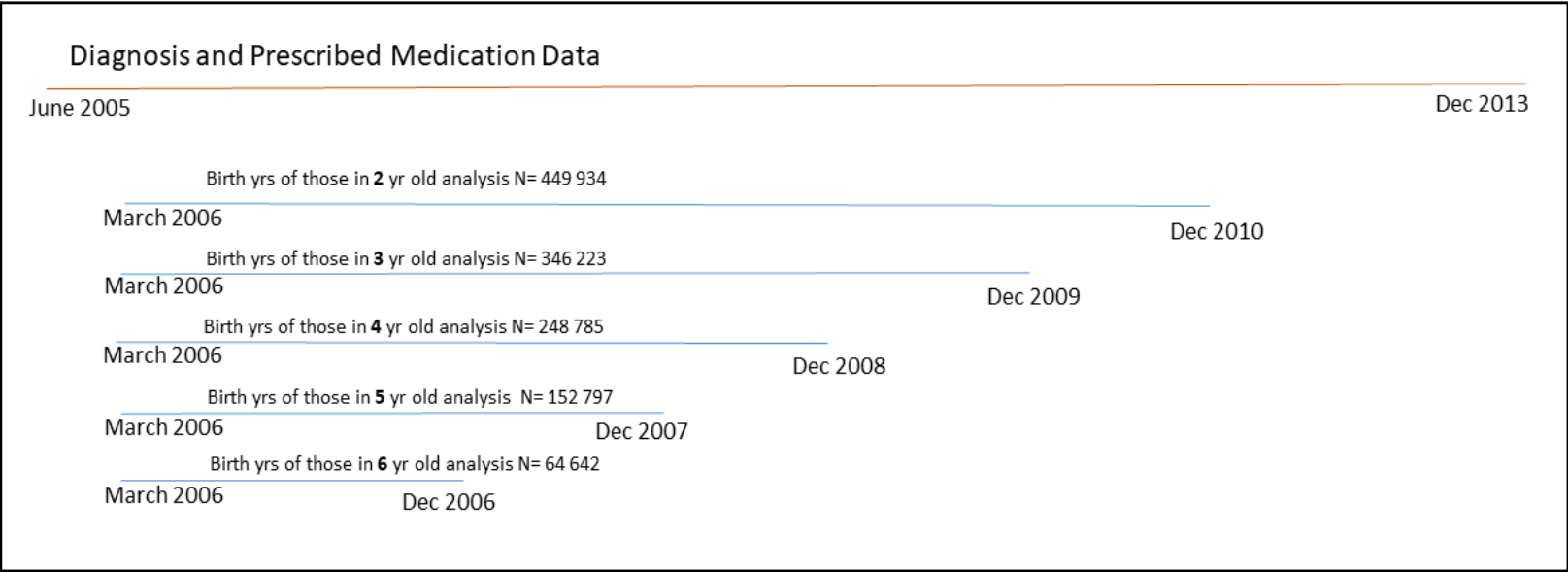


Online data supplement

Prescribed analgesics in pregnancy and risk of childhood asthma

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Figure E1: Data available for analysis



Footnote: Numbers refer to adjusted analyses (complete data on covariates)

Table E1. Three classes of analgesics included in the analyses

	ATC codes	Generic drug name
Opioids	N02AA59	Codeine, combinations excluding psycholeptics
	N02AA79	Codeine, combinations with psycholeptics
	N02AA08	Dihydrocodeine
	N02AA58	Dihydrocodeine, combinations
	N02AC04	Dextropropoxyphene
	N02AC54	Dextropropoxyphene, combinations excluding psycholeptics
	N02AX02	Tramadol
Anti-migraine	N02CA01	Dihydroergotamine
	N02CA02	Ergotamine
	N02CA04	Methysergide
	N02CA07	Lisuride
	N02CA51	Dihydroergotamine, combinations
	N02CA52	Ergotamine, combinations excluding psycholeptics
	N02CA72	Ergotamine, combinations with psycholeptics
	N02CC01	Sumatriptan
	N02CC02	Naratriptan
	N02CC03	Zolmitriptan
	N02CC04	Rizatriptan
	N02CC05	Almotriptan
	N02CC06	Eletriptan
	N02CC07	Frovatriptan
	N02CX01	Pizotifen
	N02CX02	Clonidine
	N02CX03	Ipazochrome
	N02CX05	Dimetotiazine
	N02CX06	Oxetorone
	N02CB01	Flumetoxone
Paracetamol	N02BE01	Paracetamol
	N02BE51	Paracetamol, combinations excluding psycholeptics
	N02BE71	Paracetamol, combinations with psycholeptics

Table E2. Frequency of analgesic classes prescribed to the mother during pregnancy

Opioids	Anti-migraine	Paracetamol	N	%
No	No	No	459,690	93.2
No	No	Yes	9,091	1.8
Yes	No	No	15,405	3.1
No	Yes	No	2,343	0.5
Yes	No	Yes	5,091	1.0
No	Yes	Yes	225	0.0
Yes	Yes	No	829	0.2
Yes	Yes	Yes	325	0.1

Table E3. Associations between prescribed analgesics in pregnancy and childhood asthma/wheeze (whole cohort; unadjusted analysis)

Asthma/wheeze		Opioids		Anti-migraine		Paracetamol	
Age (years)	n	OR ¹	(95% CI)	OR ¹	(95% CI)	OR ¹	(95% CI)
2	492, 999	1.72	(1.64, 1.79)	1.50	(1.34, 1.67)	1.71	(1.62, 1.80)
3	381 729	1.67	(1.59, 1.76)	1.55	(1.37, 1.75)	1.75	(1.65, 1.86)
4	276 333	1.58	(1.49, 1.68)	1.42	(1.22, 1.65)	1.65	(1.54, 1.78)
5	173 131	1.61	(1.48, 1.74)	1.74	(1.45, 2.09)	1.67	(1.52, 1.83)
6	72 778	1.65	(1.45, 1.87)	1.78	(1.32, 2.39)	1.71	(1.48, 2.00)

Table E4. Associations between prescribed analgesics in pregnancy and childhood asthma/wheeze (whole cohort), mutually adjusted for the other analgesics

Asthma/wheeze		Opioids		Anti-migraine		Paracetamol	
Age (years)	n	OR ¹	(95% CI)	OR ¹	(95% CI)	OR ¹	(95% CI)
2	449 934	1.37	(1.30-1.44)	1.15	(1.03-1.30)	1.34	(1.26-1.43)
3	346 223	1.33	(1.26-1.41)	1.21	(1.06-1.38)	1.41	(1.32-1.51)
4	248 785	1.29	(1.20-1.38)	1.07	(0.91-1.27)	1.34	(1.24-1.36)
5	152 797	1.30	(1.18-1.42)	1.34	(1.09-1.65)	1.36	(1.21-1.51)
6	64 642	1.28	(1.11-1.49)	1.27	(0.90-1.80)	1.33	(1.11-1.58)

¹ Odds ratio adjusted for maternal birth country, education, asthma, BMI in early pregnancy, parity, smoking during pregnancy, age at delivery and **mutual adjustment for the other analgesics**

Table E5. Associations between prescribed analgesics in pregnancy and childhood asthma/wheeze (whole cohort), with exposure being defined by the drug having been dispensed at least twice during pregnancy

Asthma/wheeze		Opioids		Anti-migraine		Paracetamol	
Age (years)	n	OR ¹	(95% CI)	OR ¹	(95% CI)	OR ¹	(95% CI)
2	449 934	1.57	(1.44-1.71)	1.39	(1.16-1.67)	1.61	(1.47-1.76)
3	346 223	1.59	(1.44-1.75)	1.39	(1.12-1.72)	1.70	(1.54-1.89)
4	248 785	1.50	(1.34-1.70)	1.29	(0.99-1.68)	1.68	(1.48-1.91)
5	152 797	1.47	(1.26-1.72)	1.60	(1.16-2.22)	1.61	(1.35-1.90)
6	64 642	1.54	(1.22-1.96)	1.18	(0.65-2.15)	1.68	(1.29-2.18)

¹ Odds ratio adjusted for maternal birth country, education, asthma, BMI in early pregnancy, parity, smoking during pregnancy and age at delivery

Table E6. Odds ratios (OR) and 95% confidence intervals (CI) from logistic regression of asthma/wheeze at age 2-6 years by number of classes of analgesic drugs (opioids, anti-migraine, paracetamol)

Asthma/wheeze		Number of classes of analgesics					
		One		Two		Three	
Age (years)	n	OR ¹	(95% CI)	OR ¹	(95% CI)	OR ¹	(95% CI)
2	449 934	1.42	(1.36-1.48)	1.67	(1.54-1.81)	1.69	(1.21-2.36)
3	346 223	1.42	(1.35-1.49)	1.61	(1.44-1.81)	2.00	(1.38-2.90)
4	248 785	1.34	(1.26-1.42)	1.39	(1.30-1.49)	1.28	(0.74-2.19)
5	152 797	1.36	(1.26-1.48)	1.69	(1.45-1.28)	1.94	(1.03-3.68)
6	64 642	1.36	(1.19-1.55)	1.62	(1.27-2.06)	1.36	(0.41-4.52)

¹ Adjusted for maternal birth country, education, asthma, BMI in early pregnancy, parity, smoking during pregnancy and age at delivery

Table E7. Associations between prescribed analgesics in pregnancy and childhood asthma/wheeze (first born children only)

Asthma/wheeze		Opioids		Anti-migraine		Paracetamol	
Age (years)	n	OR ¹	(95% CI)	OR ¹	(95% CI)	OR ¹	(95% CI)
2	197 505	1.48	(1.37, 1.60)	1.27	(1.07, 1.52)	1.51	(1.37-1.66)
3	152 056	1.39	(1.27, 1.52)	1.40	(1.16, 1.70)	1.55	(1.39, 1.72)
4	109, 104	1.32	(1.19, 1.47)	1.32	(1.05, 1.67)	1.45	(1.28, 1.66)
5	66 552	1.41	(1.23, 1.62)	1.51	(1.12, 2.03)	1.48	(1.25, 1.75)
6	28 156	1.45	(1.17, 1.80)	1.40	(0.85, 2.31)	1.54	(1.18, 2.02)

¹ Odds ratio adjusted for maternal birth country, education, asthma, BMI in early pregnancy, smoking during pregnancy and age at delivery

Table E8: Age-varying hazard ratios (HR) from Cox proportional hazards regression of association between incident maternal analgesic prescription and asthma/wheeze incidence

a. HRs adjusted for measured confounders¹ (n=656,440, events=55,761)						
Age band (years)	Opioids		Anti-migraine		Paracetamol	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
0-1	1.52	(1.44, 1.60)	1.32	(1.16, 1.51)	1.57	(1.48, 1.67)
1-2	1.46	(1.38, 1.55)	1.27	(1.10, 1.46)	1.37	(1.28, 1.47)
>2	1.35	(1.26, 1.44)	1.44	(1.25, 1.67)	1.37	(1.27, 1.48)

b. Sibling comparison: HRs adjusted for factors shared by siblings, using stratified models, and measured confounders not shared by siblings² (n=658,898, events=55,990)						
Age band (years)	Opioids		Anti-migraine		Paracetamol	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
0-1	1.10	(0.97, 1.27)	1.28	(0.90, 1.82)	1.11	(0.95, 1.29)
1-2	0.96	(0.81, 1.14)	0.70	(0.45, 1.11)	1.03	(0.84, 1.27)
>2	0.94	(0.73, 1.21)	1.12	(0.59, 2.13)	0.88	(0.64, 1.21)

¹ maternal birth country, education, asthma, BMI in early pregnancy, parity, smoking during pregnancy and age at delivery

² BMI in early pregnancy, parity, smoking during pregnancy and age at delivery