

Supplemental Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Sources of Data

Information on live- and stillbirths was obtained from the Medical Birth Register. This register, established in 1968, contains data on all births by women living in Denmark and includes information on the personal identification numbers of the newborn and the parents, date of birth, multiple births, gestational age, birth weight and maternal smoking status.¹ Gestational age is recorded on the basis of maternal report of the first day of the last menstrual period; this date is subsequently confirmed by ultrasonographic measurements at antenatal screening in the vast majority of women. In a study of the use of prenatal ultrasound scanning among pregnant women in Denmark, more than 93% underwent a scan in the year 2000.² The National Prescription Registry contains individual-level information on all drug prescriptions filled at all Danish pharmacies since 1995,³ including data on the anatomical therapeutic chemical (ATC) code of the dispensed drug and the date when the prescription was filled. The ATC code for metoclopramide is A03FA01. The National Patient Register holds individual-level information on outpatient and emergency department visits and inpatient admissions to all hospitals in Denmark; physician-assigned diagnoses are coded according to the International Classification of Diseases;⁴ the tenth revision (ICD-10) was used throughout the study period. From this register, we obtained diagnostic information on pregnancies with abortive outcome, congenital malformations, and maternal medical conditions. For pregnancies with abortive outcome, gestational age is recorded in the National Patient Register using a supplementary code. The Central Person Register⁵ (the main administrative register in Denmark) was used to obtain information on age, county of residence, and country of birth of the women. Statistics Denmark provided data on women's educational level, gross household income, and civil status. By the use of the personal identification number assigned to all inhabitants in Denmark, we linked individual-level information between these data sources.

eMethods. Classification of Major Congenital Malformations

We identified cases of major congenital malformations from the National Patient Register, allowing for a 1-year follow-up after birth for all participants. A validation study of the National Patient Register found that registrations were correct for 88% of malformation diagnoses overall and 90% for cardiac defects overall.^{6,7} ICD-10 codes used for the identification of major congenital malformations in this study are summarized in eTable 1. Major congenital malformations were defined according to the European Surveillance of Congenital Anomalies (EUROCAT) classification for subgroups of major congenital anomalies,⁸ with the study outcome defined as the first registered diagnosis of any major congenital malformation. For the purpose of our study, some modifications of the EUROCAT classification were performed in order to exclude malformations for which causes are known. Thus, infants with chromosomal aberrations (D821, Q90-99), genetic syndromes (Q447B, Q619A, Q751, Q754, Q771, Q772, Q780, Q796, Q85, Q87), malformation syndromes with known causes (Q86) and congenital virus infections with possible association with malformations (P350, P351, P352, P371) were identified and excluded from the analyses of malformations.

All minor congenital anomalies were excluded from evaluation according to the EUROCAT minor anomalies exclusion list (i.e. infants diagnosed with such defects were considered as non-cases but were not excluded from the study).⁹ Due to minor inconsistencies between the ICD-10-British Pediatric Association version used by EUROCAT, and the standard ICD-10 used in Denmark, some EUROCAT exclusions could not be performed: synophrys (Q1880), crocodile tears (Q0782), functional gastrointestinal disorders (Q4021, Q4320, Q4381 and Q4382), and bifid scrotum (Q5521). In addition, hip dislocation and dysplasia (Q65), which are included in the EUROCAT limb malformation subgroup, were excluded from evaluation due to poor validity in the National Patient Register.⁶

eMethods. *ICD-10* Codes for Abortive Pregnancy Outcomes

We used the National Patient Register to identify abortive outcomes of pregnancy, which included spontaneous abortion (ICD-10 codes: 0021 and 003) as well as other abortive outcomes (ectopic pregnancy [000], hydatidiform mole [001], other abnormal products of gestation [0020, 0028-029], and induced abortion [004-08]). A validation study of the National Patient Register found that registrations were correct for 99% of diagnoses of spontaneous abortion, when confirmed by review of medical records.¹⁰ The gestational age cutoff for the definitions of spontaneous abortion and stillbirth in Denmark changed during the study period; between 1997 and 2003, fetal death through week 28 was defined as spontaneous abortion and later fetal death as stillbirth, from 2004 fetal death up through week 22 is defined as spontaneous abortion. In this study, spontaneous abortion was at all times defined as fetal death occurring through 22 gestational weeks.

eMethods. Malformations Identified Among Induced Abortions and Stillbirths

In Denmark, diagnoses of induced abortions are registered in the National Patient Register. For induced abortions prior to 12 gestational weeks, the reason for termination is not registered. However, for induced abortions between weeks 13 and 22, a specific ICD code has been in use since April, 2004, to indicate the reason for termination. In cases where the reason for induced abortion is medical (“hereditary predisposition in fetus” [ICD-10 code O053] or “fetal injury or disease” [O054]), the diagnosing physician is required to indicate additional supplementary codes to specify the presence or absence of congenital malformation. These include codes indicating a) confirmed malformation (and ICD-10 code to specify the malformation), b) no malformation, c) suspect malformation, and d) malformation information missing.

Malformations diagnoses among stillborn infants are registered in the Medical Birth Register (ICD-10 codes are used).

For sensitivity analyses of major congenital malformation overall and those individual malformation categories of which >10% are terminated in Denmark,¹¹ we included (in addition to live-born infants) all induced abortions for medical reasons and all stillbirths in a subcohort with delivery dates between April, 2004, and March, 2011. Among induced abortions for medical reasons, we defined those with codes indicating confirmed defects as cases (in addition to ICD-10 code for the defect) and those without such codes as non-cases. It should be noted, however, that the completeness and validity of registration of malformations among induced abortions and stillbirths have not been investigated why results from this sensitivity analysis should be interpreted with caution.

eMethods. Exposures During Pregnancy

Estimates were adjusted for the following exposures during pregnancy (within the respective exposure time window of each analysis): hospitalization for hyperemesis gravidarum (ICD-10 code O21) or nausea and vomiting (R11) and use of other antiemetics (antiemetic antihistamines [R06AE03, R06AD02, R06AE05, N07CA02], ondansetron [ATC code A04AA01], scopolamine [A04AD01], and domperidone [A03FA03]).

eTable 1. Congenital Malformations: Categorization, *ICD-10* Codes, and Exclusions

Malformation subgroups included in category major malformations overall	ICD-10 codes	ICD-10 codes for minor defects excluded from evaluation
Nervous system	Q00-Q07	
Eye	Q10-Q15	Q101-Q103, Q105, Q135
Ear, face and neck	Q16-Q18	Q170-Q175, Q179, Q180-Q182, Q184-Q187, Q189
Congenital heart defects	Q20-Q26	Q211C, Q250
Respiratory	Q30-34	Q314, Q315, Q320, Q331
Orofacial clefts	Q35-37	
Digestive system	Q38-45, Q790	Q381, Q382, Q385, Q400, Q401, Q430
Abdominal wall defects	Q792, Q793, Q795	
Urinary	Q60-64, Q794	Q610, Q627, Q633
Genital	Q50-52, Q54-56	Q523, Q525, Q552F
Limb	Q66-74	Q662-Q669, Q670-Q678, Q680, Q682A, Q683-Q685, Q740G
Other	Q750, Q77, Q780, Q782-Q788, Q798, Q80-82, Q893, Q894	Q825, Q8280

eTable 2. Individual Malformations Categories and Their Occurrence in the Background Cohort

Malformation (ICD-10 code)	Occurrence of malformation in background cohort (n=879,235)		Fulfilled power criterion of ≥ 0.3 cases per 1000 and included in analyses
	No.	No. per 1000	
Neural tube defects (Q00, Q01, Q05)	336	0.38	Yes
Hydrocephalus (Q03)	369	0.42	Yes
Microcephaly (Q02)	222	0.25	
Arhinencephaly/holoprosencephaly (Q041,Q042)	19	0.02	
Anophthalmus/micropthalmus (Q110, Q111, Q112)	107	0.12	
Congenital cataract (Q120)	268	0.30	Yes
Congenital glaucoma (Q150)	86	0.10	
Anotia (Q160)	25	0.03	
Common arterial truncus (Q200)	63	0.07	
Transposition of great vessels (Q203)	330	0.38	Yes
Single ventricle (Q204)	111	0.13	
Ventricular septal defect (Q210)	2,849	3.24	Yes
Atrial septal defect (Q211)	2,631	2.99	Yes
Atrioventricular septal defect (Q212)	252	0.29	
Tetralogy of Fallot (Q213)	274	0.31	Yes
Tricuspid atresia and stenosis (Q224)	35	0.04	
Ebstein's anomaly (Q225)	44	0.05	
Pulmonary valve stenosis (Q221)	579	0.66	Yes
Pulmonary valve atresia (Q220)	111	0.13	
Aortic valve atresia/stenosis (Q230)	169	0.19	
Hypoplastic left heart (Q234)	157	0.18	
Hypoplastic right heart (Q226)	57	0.06	
Coarctation of aorta (Q251)	390	0.44	Yes
Total anomalous pulmonary venous return (Q262)	54	0.06	
Choanal atresia (Q300)	150	0.17	
Cleft lip with or without cleft palate (Q36, Q37)	1,143	1.30	Yes
Cleft palate (Q35)	461	0.52	Yes
Esophageal atresia (Q390, Q391)	201	0.23	
Duodenal atresia or stenosis (Q410)	138	0.16	
Atresia or stenosis of other part of small intestine (Q411-Q418)	93	0.11	
Anorectal atresia and stenosis (Q420-Q423)	322	0.37	Yes
Hirschprung's disease (Q431)	243	0.28	
Atresia of bile ducts (Q442)	88	0.10	
Annular pancreas (Q451)	18	0.02	
Diaphragmatic hernia (Q790)	188	0.21	
Gastroschisis (Q793)	157	0.18	
Omphalocele (Q792)	97	0.11	
Renal agenesis (Q601, Q606)	36	0.04	
Renal dysplasia (Q614)	117	0.13	
Congenital hydronephrosis (Q620)	1,761	2.00	Yes
Bladder exstrophy and/or epispadia (Q640, Q641)	79	0.09	
Posterior urethral valve and/or prune belly (Q642, Q794)	117	0.13	
Hypospadias (Q54)	2,105	4.67 ^a	Yes
Indeterminate sex (Q56)	19	0.02	
Limb reduction (Q71, Q72, Q73)	504	0.57	Yes
Club foot (Q660)	1,410	1.60	Yes
Polydactyly (Q69)	557	0.63	Yes
Syndactyly (Q70)	633	0.72	Yes
Skeletal dysplasias (Q770, Q773-Q779, Q782-Q788)	76	0.09	
Craniosynostosis (Q750)	669	0.76	Yes
Other malformations of musculoskeletal system (Q798)	96	0.11	
Congenital skin disorders (Q80-82)	359	0.41	Yes
Situs inversus (Q893)	35	0.04	

^aAmong boys.

eTable 3. Variables Included in Propensity Score With Categories, Sources of Data, and Missing Values

Covariate	Categories	Source of data	No. (%) missing ^c
Demographics			
Age at pregnancy onset	≤24, 25-29, 30-34, 35-39, ≥40	Central Person Register	182 (0.01)
Place of birth	Denmark, Europe, Other	Central Person Register	3829 (0.31)
County of residence	Capital, Mid Jutland, North Jutland, Sealand, Southern Denmark	Central Person Register	10,421 (0.85)
Married or living with partner	yes/no	Statistics Denmark	13,626 (1.11)
Level of education	Primary school, Secondary school, Vocational or short tertiary education, Medium or long tertiary education	Statistics Denmark	40,112 (3.28)
Calendar year of delivery or abortive outcome	3-year categories	National Patient Register and Medical Birth Register	0
Gross household income	quintiles	Statistics Denmark	0
Pregnancy history			
Parity	0, 1, 2, ≥ 3	Medical Birth Register	0
Spontaneous abortion in previous pregnancy ^a	yes/no	National Patient Register	0
Stillbirth in previous pregnancy ^a	yes/no	Medical Birth Register	0
Any congenital malformation in previous pregnancy ^a	yes/no	National Patient Register	0
Preterm birth in previous pregnancy ^a	yes/no	Medical Birth Register	0
Low birth weight in previous pregnancy ^a	yes/no	Medical Birth Register	0
Small for gestational age in previous pregnancy ^a	yes/no	Medical Birth Register	0
Smoking ^b	yes/no	Medical Birth Register	27,366 (3.10)
Medical history			
Diabetes mellitus (any)	yes/no (ICD-10 codes O24, E10-14 or at least two prescription fills for ATC code: A10)	National Patient Register and National Prescription Registry	0
Use of PPI/H2-blocker in past 3 months	yes/no (ATC codes: A02BA, A02BC)	National Prescription Registry	0
Use of NSAID in past 3 months	yes/no (ATC codes: M01A, N02BA)	National Prescription Registry	0
Use of antimigraine drug in past 3 months	yes/no (ATC code: N02C)	National Prescription Registry	0
Use of IVF drug in past 3 months	yes/no (ATC codes: G03G, G03DA04, H01AA, H01CC, L02AE01)	National Prescription Registry	0
Health care utilization			
Hospital admissions in last year	0, 1-2, ≥ 3	National Patient Register	0
Outpatient hospital contacts in last year	0, 1-2, ≥ 3	National Patient Register	0
Prescription drugs used in last 6 months	0, 1-2, 3-4, ≥ 5	National Prescription Registry	0
Interactions			
Between age at pregnancy onset and place of birth; county of residence; married or living with partner; level of education; gross household income (5 distinct interactions).			
Between place of birth and county of residence; married or living with partner; level of education; gross household income (4 distinct interactions)			
Between county of residence and married or living with partner; level of education; gross household income (3 distinct interactions)			
Between married or living with partner and level of education; gross household income (2 distinct interactions)			
Between level of education and gross household income (1 interaction)			

ICD: international classification of diseases; ATC: anatomic therapeutic chemical; PPI: proton pump inhibitor; H2-blocker: histamine-2 receptor blocker; NSAID: non-steroidal anti-inflammatory drug; IVF: in vitro fertilization. ^aThe respective history of each adverse outcome in a previous pregnancy (if any) was included in the respective propensity score for the analysis of each outcome. Thus, for the analysis of spontaneous abortion, only history of spontaneous abortion was included (not history of other outcomes). However, for the analyses involving birth weight (the outcomes of small for gestational age and low birth weight), history of low birth weight and small for gestational age were both included. ^bAvailable for analyses based on live births (malformations, preterm birth, small for gestational age, low birth weight); smoking data were not available for pregnancies with abortive outcomes. ^cNumbers and percentages refer to those among the study cohort of 1,222,503 pregnancies for all variables, except for smoking, which is among live births (881,945).

eTable 4A and B. Characteristics of Pregnant Women in Study Cohort Before Matching

	Time window of exposure to metoclopramide					
	First trimester (included in analysis of congenital malformations)		7 to 22 weeks (included in analysis of spontaneous abortion)		7 weeks to birth (included in analysis of stillbirth)	
	Unexposed (n=850,730)	Exposed (n=28,505)	Unexposed (n=1,179,862)	Exposed (n=37,958)	Unexposed (n=1,177,501)	Exposed (n=40,319)
Age at pregnancy onset, mean (SD)	29.6 (4.8)	28.9 (4.8)	29.6 (5.5)	28.7 (5.2)	29.6 (5.5)	28.7 (5.2)
Place of birth						
Denmark	85.8	76.0	85.1	76.9	85.1	77.3
Europe	3.2	2.3	3.3	2.4	3.3	2.4
Other	11.0	21.6	11.6	20.7	11.6	20.3
County of residence						
Capital	32.7	29.7	33.8	31.1	33.9	30.7
Mid Jutland	23.2	23.4	22.3	22.3	22.3	22.4
North Jutland	10.0	9.8	9.7	9.9	9.7	10.1
Sealand	13.1	13.5	13.4	13.8	13.4	13.7
Southern Denmark	20.8	23.4	19.9	22.8	19.9	22.9
Married or living with partner	87.7	86.4	81.3	81.6	81.3	81.6
Level of education						
Primary school	21.3	30.3	24.9	32.4	24.9	32.3
Secondary school	9.4	9.9	9.6	10.0	9.6	9.9
Vocational or short tertiary education	36.9	36.9	35.8	36.0	35.8	36.1
Medium or long tertiary education	32.4	22.8	29.7	21.6	29.7	21.7
Gross household income						
1st quintile	15.0	18.7	19.9	22.5	19.9	22.5
2nd quintile	19.3	24.2	19.9	23.7	19.9	23.5
3rd quintile	21.8	22.1	20.0	20.9	20.0	21.0
4th quintile	22.2	19.3	20.1	18.1	20.1	18.1
5th quintile	21.6	15.6	20.2	14.9	20.2	14.9
Calendar year						
1997 - 1999	21.7	19.0	21.9	19.4	21.9	19.7
2000 - 2002	21.2	22.9	21.3	22.8	21.3	22.9
2003 - 2005	20.8	22.8	20.9	22.3	20.9	22.1
2006 - 2008	21.0	19.9	20.9	19.9	20.9	19.8
2009 - March 2011	15.2	15.4	14.9	15.6	14.9	15.6
Pregnancy history						
Parity						
1	36.7	38.4	33.5	35.7	33.5	35.8
2	13.7	14.2	15.9	14.8	15.9	14.7
≥ 3	4.3	4.9	5.9	5.4	5.9	5.4
Malformation in previous pregnancy	5.1	5.5	n.a.	n.a.	n.a.	n.a.
Spontaneous abortion in previous pregnancy	n.a.	n.a.	14.9	14.8	n.a.	n.a.
Stillbirth in previous pregnancy	n.a.	n.a.	n.a.	n.a.	0.7	0.4
Smoking during pregnancy	18.1	13.4	-	-	-	-
Medical history						
Diabetes mellitus	1.5	1.2	1.5	1.2	1.5	1.3
Use of PPI/H2-blocker in past 3 months	1.0	2.3	1.1	2.2	1.1	2.2
Use of NSAID in past 3 months	4.7	7.9	4.8	7.8	4.8	7.8
Use of antimigraine drug in past 3 months	0.8	2.1	0.8	2.0	0.8	2.1
Use of IVF drug in past 3 months	4.3	3.5	3.7	3.3	3.7	3.3
Health care utilization						
Hospital admissions in past year						
1-2	8.3	10.2	8.2	10.1	8.2	10.1
≥3	11.5	10.9	12.1	11.3	12.1	11.6
Outpatient hospital contacts in past year						
1-2	13.9	15.6	14.0	15.5	14.0	15.6
≥3	14.4	16.5	14.8	16.5	14.8	16.6
Prescription drugs in past 6 months						
1-2	44.3	42.7	44.1	42.6	44.1	42.4
3-4	15.4	19.6	15.5	19.5	15.5	19.6
≥ 5	6.6	10.8	6.8	10.8	6.8	11.1
Exposures during pregnancy						
Hospital admission for hyperemesis or nausea/vomiting	0.4	11.0	0.4	10.9	0.5	11.2
Use of other antiemetics	0.3	3.2	0.3	3.6	0.4	3.7

Characteristics are shown as per cent unless stated otherwise.

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eTable 4A and B. Characteristics of Pregnant Women in Study Cohort Before Matching (cont'd)

	Time window of exposure to metoclopramide			
	0 to 37 weeks (included in analysis of preterm birth)		0 weeks to birth (included in analyses of low birth weight and small for gestational age)	
	Unexposed (n=845,086)	Exposed (n=36,859)	Unexposed (n=840,860)	Exposed (n=36,879)
Age at pregnancy onset, mean (SD)	29.6 (4.8)	28.8 (4.9)	29.6 (4.8)	28.8 (4.9)
Place of birth				
Denmark	85.8	77.0	85.8	77.1
Europe	3.2	2.4	3.2	2.4
Other	10.9	20.6	10.9	20.5
County of residence				
Capital	32.8	29.2	32.8	29.1
Mid Jutland	23.2	23.2	23.2	23.1
North Jutland	9.9	10.4	9.9	10.4
Sealand	13.1	13.5	13.1	13.5
Southern Denmark	20.8	23.7	20.8	23.7
Married or living with partner	87.7	85.7	87.7	85.8
Level of education				
Primary school	21.2	30.9	21.2	30.8
Secondary school	9.4	9.7	9.4	9.7
Vocational or short tertiary education	36.9	37.0	36.8	37.0
Medium or long tertiary education	32.5	22.4	32.5	22.4
Gross household income				
1st quintile	15.0	19.2	14.9	19.2
2nd quintile	19.3	24.0	19.3	23.9
3rd quintile	21.8	22.3	21.8	22.3
4th quintile	22.2	19.3	22.3	19.3
5th quintile	21.7	15.2	21.7	15.3
Calendar year				
1997 - 1999	21.7	19.6	21.7	19.6
2000 - 2002	21.2	23.1	21.2	23.1
2003 - 2005	20.8	22.4	20.9	22.3
2006 - 2008	21.0	19.7	21.0	19.7
2009 - March 2011	15.2	15.2	15.2	15.2
Pregnancy history				
Parity				
1	36.7	37.8	36.7	37.8
2	13.7	13.6	13.7	13.6
≥ 3	4.4	4.8	4.4	4.9
Preterm birth in previous pregnancy	4.0	4.1	n.a.	n.a.
Low birth weight in previous pregnancy	n.a.	n.a.	3.3	3.3
Small for gestational age in previous pregnancy	n.a.	n.a.	9.0	9.4
Smoking during pregnancy	18.1	15.4	18.1	15.4
Medical history				
Diabetes mellitus	1.5	1.3	1.5	1.3
Use of PPI/H2-blocker in past 3 months	1.0	2.3	1.0	2.3
Use of NSAID in past 3 months	4.7	8.1	4.7	8.1
Use of antimigraine drug in past 3 months	0.8	2.2	0.8	2.2
Use of IVF drug in past 3 months	4.3	3.7	4.3	3.7
Health care utilization				
Hospital admissions in past year				
1-2	8.2	10.2	8.2	10.2
≥3	11.5	11.4	11.5	11.4
Outpatient hospital contacts in past year				
1-2	13.9	15.6	13.9	15.7
≥3	14.4	16.7	14.4	16.7
Prescription drugs in past 6 months				
1-2	44.4	42.3	44.4	42.3
3-4	15.4	19.8	15.3	19.9
≥ 5	6.6	11.3	6.6	11.3
Exposures during pregnancy				
Hospital admission for hyperemesis or nausea/vomiting	0.6	12.0	0.7	12.5
Use of other antiemetics	0.5	4.0	0.5	4.0

Characteristics are shown as per cent unless stated otherwise.

eTable 5. Characteristics of Women Included in Matched Analyses of Preterm Birth, Low Birth Weight, and SGA*

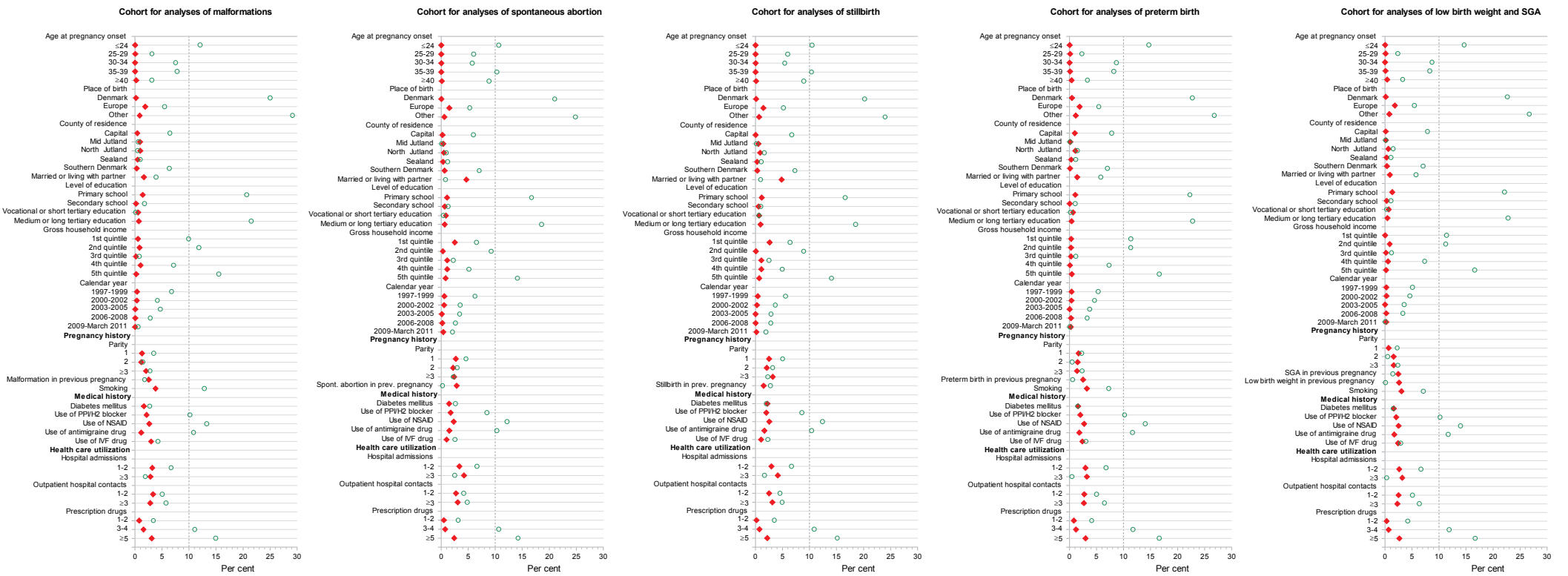
	Time window of exposure to metoclopramide			
	0 to 37 weeks (included in analysis of preterm birth)		0 weeks to birth (included in analyses of low birth weight and small for gestational age)	
	Unexposed (n=146,908)	Exposed (n=36,839)	Unexposed (n=147,016)	Exposed (n=36,864)
Age at pregnancy onset, mean (SD)	28.8 (4.9)	28.8 (4.9)	28.8 (4.9)	28.8 (4.9)
Place of birth				
Denmark	76.9	77.1	77.1	77.1
Europe	2.1	2.4	2.1	2.4
Other	21.0	20.6	20.8	20.5
County of residence				
Capital	29.6	29.2	29.2	29.1
Mid Jutland	23.2	23.2	23.2	23.2
North Jutland	10.0	10.4	10.2	10.4
Sealand	13.4	13.5	13.4	13.5
Southern Denmark	23.6	23.7	23.9	23.7
Married or living with partner	86.2	85.7	86.1	85.8
Level of education				
Primary school	30.4	30.9	30.2	30.8
Secondary school	9.7	9.7	9.8	9.7
Vocational or short tertiary education	37.3	37.0	37.3	37.0
Medium or long tertiary education	22.6	22.4	22.6	22.4
Gross household income				
1st quintile	19.1	19.2	19.2	19.2
2nd quintile	23.8	24.0	23.5	23.9
3rd quintile	22.4	22.3	22.4	22.3
4th quintile	19.2	19.3	19.5	19.3
5th quintile	15.4	15.3	15.4	15.3
Calendar year				
1997 - 1999	19.7	19.6	19.7	19.6
2000 - 2002	22.9	23.1	23.0	23.1
2003 - 2005	22.4	22.4	22.3	22.3
2006 - 2008	19.8	19.7	19.8	19.7
2009 - March 2011	15.1	15.2	15.2	15.2
Pregnancy history				
Parity				
1	38.6	37.8	38.1	37.8
2	13.1	13.6	13.0	13.6
≥ 3	4.5	4.8	4.5	4.8
Preterm birth in previous pregnancy	3.6	4.1	n.a.	n.a.
Low birth weight in previous pregnancy	n.a.	n.a.	2.8	3.3
Small for gestational age in previous pregnancy	n.a.	n.a.	8.7	9.4
Smoking during pregnancy	14.2	15.4	14.3	15.4
Medical history				
Diabetes mellitus	1.1	1.3	1.1	1.3
Use of PPI/H2-blocker in past 3 months	2.0	2.3	2.0	2.3
Use of NSAID in past 3 months	7.3	8.0	7.4	8.0
Use of antimigraine drug in past 3 months	1.9	2.2	2.0	2.2
Use of IVF drug in past 3 months	3.3	3.7	3.3	3.7
Health care utilization				
Hospital admissions in past year				
1-2	9.3	10.2	9.4	10.1
≥3	10.4	11.4	10.4	11.4
Outpatient hospital contacts in past year				
1-2	14.6	15.6	14.8	15.7
≥3	15.7	16.7	15.8	16.6
Prescription drugs in past 6 months				
1-2	42.8	42.4	42.5	42.3
3-4	19.3	19.8	19.6	19.9
≥ 5	10.3	11.2	10.4	11.3
Exposures during pregnancy				
Hospital admission for hyperemesis or nausea/vomiting	0.8	12.0	0.9	12.5
Use of other antiemetics	0.6	4.0	0.6	4.0

Characteristics are shown as per cent unless stated otherwise.

*Each metoclopramide-exposed pregnancy was matched to up to 4 unexposed on the basis of age, calendar year and propensity score.

eFigure. Standardized Differences Between Metoclopramide-Exposed and Unexposed Participants Before and After Matching Based on Age, Calendar Year, and Propensity Score

○ Unmatched
◆ Matched



eTable 6. Characteristics of Women Included in Matched Sensitivity Analyses of Major Congenital Malformations, Including Cases From Stillbirths and Induced Abortions; Subcohort April 2004 to March 2011*

	Unexposed (n=48,640)	Metoclopramide (n=12,187)
Pregnancy outcome, no (%)		
Live birth	48,251 (99.2)	12,105 (99.3)
Stillbirth	201 (0.4)	46 (0.4)
Induced abortion	188 (0.4)	36 (0.3)
Age at pregnancy onset, mean (SD)	29.3 (5.0)	29.2 (5.0)
Place of birth		
Denmark	78.4	77.8
Europe	2.5	2.8
Other	19.2	19.5
County of residence		
Capital	31.4	31.4
Mid Jutland	23.2	23.0
North Jutland	10.3	10.4
Sealand	14.1	14.1
Southern Denmark	20.9	21.0
Married or living with partner	84.9	84.7
Level of education		
Primary school	30.2	30.3
Secondary school	10.4	10.8
Vocational or short tertiary education	34.0	33.7
Medium or long tertiary education	25.4	25.2
Gross household income		
1st quintile	18.7	18.9
2nd quintile	22.9	23.2
3rd quintile	22.8	22.7
4th quintile	20.2	19.8
5th quintile	15.4	15.4
Calendar year		
April, 2004 - 2005	17.1	17.0
2006 - 2008	46.8	46.8
2009 - March 2011	36.1	36.3
Pregnancy history		
Parity		
1	39.6	38.6
2	13.4	14.1
≥ 3	5.3	5.5
Malformation in previous pregnancy	5.4	6.0
Medical history		
Diabetes mellitus	1.6	2.0
Use of PPI/H2-blocker in past 3 months	2.4	2.6
Use of NSAID in past 3 months	7.6	8.2
Use of antimigraine drug in past 3 months	2.2	2.4
Use of IVF drug in past 3 months	4.0	4.5
Health care utilization		
Hospital admissions in past year		
1-2	8.3	8.9
≥3	10.3	11.4
Outpatient hospital contacts in past year		
1-2	15.6	16.3
≥3	20.3	21.4
Prescription drugs in past 6 months		
1-2	42.8	42.5
3-4	19.8	20.1
≥ 5	11.9	12.3
Exposures during pregnancy		
Hospital admission for hyperemesis or nausea/vomiting	0.6	9.7
Use of other antiemetics	0.5	5.3

Characteristics are shown as per cent unless stated otherwise.

*Each metoclopramide-exposed pregnancy was matched to up to 4 unexposed on the basis of age, calendar year and propensity score.

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eTable 7. Characteristics of Women Included in Sensitivity Analysis of Spontaneous Abortion Comparing Metoclopramide vs Antiemetic Antihistamines

	Antihistamine (n=2,054)	Metoclopramide (n=37,397)
Age at pregnancy onset, mean (SD)	29.2 (5.2)	28.7 (5.2)
Place of birth		
Denmark	79.4	76.9
Europe	3.1	2.4
Other	17.6	20.7
County of residence		
Capital	33.6	31.0
Mid Jutland	20.5	22.4
North Jutland	10.0	10.0
Sealand	13.6	13.8
Southern Denmark	22.1	22.7
Married or living with partner	83.8	81.5
Level of education		
Primary school	28.3	32.4
Secondary school	9.6	10.0
Vocational or short tertiary education	36.7	36.0
Medium or long tertiary education	25.4	21.6
Gross household income		
1st quintile	19.8	22.6
2nd quintile	23.0	23.7
3rd quintile	20.5	20.8
4th quintile	19.9	18.0
5th quintile	16.7	14.8
Calendar year		
1997 - 1999	16.4	19.5
2000 - 2002	18.0	22.9
2003 - 2005	19.4	22.3
2006 - 2008	25.9	19.8
2009 - March 2011	20.3	15.5
Pregnancy history		
Parity		
1	36.5	35.6
2	13.4	14.8
≥ 3	4.4	5.4
Spontaneous abortion in previous pregnancy	14.6	14.8
Medical history		
Diabetes mellitus	1.9	1.2
Use of PPI/H2-blocker in past 3 months	2.9	2.1
Use of NSAID in past 3 months	7.9	7.8
Use of antimigraine drug in past 3 months	1.5	2.1
Use of IVF drug in past 3 months	4.2	3.2
Health care utilization		
Hospital admissions in past year		
1-2	10.0	10.1
≥3	10.5	11.4
Outpatient hospital contacts in past year		
1-2	16.1	15.5
≥3	18.5	16.5
Prescription drugs in past 6 months		
1-2	41.8	42.6
3-4	18.9	19.5
≥ 5	14.8	10.7
Exposures during pregnancy		
Hospital admission for hyperemesis or nausea/vomiting	11.3	10.5

Characteristics are shown as per cent unless stated otherwise.

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