.45)	530	12,454	42.56 (39.01 - 46.10)
Unexposed	48,996	1,532,133	31.98 (31.70 - 32.26)	43,470	1,165,222	37.31 (36.96 - 37.65)
Any Cardiovascular Malformation						
Exposed	768	70,447	10.90 (10.13 - 11.67)	144	12,454	11.56 (9.68 - 13.44)
Unexposed	12,800	1,532,133	8.35 (8.21 - 8.50)	10,521	1,165,222	9.03 (8.86 - 9.20)
Ventricular Septal Defect						
Exposed	343	70,447	4.87 (4.35 - 5.38)	79	12,454	6.34 (4.95 - 7.74)
Unexposed	5,973	1,532,133	3.90 (3.80 - 4.00)	5,778	1,165,222	4.96 (4.83 - 5.09)
Secundum Atrial Septal Defect/Patent Foramen Ovale						
Exposed	181	70,447	2.57 (2.20 - 2.94)	34	12,454	2.73 (1.81 - 3.65)
Unexposed	2,736	1,532,133	1.79 (1.72 - 1.85)	2,854	1,165,222	2.45 (2.36 - 2.54)
Neural Tube Defect						
Exposed	28	70,447	0.40 (0.25 - 0.54)	6	12,454	0.48 (0.10 - 0.87)
Unexposed	553	1,532,133	0.36 (0.33 - 0.39)	424	1,165,222	0.36 (0.33 - 0.40)
Club Foot						
Exposed	155	70,447	2.20 (1.85 - 2.55)	20	12,454	1.61 (0.90 - 2.31)
Unexposed	2,356	1,532,133	1.54 (1.48 - 1.60)	1,781	1,165,222	1.53 (1.46 - 1.60)
Oral Cleft						
Exposed	109	70,447	1.55 (1.26 - 1.84)	28	12,454	2.25 (1.42 - 3.08)
Unexposed	1,702	1,532,133	1.11 (1.06 - 1.16)	1,441	1,165,222	1.24 (1.17 - 1.30)

Abbreviations: CI, confidence interval; no., number.

eTable 6 Risk of Congenital Malformations (Primary Outcomes) in Infants Following Exposure to Opioids During the First Trimester: Sensitivity Analyses.

	Unadjusted			Propensity Score Weighted		
	Exposed to Opioids	**Unexposed**	**Relative Risk (95% CI)**	**Exposed to Opioids**	**Unexposed**	**Relative Risk (95% CI)**
	No. of Events / Total No. Of Infants	No. of Events / Total No. Of Infants		No. of Events / Total No. Of Infants	No. of Events / Total No. Of Infants	
A) ANY CONGENITAL MALFORMATION						
Hd-PS estimate						
MAX	N/A	N/A	N/A	2869 / 70112	48996 / 1532133	1.10 (1.05 - 1.15)
MarketScan	N/A	N/A	N/A	529 / 12427	43470 / 1165221	1.01 (0.93 - 1.11)
Pooled	N/A	N/A	N/A	3398 / 82539	92466 / 2697354	1.08 (1.04 - 1.13)
Discontinuers as referent						
MAX	2037 / 48279	8169 / 223569	1.15 (1.10 - 1.21)	2033 / 48226	8168 / 223454	1.00 (0.95 - 1.06)
MarketScan	311 / 7451	3807 / 92713	1.02 (0.91 - 1.14)	311 / 7449	3793 / 92436	0.93 (0.82 - 1.05)
Pooled	2348 / 55730	11976 / 316282	1.13 (1.08 - 1.18)	2344 / 55675	11961 / 315890	0.99 (0.94 - 1.04)
Excluding women with aberrant opioid filling patterns						
MAX	2213 / 54800	48996 / 1532133	1.26 (1.21 - 1.32)	2209 / 54735	48996 / 1532114	1.07 (1.02 - 1.12)
MarketScan	509 / 12016	43470 / 1165222	1.14 (1.04 - 1.24)	508 / 12006	42929 / 1153073	1.01 (0.92 - 1.10)
Pooled	2722 / 66816	92466 / 2697355	1.24 (1.19 - 1.28)	2717 / 66741	91925 / 2685187	1.06 (1.01 - 1.10)
Restriction to women with folate supplementation						
MAX	1570 / 37659	22750 / 679575	1.25 (1.18 - 1.31)	1570 / 37659	22717 / 678358	1.05 (0.99 - 1.12)
MarketScan	196 / 4885	15045 / 402624	1.07 (0.94 - 1.23)	196 / 4874	14801 / 396869	0.97 (0.84 - 1.12)
Pooled	1766 / 42544	37795 / 1082199	1.22 (1.17 - 1.28)	1766 / 42533	37518 / 1075227	1.04 (0.98 - 1.10)
Late first trimester exposure						
MAX	1999 / 48148	48996 / 1532133	1.30 (1.24 - 1.36)	1991 / 47982	48996 / 1532133	1.09 (1.03 - 1.15)
MarketScan	349 / 8052	43470 / 1165222	1.16 (1.05 - 1.29)	348 / 8033	42604 / 1145452	1.03 (0.93 - 1.16)
Pooled	2348 / 56200	92466 / 2697355	1.28 (1.23 - 1.33)	2339 / 56015	91600 / 2677585	1.08 (1.03 - 1.13)
Outcome assessment to 365 days						
MAX	3696 / 56921	63361 / 1238327	1.27 (1.23 - 1.31)	3696 / 56895	63353 / 1237985	0.97 (0.94 - 1.00)
MarketScan	776 / 8983	64228 / 851107	1.14 (1.07 - 1.22)	776 / 8983	63877 / 847613	0.97 (0.91 - 1.04)
Pooled	4472 / 65904	127589 / 2089434	1.25 (1.21 - 1.28)	4472 / 65878	127230 / 2085598	0.97 (0.94 - 1.00)

Negative control analysis						
MAX	935 / 26147	43030 / 1354414	1.13 (1.06 - 1.20)	935 / 26147	42960 / 1352772	1.04 (0.98 - 1.11)
MarketScan	259 / 7695	40319 / 1082135	0.90 (0.80 - 1.02)	259 / 7695	40287 / 1081268	0.92 (0.81 - 1.03)
Pooled	1194 / 33842	83349 / 2436549	1.07 (1.01 - 1.13)	1194 / 33842	83247 / 2434040	1.01 (0.96 - 1.07)
Hydrocodone						
MAX	1449 / 35259	48996 / 1532133	1.29 (1.22 - 1.35)	1444 / 35066	48817 / 1525321	1.06 (0.99 - 1.13)
MarketScan	234 / 5775	43470 / 1165222	1.09 (0.96 - 1.23)	234 / 5774	42763 / 1148210	0.93 (0.82 - 1.06)
Pooled	1683 / 41034	92466 / 2697355	1.25 (1.20 - 1.32)	1678 / 40840	91580 / 2673531	1.03 (0.98 - 1.09)
Oxycodone						
MAX	288 / 7019	48996 / 1532133	1.28 (1.15 - 1.44)	281 / 6945	44313 / 1357932	1.00 (0.87 - 1.14)
MarketScan	80 / 1467	43470 / 1165222	1.46 (1.18 - 1.81)	80 / 1440	33409 / 872696	1.20 (0.96 - 1.50)
Pooled	368 / 8486	92466 / 2697355	1.32 (1.19 - 1.46)	361 / 8385	77722 / 2230628	1.05 (0.94 - 1.18)
Codeine						
MAX	352 / 9501	48996 / 1532133	1.16 (1.05 - 1.28)	346 / 9431	48541 / 1520158	1.05 (0.94 - 1.17)
MarketScan	57 / 1549	43470 / 1165222	0.99 (0.76 - 1.27)	57 / 1529	43035 / 1155583	0.87 (0.67 - 1.13)
Pooled	409 / 11050	92466 / 2697355	1.13 (1.03 - 1.25)	403 / 10960	91576 / 2675741	1.02 (0.92 - 1.13)
Dose Analysis: <= 300 MME						
MAX	1078 / 27495	48996 / 1532133	1.23 (1.16 - 1.30)	1075 / 27436	48729 / 1524384	1.07 (1.00 - 1.14)
MarketScan	130 / 3297	43470 / 1165222	1.06 (0.89 - 1.25)	130 / 3296	42862 / 1152097	0.95 (0.80 - 1.13)
Pooled	1208 / 30792	92466 / 2697355	1.21 (1.14 - 1.28)	1205 / 30732	91591 / 2676481	1.05 (0.99 - 1.12)
Dose Analysis: >300 MME - <=600 MME						
MAX	620 / 14568	48996 / 1532133	1.33 (1.23 - 1.44)	616 / 14483	48751 / 1523762	1.09 (1.00 - 1.19)
MarketScan	91 / 2133	43470 / 1165222	1.14 (0.94 - 1.40)	91 / 2129	42214 / 1136288	1.02 (0.83 - 1.26)
Pooled	711 / 16701	92466 / 2697355	1.31 (1.21 - 1.40)	707 / 16612	90965 / 2660050	1.08 (0.99 - 1.17)
Dose Analysis: >600 - <=1200 MME						
MAX	475 / 11337	48996 / 1532133	1.31 (1.20 - 1.43)	473 / 11311	48995 / 1532132	1.04 (0.95 - 1.15)
MarketScan	79 / 1825	43470 / 1165222	1.16 (0.94 - 1.44)	79 / 1818	43463 / 1165114	1.03 (0.82 - 1.29)
Pooled	554 / 13162	92466 / 2697355	1.29 (1.18 - 1.40)	552 / 13129	92458 / 2697246	1.04 (0.95 - 1.14)
Dose Analysis: >1200 MME						
MAX	667 / 15808	48996 / 1532133	1.32 (1.22 - 1.42)	664 / 15759	48918 / 1528506	1.04 (0.94 - 1.14)
MarketScan	208 / 4685	43470 / 1165222	1.19 (1.04 - 1.36)	208 / 4657	42822 / 1150112	1.02 (0.88 - 1.18)

Pooled	875 / 20493	92466 / 2697355	1.29 (1.21 - 1.37)	872 / 20416	91740 / 2678618	1.03 (0.95 - 1.11)

B) ANY CARDIOVASCULAR MALFORMATION						
Hd-PS estimate						
MAX	N/A	N/A	N/A	763 / 70112	12800 / 1532133	1.09 (0.99 - 1.19)
MarketScan	N/A	N/A	N/A	144 / 12427	10521 / 1165221	1.12 (0.94 - 1.35)
Pooled	N/A	N/A	N/A	907 / 82539	23321 / 2697354	1.09 (1.01 - 1.19)
Discontinuers as referent						
MAX	553 / 48279	2181 / 223569	1.17 (1.07 - 1.29)	552 / 48226	2181 / 223454	0.99 (0.89 - 1.10)
MarketScan	93 / 7451	976 / 92713	1.19 (0.96 - 1.46)	93 / 7449	972 / 92436	1.07 (0.84 - 1.35)
Pooled	646 / 55730	3157 / 316282	1.18 (1.08 - 1.28)	645 / 55675	3153 / 315890	1.00 (0.91 - 1.10)
Excluding women with aberrant opioid filling patterns						
MAX	594 / 54800	12800 / 1532133	1.30 (1.20 - 1.41)	593 / 54735	12800 / 1532114	1.09 (0.99 - 1.20)
MarketScan	135 / 12016	10521 / 1165222	1.24 (1.05 - 1.47)	135 / 12006	10407 / 1153073	1.10 (0.92 - 1.33)
Pooled	729 / 66816	23321 / 2697355	1.29 (1.20 - 1.39)	728 / 66741	23207 / 2685187	1.09 (1.00 - 1.19)
Restriction to women with folate supplementation						
MAX	401 / 37659	5822 / 679575	1.24 (1.12 - 1.37)	401 / 37659	5814 / 678358	1.04 (0.92 - 1.18)
MarketScan	53 / 4885	3689 / 402624	1.18 (0.90 - 1.55)	53 / 4874	3642 / 396869	1.10 (0.82 - 1.48)
Pooled	454 / 42544	9511 / 1082199	1.24 (1.12 - 1.36)	454 / 42533	9456 / 1075227	1.05 (0.94 - 1.18)
Late first trimester exposure						
MAX	537 / 48148	12800 / 1532133	1.34 (1.23 - 1.45)	534 / 47982	12800 / 1532133	1.12 (1.01 - 1.24)
MarketScan	99 / 8052	10521 / 1165222	1.36 (1.12 - 1.66)	99 / 8033	10341 / 1145452	1.20 (0.97 - 1.49)
Pooled	636 / 56200	23321 / 2697355	1.34 (1.24 - 1.45)	633 / 56015	23141 / 2677585	1.13 (1.03 - 1.24)
Outcome assessment to 365 days						
MAX	907 / 56921	15259 / 1238327	1.29 (1.21 - 1.38)	907 / 56895	15258 / 1237985	1.05 (0.98 - 1.12)
MarketScan	160 / 8983	12232 / 851107	1.24 (1.06 - 1.45)	160 / 8983	12169 / 847613	1.15 (0.99 - 1.35)
Pooled	1067 / 65904	27491 / 2089434	1.28 (1.21 - 1.37)	1067 / 65878	27427 / 2085598	1.06 (1.00 - 1.13)
Negative control analysis						
MAX	241 / 26147	11266 / 1354414	1.11 (0.98 - 1.26)	241 / 26147	11245 / 1352772	1.05 (0.92 - 1.19)
MarketScan	57 / 7695	9749 / 1082135	0.82 (0.63 - 1.07)	57 / 7695	9740 / 1081268	0.82 (0.63 - 1.06)
Pooled	298 / 33842	21015 / 2436549	1.05 (0.93 - 1.17)	298 / 33842	20985 / 2434040	1.00 (0.89 - 1.12)
Hydrocodone						

MAX	374 / 35259	12800 / 1532133	1.27 (1.15 - 1.41)	372 / 35066	12751 / 1525321	1.01 (0.89 - 1.14)
MarketScan	65 / 5775	10521 / 1165222	1.25 (0.98 - 1.59)	65 / 5774	10371 / 1148210	1.08 (0.83 - 1.39)
Pooled	439 / 41034	23321 / 2697355	1.27 (1.15 - 1.39)	437 / 40840	23122 / 2673531	1.02 (0.91 - 1.14)
Oxycodone						
MAX	75 / 7019	12800 / 1532133	1.28 (1.02 - 1.60)	73 / 6945	11576 / 1357932	0.99 (0.76 - 1.28)
MarketScan	20 / 1467	10521 / 1165222	1.51 (0.98 - 2.33)	20 / 1440	7964 / 872696	1.30 (0.82 - 2.06)
Pooled	95 / 8486	23321 / 2697355	1.32 (1.08 - 1.62)	93 / 8385	19540 / 2230628	1.05 (0.84 - 1.32)
Codeine						
MAX	110 / 9501	12800 / 1532133	1.39 (1.15 - 1.67)	108 / 9431	12679 / 1520158	1.23 (1.01 - 1.50)
MarketScan	12 / 1549	10521 / 1165222	0.86 (0.49 - 1.51)	12 / 1529	10406 / 1155583	0.72 (0.40 - 1.28)
Pooled	122 / 11050	23321 / 2697355	1.32 (1.11 - 1.58)	120 / 10960	23085 / 2675741	1.16 (0.97 - 1.40)
Dose Analysis: <= 300 MME						
MAX	263 / 27495	12800 / 1532133	1.15 (1.01 - 1.29)	262 / 27436	12734 / 1524384	1.00 (0.87 - 1.14)
MarketScan	32 / 3297	10521 / 1165222	1.07 (0.76 - 1.52)	32 / 3296	10387 / 1152097	0.97 (0.69 - 1.37)
Pooled	295 / 30792	23321 / 2697355	1.14 (1.01 - 1.28)	294 / 30732	23121 / 2676481	0.99 (0.88 - 1.13)
Dose Analysis: >300 MME - <=600 MME						
MAX	179 / 14568	12800 / 1532133	1.47 (1.27 - 1.70)	178 / 14483	12738 / 1523762	1.22 (1.04 - 1.44)
MarketScan	23 / 2133	10521 / 1165222	1.19 (0.80 - 1.79)	23 / 2129	10258 / 1136288	1.06 (0.70 - 1.60)
Pooled	202 / 16701	23321 / 2697355	1.44 (1.25 - 1.65)	201 / 16612	22996 / 2660050	1.20 (1.03 - 1.40)
Dose Analysis: >600 - <=1200 MME						
MAX	129 / 11337	12800 / 1532133	1.36 (1.15 - 1.62)	128 / 11311	12800 / 1532132	1.04 (0.86 - 1.25)
MarketScan	24 / 1825	10521 / 1165222	1.46 (0.98 - 2.17)	24 / 1818	10520 / 1165114	1.25 (0.82 - 1.92)
Pooled	153 / 13162	23321 / 2697355	1.38 (1.18 - 1.61)	152 / 13129	23320 / 2697246	1.07 (0.90 - 1.27)
Dose Analysis: >1200 MME						
MAX	179 / 15808	12800 / 1532133	1.36 (1.17 - 1.57)	177 / 15759	12782 / 1528506	0.99 (0.82 - 1.18)
MarketScan	59 / 4685	10521 / 1165222	1.39 (1.08 - 1.80)	59 / 4657	10374 / 1150112	1.21 (0.91 - 1.62)
Pooled	238 / 20493	23321 / 2697355	1.37 (1.20 - 1.55)	236 / 20416	23156 / 2678618	1.04 (0.90 - 1.22)

C) VENTRICULAR SEPTAL DEFECT						
Hd-PS estimate						
MAX	N/A	N/A	N/A	340 / 70112	5973 / 1532133	1.10 (0.96 - 1.26)
MarketScan	N/A	N/A	N/A	79 / 12427	5778 / 1165221	1.12 (0.87 - 1.44)

Pooled	N/A	N/A	N/A	419 / 82539	11751 / 2697354	1.10 (0.98 - 1.24)
Discontinuers as referent						
MAX	242 / 48279	1023 / 223569	1.10 (0.95 - 1.26)	241 / 48226	1023 / 223454	0.93 (0.78 - 1.09)
MarketScan	51 / 7451	489 / 92713	1.30 (0.97 - 1.73)	51 / 7449	488 / 92436	1.21 (0.86 - 1.68)
Pooled	293 / 55730	1512 / 316282	1.13 (1.00 - 1.28)	292 / 55675	1511 / 315890	0.97 (0.84 - 1.13)
Excluding women with aberrant opioid filling patterns						
MAX	267 / 54800	5973 / 1532133	1.25 (1.11 - 1.41)	267 / 54735	5973 / 1532114	1.08 (0.94 - 1.25)
MarketScan	74 / 12016	5778 / 1165222	1.24 (0.99 - 1.56)	74 / 12006	5716 / 1153073	1.10 (0.85 - 1.42)
Pooled	341 / 66816	11751 / 2697355	1.25 (1.12 - 1.39)	341 / 66741	11689 / 2685187	1.09 (0.96 - 1.23)
Restriction to women with folate supplementation						
MAX	180 / 37659	2741 / 679575	1.19 (1.02 - 1.38)	180 / 37659	2736 / 678358	1.04 (0.86 - 1.26)
MarketScan	34 / 4885	2062 / 402624	1.36 (0.97 - 1.91)	34 / 4874	2041 / 396869	1.12 (0.77 - 1.62)
Pooled	214 / 42544	4803 / 1082199	1.21 (1.06 - 1.39)	214 / 42533	4777 / 1075227	1.05 (0.89 - 1.25)
Late first trimester exposure						
MAX	242 / 48148	5973 / 1532133	1.29 (1.13 - 1.47)	240 / 47982	5973 / 1532133	1.12 (0.96 - 1.31)
MarketScan	52 / 8052	5778 / 1165222	1.30 (0.99 - 1.71)	52 / 8033	5676 / 1145452	1.14 (0.84 - 1.55)
Pooled	294 / 56200	11751 / 2697355	1.29 (1.15 - 1.45)	292 / 56015	11649 / 2677585	1.13 (0.98 - 1.29)
Outcome assessment to 365 days						
MAX	342 / 56921	6221 / 1238327	1.20 (1.07 - 1.33)	342 / 56895	6221 / 1237985	1.08 (0.97 - 1.20)
MarketScan	83 / 8983	5709 / 851107	1.38 (1.11 - 1.71)	83 / 8983	5683 / 847613	1.29 (1.04 - 1.61)
Pooled	425 / 65904	11930 / 2089434	1.23 (1.12 - 1.36)	425 / 65878	11904 / 2085598	1.12 (1.01 - 1.23)
Negative control analysis						
MAX	107 / 26147	5278 / 1354414	1.05 (0.87 - 1.27)	107 / 26147	5269 / 1352772	1.00 (0.83 - 1.22)
MarketScan	24 / 7695	5379 / 1082135	0.63 (0.42 - 0.94)	24 / 7695	5373 / 1081268	0.62 (0.42 - 0.93)
Pooled	131 / 33842	10657 / 2436549	0.95 (0.80 - 1.13)	131 / 33842	10642 / 2434040	0.92 (0.77 - 1.09)
Hydrocodone						
MAX	161 / 35259	5973 / 1532133	1.17 (1.00 - 1.37)	159 / 35066	5954 / 1525321	0.99 (0.81 - 1.20)
MarketScan	33 / 5775	5778 / 1165222	1.15 (0.82 - 1.62)	33 / 5774	5694 / 1148210	1.01 (0.70 - 1.45)
Pooled	194 / 41034	11751 / 2697355	1.17 (1.01 - 1.35)	192 / 40840	11648 / 2673531	0.99 (0.83 - 1.18)
Oxycodone						
MAX	34 / 7019	5973 / 1532133	1.24 (0.89 - 1.74)	32 / 6945	5385 / 1357932	0.93 (0.61 - 1.40)

MarketScan	13 / 1467	5778 / 1165222	1.79 (1.04 - 3.07)	13 / 1440	4328 / 872696	1.69 (0.91 - 3.15)
Pooled	47 / 8486	11751 / 2697355	1.37 (1.03 - 1.83)	45 / 8385	9713 / 2230628	1.11 (0.79, 1.57)
Codeine						
MAX	49 / 9501	5973 / 1532133	1.32 (1.00 - 1.75)	47 / 9431	5914 / 1520158	1.20 (0.88 - 1.62)
MarketScan	6 / 1549	5778 / 1165222	0.78 (0.35 - 1.74)	6 / 1529	5708 / 1155583	0.68 (0.30 - 1.55)
Pooled	55 / 11050	11751 / 2697355	1.25 (0.96 - 1.63)	53 / 10960	11622 / 2675741	1.12 (0.84 - 1.49)
Dose Analysis: <= 300 MME						
MAX	122 / 27495	5973 / 1532133	1.14 (0.95 - 1.36)	121 / 27436	5940 / 1524384	1.06 (0.87 - 1.29)
MarketScan	14 / 3297	5778 / 1165222	0.86 (0.51 - 1.45)	14 / 3296	5699 / 1152097	0.78 (0.46 - 1.32)
Pooled	136 / 30792	11751 / 2697355	1.10 (0.93 - 1.31)	135 / 30732	11639 / 2676481	1.02 (0.85 - 1.23)
Dose Analysis: >300 MME - <=600 MME						
MAX	67 / 14568	5973 / 1532133	1.18 (0.93 - 1.50)	66 / 14483	5946 / 1523762	1.04 (0.80 - 1.36)
MarketScan	15 / 2133	5778 / 1165222	1.42 (0.86 - 2.35)	15 / 2129	5629 / 1136288	1.26 (0.74 - 2.13)
Pooled	82 / 16701	11751 / 2697355	1.22 (0.98 - 1.52)	81 / 16612	11575 / 2660050	1.08 (0.85 - 1.37)
Dose Analysis: >600 - <=1200 MME						
MAX	58 / 11337	5973 / 1532133	1.31 (1.01 - 1.70)	57 / 11311	5973 / 1532132	1.05 (0.79 - 1.41)
MarketScan	16 / 1825	5778 / 1165222	1.77 (1.08 - 2.88)	16 / 1818	5778 / 1165114	1.62 (0.95 - 2.76)
Pooled	74 / 13162	11751 / 2697355	1.40 (1.11 - 1.76)	73 / 13129	11751 / 2697246	1.16 (0.90 - 1.50)
Dose Analysis: >1200 MME						
MAX	85 / 15808	5973 / 1532133	1.38 (1.11 - 1.71)	83 / 15759	5964 / 1528506	1.01 (0.76 - 1.33)
MarketScan	30 / 4685	5778 / 1165222	1.29 (0.90 - 1.85)	30 / 4657	5698 / 1150112	1.05 (0.67 - 1.64)
Pooled	115 / 20493	11751 / 2697355	1.36 (1.13 - 1.63)	113 / 20416	11662 / 2678618	1.02 (0.81 - 1.29)

D) SECUNDUM ATRIAL SEPTAL DEFECT/PATENT FORAMEN OVALE						
Hd-PS estimate						
MAX	N/A	N/A	N/A	180 / 70112	2736 / 1532133	1.08 (0.89 - 1.31)
MarketScan	N/A	N/A	N/A	34 / 12427	2854 / 1165221	1.07 (0.74 - 1.56)
Pooled	N/A	N/A	N/A	214 / 82539	5590 / 2697354	1.08 (0.91 - 1.28)
Discontinuers as referent						
MAX	134 / 48279	510 / 223569	1.22 (1.01 - 1.47)	134 / 48226	510 / 223454	1.01 (0.80 - 1.26)
MarketScan	22 / 7451	263 / 92713	1.04 (0.67 - 1.61)	22 / 7449	262 / 92436	0.86 (0.53 - 1.39)
Pooled	156 / 55730	773 / 316282	1.19 (1.00 - 1.41)	156 / 55675	772 / 315890	0.98 (0.80 - 1.20)

Excluding women with aberrant opioid filling patterns						
MAX	133 / 54800	2736 / 1532133	1.36 (1.14 - 1.62)	133 / 54735	2736 / 1532114	1.03 (0.84 - 1.25)
MarketScan	30 / 12016	2854 / 1165222	1.02 (0.71 - 1.46)	30 / 12006	2808 / 1153073	1.00 (0.67 - 1.47)
Pooled	163 / 66816	5590 / 2697355	1.29 (1.10 - 1.50)	163 / 66741	5544 / 2685187	1.02 (0.85 - 1.22)
Restriction to women with folate supplementation						
MAX	102 / 37659	1299 / 679575	1.42 (1.16 - 1.73)	102 / 37659	1297 / 678358	1.08 (0.84 - 1.39)
MarketScan	7 / 4885	981 / 402624	0.59 (0.28 - 1.24)	7 / 4874	962 / 396869	0.62 (0.28 - 1.39)
Pooled	109 / 42544	2280 / 1082199	1.33 (1.10 - 1.62)	109 / 42533	2259 / 1075227	1.03 (0.81 - 1.31)
Late first trimester exposure						
MAX	124 / 48148	2736 / 1532133	1.44 (1.21 - 1.73)	124 / 47982	2736 / 1532133	1.08 (0.88 - 1.34)
MarketScan	26 / 8052	2854 / 1165222	1.32 (0.90 - 1.94)	26 / 8033	2791 / 1145452	1.29 (0.84 - 1.99)
Pooled	150 / 56200	5590 / 2697355	1.42 (1.21 - 1.67)	150 / 56015	5527 / 2677585	1.12 (0.93 - 1.35)
Outcome assessment to 365 days						
MAX	326 / 56921	5231 / 1238327	1.36 (1.21 - 1.52)	326 / 56895	5231 / 1237985	1.00 (0.90 - 1.12)
MarketScan	58 / 8983	4979 / 851107	1.10 (0.85 - 1.43)	58 / 8983	4944 / 847613	1.08 (0.83 - 1.39)
Pooled	384 / 65904	10210 / 2089434	1.31 (1.18 - 1.45)	384 / 65878	10175 / 2085598	1.01 (0.92 - 1.12)
Negative control analysis						
MAX	56 / 26147	2380 / 1354414	1.22 (0.94 - 1.59)	56 / 26147	2371 / 1352772	1.10 (0.84 - 1.44)
MarketScan	15 / 7695	2622 / 1082135	0.80 (0.48 - 1.34)	15 / 7695	2619 / 1081268	0.87 (0.52 - 1.44)
Pooled	71 / 33842	5002 / 2436549	1.12 (0.88 - 1.41)	71 / 33842	4990 / 2434040	1.04 (0.82 - 1.32)
Hydrocodone						
MAX	90 / 35259	2736 / 1532133	1.43 (1.16 - 1.76)	90 / 35066	2729 / 1525321	0.92 (0.71 - 1.20)
MarketScan	16 / 5775	2854 / 1165222	1.13 (0.69 - 1.85)	16 / 5774	2806 / 1148210	1.06 (0.63 - 1.78)
Pooled	106 / 41034	5590 / 2697355	1.38 (1.14 - 1.67)	106 / 40840	5535 / 2673531	0.95 (0.75 - 1.20)
Oxycodone						
MAX	17 / 7019	2736 / 1532133	1.36 (0.84 - 2.18)	17 / 6945	2483 / 1357932	1.03 (0.59 - 1.80)
MarketScan	6 / 1467	2854 / 1165222	1.67 (0.75 - 3.71)	6 / 1440	2134 / 872696	1.92 (0.85 - 4.30)
Pooled	23 / 8486	5590 / 2697355	1.43 (0.95 - 2.16)	23 / 8385	4617 / 2230628	1.26 (0.80 - 1.99)
Codeine						
MAX	24 / 9501	2736 / 1532133	1.41 (0.95 - 2.11)	24 / 9431	2695 / 1520158	1.23 (0.80 - 1.89)
MarketScan	5 / 1549	2854 / 1165222	1.32 (0.55 - 3.16)	5 / 1529	2826 / 1155583	1.30 (0.51 - 3.31)

Pooled	29 / 11050	5590 / 2697355	1.40 (0.97 - 2.01)	29 / 10960	5521 / 2675741	1.24 (0.84 - 1.83)
Dose Analysis: <= 300 MME						
MAX	68 / 27495	2736 / 1532133	1.39 (1.09 - 1.76)	68 / 27436	2716 / 1524384	1.02 (0.77 - 1.34)
MarketScan	10 / 3297	2854 / 1165222	1.24 (0.67 - 2.30)	10 / 3296	2812 / 1152097	1.27 (0.68 - 2.38)
Pooled	78 / 30792	5590 / 2697355	1.36 (1.09 - 1.71)	78 / 30732	5528 / 2676481	1.05 (0.82 - 1.36)
Dose Analysis: >300 MME - <=600 MME						
MAX	38 / 14568	2736 / 1532133	1.46 (1.06 - 2.01)	38 / 14483	2719 / 1523762	1.06 (0.74 - 1.52)
MarketScan	5 / 2133	2854 / 1165222	0.96 (0.40 - 2.30)	5 / 2129	2765 / 1136288	1.02 (0.41 - 2.54)
Pooled	43 / 16701	5590 / 2697355	1.39 (1.03 - 1.88)	43 / 16612	5484 / 2660050	1.06 (0.76 - 1.47)
Dose Analysis: >600 - <=1200 MME						
MAX	32 / 11337	2736 / 1532133	1.58 (1.12 - 2.24)	32 / 11311	2736 / 1532132	1.09 (0.74 - 1.60)
MarketScan	4 / 1825	2854 / 1165222	0.89 (0.34 - 2.38)	4 / 1818	2854 / 1165114	0.94 (0.33 - 2.68)
Pooled	36 / 13162	5590 / 2697355	1.48 (1.07 - 2.06)	36 / 13129	5590 / 2697246	1.07 (0.74 - 1.54)
Dose Analysis: >1200 MME						
MAX	38 / 15808	2736 / 1532133	1.35 (0.98 - 1.85)	38 / 15759	2732 / 1528506	0.88 (0.60 - 1.31)
MarketScan	13 / 4685	2854 / 1165222	1.13 (0.66 - 1.95)	13 / 4657	2807 / 1150112	1.09 (0.59 - 2.02)
Pooled	51 / 20493	5590 / 2697355	1.29 (0.98 - 1.70)	51 / 20416	5539 / 2678618	0.94 (0.68 - 1.31)

E) NEURAL TUBE DEFECT						
Hd-PS estimate						
MAX	N/A	N/A	N/A	28 / 70112	553 / 1532133	0.79 (0.48 - 1.30)
MarketScan	N/A	N/A	N/A	6 / 12427	424 / 1165221	1.10 (0.43 - 2.86)
Pooled	N/A	N/A	N/A	34 / 82539	977 / 2697354	0.85 (0.54 - 1.32)
Discontinuers as referent						
MAX	22 / 48279	101 / 223569	1.01 (0.64 - 1.60)	22 / 48226	101 / 223454	0.75 (0.44 - 1.30)
MarketScan	2 / 7451	40 / 92713	0.62 (0.15 - 2.57)	2 / 7449	40 / 92436	0.73 (0.18 - 2.98)
Pooled	24 / 55730	141 / 316282	0.96 (0.62 - 1.49)	24 / 55675	141 / 315890	0.75 (0.45 - 1.25)
Excluding women with aberrant opioid filling patterns						
MAX	18 / 54800	553 / 1532133	0.91 (0.57 - 1.46)	18 / 54735	553 / 1532114	0.64 (0.37 - 1.11)
MarketScan	6 / 12016	424 / 1165222	1.37 (0.61 - 3.07)	6 / 12006	420 / 1153073	1.11 (0.43 - 2.86)
Pooled	24 / 66816	977 / 2697355	1.01 (0.67 - 1.51)	24 / 66741	973 / 2685187	0.73 (0.45 - 1.19)
Restriction to women with folate supplementation						

MAX	12 / 37659	260 / 679575	0.83 (0.47 - 1.49)	12 / 37659	260 / 678358	0.55 (0.25 - 1.23)
MarketScan	1 / 4885	149 / 402624	0.55 (0.08 - 3.95)	1 / 4874	147 / 396869	0.25 (0.01 - 5.30)
Pooled	13 / 42544	409 / 1082199	0.81 (0.46 - 1.40)	13 / 42533	407 / 1075227	0.53 (0.24 - 1.14)
Late first trimester exposure						
MAX	19 / 48148	553 / 1532133	1.09 (0.69 - 1.73)	19 / 47982	553 / 1532133	0.87 (0.51 - 1.50)
MarketScan	5 / 8052	424 / 1165222	1.71 (0.71 - 4.12)	5 / 8033	417 / 1145452	1.73 (0.66 - 4.55)
Pooled	24 / 56200	977 / 2697355	1.20 (0.80 - 1.80)	24 / 56015	970 / 2677585	1.03 (0.64 - 1.65)
Outcome assessment to 365 days						
MAX	27 / 56921	609 / 1238327	0.96 (0.66 - 1.42)	27 / 56895	609 / 1237985	0.63 (0.43 - 0.92)
MarketScan	6 / 8983	441 / 851107	1.29 (0.58 - 2.88)	6 / 8983	438 / 847613	1.70 (0.76 - 3.81)
Pooled	33 / 65904	1050 / 2089434	1.02 (0.72 - 1.44)	33 / 65878	1047 / 2085598	0.75 (0.53 - 1.07)
Negative control analysis						
MAX	<11* / 26147	478 / 1354414	0.76 (0.36 - 1.60)	<11* / 26147	477 / 1352772	0.65 (0.31 - 1.39)
MarketScan	8 / 7695	382 / 1082135	2.95 (1.46 - 5.93)	8 / 7695	382 / 1081268	2.68 (1.34 - 5.38)
Pooled	* / 33842	860 / 2436549	1.56 (0.94 - 2.60)	* / 33842	859 / 2434040	1.40 (0.84 - 2.34)
Hydrocodone						
MAX	15 / 35259	553 / 1532133	1.18 (0.71 - 1.97)	15 / 35066	551 / 1525321	0.78 (0.41 - 1.49)
MarketScan	2 / 5775	424 / 1165222	0.95 (0.24 - 3.82)	2 / 5774	421 / 1148210	0.98 (0.24 - 3.92)
Pooled	17 / 41034	977 / 2697355	1.15 (0.71 - 1.86)	17 / 40840	972 / 2673531	0.81 (0.45 - 1.46)
Oxycodone						
MAX	<11* / 7019	553 / 1532133	1.97 (0.82 - 4.76)	<11* / 6945	488 / 1357932	1.02 (0.34 - 3.01)
MarketScan	0 / 1467	424 / 1165222	N/A	0 / 1440	320 / 872696	N/A
Pooled	<11* / 8486	977 / 2697355	N/A	<11* / 8385	808 / 2230628	N/A
Codeine						
MAX	<11* / 9501	553 / 1532133	0.29 (0.04 - 2.07)	<11* / 9431	552 / 1520158	0.28 (0.04 - 1.85)
MarketScan	0 / 1549	424 / 1165222	N/A	0 / 1529	422 / 1155583	N/A
Pooled	<11* / 11050	977 / 2697355	N/A	<11* / 10960	974 / 2675741	N/A
Dose Analysis: <= 300 MME						
MAX	<11* / 27495	553 / 1532133	0.91 (0.47 - 1.75)	<11* / 27436	552 / 1524384	0.70 (0.34 - 1.45)
MarketScan	2 / 3297	424 / 1165222	1.67 (0.42 - 6.68)	2 / 3296	418 / 1152097	1.26 (0.29 - 5.46)
Pooled	* / 30792	977 / 2697355	1.01 (0.56 - 1.84)	* / 30732	970 / 2676481	0.79 (0.41 - 1.51)

Dose Analysis: >300 MME - <=600 MME						
MAX	<11* / 14568	553 / 1532133	0.76 (0.28 - 2.03)	<11* / 14483	551 / 1523762	0.49 (0.16 - 1.47)
MarketScan	3 / 2133	424 / 1165222	3.87 (1.24 - 12.02)	3 / 2129	415 / 1136288	2.74 (0.76 - 9.87)
Pooled	* / 16701	977 / 2697355	1.53 (0.73 - 3.21)	* / 16612	966 / 2660050	1.01 (0.44 – 2.34)
Dose Analysis: >600 - <=1200 MME						
MAX	<11* / 11337	553 / 1532133	1.22 (0.51 - 2.95)	<11* / 11311	553 / 1532132	0.73 (0.27 - 1.95)
MarketScan	0 / 1825	424 / 1165222	N/A	0 / 1818	424 / 1165114	N/A
Pooled	<11* / 13162	977 / 2697355	N/A	<11* / 13129	977 / 2697246	N/A
Dose Analysis: >1200 MME						
MAX	<11* / 15808	553 / 1532133	1.75 (0.94 - 3.28)	<11* / 15759	553 / 1528506	1.13 (0.50 - 2.55)
MarketScan	1 / 4685	424 / 1165222	0.59 (0.08 - 4.17)	1 / 4657	418 / 1150112	0.80 (0.12 - 5.41)
Pooled	* / 20493	977 / 2697355	1.58 (0.87 - 2.87)	* / 20416	971 / 2678618	1.07 (0.51 - 2.27)

F) CLUB FOOT						
Hd-PS estimate						
MAX	N/A	N/A	N/A	154 / 70112	2356 / 1532133	1.28 (1.05 - 1.56)
MarketScan	N/A	N/A	N/A	20 / 12427	1781 / 1165221	0.82 (0.50 - 1.35)
Pooled	N/A	N/A	N/A	174 / 82539	4137 / 2697354	1.20 (1.00 - 1.44)
Discontinuers as referent						
MAX	119 / 48279	420 / 223569	1.31 (1.07 - 1.61)	119 / 48226	420 / 223454	1.14 (0.89 - 1.46)
MarketScan	12 / 7451	139 / 92713	1.07 (0.60 - 1.94)	12 / 7449	139 / 92436	0.90 (0.48 - 1.68)
Pooled	131 / 55730	559 / 316282	1.28 (1.06 - 1.56)	131 / 55675	559 / 315890	1.10 (0.87 - 1.39)
Excluding women with aberrant opioid filling patterns						
MAX	120 / 54800	2356 / 1532133	1.42 (1.19 - 1.71)	120 / 54735	2356 / 1532114	1.11 (0.90 - 1.38)
MarketScan	20 / 12016	1781 / 1165222	1.09 (0.70 - 1.69)	20 / 12006	1766 / 1153073	0.89 (0.55 - 1.45)
Pooled	140 / 66816	4137 / 2697355	1.37 (1.16 - 1.62)	140 / 66741	4122 / 2685187	1.07 (0.88 - 1.31)
Restriction to women with folate supplementation						
MAX	92 / 37659	1121 / 679575	1.48 (1.20 - 1.83)	92 / 37659	1121 / 678358	1.12 (0.86 - 1.47)
MarketScan	8 / 4885	621 / 402624	1.06 (0.53 - 2.13)	8 / 4874	614 / 396869	1.06 (0.52 - 2.17)
Pooled	100 / 42544	1742 / 1082199	1.44 (1.18 - 1.76)	100 / 42533	1735 / 1075227	1.11 (0.86 - 1.44)
Late first trimester exposure						

MAX	106 / 48148	2356 / 1532133	1.43 (1.18 - 1.74)	105 / 47982	2356 / 1532133	1.10 (0.87 - 1.39)
MarketScan	13 / 8052	1781 / 1165222	1.06 (0.61 - 1.82)	13 / 8033	1750 / 1145452	0.87 (0.48 - 1.59)
Pooled	119 / 56200	4137 / 2697355	1.38 (1.15 - 1.66)	118 / 56015	4106 / 2677585	1.07 (0.86 - 1.33)
Outcome assessment to 365 days						
MAX	164 / 56921	2495 / 1238327	1.43 (1.22 - 1.67)	164 / 56895	2495 / 1237985	1.36 (1.16 - 1.59)
MarketScan	18 / 8983	1601 / 851107	1.07 (0.67 - 1.69)	18 / 8983	1595 / 847613	0.84 (0.53 - 1.34)
Pooled	182 / 65904	4096 / 2089434	1.39 (1.19 - 1.61)	182 / 65878	4090 / 2085598	1.29 (1.11 - 1.50)
Negative control analysis						
MAX	50 / 26147	2062 / 1354414	1.26 (0.95 - 1.66)	50 / 26147	2060 / 1352772	1.15 (0.86 - 1.52)
MarketScan	7 / 7695	1647 / 1082135	0.60 (0.28 - 1.26)	7 / 7695	1646 / 1081268	0.57 (0.27 - 1.20)
Pooled	57 / 33842	3709 / 2436549	1.14 (0.88 - 1.49)	57 / 33842	3706 / 2434040	1.05 (0.81 - 1.37)
Hydrocodone						
MAX	93 / 35259	2356 / 1532133	1.72 (1.39 - 2.11)	93 / 35066	2351 / 1525321	1.26 (0.96 - 1.65)
MarketScan	9 / 5775	1781 / 1165222	1.02 (0.53 - 1.96)	9 / 5774	1765 / 1148210	0.80 (0.39 - 1.64)
Pooled	102 / 41034	4137 / 2697355	1.64 (1.34 - 1.99)	102 / 40840	4116 / 2673531	1.19 (0.92 - 1.53)
Oxycodone						
MAX	14 / 7019	2356 / 1532133	1.30 (0.77 - 2.19)	14 / 6945	2103 / 1357932	0.74 (0.35 - 1.55)
MarketScan	4 / 1467	1781 / 1165222	1.78 (0.67 - 4.75)	4 / 1440	1362 / 872696	1.52 (0.46 - 5.00)
Pooled	18 / 8486	4137 / 2697355	1.39 (0.88 - 2.21)	18 / 8385	3465 / 2230628	0.91 (0.48 - 1.70)
Codeine						
MAX	17 / 9501	2356 / 1532133	1.16 (0.72 - 1.87)	17 / 9431	2335 / 1520158	1.01 (0.62 - 1.63)
MarketScan	3 / 1549	1781 / 1165222	1.27 (0.41 - 3.93)	3 / 1529	1764 / 1155583	1.10 (0.35 - 3.47)
Pooled	20 / 11050	4137 / 2697355	1.18 (0.76 - 1.83)	20 / 10960	4099 / 2675741	1.02 (0.65 - 1.59)
Dose Analysis: <= 300 MME						
MAX	50 / 27495	2356 / 1532133	1.18 (0.89 - 1.56)	50 / 27436	2344 / 1524384	1.00 (0.74 - 1.34)
MarketScan	5 / 3297	1781 / 1165222	0.99 (0.41 - 2.39)	5 / 3296	1762 / 1152097	0.89 (0.37 - 2.13)
Pooled	55 / 30792	4137 / 2697355	1.16 (0.89 - 1.52)	55 / 30732	4106 / 2676481	0.98 (0.74 - 1.31)
Dose Analysis: >300 MME - <=600 MME						
MAX	37 / 14568	2356 / 1532133	1.65 (1.19 - 2.28)	37 / 14483	2345 / 1523762	1.30 (0.90 - 1.86)
MarketScan	4 / 2133	1781 / 1165222	1.23 (0.46 - 3.27)	4 / 2129	1741 / 1136288	1.01 (0.37 - 2.77)
Pooled	41 / 16701	4137 / 2697355	1.60 (1.18 - 2.18)	41 / 16612	4086 / 2660050	1.26 (0.90 - 1.77)

Dose Analysis: >600 - <=1200 MME						
MAX	28 / 11337	2356 / 1532133	1.61 (1.11 - 2.33)	28 / 11311	2356 / 1532132	1.22 (0.78 - 1.89)
MarketScan	0 / 1825	1781 / 1165222	N/A	0 / 1818	1780 / 1165114	N/A
Pooled	28 / 13162	4137 / 2697355	N/A	28 / 13129	4136 / 2697246	N/A
Dose Analysis: >1200 MME						
MAX	39 / 15808	2356 / 1532133	1.60 (1.17 - 2.20)	39 / 15759	2354 / 1528506	1.22 (0.81 - 1.83)
MarketScan	10 / 4685	1781 / 1165222	1.40 (0.75 - 2.60)	10 / 4657	1763 / 1150112	1.05 (0.50 - 2.19)
Pooled	49 / 20493	4137 / 2697355	1.56 (1.18 - 2.07)	49 / 20416	4117 / 2678618	1.18 (0.82 - 1.68)

G) ORAL CLEFT						
Hd-PS estimate						
MAX	N/A	N/A	N/A	109 / 70112	1702 / 1532133	1.12 (0.89 - 1.42)
MarketScan	N/A	N/A	N/A	28 / 12427	1441 / 1165221	1.69 (1.13 - 2.51)
Pooled	N/A	N/A	N/A	137 / 82539	3143 / 2697354	1.25 (1.02 - 1.52)
Discontinuers as referent						
MAX	87 / 48279	281 / 223569	1.43 (1.13 - 1.82)	87 / 48226	281 / 223454	1.17 (0.88 - 1.55)
MarketScan	16 / 7451	103 / 92713	1.93 (1.14 - 3.27)	16 / 7449	103 / 92436	1.61 (0.93 - 2.78)
Pooled	103 / 55730	384 / 316282	1.51 (1.21 - 1.90)	103 / 55675	384 / 315890	1.25 (0.97 - 1.62)
Excluding women with aberrant opioid filling patterns						
MAX	86 / 54800	1702 / 1532133	1.41 (1.14 - 1.75)	86 / 54735	1702 / 1532114	1.13 (0.88 - 1.45)
MarketScan	26 / 12016	1441 / 1165222	1.75 (1.19 - 2.58)	26 / 12006	1421 / 1153073	1.62 (1.05 - 2.49)
Pooled	112 / 66816	3143 / 2697355	1.49 (1.23 - 1.80)	112 / 66741	3123 / 2685187	1.24 (0.99 - 1.54)
Restriction to women with folate supplementation						
MAX	61 / 37659	814 / 679575	1.35 (1.04 - 1.75)	61 / 37659	813 / 678358	1.04 (0.75 - 1.43)
MarketScan	10 / 4885	493 / 402624	1.67 (0.89 - 3.12)	10 / 4874	483 / 396869	1.70 (0.81 - 3.58)
Pooled	71 / 42544	1307 / 1082199	1.40 (1.10 - 1.77)	71 / 42533	1296 / 1075227	1.12 (0.84 - 1.51)
Late first trimester exposure						
MAX	77 / 48148	1702 / 1532133	1.44 (1.15 - 1.81)	77 / 47982	1702 / 1532133	1.25 (0.95 - 1.64)
MarketScan	17 / 8052	1441 / 1165222	1.71 (1.06 - 2.75)	17 / 8033	1414 / 1145452	1.59 (0.94 - 2.71)
Pooled	94 / 56200	3143 / 2697355	1.49 (1.21 - 1.83)	94 / 56015	3116 / 2677585	1.32 (1.03 - 1.68)
Outcome assessment to 365 days						

MAX	92 / 56921	1610 / 1238327	1.24 (1.01 - 1.53)	92 / 56895	1609 / 1237985	1.11 (0.90 - 1.37)
MarketScan	24 / 8983	1204 / 851107	1.89 (1.26 - 2.83)	24 / 8983	1198 / 847613	1.91 (1.28 - 2.86)
Pooled	116 / 65904	2814 / 2089434	1.36 (1.13 - 1.64)	116 / 65878	2807 / 2085598	1.25 (1.04 - 1.50)
Negative control analysis						
MAX	36 / 26147	1473 / 1354414	1.27 (0.91 - 1.76)	36 / 26147	1472 / 1352772	1.08 (0.78 - 1.51)
MarketScan	9 / 7695	1336 / 1082135	0.95 (0.49 - 1.82)	9 / 7695	1335 / 1081268	0.89 (0.46 - 1.73)
Pooled	45 / 33842	2809 / 2436549	1.19 (0.89 - 1.60)	45 / 33842	2807 / 2434040	1.04 (0.77 - 1.40)
Hydrocodone						
MAX	65 / 35259	1702 / 1532133	1.66 (1.30 - 2.13)	65 / 35066	1697 / 1525321	1.31 (0.96 - 1.79)
MarketScan	14 / 5775	1441 / 1165222	1.96 (1.16 - 3.32)	14 / 5774	1415 / 1148210	1.68 (0.97 - 2.90)
Pooled	79 / 41034	3143 / 2697355	1.71 (1.37 - 2.14)	79 / 40840	3112 / 2673531	1.39 (1.06 - 1.83)
Oxycodone						
MAX	11 / 7019	1702 / 1532133	1.41 (0.78 - 2.55)	11 / 6945	1504 / 1357932	0.82 (0.37 - 1.80)
MarketScan	5 / 1467	1441 / 1165222	2.76 (1.15 - 6.62)	5 / 1440	1086 / 872696	2.98 (1.09 - 8.18)
Pooled	16 / 8486	3143 / 2697355	1.74 (1.07 - 2.84)	16 / 8385	2590 / 2230628	1.34 (0.72 - 2.50)
Codeine						
MAX	<11* / 9501	1702 / 1532133	0.76 (0.38 - 1.52)	<11* / 9431	1690 / 1520158	0.56 (0.27 - 1.17)
MarketScan	3 / 1549	1441 / 1165222	1.57 (0.51 - 4.86)	3 / 1529	1430 / 1155583	1.39 (0.46 - 4.21)
Pooled	* / 11050	3143 / 2697355	0.93 (0.51 - 1.67)	* / 10960	3120 / 2675741	0.74 (0.40 - 1.37)
Dose Analysis: <= 300 MME						
MAX	33 / 27495	1702 / 1532133	1.08 (0.77 - 1.52)	33 / 27436	1696 / 1524384	0.93 (0.66 - 1.33)
MarketScan	4 / 3297	1441 / 1165222	0.98 (0.37 - 2.62)	4 / 3296	1422 / 1152097	0.94 (0.36 - 2.49)
Pooled	37 / 30792	3143 / 2697355	1.07 (0.77 - 1.48)	37 / 30732	3118 / 2676481	0.94 (0.67 - 1.31)
Dose Analysis: >300 MME - <=600 MME						
MAX	29 / 14568	1702 / 1532133	1.79 (1.24 - 2.59)	29 / 14483	1697 / 1523762	1.20 (0.76 - 1.88)
MarketScan	6 / 2133	1441 / 1165222	2.27 (1.02 - 5.07)	6 / 2129	1394 / 1136288	2.19 (0.94 - 5.12)
Pooled	35 / 16701	3143 / 2697355	1.87 (1.34 - 2.61)	35 / 16612	3091 / 2660050	1.37 (0.92 - 2.04)
Dose Analysis: >600 - <=1200 MME						
MAX	17 / 11337	1702 / 1532133	1.35 (0.84 - 2.18)	17 / 11311	1702 / 1532132	1.03 (0.61 - 1.75)
MarketScan	7 / 1825	1441 / 1165222	3.10 (1.48 - 6.51)	7 / 1818	1441 / 1165114	2.97 (1.36 - 6.46)
Pooled	24 / 13162	3143 / 2697355	1.72 (1.15 - 2.57)	24 / 13129	3143 / 2697246	1.44 (0.93 - 2.24)

Dose Analysis: >1200 MME						
MAX	29 / 15808	1702 / 1532133	1.65 (1.14 - 2.38)	29 / 15759	1699 / 1528506	1.24 (0.76 - 2.02)
MarketScan	9 / 4685	1441 / 1165222	1.55 (0.81 - 2.99)	9 / 4657	1420 / 1150112	1.56 (0.75 - 3.22)
Pooled	38 / 20493	3143 / 2697355	1.63 (1.18 - 2.24)	38 / 20416	3119 / 2678618	1.33 (0.89 - 2.00)

* Cell size <11 for MAX cohort. Numbers suppressed in accord with the CMS cell size suppression policy.
Abbreviations: Hd-PS, High-dimensional propensity score; MME, morphine milligram equivalent; N/A, not applicable; no., number.

eTable 7 Risk of Congenital Malformations (Oral Cleft Subgroups) in Infants Following Exposure to Opioids During the First Trimester: Sensitivity Analyses.

	Propensity Score Weighted		
	Exposed to Opioids	**Unexposed**	**Relative Risk (95% CI)**
	No. of Events / Total No. Of Infants	No. of Events / Total No. Of Infants	
A) CLEFT PALATE			
Main analysis (adjusted)			
MAX	64 / 70,074	827 / 1,532,118	1.33 (0.95 - 1.87)
MarketScan	21 / 12,430	716 / 1,152,470	2.50 (1.52 - 4.10)
Pooled	85 / 82,504	1,543 / 2,684,588	1.62 (1.23 - 2.14)
Hd-PS estimate			
MAX	64 / 70,112	827 / 1,532,133	1.40 (1.02 - 1.90)
MarketScan	21 / 12,427	732 / 1,165,221	2.36 (1.46 - 3.80)
Pooled	85 / 82,539	1,559 / 2,697,354	1.63 (1.26 - 2.11)
Discontinuers as referent			
MAX	50 / 48,226	153 / 223,454	1.25 (0.85 - 1.84)
MarketScan	12 / 7,449	50 / 92,436	2.63 (1.34 - 5.14)
Pooled	62 / 55,675	203 / 315,890	1.51 (1.08 - 2.10)
Excluding women with aberrant opioid filling patterns			
MAX	47 / 54,735	827 / 1,532,114	1.36 (0.96 - 1.91)
MarketScan	19 / 12,006	717 / 1,153,073	2.29 (1.35 - 3.87)
Pooled	66 / 66,741	1,544 / 2,685,187	1.59 (1.19 - 2.11)
Restriction to women with folate supplementation			
MAX	39 / 37,659	397 / 678,358	1.40 (0.93 - 2.11)
MarketScan	9 / 4,874	247 / 396,869	2.58 (1.12 - 5.97)
Pooled	48 / 42,533	644 / 1,075,227	1.58 (1.09 - 2.28)
Late first trimester exposure			
MAX	46 / 47,982	827 / 1,532,133	1.50 (1.04 - 2.17)
MarketScan	13 / 8,033	711 / 1,145,452	2.39 (1.26 - 4.53)
Pooled	59 / 56,015	1,538 / 2,677,585	1.69 (1.22 - 2.32)
Outcome assessment to 365 days			
MAX	60 / 56,895	965 / 1,237,985	1.20 (0.86 - 1.67)
MarketScan	15 / 8,983	509 / 847,613	2.79 (1.51 - 5.17)
Pooled	75 / 65,878	1,474 / 2,085,598	1.45 (1.08 - 1.94)
Negative control analysis			
MAX	20 / 26,147	712 / 1,352,772	1.25 (0.80 - 1.95)
MarketScan	7 / 7,695	683 / 1,081,268	1.35 (0.64 - 2.85)
Pooled	27 / 33,842	1,395 / 2,434,040	1.28 (0.87 - 1.87)
Hydrocodone			
MAX	42 / 35,066	825 / 1,525,321	1.72 (1.13 - 2.62)
MarketScan	10 / 5,774	715 / 1,148,210	2.49 (1.23 - 5.05)
Pooled	52 / 40,840	1,540 / 2,673,531	1.89 (1.32 - 2.72)

Oxycodone			
MAX	<11* / 6,945	740 / 1,357,932	1.32 (0.45 - 3.83)
MarketScan	3 / 1,440	570 / 872,696	3.69 (0.88 - 15.48)
Pooled	<11* / 8,385	1,310 / 2,230,628	1.90 (0.81 - 4.47)
Codeine			
MAX	<11* / 9,431	820 / 1,520,158	1.03 (0.45 - 2.35)
MarketScan	2 / 1,529	724 / 1,155,583	2.11 (0.53 - 8.36)
Pooled	<11* / 10,960	1,544 / 2,675,741	1.24 (0.61 - 2.53)
Dose Analysis: <= 300 MME			
MAX	17 / 27,436	825 / 1,524,384	1.05 (0.64 - 1.73)
MarketScan	2 / 3,296	719 / 1,152,097	0.94 (0.24 - 3.74)
Pooled	19 / 30,732	1,544 / 2,676,481	1.04 (0.65 - 1.66)
Dose Analysis: >300 MME - <=600 MME			
MAX	15 / 14,483	825 / 1,523,762	1.21 (0.60 - 2.42)
MarketScan	4 / 2,129	702 / 1,136,288	2.94 (1.07 - 8.07)
Pooled	19 / 16,612	1,527 / 2,660,050	1.61 (0.91 - 2.85)
Dose Analysis: >600 - <=1200 MME			
MAX	<11* / 11,311	827 / 1,532,132	1.28 (0.63 - 2.61)
MarketScan	7 / 1,818	732 / 1,165,114	6.32 (2.77 - 14.40)
Pooled	* / 13,129	1,559 / 2,697,246	2.54 (1.48 - 4.35)
Dose Analysis: >1200 MME			
MAX	23 / 15,759	827 / 1,528,506	2.19 (1.21 - 3.97)
MarketScan	6 / 4,657	721 / 1,150,112	2.05 (0.80 - 5.26)
Pooled	29 / 20,416	1,548 / 2,678,618	2.15 (1.30 - 3.55)
B) CLEFT LIP			
Main analysis (adjusted)			
MAX	33 / 70,074	530 / 1,532,118	0.98 (0.64 - 1.52)
MarketScan	6 / 12,430	467 / 1,152,470	1.18 (0.51 - 2.75)
Pooled	39 / 82,504	997 / 2,684,588	1.02 (0.69 - 1.51)
Hd-PS estimate			
MAX	33 / 70,112	530 / 1,532,133	0.99 (0.65 - 1.52)
MarketScan	6 / 12,427	472 / 1,165,221	1.25 (0.54 - 2.87)
Pooled	39 / 82,539	1,002 / 2,697,354	1.04 (0.71 - 1.52)
Discontinuers as referent			
MAX	24 / 48,226	84 / 223,454	1.21 (0.70 - 2.08)
MarketScan	2 / 7,449	32 / 92,436	0.75 (0.17 - 3.34)
Pooled	26 / 55,675	116 / 315,890	1.14 (0.69 - 1.90)
Excluding women with aberrant opioid filling patterns			
MAX	30 / 54,735	530 / 1,532,114	1.09 (0.70 - 1.70)
MarketScan	6 / 12,006	467 / 1,153,073	1.29 (0.54 - 3.06)
Pooled	36 / 66,741	997 / 2,685,187	1.13 (0.76 - 1.68)
Restriction to women with folate supplementation			

MAX	21 / 37,659	257 / 678,358	1.23 (0.71 - 2.13)
MarketScan	1 / 4,874	173 / 396,869	0.77 (0.11 - 5.68)
Pooled	22 / 42,533	430 / 1,075,227	1.19 (0.70 - 2.02)
Late first trimester exposure			
MAX	20 / 47,982	530 / 1,532,133	1.09 (0.67 - 1.78)
MarketScan	4 / 8,033	466 / 1,145,452	1.24 (0.43 - 3.52)
Pooled	24 / 56,015	996 / 2,677,585	1.12 (0.72 - 1.74)
Outcome assessment to 365 days			
MAX	34 / 56,895	635 / 1,237,985	1.03 (0.68 - 1.58)
MarketScan	4 / 8,983	341 / 847,613	1.26 (0.44 - 3.61)
Pooled	38 / 65,878	976 / 2,085,598	1.06 (0.71 - 1.58)
Negative control analysis			
MAX	11 / 26,147	463 / 1,352,772	1.01 (0.55 - 1.85)
MarketScan	0 / 7,695	437 / 1,081,268	N/A
Pooled	11 / 33,842	900 / 2,434,040	1.01 (0.55 - 1.85)
Hydrocodone			
MAX	19 / 35,066	528 / 1,525,321	1.18 (0.70 - 1.99)
MarketScan	3 / 5,774	463 / 1,148,210	1.10 (0.38 - 3.25)
Pooled	22 / 40,840	991 / 2,673,531	1.16 (0.73 - 1.86)
Oxycodone			
MAX	<11* / 6,945	461 / 1,357,932	0.73 (0.22 - 2.43)
MarketScan	1 / 1,440	342 / 872,696	1.71 (0.22 - 13.17)
Pooled	<11* / 8,385	803 / 2,230,628	0.91 (0.32 - 2.56)
Codeine			
MAX	<11* / 9,431	523 / 1,520,158	0.26 (0.04 - 1.63)
MarketScan	0 / 1,529	467 / 1,155,583	N/A
Pooled	<11* / 10,960	990 / 2,675,741	0.26 (0.04 - 1.63)
Dose Analysis: <= 300 MME			
MAX	17 / 27,436	526 / 1,524,384	1.52 (0.93 - 2.48)
MarketScan	1 / 3,296	465 / 1,152,097	0.72 (0.10 - 4.99)
Pooled	18 / 30,732	991 / 2,676,481	1.45 (0.90 - 2.34)
Dose Analysis: >300 MME - <=600 MME			
MAX	<11* / 14,483	527 / 1,523,762	0.51 (0.17 - 1.51)
MarketScan	2 / 2,129	457 / 1,136,288	2.32 (0.52 - 10.37)
Pooled	<11* / 16,612	984 / 2,660,050	0.86 (0.36 - 2.07)
Dose Analysis: >600 - <=1200 MME			
MAX	<11* / 11,311	530 / 1,532,132	0.98 (0.41 - 2.35)
MarketScan	0 / 1,818	472 / 1,165,114	N/A
Pooled	<11* / 13,129	1,002 / 2,697,246	0.98 (0.41 - 2.35)
Dose Analysis: >1200 MME			
MAX	<11* / 15,759	529 / 1,528,506	0.22 (0.05 - 1.04)
MarketScan	3 / 4,657	465 / 1,150,112	1.80 (0.54 - 6.00)

Pooled	<11* / 20,416	994 / 2,678,618	0.82 (0.32 - 2.12)
C) CLEFT PALATE WITH CLEFT LIP			
Main analysis (adjusted)			
MAX	48 / 70,074	802 / 1,532,118	1.05 (0.74 - 1.49)
MarketScan	10 / 12,430	595 / 1,152,470	1.20 (0.61 - 2.36)
Pooled	58 / 82,504	1,397 / 2,684,588	1.08 (0.79 - 1.47)
Hd-PS estimate			
MAX	48 / 70,112	802 / 1,532,133	1.11 (0.79 - 1.56)
MarketScan	10 / 12,427	602 / 1,165,221	1.15 (0.61 - 2.17)
Pooled	58 / 82,539	1,404 / 2,697,354	1.12 (0.83 - 1.51)
Discontinuers as referent			
MAX	38 / 48,226	136 / 223,454	1.05 (0.69 - 1.58)
MarketScan	6 / 7,449	50 / 92,436	1.06 (0.46 - 2.47)
Pooled	44 / 55,675	186 / 315,890	1.05 (0.73 - 1.52)
Excluding women with aberrant opioid filling patterns			
MAX	43 / 54,735	802 / 1,532,114	1.16 (0.81 - 1.65)
MarketScan	9 / 12,006	595 / 1,153,073	1.08 (0.52 - 2.21)
Pooled	52 / 66,741	1,397 / 2,685,187	1.14 (0.83 - 1.57)
Restriction to women with folate supplementation			
MAX	27 / 37,659	371 / 678,358	0.95 (0.59 - 1.53)
MarketScan	3 / 4,874	191 / 396,869	1.06 (0.28 - 4.01)
Pooled	30 / 42,533	562 / 1,075,227	0.96 (0.61 - 1.51)
Late first trimester exposure			
MAX	32 / 47,982	802 / 1,532,133	1.21 (0.82 - 1.79)
MarketScan	6 / 8,033	594 / 1,145,452	1.07 (0.45 - 2.54)
Pooled	38 / 56,015	1,396 / 2,677,585	1.18 (0.83 - 1.69)
Outcome assessment to 365 days			
MAX	44 / 56,895	776 / 1,237,985	0.96 (0.67 - 1.39)
MarketScan	8 / 8,983	448 / 847,613	1.27 (0.59 - 2.74)
Pooled	52 / 65,878	1,224 / 2,085,598	1.01 (0.72 - 1.41)
Negative control analysis			
MAX	13 / 26,147	697 / 1,352,772	0.82 (0.47 - 1.43)
MarketScan	2 / 7,695	550 / 1,081,268	0.45 (0.11 - 1.89)
Pooled	15 / 33,842	1,247 / 2,434,040	0.76 (0.45 - 1.27)
Hydrocodone			
MAX	28 / 35,066	801 / 1,525,321	1.26 (0.82 - 1.94)
MarketScan	5 / 5,774	594 / 1,148,210	1.18 (0.47 - 2.93)
Pooled	33 / 40,840	1,395 / 2,673,531	1.24 (0.84 - 1.84)
Oxycodone			
MAX	<11* / 6,945	698 / 1,357,932	0.52 (0.16 - 1.69)
MarketScan	1 / 1,440	451 / 872,696	1.27 (0.17 - 9.26)
Pooled	<11* / 8,385	1,149 / 2,230,628	0.66 (0.24 - 1.81)

Codeine			
MAX	<11* / 9,431	800 / 1,520,158	0.32 (0.09 - 1.16)
MarketScan	1 / 1,529	601 / 1,155,583	0.84 (0.12 - 5.76)
Pooled	<11* / 10,960	1,401 / 2,675,741	0.43 (0.15 - 1.26)
Dose Analysis: <= 300 MME			
MAX	13 / 27,436	801 / 1,524,384	0.75 (0.43 - 1.29)
MarketScan	1 / 3,296	596 / 1,152,097	0.48 (0.07 - 3.30)
Pooled	14 / 30,732	1,397 / 2,676,481	0.73 (0.43 - 1.22)
Dose Analysis: >300 MME - <=600 MME			
MAX	15 / 14,483	802 / 1,523,762	1.35 (0.77 - 2.36)
MarketScan	3 / 2,129	583 / 1,136,288	1.92 (0.57 - 6.52)
Pooled	18 / 16,612	1,385 / 2,660,050	1.43 (0.86 - 2.38)
Dose Analysis: >600 - <=1200 MME			
MAX	<11* / 11,311	802 / 1,532,132	1.13 (0.58 - 2.20)
MarketScan	0 / 1,818	602 / 1,165,114	N/A
Pooled	<11* / 13,129	1,404 / 2,697,246	1.13 (0.58 - 2.20)
Dose Analysis: >1200 MME			
MAX	<11* / 15,759	800 / 1,528,506	0.88 (0.43 - 1.80)
MarketScan	5 / 4,657	592 / 1,150,112	1.69 (0.63 - 4.53)
Pooled	* / 20,416	1,392 / 2,678,618	1.10 (0.62 - 1.97)

* Cell size <11 for MAX cohort. Numbers suppressed in accord with the CMS cell size suppression policy.
Abbreviations: Hd-PS, High-dimensional propensity score; MME, morphine milligram equivalent; N/A, not applicable; no., number.

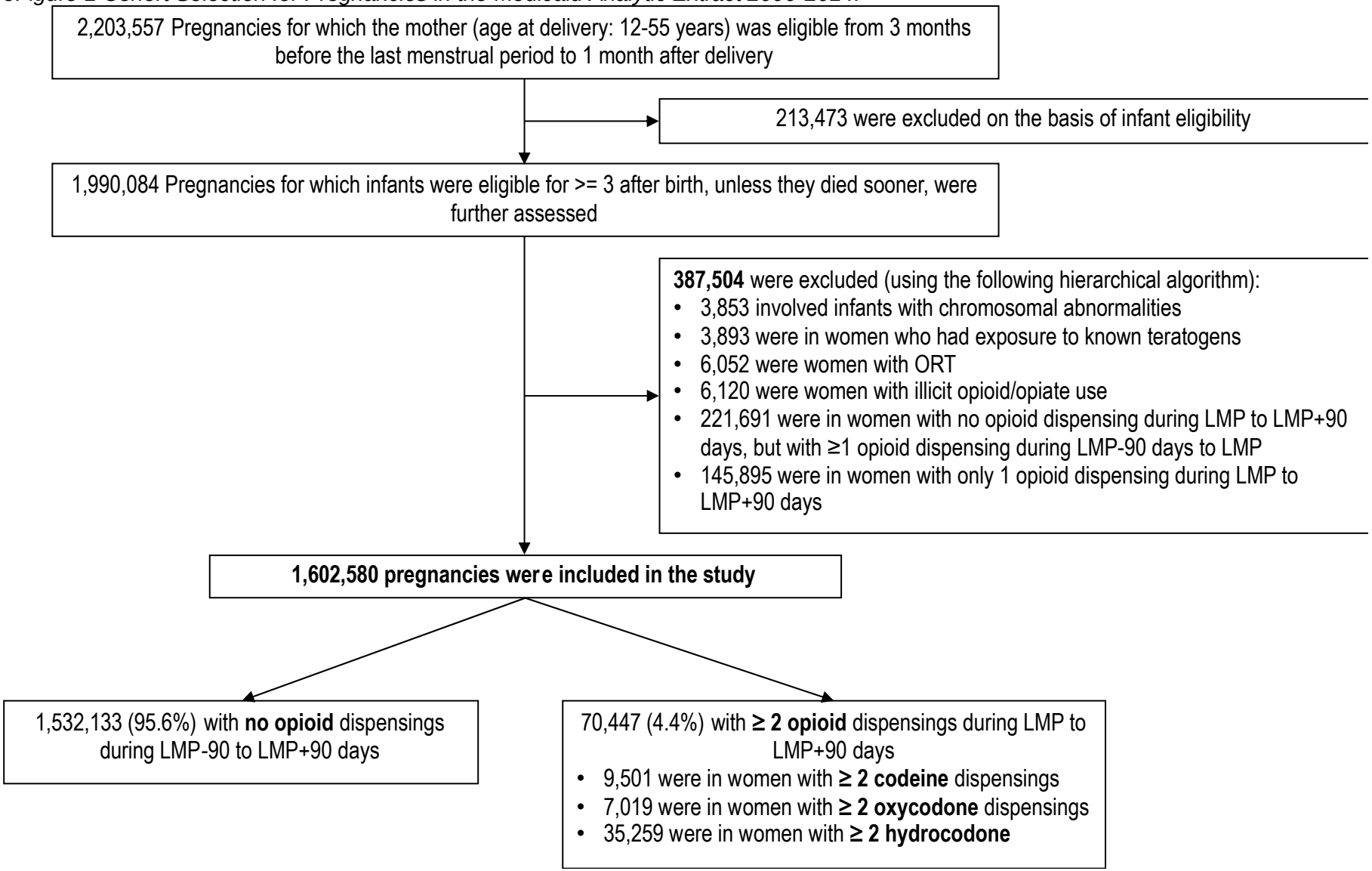
eTable 8 Absolute Risk of Congenital Malformations (Secondary Outcomes) Among Infants Born to Mothers With and Without Exposure to Opioids.

	MAX 2000-2014			MarketScan 2003-2015		
	Events	Total	Risk	Events	Total	Risk
	no. of affected infants	*no. of pregnancies*	*no./1,000 infants (95 % CI)*	*no. of affected infants*	*no. of pregnancies*	*no./1,000 infants (95 % CI)*
Conotruncal Defect						
Exposed	61	70,447	0.87 (0.65 - 1.08)	13	12,454	1.04 (0.48 - 1.61)
Unexposed	1,158	1,532,133	0.76 (0.71 - 0.80)	1,064	1,165,222	0.91 (0.86 - 0.97)
Single Ventricle Defect						
Exposed	11	70,447	0.16 (0.06 - 0.25)	1	12,454	0.08 (-0.08 - 0.24)
Unexposed	237	1,532,133	0.15 (0.13 - 0.17)	172	1,165,222	0.15 (0.13 - 0.17)
Atrioventricular Septal Defect						
Exposed	16	70,447	0.23 (0.12 - 0.34)	-	12,454	-
Unexposed	356	1,532,133	0.23 (0.21 - 0.26)	245	1,165,222	0.21 (0.18 - 0.24)
Right-Sided Defect						
Exposed	77	70,447	1.09 (0.85 - 1.34)	16	12,454	1.28 (0.66 - 1.91)
Unexposed	1,473	1,532,133	0.96 (0.91 - 1.01)	1,211	1,165,222	1.04 (0.98 - 1.10)
Left-Sided Defect						
Exposed	88	70,447	1.25 (0.99 - 1.51)	17	12,454	1.37 (0.72 - 2.01)
Unexposed	1,473	1,532,133	0.96 (0.91 - 1.01)	1,294	1,165,222	1.11 (1.05 - 1.17)
Persistent Ductus Arteriosus						
Exposed	68	70,447	0.97 (0.74 - 1.19)	16	12,454	1.28 (0.66 - 1.91)
Unexposed	1,416	1,532,133	0.92 (0.88 - 0.97)	1,251	1,165,222	1.07 (1.01 - 1.13)
Persistent Pulmonary Hypertension of the Newborn						
Exposed	93	70,447	1.32 (1.05 - 1.59)	13	12,454	1.04 (0.48 - 1.61)
Unexposed	1,197	1,532,133	0.78 (0.74 - 0.83)	521	1,165,222	0.45 (0.41 - 0.49)
Anomalous Pulmonary Venous Return						
Exposed	17	70,447	0.24 (0.13 - 0.36)	2	12,454	0.16 (-0.06 - 0.38)
Unexposed	287	1,532,133	0.19 (0.17 - 0.21)	187	1,165,222	0.16 (0.14 - 0.18)
Other Cardiac Defect						
Exposed	102	70,447	1.45 (1.17 - 1.73)	16	12,454	1.28 (0.66 - 1.91)
Unexposed	1,844	1,532,133	1.20 (1.15 - 1.26)	1,059	1,165,222	0.91 (0.85 - 0.96)

	MAX 2000-2014			MarketScan 2003-2015		
	Events	Total	Risk	Events	Total	Risk
	no. of affected infants	*no. of pregnancies*	*no./1,000 infants (95 % CI)*	*no. of affected infants*	*no. of pregnancies*	*no./1,000 infants (95 % CI)*
Cardiac Defect NOS						
Exposed	137	70,447	1.94 (1.62 - 2.27)	20	12,454	1.61 (0.90 - 2.31)
Unexposed	2,148	1,532,133	1.40 (1.34 - 1.46)	1,445	1,165,222	1.24 (1.18 - 1.30)
Gastroschisis						
Exposed	34	70,447	0.48 (0.32 - 0.64)	1	12,454	0.08 (-0.08 - 0.24)
Unexposed	663	1,532,133	0.43 (0.40 - 0.47)	122	1,165,222	0.10 (0.09 - 0.12)
Any Central Nervous System Malformation						
Exposed	167	70,447	2.37 (2.01 - 2.73)	22	12,454	1.77 (1.03 - 2.50)
Unexposed	2,880	1,532,133	1.88 (1.81 - 1.95)	1,465	1,165,222	1.26 (1.19 - 1.32)
Microcephaly						
Exposed	34	70,447	0.48 (0.32 - 0.64)	3	12,454	0.24 (-0.03 - 0.51)
Unexposed	580	1,532,133	0.38 (0.35 - 0.41)	208	1,165,222	0.18 (0.15 - 0.20)
Hydrocephaly						
Exposed	72	70,447	1.02 (0.79 - 1.26)	10	12,454	0.80 (0.31 - 1.30)
Unexposed	1,064	1,532,133	0.69 (0.65 - 0.74)	466	1,165,222	0.40 (0.36 - 0.44)
Reduction Deformity of Brain						
Exposed	11	70,447	0.16 (0.06 - 0.25)	2	12,454	0.16 (-0.06 - 0.38)
Unexposed	299	1,532,133	0.20 (0.17 - 0.22)	185	1,165,222	0.16 (0.14 - 0.18)
Cleft Palate						
Exposed	64	70,447	0.91 (0.69 - 1.13)	21	12,454	1.69 (0.97 - 2.41)
Unexposed	827	1,532,133	0.54 (0.50 - 0.58)	732	1,165,222	0.63 (0.58 - 0.67)
Cleft Lip						
Exposed	33	70,447	0.47 (0.31 - 0.63)	6	12,454	0.48 (0.10 - 0.87)
Unexposed	530	1,532,133	0.35 (0.32 - 0.38)	472	1,165,222	0.41 (0.37 - 0.44)
Cleft Palate with Cleft Lip						
Exposed	48	70,447	0.68 (0.49 - 0.87)	10	12,454	0.80 (0.31 - 1.30)
Unexposed	802	1,532,133	0.52 (0.49 - 0.56)	602	1,165,222	0.52 (0.48 - 0.56)

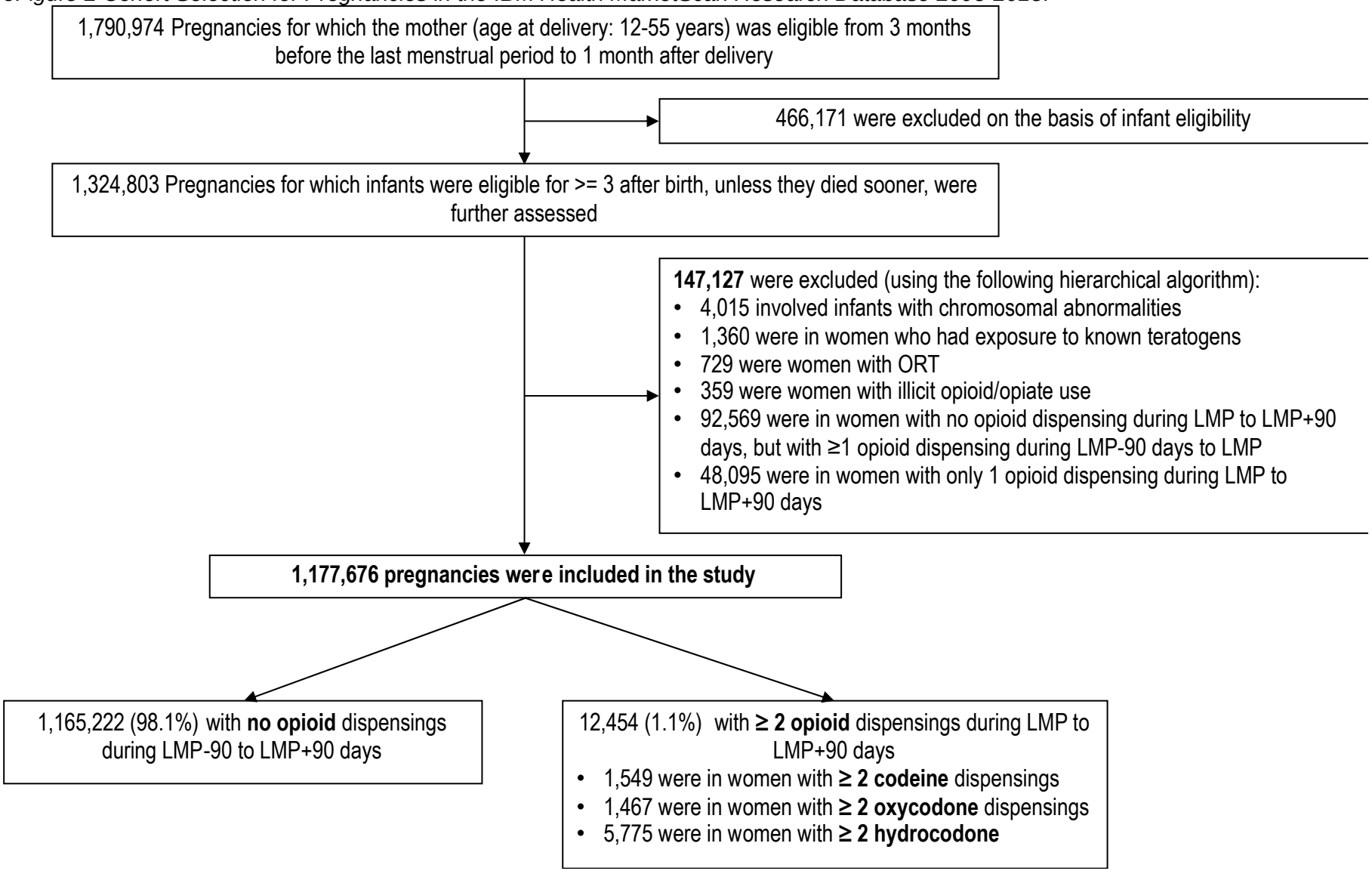
Abbreviations: CI, confidence interval; no., number; NOS, not otherwise specified.

eFigure 1 Cohort Selection for Pregnancies in the Medicaid Analytic Extract 2000-2014.



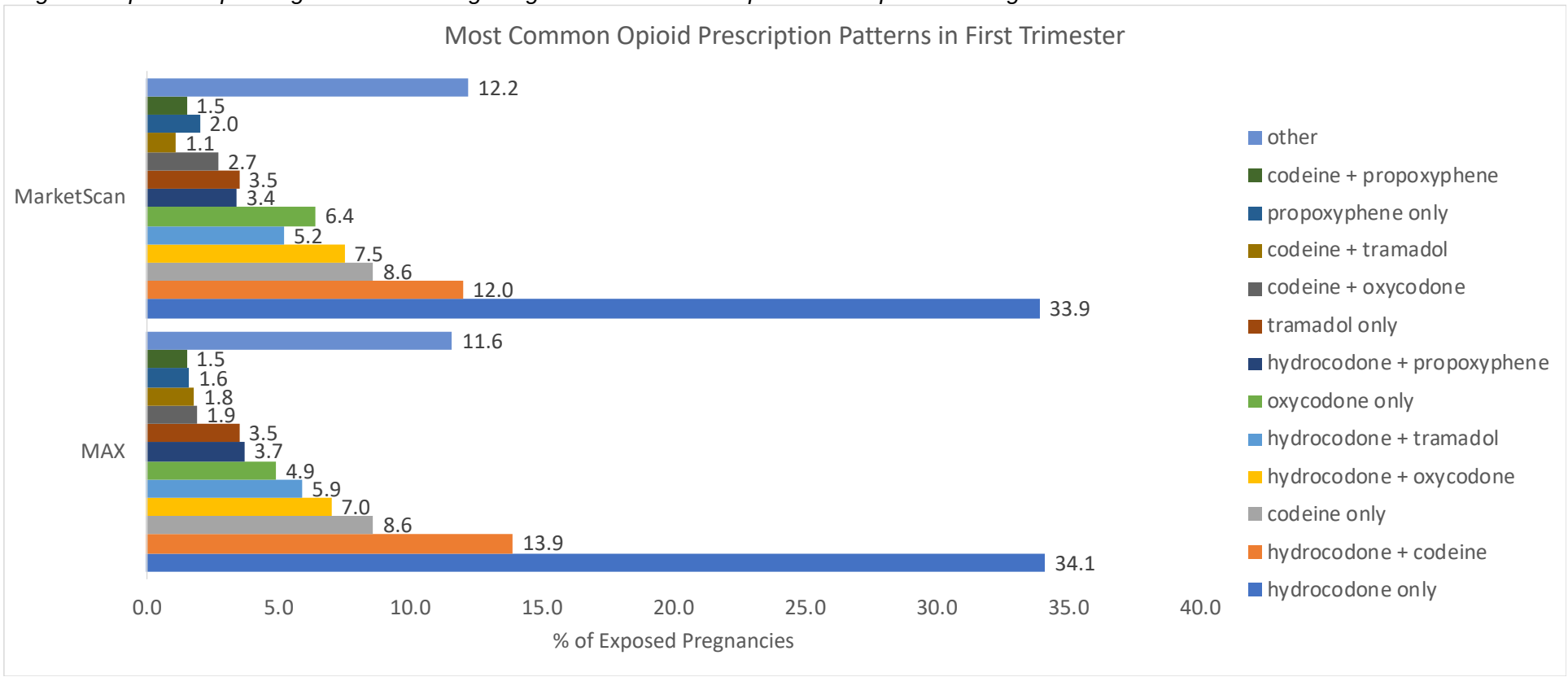
Abbreviations: LMP, last menstrual period; ORT, opioid replacement therapy.

eFigure 2 Cohort Selection for Pregnancies in the IBM Health MarketScan Research Database 2003-2015.

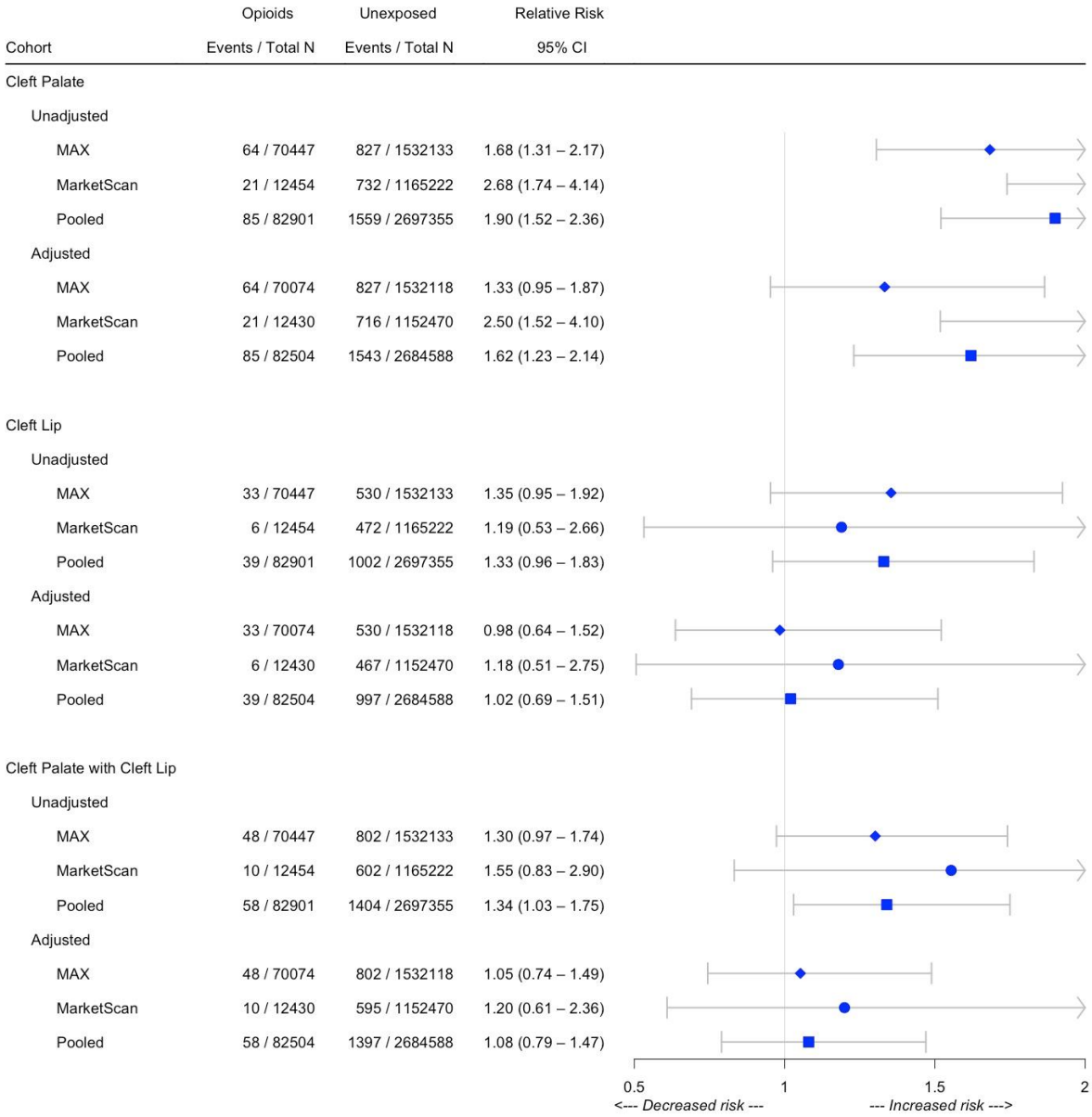


Abbreviations: LMP, last menstrual period; ORT, opioid replacement therapy.

eFigure 3 Opioid Dispensing Patterns Among Pregnancies With >=2 Opioid Prescriptions During the First Trimester.

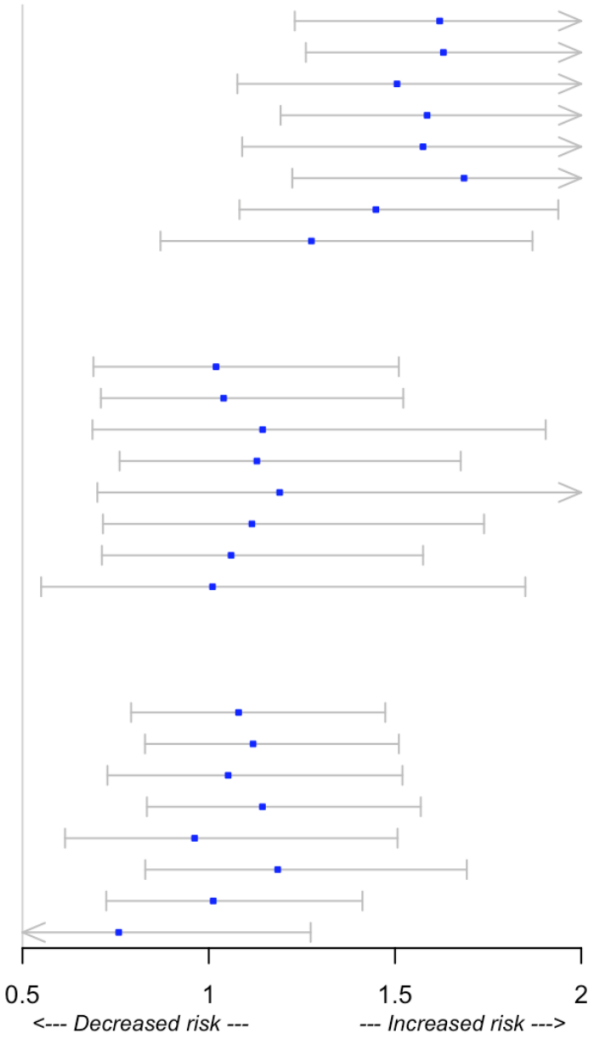


eFigure 4 Risk of Congenital Malformations (Oral Cleft Subgroups) in Infants Following Exposure to Opioids During the First Trimester: Main Analyses (Unadjusted and Propensity Score Stratified).



eFigure 5 Risk of Congenital Malformations (Oral Cleft Subgroups) in Infants Following Exposure to Opioids During the First Trimester: Sensitivity Analyses (Pooled Estimates, Propensity Score Stratified).

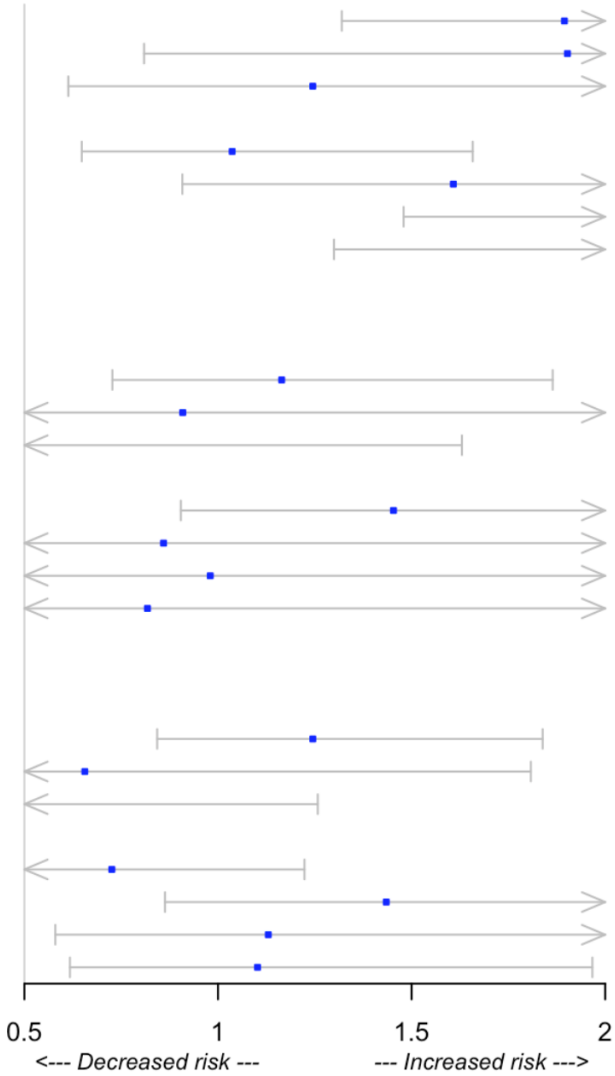
Cohort	Opioids Events / Total N	Unexposed Events / Total N	Relative Risk 95% CI
Cleft Palate			
Main analysis (adjusted)	85 / 82504	1543 / 2684588	1.62 (1.23 - 2.14)
Hd-PS estimate	85 / 82539	1559 / 2697354	1.63 (1.26 - 2.11)
Discontinuers as referent	62 / 55675	203 / 315890	1.51 (1.08 - 2.10)
Excluding women with aberrant opioid filling patterns	66 / 66741	1544 / 2685187	1.59 (1.19 - 2.11)
Restriction to women with folate supplementation	48 / 42533	644 / 1075227	1.58 (1.09 - 2.28)
Late first trimester exposure	59 / 56015	1538 / 2677585	1.69 (1.22 - 2.32)
Outcome assessment to 365 days	75 / 65878	1474 / 2085598	1.45 (1.08 - 1.94)
Negative control analysis	27 / 33842	1395 / 2434040	1.28 (0.87 - 1.87)
Cleft Lip			
Main analysis (adjusted)	39 / 82504	997 / 2684588	1.02 (0.69 - 1.51)
Hd-PS estimate	39 / 82539	1002 / 2697354	1.04 (0.71 - 1.52)
Discontinuers as referent	26 / 55675	116 / 315890	1.14 (0.69 - 1.90)
Excluding women with aberrant opioid filling patterns	36 / 66741	997 / 2685187	1.13 (0.76 - 1.68)
Restriction to women with folate supplementation	22 / 42533	430 / 1075227	1.19 (0.70 - 2.02)
Late first trimester exposure	24 / 56015	996 / 2677585	1.12 (0.72 - 1.74)
Outcome assessment to 365 days	38 / 65878	976 / 2085598	1.06 (0.71 - 1.58)
Negative control analysis	11** / 33842	900 / 2434040	1.01 (0.55 - 1.85)
Cleft Palate with Cleft Lip			
Main analysis (adjusted)	58 / 82504	1397 / 2684588	1.08 (0.79 - 1.47)
Hd-PS estimate	58 / 82539	1404 / 2697354	1.12 (0.83 - 1.51)
Discontinuers as referent	44 / 55675	186 / 315890	1.05 (0.73 - 1.52)
Excluding women with aberrant opioid filling patterns	52 / 66741	1397 / 2685187	1.14 (0.83 - 1.57)
Restriction to women with folate supplementation	30 / 42533	562 / 1075227	0.96 (0.61 - 1.51)
Late first trimester exposure	38 / 56015	1396 / 2677585	1.18 (0.83 - 1.69)
Outcome assessment to 365 days	52 / 65878	1224 / 2085598	1.01 (0.72 - 1.41)
Negative control analysis	15 / 33842	1247 / 2434040	0.76 (0.45 - 1.27)



** Results presented here are not pooled but represent results in the MAX cohort as there were no outcomes among exposed in the MarketScan cohort.
Aberrant opioid filling patterns were defined based on an average of >120 milligrams oral morphine equivalents (MME) for ≥90 consecutive days or use of >3 pharmacies or >3 prescribers for opioid prescriptions between 3 months prior to pregnancy and the end of the first trimester.
Abbreviations: HdPS, High-dimensional Propensity Score.

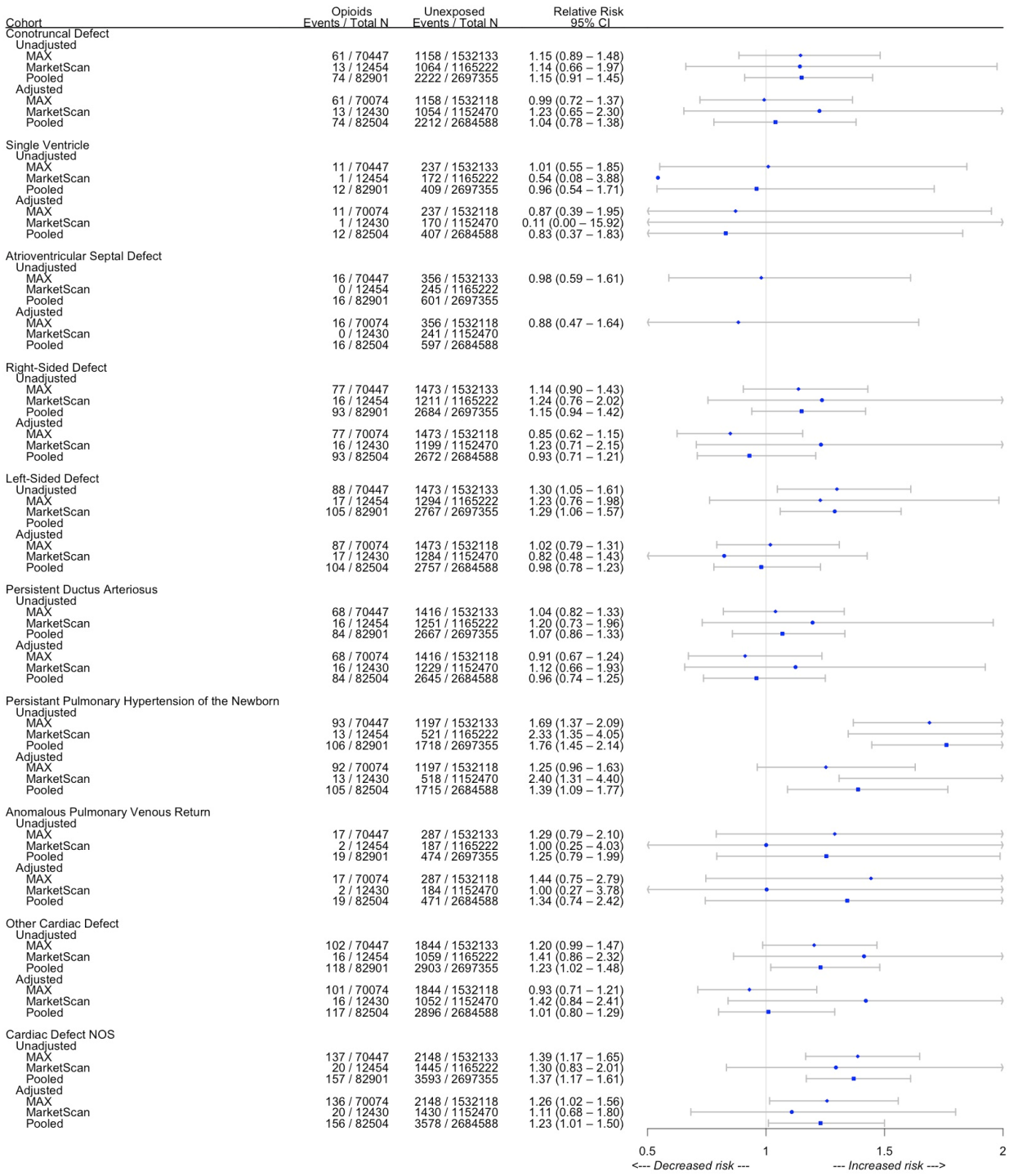
eFigure 6 Risk of Congenital Malformations (Oral Cleft Subgroups) in Infants Following Exposure to Opioids During the First Trimester: Subgroup Analyses (Pooled Estimates, Propensity Score Stratified).

Cohort	Opioids Events / Total N	Unexposed Events / Total N	Relative Risk 95% CI
Cleft Palate			
Hydrocodone	52 / 40840	1540 / 2673531	1.89 (1.32 - 2.72)
Oxycodone	<11* / 8385	1310 / 2230628	1.90 (0.81 - 4.47)
Codeine	<11* / 10960	1544 / 2675741	1.24 (0.61 - 2.53)
Dose Analysis			
<=300 MME	19 / 30732	1544 / 2676481	1.04 (0.65 - 1.66)
>300 – <=600 MME	19 / 16612	1527 / 2660050	1.61 (0.91 - 2.85)
>600 – <=1200 MME	* / 13129	1559 / 2697246	2.54 (1.48 - 4.35)
>1200 MME	29 / 20416	1548 / 2678618	2.15 (1.30 - 3.55)
Cleft Lip			
Hydrocodone	22 / 40840	991 / 2673531	1.16 (0.73 - 1.86)
Oxycodone	<11* / 8385	803 / 2230628	0.91 (0.32 - 2.56)
Codeine	<11*,** / 10960	990 / 2675741	0.26 (0.04 - 1.63)
Dose Analysis			
<=300 MME	18 / 30732	991 / 2676481	1.45 (0.90 - 2.34)
>300 – <=600 MME	<11* / 16612	984 / 2660050	0.86 (0.36 - 2.07)
>600 – <=1200 MME	<11*,** / 13129	1002 / 2697246	0.98 (0.41 - 2.35)
>1200 MME	<11* / 20416	994 / 2678618	0.82 (0.32 - 2.12)
Cleft Palate with Cleft Lip			
Hydrocodone	33 / 40840	1395 / 2673531	1.24 (0.84 - 1.84)
Oxycodone	<11* / 8385	1149 / 2230628	0.66 (0.24 - 1.81)
Codeine	<11* / 10960	1401 / 2675741	0.43 (0.15 - 1.26)
Dose Analysis			
<=300 MME	14 / 30732	1397 / 2676481	0.73 (0.43 - 1.22)
>300 – <=600 MME	18 / 16612	1385 / 2660050	1.43 (0.86 - 2.38)
>600 – <=1200 MME	<11*,** / 13129	1404 / 2697246	1.13 (0.58 - 2.20)
>1200 MME	* / 20416	1392 / 2678618	1.10 (0.62 - 1.97)



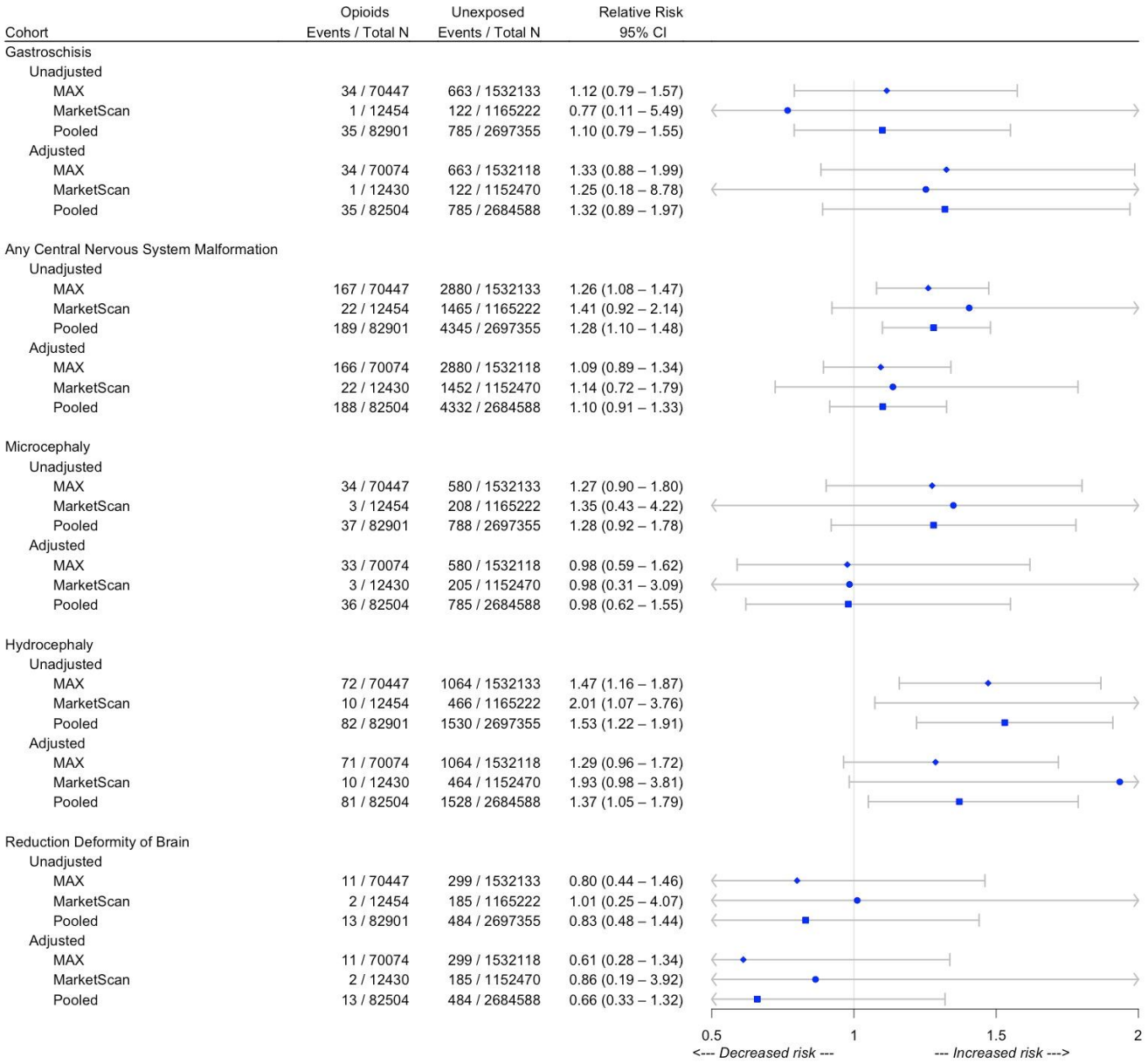
* Cell size <11 in MAX cohort. Numbers are suppressed in accord with the CMS cell size suppression policy.
** Results presented here are not pooled but represent results in the MAX cohort as there were no outcomes among exposed in the MarketScan cohort.
Abbreviation: MME, morphine milligram equivalent.

eFigure 7 Risk of Congenital Malformations (Secondary Outcomes – Cardiac Malformations) in Infants Following Exposure to Opioids During the First Trimester: Main Analyses (Unadjusted and Propensity Score Stratified).



Abbreviations: NOS, not otherwise specified.

eFigure 8 Risk of Congenital Malformations (Secondary Outcomes – Non-Cardiac Malformations) in Infants Following Exposure to Opioids During the First Trimester: Main Analyses (Unadjusted and Propensity Score Stratified).



Appendix 1 Cohort Selection

Cohorts were restricted to women aged 12 to 55 years. To ensure accurate capture of relevant diagnoses, procedures, and medication exposures, we required women in the cohorts to have insurance coverage from at least 3 months prior to the date of the estimated last menstrual period (LMP) to at least 1 month after delivery. We also required that infants had insurance coverage for at least the first 3 months after birth (unless they died sooner in which case a shorter period of coverage was allowed). For Medicaid beneficiaries, we restricted our analysis to women and infants without restricted benefits, private insurance, or certain capitated managed care programs that underreport claims to the Medicaid Analytic eXtract.(1) We excluded pregnancies in which mothers were exposed to known teratogens during the first trimester and pregnancies with an infant with a chromosomal abnormality. Finally, we excluded pregnancies of women with diagnoses indicating an opioid use disorder or who were treated with opioid replacement therapy (as shown in Supplementary Figures 1-2) given that the focus of the present study is on the risks associated with prescription opioid analgesics.

Appendix 2 Validation Study Description and Results

As part of this study, we validated claims-based algorithms for identifying the primary outcomes of interest - Ventricular Septal Defects (VSD), Secundum Atrial Septal Defects/Patent Foramen Ovale (ASD/PFO), Neural Tube Defects (NTD), Club Foot, and Oral Clefts - using hospital medical records.

Using the Mass General Brigham (MGB) Research Patient Data Registry – a centralized clinical data warehouse of patients receiving care at MGB affiliated hospitals in the Boston area – we identified infants born between 2008 and 2014 who had a malformation of interest based on algorithms using ICD-9 and CPT diagnostic and procedural codes in the infant claims (as described in Supplementary Table 1). To avoid inclusion of rule-out diagnosis or coding errors, a malformation was considered present if a diagnosis was recorded on ≥ 2 different dates, or if only recorded on 1 date, associated with a specific therapeutic procedure or surgery code or infant death shortly after birth. Since we cannot distinguish ASD from prematurity-related PFO based on ICD-9 codes, we excluded ASD/PFO diagnoses in preterm infants and required diagnostic codes to persist for ≥ 6 weeks. Medical charts of algorithm-identified cases were independently reviewed by two physicians to assess the presence of the outcome. Reviewer pairs were asked to reevaluate cases together and attempt to achieve consensus whenever there was disagreement. Positive predictive values (PPVs) and 95% confidence intervals (CIs) were calculated, using medical charts as the gold standard.

50 randomly sampled cases were considered for each outcome, except for NTD for which all 24 cases identified in the database were reviewed. Medical charts were missing for 1 case of VSD, 1 case of NTD and 1 case of Oral Cleft. All 49 retrievable VSDs were classified as true positives (PPV=100%; 95% CI=91%, 100%). All 50 ASD/PFO cases were either true ASDs (N=18) or PFOs (N=32), resulting in a PPV of 100% (91%, 100%). PPVs were 74% (51%, 89%) for NTD, 98% (88%, 100%) for Club Foot and 96% (85%, 99%) for Oral Cleft, see Appendix Table 1.

Appendix Table 1 Positive Predicted Values of Validated Malformations.

Malformation	# True Positives	# False Positives	Total	Charts N/A	PPV (95% CI)
Ventricular Septal Defect	49	0	49	1	1.00 (0.91 - 1.00)
Neural Tube Defect	17	6	23	1	0.74 (0.51 - 0.89)
Club Foot	49	1	50	0	0.98 (0.88 - 1.00)
Secundum Atrial Septal Defect/Patent Foramen Ovale	18 ASD/32 PFO	0	50	0	1.00 (0.91 - 1.00)
Oral Cleft	47	2	49	1	0.96 (0.85 - 0.99)

Abbreviations: ASD, secundum atrial septal defect; CI, confidence interval; N/A, not available; PFO, patent foramen ovale; PPV, positive predictive value.

Appendix 3 Quantifying the Potential Effect of Restriction to Live Births

The study cohorts consisted of live births and did not include pregnancies ending in stillbirth, spontaneous abortion or therapeutic abortion.

If the frequency of live births is the same among opioid-exposed and unexposed pregnancies, within levels of covariates included as potential confounders, then the relative risk (RR) estimates as they were obtained from our analyses are unbiased.
If, however, non-live births occur with a higher frequency among opioid-exposed vs. unexposed pregnancies, then estimates from our main analyses may be biased towards the null. To assess this potential bias, we quantified the potential impact of missing non-live births (including stillbirth, spontaneous abortion and therapeutic abortion) using methods that have previously been described in detail and have been employed by our team in prior evaluations of teratogenic potential of select medications(2-6). The approach used estimates the true (corrected) RR at the time of the occurrence of the defect as a function of the observed association and the probabilities of survival until birth as follows:
Corrected RR = observed RR * (S10*S01/S11*S00), with
S10 being the probability of livebirth among unexposed infants with the malformation of interest;
S11 being the probability of livebirth among exposed infants with the malformation of interest;
S00 being the probability of livebirth among unexposed infants without the malformation of interest;
S01 being the probability of livebirth among exposed infants without the malformation of interest.

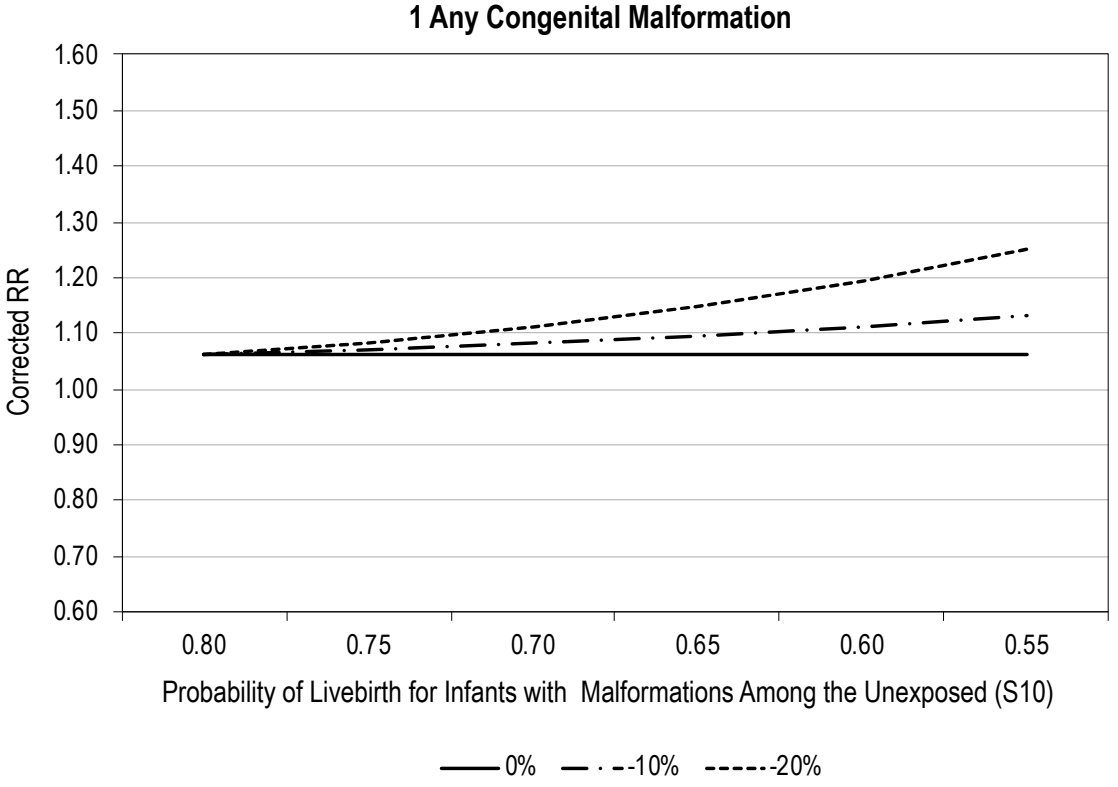
Bias does not occur unless both the malformation of interest and the exposure affect the probability of livebirth. The selection probabilities would otherwise cancel out.
In the approach used we assumed a frequency of non-live births in non-malformed fetuses of 20%, corresponding to a livebirth probability of 80%. Using literature-based estimates of the frequency of termination for recognized malformations, we modeled a range of livebirth probabilities in the unexposed malformed, from 55% to 80% for all malformations of interest (lower probabilities are considered unrealistic)(7). We then assessed the potential impact of a 10% to 20% lower frequency of livebirths among the opioid exposed (within levels of covariates adjusted for through the use of propensity scores) on the fully adjusted RR (see Appendix Table 2).

Appendix Figures 1 through 6 show the range of plausible values for the corrected RR. Even under the most extreme assumption of at least 45% non-live births among unexposed infants with the malformation of interest and 65% non-live births among opioid-exposed infants, the RR would remain below 1.30 for all malformations of interest.
Of note, this analysis was not conducted for oral clefts as non-syndromic oral clefts do not result in fetal death and are rarely a reason for terminations.(7, 8)

Appendix Table 2 Probability of Live Birth

Pregnancies with malformation		**Pregnancies without malformation**	
Unexposed (S10)	**Exposed (S11)**	**Unexposed (S00)**	**Exposed (S01)**
55-80%	S10-20%	80%	S00-20%
	S10-10%		S00-10%
	S10		S00

Appendix Figures 1-6 Corrected Relative Risk for the Association Between Opioid Exposure During the First Trimester and Congenital Malformations, Starting from the Observed Adjusted Relative Risk.



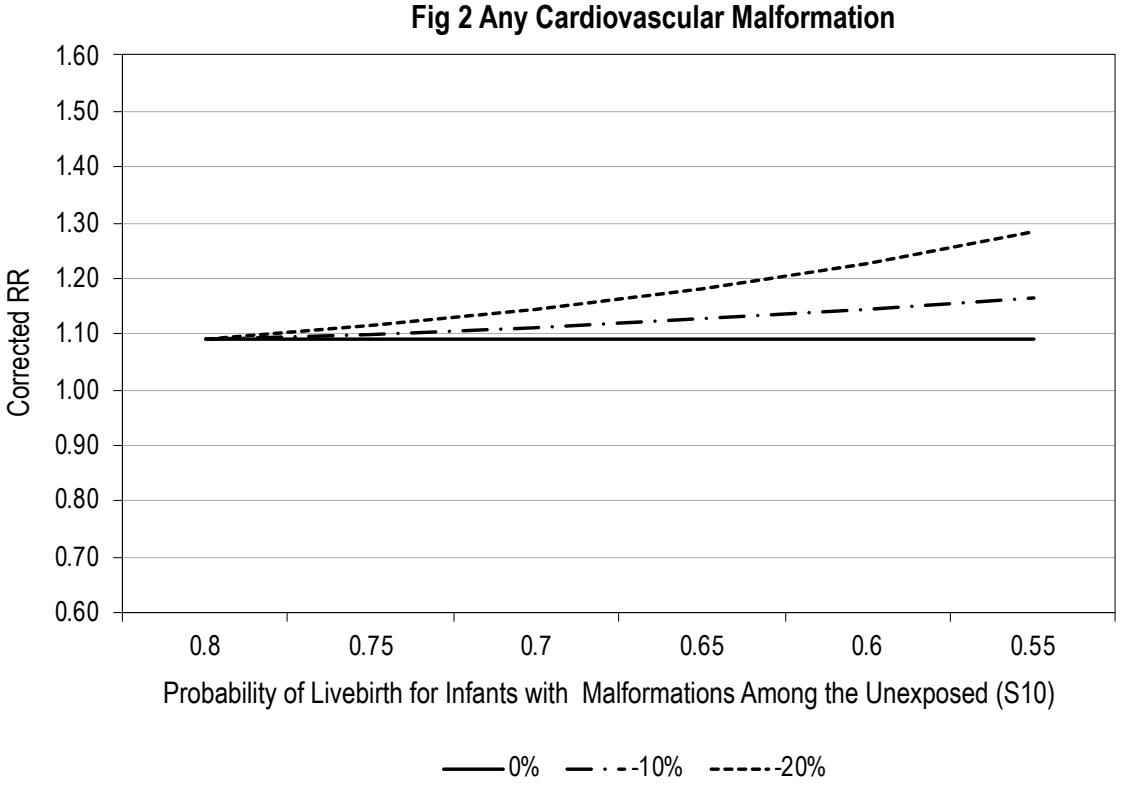


Fig 3 Ventricular Septal Defect

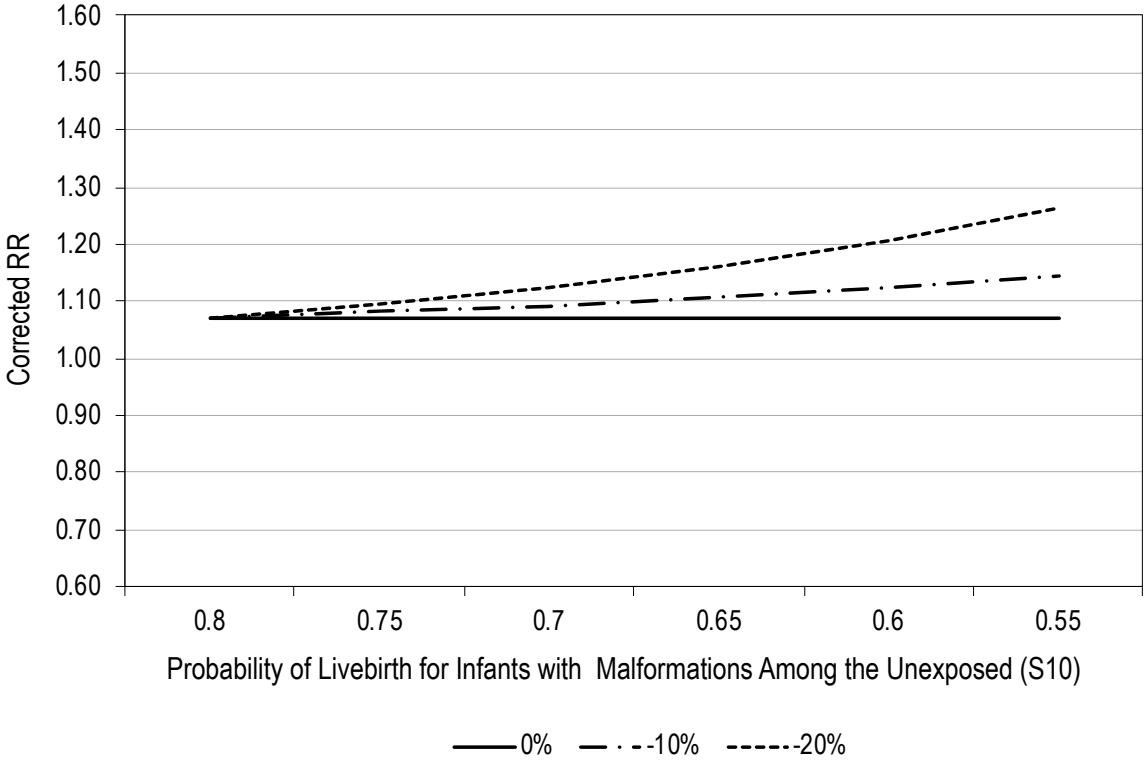


Fig 4 Secundum Atrial Septal Defect/Patent Foramen Ovale

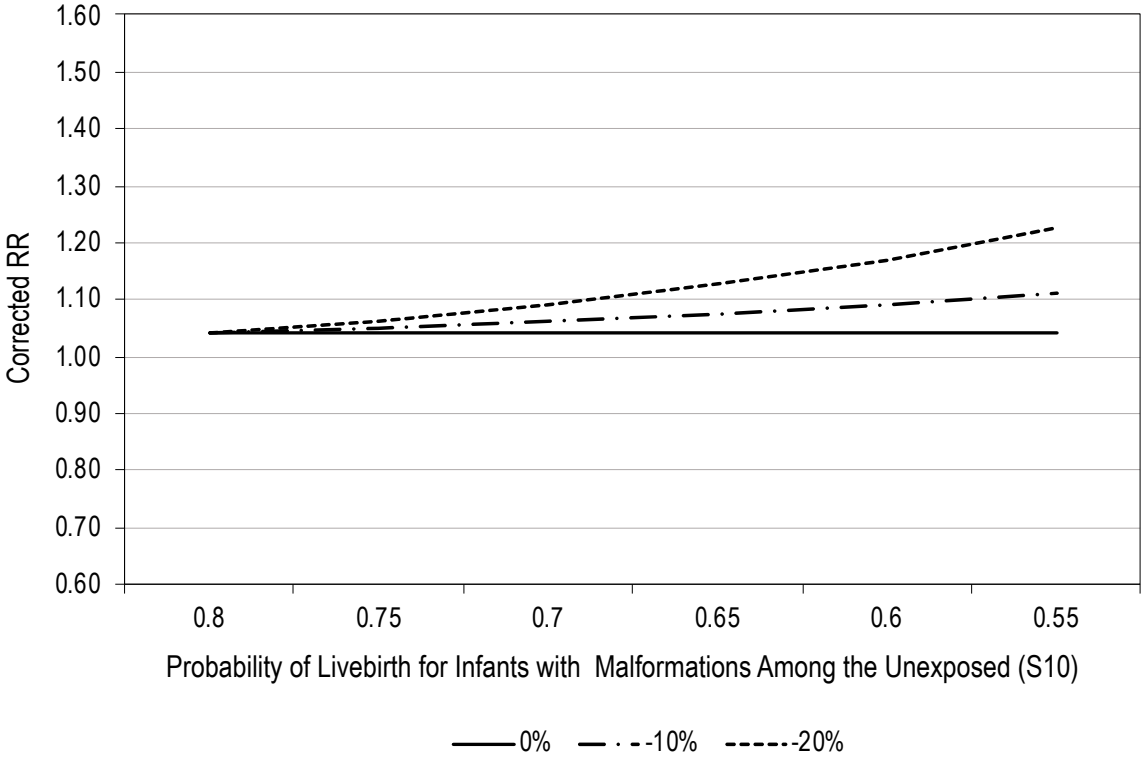


Fig 5 Neural Tube Defect

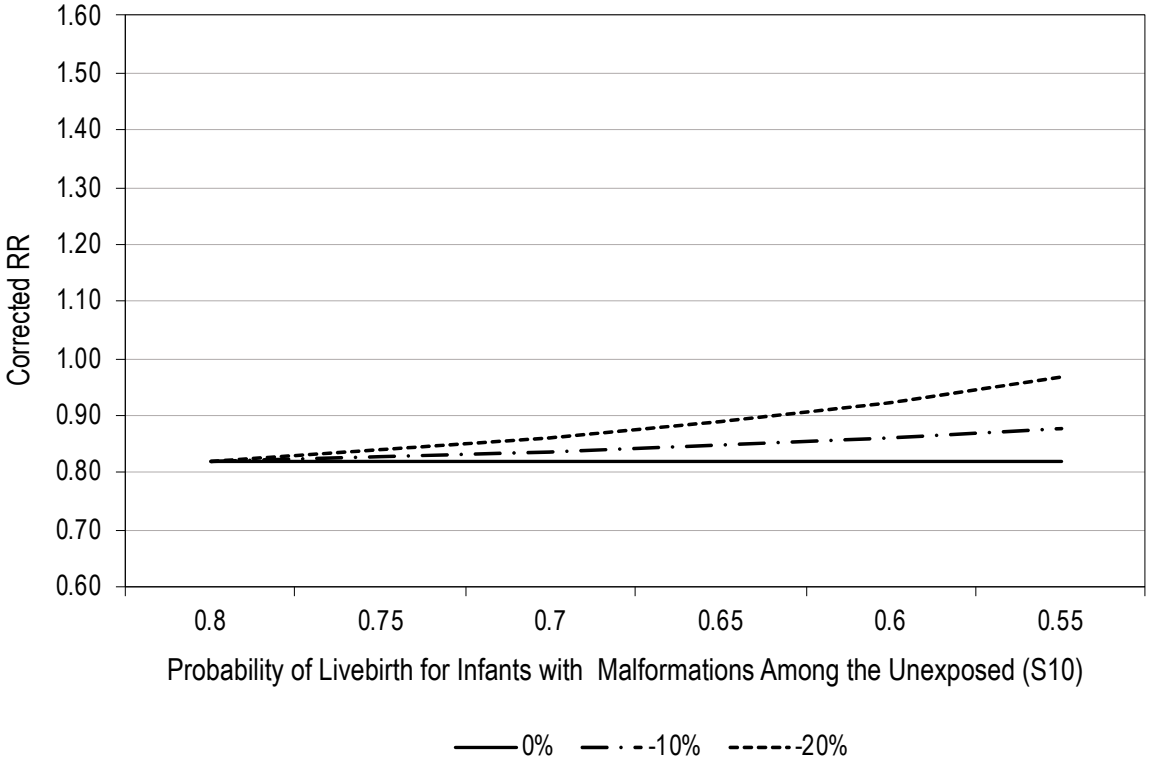
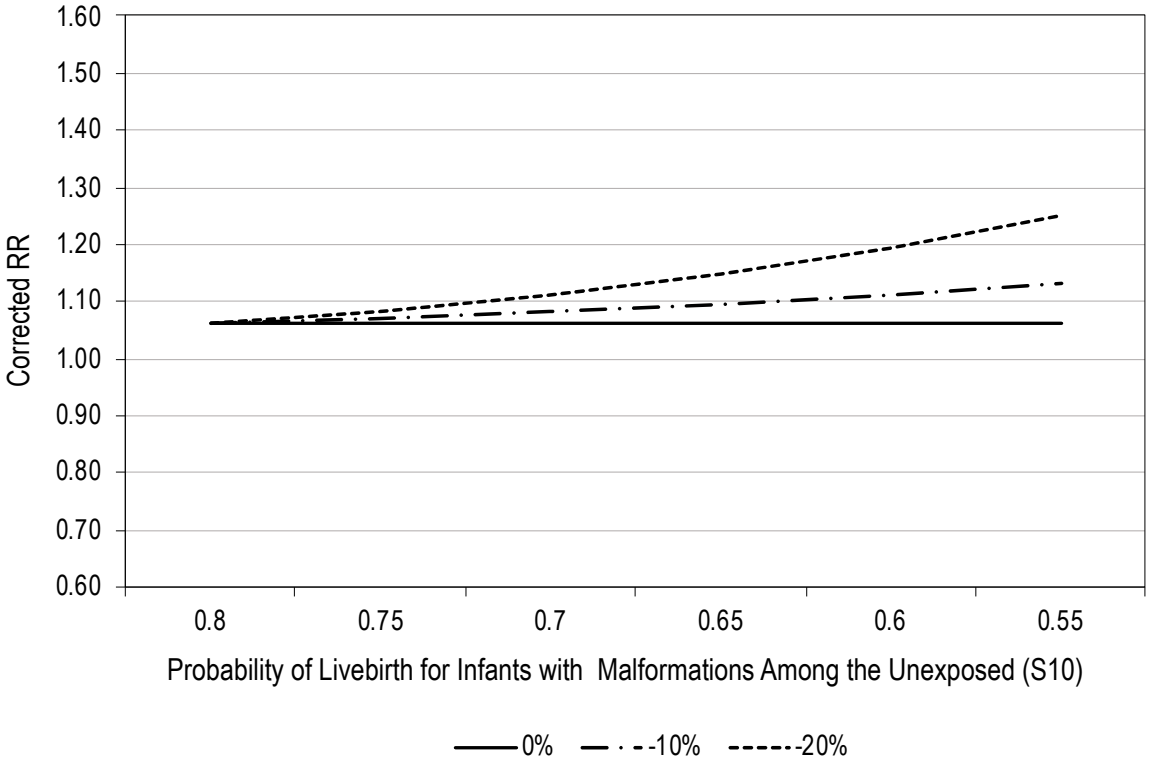


Fig 6 Club Foot



Appendix 4 Sensitivity Analysis of Residual Confounding to Explain Increase in Oral Clefts

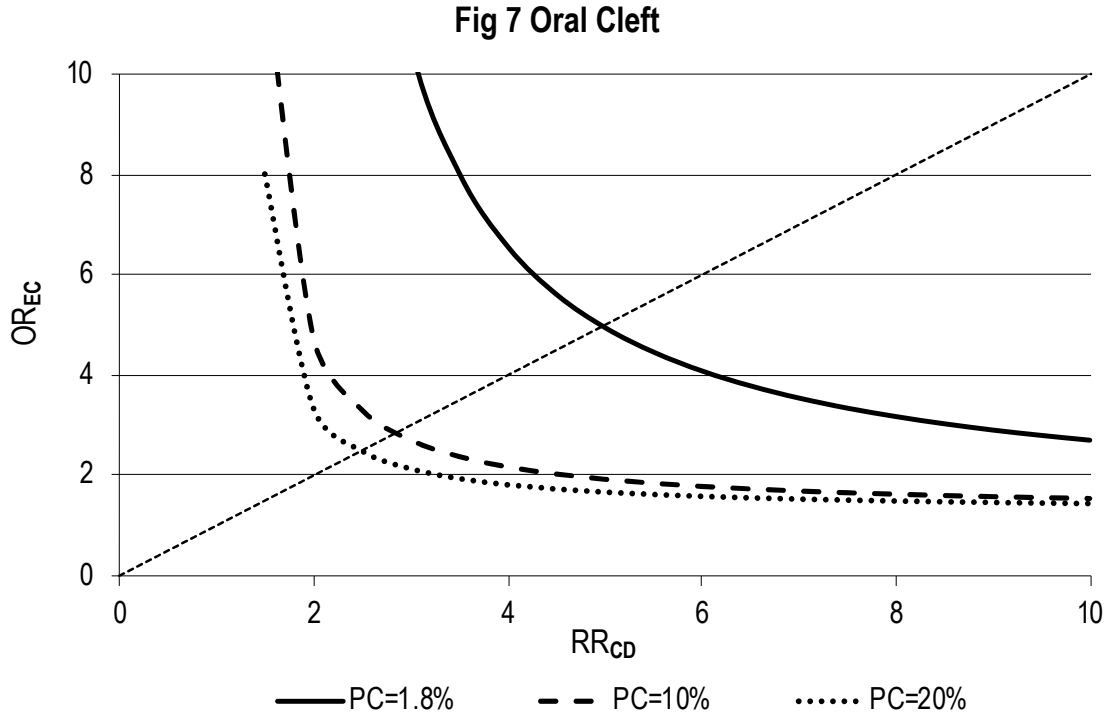
With an observed prevalence of 12.8% among exposed and 2.2% among unexposed Medicaid insured women, and 4.95% among exposed and 0.48% among unexposed commercially insured women, tobacco use is likely to be incompletely captured in claims data. The Centers from Disease Control and Prevention estimate that 7.2% of women smoke cigarettes during pregnancy, with strong variations by race/ethnicity, maternal age and social economic status.(9)

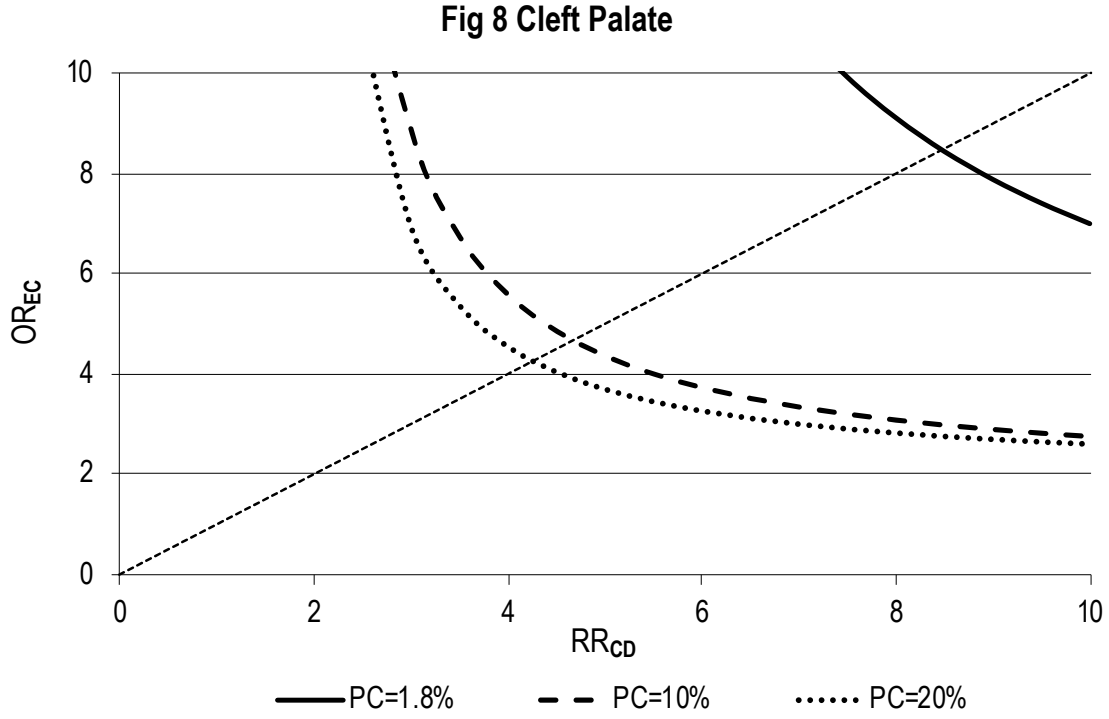
To quantify the potential impact of residual confounding (e.g., by incompletely measured tobacco use or other factors), an approach that has been referred to as the target-adjustment sensitivity analysis(10, 11) will be used. This approach assesses the extent of confounding necessary to fully explain the observed findings if in truth there is no association, i.e. under the null.

Appendix Figures 7 and 8 display the strengths of the association between opioid exposure during the first trimester and a potential unmeasured/incompletely captured confounder (e.g., tobacco use) (displayed as odds ratio (OREC)) and the association between the potential confounder and the outcomes of interest (oral cleft overall & cleft palate) (displayed as relative risk (RRCD)) that would be required to fully explain the observed increased risk of the outcome associated with opioid exposure (pooled adjusted RR=1.21 for oral cleft & 1.62 for cleft palate) if in truth no such increase existed ("True" RR=1).

For an unmeasured confounder present in 10% or 20% of the population, relative risks of 2.5 or more linking the hypothetical confounder to both opioid exposure and oral cleft (and approximately 4 for cleft palate) would be needed to fully explain the observed association. For a confounder present in 1.8% of the population (which would correspond to the observed prevalence of tobacco use among exposed and unexposed women in both cohorts together), relative risks of at least 5 for oral clefts and greater than 8 for cleft palates would be needed. These required associations are unrealistically high, especially since previous literature suggested only a modest association between smoking and oral cleft (OR=1.22).(12)

Appendix Figures 8-9 Sensitivity analysis of residual confounding by and unmeasured or incompletely measured confounder such as tobacco use (rule-out approach) for the estimated pooled adjusted relative risk of 1.21 for oral cleft and 1.77 for cleft palate and different levels of confounder prevalence (PC=1.8%, 10%, 20%).





Note: Each line splits the area into two. The upper right area represents all combinations of an association between exposure and confounder (OREC) and an association between confounder and outcome (RRCD) that would create confounding by an unmeasured factor strong enough to move the point estimate of RR to the null value (RR = 1) or beyond. The area to the lower left represents all parameter combinations that would not be able to move the estimated RR toward the null.

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