Original Investigation

Metoclopramide in Pregnancy and Risk of Major Congenital Malformations and Fetal Death

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IMPORTANCE Metoclopramide, a drug frequently used for nausea and vomiting in pregnancy, is thought to be safe, but information on the risk of specific malformations and fetal death is lacking.

OBJECTIVE To investigate the safety of metoclopramide use in pregnancy.

DESIGN, SETTING, AND PARTICIPANTS Register-based cohort study in Denmark, 1997-2011. From a cohort of 1 222 503 pregnancies, metoclopramide-exposed and unexposed women were matched (1:4 ratio) on the basis of age, calendar year, and propensity scores.

MAIN OUTCOMES AND MEASURES Primary outcomes were major congenital malformations overall, 20 individual malformation categories (selected according to power criteria), spontaneous abortion, and stillbirth. In matched analyses, logistic regression was used to estimate prevalence odds ratios of malformations and Cox regression to estimate hazard ratios (HRs) of spontaneous abortion.

RESULTS Among 28 486 women exposed to metoclopramide in the first trimester, 721 had an infant with a major congenital malformation (25.3 [95% CI, 23.5-27.1] cases per 1000 births), compared with 3024 among 113 698 unexposed women (26.6 [95% CI, 25.7-27.5] per 1000 births). There were no significant associations between metoclopramide use and malformations overall (prevalence odds ratio, 0.93 [95% CI, 0.86-1.02]) or any of the 20 individual malformation categories, eg, neural tube defects, transposition of great vessels, ventricular septal defect, atrial septal defect, tetralogy of Fallot, coarctation of the aorta, cleft lip, cleft palate, anorectal atresia/stenosis, and limb reduction (upper limit of 95% CI below 2.0 for 17 of 20 categories). Metoclopramide was not associated with increased risk of spontaneous abortion (757 cases [20.0 {95% CI, 18.5-21.4} per 1000] among 37 946 metoclopramide-exposed women and 9414 cases [62.1 {95% CI, 60.9-63.3} per 1000] among 151 661 unexposed women; HR, 0.35 [95% CI, 0.33-0.38]) and stillbirth (142 cases [3.5 {95% CI, 2.9-4.1} per 1000] among 40 306 metoclopramide-exposed women and 634 cases [3.9 {95% CI, 3.6-4.2} per 1000] among 161 098 unexposed women; HR, 0.90 [95% CI, 0.74-1.08]).

CONCLUSIONS AND RELEVANCE Metoclopramide use in pregnancy was not associated with increased risk of major congenital malformations overall, any of the 20 individual malformation categories assessed, spontaneous abortion, or stillbirth. These safety data may help inform decision making when treatment with metoclopramide is considered in pregnancy.

JAMA. 2013;310(15):1601-1611. doi:10.1001/jama.2013.278343

Author Audio Interview at jama.com

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More than 50% of pregnant women experience nausea and vomiting, which typically present in early pregnancy.[1,2] The care of most women is managed conservatively, but 10% to 15% of those with nausea and vomiting will eventually receive drug treatment.[2,3] Metoclopramide is often recommended if treatment with an antihistamine or vitamin B_6 has failed.[2,4] Despite metoclopramide being one of the most commonly used prescription medications in pregnancy,[5,6] data on the safety of its use in pregnancy are limited. The published analytical studies, which include 5 cohort studies with a total of 4261 women exposed in pregnancy and 1 case-control study with a total of 15 metoclopramide-exposed cases of congenital malformation, have not found significantly increased risks of major adverse pregnancy and fetal outcomes.[3,6-10] Although these findings are generally reassuring and indicate that metoclopramide does not increase the risk of congenital malformations when these outcomes are assessed in aggregate, malformations are a heterogeneous group of disorders and preferably should be studied individually.[11] Furthermore, no sufficiently powered study has investigated the risk of fetal death associated with metoclopramide exposure in pregnancy.

We used nationwide administrative and health care registers in Denmark to investigate associations between metoclopramide use in pregnancy and serious adverse outcomes. The primary outcomes were major congenital malformations, spontaneous abortion, and stillbirth. For the outcome of malformations, we studied malformations overall and those individual defects that fulfilled a prespecified power criterion. Secondary outcomes were preterm birth, low birth weight, and small for gestational age (SGA).

Methods

Cohort

We conducted a register-based cohort study, including all pregnancies in Denmark with delivery dates or dates of abortive outcome January 1, 1997, through March 31, 2011. Individual-level information was obtained from nationwide registers and linked using unique personal identifiers. The cohort was constructed by identifying all singleton live births and stillbirths in the Medical Birth Register[12] and pregnancies with abortive outcomes in the National Patient Register[13]; subsequently, using information on the gestational age at which these events occurred, we could define the onset of pregnancy (ie, the first day of the last menstrual period) and hence follow the cohort from pregnancy onset. Analyses of fetal death outcomes were based on all pregnancies in the cohort, whereas analyses of malformations, preterm birth, low birth weight, and SGA were based on live births. The data sources for this study, which also included the National Prescription Registry,[14] the Central Person Register,[15] and Statistics Denmark, are described in the eMethods in the Supplement.

We excluded pregnancies for which information on gestational age was missing or implausible (<22 and >45 weeks for births, >22 weeks for spontaneous abortions), pregnancies with multiple records on overlapping dates, and women diagnosed with cancer within 6 months prior to pregnancy onset (who are more likely to use metoclopramide for an indication unrelated to pregnancy and to experience adverse pregnancy and fetal events). For the analyses of spontaneous abortion and stillbirth, we also excluded women whose abortions occurred at a gestational age of less than 6 completed weeks of gestation (many early pregnancy losses are not recognized clinically; thus, these outcomes would have been subject to misclassification) and those exposed to metoclopramide within the first 6 weeks (follow-up for these outcomes started in week 7; consequently, inclusion of the first 6 weeks would have introduced immortal time). For analyses involving birth weight, we excluded pregnancies for which this information was missing. The study was approved by the Danish Data Protection Agency; ethics approval was not required.

Metoclopramide

We identified prescriptions for metoclopramide dispensed to women in the cohort from the National Prescription Registry, with the timing of exposure defined by the prescription fill date. The exposure time windows were the first trimester (pregnancy start through 12 gestational weeks) for the analyses of malformations; start of week 7 through week 22 for spontaneous abortion; start of week 7 until birth for stillbirth; before 37 weeks for preterm birth; and any time in pregnancy for low birth weight and SGA. Unexposed women were those who did not use metoclopramide throughout the respective exposure time window. Women who had filled metoclopramide prescriptions within 1 month before pregnancy onset were excluded.

Outcomes

Cases of major congenital malformations diagnosed within the first year of life were identified from the National Patient Register and defined according to the EUROCAT (European Surveillance of Congenital Anomalies) classification (eMethods in the Supplement).[16] Validation studies of the register have showed that registrations were correct for 88% of malformations overall and 90% of cardiac defects.[17,18] Because drug exposure is unlikely to give rise to malformations for which another cause is known, we excluded infants with chromosomal aberrations, genetic syndromes, malformation syndromes with known causes, and viral infections having a possible association with malformations (eMethods in the Supplement). The outcome of major malformations overall was defined as the first registered diagnosis of any major malformation. For individual malformations, we included those for which a 2.5-fold relative risk increase was detectable at 90% power (5% α level; power calculations were performed using OpenEpi version 3.01 [openepi.com]). Assuming the cohort would include 28 000 exposed and 112 000 unexposed pregnancies (data from preliminary analyses), this would require a minimal expected prevalence of 0.3 malformation cases per 1000 births among unexposed pregnancies. In the background nationwide study cohort, we then assessed the prevalence of 53 individual malformation categories from the EUROCAT classification[16] and of potential interest; this generated 20 categories that fulfilled the power criterion (eTable 2 in the Supplement).

Cases of spontaneous abortion (fetal death occurring through 22 gestational weeks) were identified in the National Patient Register; validation showed that registrations were correct for 99% of diagnoses of spontaneous abortion.[19] Cases of stillbirth (fetal loss after 22 completed weeks), preterm birth (delivery before 37 completed weeks), low birth weight (<2500 g), and SGA (lowest 10th percentile of the gestational age-specific birth weight in the cohort) were identified from the Medical Birth Register.

Statistical Analyses

Our strategy for control of potential confounders included matching based on age, calendar year, and propensity scores, which accounted for baseline characteristics at pregnancy onset, and multivariate adjustment, which controlled for exposures occurring during pregnancy. The propensity scores were estimated using logistic regression as the probability of metoclopramide exposure given all baseline characteristics (details on variables are reported in eTable 3 in the Supplement); additionally, all 2-way interactions between demographic variables were included in the scores. Variables with missing values (0%-3.3% missing; eTable 3 in the Supplement) were imputed using the mode value.[20] We used the nearest-neighbor matching algorithm (caliper width 0.2 of the standard deviation of the logit score)[21,22] to match each exposed pregnancy to up to 4 unexposed pregnancies according to age (5-year categories), calendar year, and propensity score. In analyses of fetal death, the risk of which is highly dependent on gestational age, we also used gestational age at first day of metoclopramide exposure as a matching criterion for each woman; ie, unexposed pregnancies that had survived through this date were eligible as matches.

The balance achieved by matching was assessed by checking standardized differences between groups before and after matching. Any given characteristic was considered well balanced if the standardized difference was less than 10%. The number of pregnancies varied according to the specific analysis (different exposure time windows and eligibility criteria); consequently, a distinct matched subcohort was created for each analysis. Estimates for final models in these matched cohorts were additionally adjusted for hospitalization for hyperemesis gravidarum or nausea and vomiting (proxy measure of severity) and use of other antiemetics during pregnancy (eMethods in the Supplement).

For analyses of spontaneous abortion and stillbirth, we generated survival curves using the Kaplan-Meier method and used Cox proportional hazards regression to estimate hazard ratios (HRs). Gestational age was the underlying time metric. Censoring criteria were an abortive outcome other than spontaneous abortion (eg, ectopic pregnancy, induced abortion) in the analysis of spontaneous abortion and any abortive outcome in the stillbirth analysis. The proportional hazards assumption was assessed using a Wald test for the interaction between treatment status and gestational age in weeks. For the analyses of malformations, preterm birth, low birth weight, and SGA, logistic regression was used to estimate prevalence odds ratios (ORs). SAS version 9.2 (SAS Institute Inc) was used for all analyses.

Preplanned sensitivity analyses included analyses of adverse outcomes according to the number of filled prescriptions (assuming that women refilling prescriptions are more likely to have used the prescribed drug); analysis of malformations overall, with the exposure time window restricted to the period of maximal susceptibility to teratogenic agents (gestational weeks 4 to 10)[23]; analyses of malformations, including malformations among terminated pregnancies and stillbirths (subcohort from April 2004 onward; details in eMethods in the Supplement); and, because nausea and vomiting are associated with decreased risk of spontaneous abortion[24,25] (which could introduce confounding by indication), analyses of spontaneous abortion comparing pregnancies exposed to metoclopramide with those exposed to antiemetic antihistamines (propensity score-adjusted analysis).

Differences were considered statistically significant when the 95% CIs did not overlap 1.0 and when $P < .05$ (2-tailed).

Results

Cohort

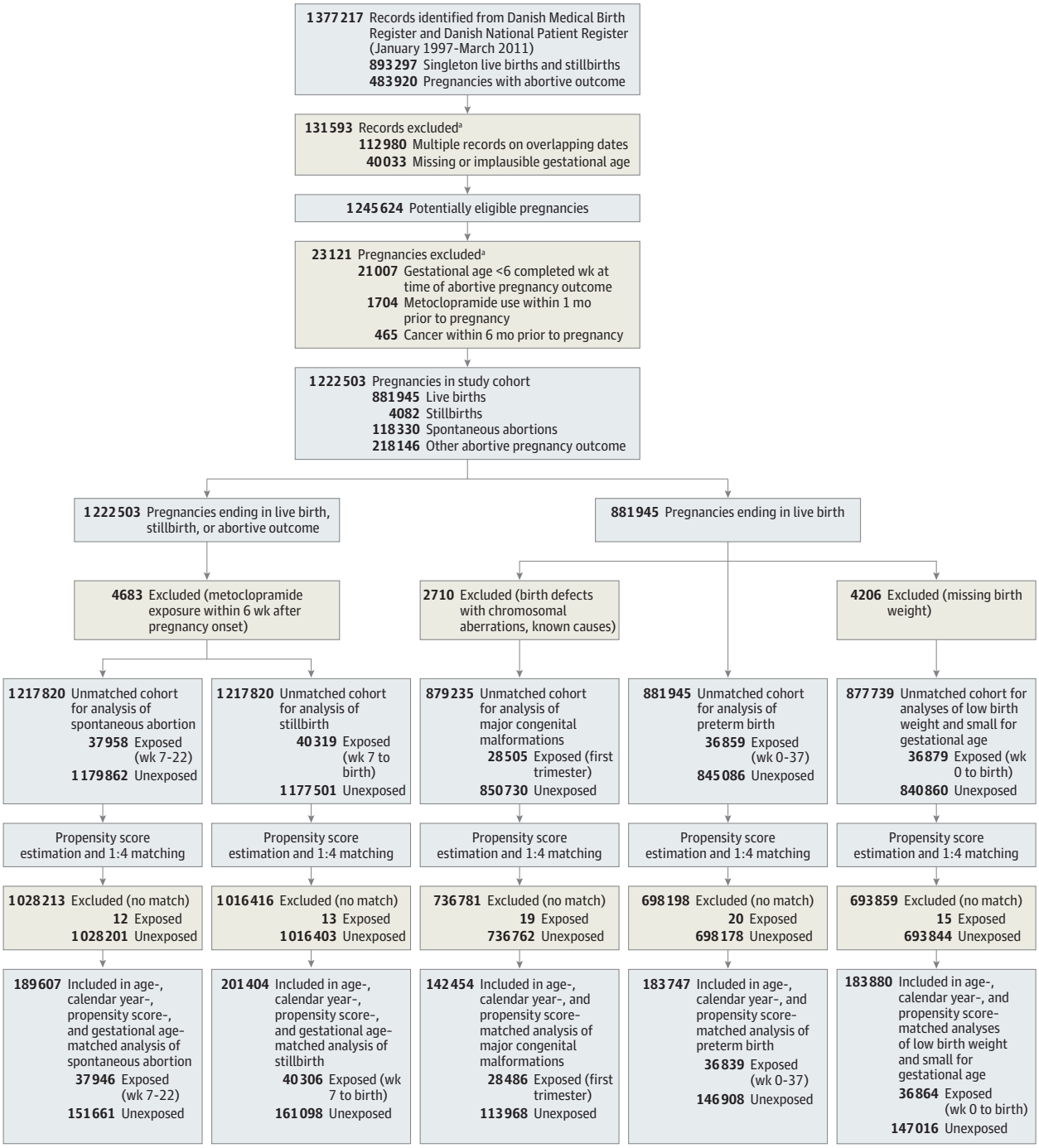
From a total of 1 377 217 potentially eligible pregnancies, 1 222 503 were included in the study cohort (**Figure 1**). Of these, 45 002 (3.7%) were exposed to metoclopramide. The first prescription was filled at approximately 8 weeks (ie, a median of 57 gestational days [interquartile range, 47-75 days]), and exposed women were dispensed a median of 40 doses (interquartile range, 30-40 doses) during pregnancy (ie, corresponding to 13 days of treatment). Subsequent application of inclusion criteria, exposure time windows, and matching specific to each analysis of individual outcomes generated 5 subcohorts (Figure 1). For all matched subcohorts, the exposed and unexposed groups were well balanced on baseline characteristics (**Table 1**; eTable 5 and eFigure in the Supplement). Among pregnant women exposed to metoclopramide, between 10.9% and 12.5% (depending on the exposure time window) were hospitalized for hyperemesis or nausea and vomiting during pregnancy and 3.2% to 4.0% used another prescription antiemetic, compared with 0.6% to 0.8% and 0.3% to 0.5%, respectively, among unexposed women (Table 1; eTable 5 in the Supplement)

Primary Outcomes

Congenital Malformations

Figure 2 shows the matched analyses of major congenital malformations, with and without additional adjustment for hospitalization for hyperemesis or nausea and vomiting and use of other antiemetics. The matched cohort included 28 486 liveborn infants exposed to metoclopramide in the first trimester of pregnancy and 113 698 unexposed infants. Of these, 721 among the exposed infants (25.3 [95% CI, 24.5-27.1] per 1000 births) and 3024 among the unexposed infants (26.6 [25.7-27.5] per 1000 births) were diagnosed with any major malformation during the first year of life (adjusted prevalence OR, 0.93 [95% CI, 0.86-1.02]).

Figure 1. Study Flow



[a]Values do not sum to total because some pregnancies were excluded for more than 1 reason.

In the analyses of individual malformation categories, there were no significant associations between metoclopramide use in the first trimester and any of the 20 malformations; the upper limits of the CIs in these analyses were below 2.0 in 17 of 20 analyses and below 2.6 in the remaining 3 analyses.

Spontaneous Abortion

The matched cohort for the analysis of spontaneous abortion included 37 946 metoclopramide-exposed pregnancies, 151 661 unexposed pregnancies, and a total of 10 171 cases. The Kaplan-Meier curves showed a lower cumulative incidence of spontaneous abortion among metoclopramide-

Table 1. Characteristics of Women Included in Matched Analyses of Congenital Malformations, Spontaneous Abortion, and Stillbirth, Denmark, January 1997-March 2011[a]

Characteristic	Time Window of Exposure to Metoclopramide, %[b]					
	First Trimester (Included in Analysis of Congenital Malformations)		7 to 22 wk (Included in Analysis of Spontaneous Abortion)		7 wk to Birth (Included in Analysis of Stillbirth)	
	Exposed (n = 28 486)	Unexposed (n = 113 968)	Exposed (n = 37 946)	Unexposed (n = 151 661)	Exposed (n = 40 306)	Unexposed (n = 161 098)
Age at pregnancy onset, mean (SD)	28.9 (4.8)	28.9 (4.8)	28.7 (5.2)	28.7 (5.3)	28.7 (5.2)	28.8 (5.2)
Place of birth						
Denmark	76.1	76.0	77.0	77.0	77.3	77.2
Europe	2.3	2.1	2.4	2.2	2.4	2.2
Other	21.6	22.0	20.6	20.9	20.3	20.6
County of residence						
Capital	29.8	30.0	31.1	30.9	30.7	30.8
Mid Jutland	23.4	23.8	22.3	22.5	22.4	22.6
North Jutland	9.8	9.5	9.9	9.8	10.1	9.9
Sealand	13.5	13.3	13.8	13.6	13.7	13.6
Southern Denmark	23.4	23.3	22.8	23.0	22.9	23.0
Married or living with partner	86.4	86.9	81.6	83.3	81.6	83.5
Level of education						
Primary school	30.3	29.6	32.4	31.9	32.3	31.8
Secondary school	9.9	10.0	10.0	9.8	9.9	9.7
Vocational or short tertiary education	36.9	37.2	36.0	36.4	36.1	36.5
Medium or long tertiary education	22.9	23.2	21.6	21.9	21.7	22.1
Gross household income, quintile						
1	18.7	18.5	22.5	21.5	22.5	21.4
2	24.2	23.8	23.7	23.5	23.5	23.5
3	22.2	22.2	20.9	21.3	21.0	21.4
4	19.3	19.7	18.1	18.5	18.1	18.6
5	15.6	15.7	14.9	15.1	14.9	15.1
Calendar year						
1997-1999	19.0	19.2	19.4	19.6	19.7	19.9
2000-2002	22.9	22.8	22.8	22.6	22.9	22.7
2003-2005	22.8	22.7	22.3	22.4	22.1	22.1
2006-2008	19.9	19.9	19.8	19.9	19.8	19.8
2009-March 2011	15.4	15.4	15.6	15.5	15.6	15.5
Pregnancy history						
Parity						
1	38.4	39.0	35.7	37.0	35.9	37.1
2	14.2	13.8	14.8	14.0	14.7	14.0
≥3	4.9	4.5	5.4	4.8	5.4	4.7
Malformation in previous pregnancy	5.5	4.9	NA	NA	NA	NA
Spontaneous abortion in previous pregnancy	NA	NA	14.8	13.8	NA	NA
Stillbirth in previous pregnancy	NA	NA	NA	NA	0.4	0.4
Smoking during pregnancy	13.5	12.2				
Medical history						
Diabetes mellitus	1.2	1.0	1.2	1.0	1.3	1.0
Medication use in past 3 mo						
PPI/H_2 blocker	2.3	2.0	2.2	1.9	2.2	1.9
NSAID	7.9	7.2	7.8	7.2	7.8	7.2
Antimigraine drug	2.1	1.9	2.0	1.8	2.0	1.8
In vitro fertilization drug	3.5	2.9	3.3	3.1	3.3	3.1

(continued)

Table 1. Characteristics of Women Included in Matched Analyses of Congenital Malformations, Spontaneous Abortion, and Stillbirth, Denmark, January 1997-March 2011[a] (continued)

Characteristic	Time Window of Exposure to Metoclopramide, %[b]					
	First Trimester (Included in Analysis of Congenital Malformations)		7 to 22 wk (Included in Analysis of Spontaneous Abortion)		7 wk to Birth (Included in Analysis of Stillbirth)	
	Exposed (n = 28 486)	Unexposed (n = 113 968)	Exposed (n = 37 946)	Unexposed (n = 151 661)	Exposed (n = 40 306)	Unexposed (n = 161 098)
Health care utilization						
Hospital admissions in past y						
1-2	10.2	9.2	10.1	9.1	10.1	9.2
≥3	10.9	10.0	11.3	10.0	11.6	10.3
Outpatient hospital contacts in past y						
1-2	15.6	14.4	15.5	14.5	15.6	14.7
≥3	16.4	15.4	16.5	15.4	16.6	15.4
Prescription drugs in past 6 mo						
1-2	42.7	43.1	42.6	42.8	42.4	42.5
3-4	19.6	19.0	19.5	19.2	19.6	19.3
≥5	10.8	9.8	10.8	10.0	11.0	10.4
Exposures during pregnancy[c,d]						
Hospital admission for hyperemesis or nausea and vomiting	11.0	0.6	10.9	0.6	11.2	0.8
Use of other antiemetics[e]	3.2	0.3	3.6	0.4	3.7	0.5

Abbreviations: H_2 blocker, histamine-2 receptor blocker; NSAID, nonsteroidal anti-inflammatory drug; NA, not applicable; PPI, proton pump inhibitor.

[a] Each metoclopramide-exposed pregnancy was matched to up to 4 unexposed pregnancies on the basis of age, calendar year, and propensity score; cohorts for analyses of miscarriage and stillbirth were also matched on gestational age at first day of metoclopramide exposure.

[b] Characteristics shown as percentages (because of rounding, percentages may not total 100) current at pregnancy onset, unless stated otherwise. Socioeconomic variables are current at the start of the year of pregnancy onset. Calendar year refers to year of delivery or fetal loss. Information on smoking was not available for pregnancies ending in spontaneous abortion or stillbirth, and this variable was hence not included in the analyses of fetal death. In each analysis, history of the studied outcome in previous pregnancy was included in the propensity score, but history of other adverse outcomes was not; eg, the propensity score for the subcohort of pregnancies included in the analysis of congenital malformation includes history of malformation in previous pregnancy but not history of spontaneous abortion and stillbirth (this is why these are designated NA). eTable 5 in the Supplement shows the characteristics of women included in matched analyses of preterm birth, low birth weight, and small for gestational age; eTable 4A and B in the Supplement shows characteristics before matching for all exposure time windows.

[c] Variable not included in propensity score.

[d] Exposure within the respective exposure time window.

[e] Antihistamines, ondansetron, scopalamine, and domperidone.

exposed pregnancies compared with unexposed pregnancies (log-rank $P < .001$); this difference was most pronounced in weeks 7 through 14 of gestation, whereas curves were similar in weeks 15 through 22 (**Figure 3**). In the planned Cox model (follow-up weeks 7-22), the adjusted HR was 0.35 (95% CI, 0.33-0.38) (unadjusted HR, 0.32 [95% 0.30-0.35]); however, the proportional hazards assumption was not fulfilled. Post hoc, follow-up was therefore divided into 3 strata; inverse associations between metoclopramide use and spontaneous abortion were observed in weeks 7 through 11 and 12 through 16 (although the proportional hazards assumption was not fulfilled for weeks 12 through 16), whereas there was no association in weeks 17 through 22 (Figure 3).

Stillbirth

The matched analysis of stillbirth included 142 cases among 40 306 metoclopramide-exposed pregnancies (3.5 [95% CI, 2.9-4.1] per 1000) and 634 cases among 161 098 unexposed pregnancies (3.9 [95% CI, 3.6-4.2] per 1000). Metoclopramide was not associated with increased risk of stillbirth (adjusted HR, 0.90 [95% CI, 0.74-1.08]; the proportional hazards assumption was fulfilled [$P = .87$]).

Secondary Outcomes

There were no significant associations between metoclopramide use in pregnancy and preterm birth, low birth weight, and SGA (**Table 2**).

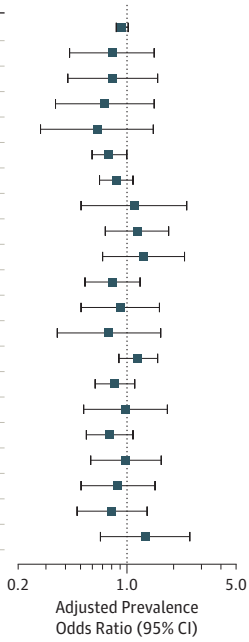
Sensitivity Analyses

Table 3 shows results of sensitivity analyses testing assumptions related to definitions of exposure and outcomes. In analyses according to the number of filled prescriptions (assuming women who refilled prescriptions were more likely to have taken the medication), estimates for all outcomes were similar between women who filled 1 prescription and those who filled 2 or more. The adjusted prevalence OR for congenital malformations overall was similar to that of the primary analysis when restricting the exposure time window to the period of maximal susceptibility to teratogenic agents.

In a subcohort that also included malformation cases among induced abortions and stillbirths, the adjusted prevalence OR for congenital malformations overall was similar to that from the primary analysis, based on live births alone. This analysis was repeated for those individual malformations (of the 20 assessed in this study) for which the proportion terminated is greater than 10% in Denmark[26]; adjusted prevalence

Figure 2. Association Between Metoclopramide Exposure in the First Trimester of Pregnancy and Major Congenital Malformations[a]

Malformation Category	Exposed (n = 28 486) No.	Exposed (n = 28 486) No. (95% CI) per 1000 Births	Unexposed (n = 113 698) No.	Unexposed (n = 113 698) No. (95% CI) per 1000 Births	Prevalence Odds Ratio (95% CI)[b]	Adjusted Prevalence Odds Ratio (95% CI)[c]
Major malformations overall	721	25.3 (23.5-27.1)	3024	26.6 (25.7-27.5)	0.95 (0.88-1.03)	0.93 (0.86-1.02)
Neural tube defects	14	0.49 (0.23-0.75)	62	0.55 (0.41-0.68)	0.90 (0.50-1.61)	0.81 (0.43-1.50)
Hydrocephalus	11	0.39 (0.16-0.61)	55	0.48 (0.36-0.61)	0.80 (0.42-1.53)	0.81 (0.42-1.58)
Congenital cataract	10	0.35 (0.13-0.57)	49	0.43 (0.31-0.55)	0.81 (0.41-1.61)	0.72 (0.35-1.50)
Transposition of great vessels	7	0.25 (0.06-0.43)	44	0.39 (0.27-0.50)	0.63 (0.29-1.41)	0.65 (0.28-1.48)
Ventricular septal defect	82	2.88 (2.26-3.50)	386	3.39 (3.06-3.73)	0.85 (0.67-1.08)	0.77 (0.60-1.00)
Atrial septal defect	83	2.91 (2.29-3.54)	377	3.32 (2.98-3.65)	0.88 (0.69-1.11)	0.86 (0.67-1.10)
Tetralogy of Fallot	10	0.35 (0.13-0.57)	30	0.26 (0.17-0.36)	1.33 (0.65-2.72)	1.12 (0.51-2.43)
Pulmonary valve stenosis	24	0.84 (0.51-1.18)	84	0.74 (0.58-0.90)	1.14 (0.72-1.08)	1.17 (0.73-1.86)
Coarctation of aorta	15	0.53 (0.26-0.79)	46	0.40 (0.29-0.52)	1.30 (0.73-2.33)	1.28 (0.70-2.35)
Cleft lip with or without cleft palate	31	1.09 (0.71-1.47)	147	1.29 (1.08-1.50)	0.84 (0.57-1.24)	0.81 (0.54-1.22)
Cleft palate	15	0.53 (0.26-0.79)	67	0.59 (0.45-0.73)	0.89 (0.51-1.56)	0.91 (0.51-1.62)
Anorectal atresia and stenosis	8	0.28 (0.09-0.48)	44	0.39 (0.27-0.50)	0.73 (0.34-1.54)	0.77 (0.36-1.66)
Congenital hydronephrosis	68	2.39 (1.82-2.96)	213	1.87 (1.62-2.12)	1.28 (0.97-1.68)	1.18 (0.89-1.58)
Hypospadias[d]	58	4.39 (3.27-5.52)	302	5.14 (4.57-5.72)	0.85 (0.64-1.13)	0.84 (0.63-1.12)
Limb reduction	13	0.46 (0.21-0.70)	56	0.49 (0.36-0.62)	0.93 (0.51-1.69)	0.99 (0.53-1.83)
Club foot	42	1.47 (1.03-1.92)	205	1.80 (1.56-2.05)	0.82 (0.59-1.14)	0.78 (0.55-1.10)
Polydactyly	20	0.70 (0.39-1.01)	76	0.67 (0.52-0.82)	1.05 (0.64-1.72)	0.99 (0.59-1.67)
Syndactyly	17	0.60 (0.31-0.88)	76	0.67 (0.52-0.82)	0.89 (0.53-1.51)	0.88 (0.51-1.52)
Craniosynostosis	19	0.67 (0.37-0.97)	91	0.80 (0.64-0.96)	0.83 (0.51-1.37)	0.80 (0.48-1.35)
Congenital skin disorders	13	0.46 (0.21-0.70)	38	0.33 (0.23-0.44)	1.37 (0.73-2.56)	1.32 (0.68-2.54)



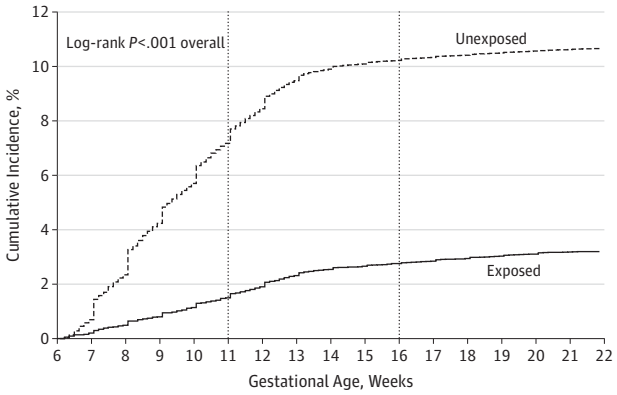
[a] Each metoclopramide-exposed pregnancy was matched to up to 4 unexposed pregnancies on the basis of age, calendar year, and propensity score. Infants underwent follow-up until age 1 year to identify major congenital malformations.

[b] Analyses of matched cohort with no further adjustment.

[c] Analyses of matched cohort with adjustment for hospitalization for hyperemesis gravidarum or nausea and vomiting and use of other antiemetics in the first trimester.

[d] Analysis performed in boys; rates are among boy offspring (of 13 201 exposed and 50 704 unexposed to metoclopramide).

Figure 3. Association Between Metoclopramide Exposure in Pregnancy and Spontaneous Abortion



	Weeks 7-11	Weeks 12-16	Weeks 17-22	Overall (Weeks 7-22)
Unexposed				
Women, No.	118726	126812	127562	151661
Events, No.	5224	3588	602	9414
Events per 1000 women, No. (95% CI)	44.0 (42.8-45.2)	28.3 (27.4-29.3)	4.7 (4.3-5.1)	62.1 (60.9-63.3)
Exposed				
Women, No.	29706	31518	32471	37946
Events, No.	259	352	146	757
Events per 1000 women, No. (95% CI)	8.7 (7.7-9.8)	11.2 (10.0-12.3)	4.5 (3.8-5.2)	20.0 (18.5-21.4)
Adjusted HR (95 CI)[a]	0.23 (0.20-0.26)	0.42 (0.37-0.47)	0.95 (0.78-1.14)	0.35 (0.33-0.38)

Each metoclopramide-exposed pregnancy was matched to up to 4 unexposed pregnancies on the basis of age, calendar year, propensity score, and gestational age at first day of metoclopramide exposure. Each tick indicates the number of completed gestational weeks; eg, 7 weeks equals 49 days.[a]Adjusted hazard ratios from analysis of matched cohort with adjustment for hospitalization for hyperemesis gravidarum or nausea and vomiting and use of other antiemetics. Wald tests for interaction between treatment status and gestational age as assessment of proportional hazards assumptions were: $P = .10$ for weeks 7 through 11, $P < .001$ for weeks 12 through 16, $P = .98$ for weeks 17 through 22, and $P < .001$ for weeks 7 through 22.

ORs for neural tube defects, hydrocephalus, anorectal atresia and stenosis, and limb reduction were all similar to those from the primary analyses, although the estimates were less precise.

To explore if the inverse association between metoclopramide exposure and spontaneous abortion observed in the primary analysis could be explained by confounding by indication, we compared metoclopramide-exposed pregnancies

Table 2. Association Between Metoclopramide Exposure in Pregnancy and Preterm Birth, Low Birth Weight, and Small for Gestational Age[a]

Outcome	Exposed			Unexposed			Prevalence OR (95% CI)	
	Participants, No.	Events		Participants, No.	Events			
		No.	No. (95% CI) per 1000 Births		No.	No. (95% CI) per 1000 Births	Unadjusted[b]	Adjusted[c]
Preterm birth	36 839	1852	50.3 (48.0-52.5)	146 908	7213	49.1 (48.0-50.2)	1.03 (0.97-1.08)	0.98 (0.93-1.04)
Low birth weight	36 864	1270	34.5 (32.6-36.3)	147 016	4985	33.9 (33.0-34.8)	1.02 (0.95-1.08)	0.98 (0.92-1.05)
Small for gestational age	36 864	3697	100.3 (97.2-103.4)	147 016	14 452	98.3 (96.8-99.8)	1.02 (0.98-1.06)	1.00 (0.96-1.04)

Abbreviation: OR, odds ratio.

[a] Each metoclopramide-exposed pregnancy was matched to up to 4 unexposed pregnancies on the basis of age, calendar year, and propensity score. The exposure time windows were pregnancy start to week 37 for the outcome of preterm birth and any time in pregnancy for the outcomes involving birth weight. Preterm birth was defined as delivery before 37 completed gestational weeks, low birth weight as less than 2500 g, and small for gestational age as the lowest 10th percentile of the gestational age–specific birth weight within the cohort.

[b] Analysis of matched cohort with no further adjustment.

[c] Analysis of matched cohort with adjustment for hospitalization for hyperemesis gravidarum or nausea and vomiting and use of other antiemetics in pregnancy.

Table 3. Sensitivity Analyses of Metoclopramide Exposure in Pregnancy and Adverse Outcomes

Analysis	Participants No.	Events		Adjusted Measure of Association (95% CI)[a]
		No.	No. (95% CI) per 1000 Participants	
According to number of filled prescriptions				
Major congenital malformations overall				
Metoclopramide				
1 prescription	21 137	544	25.7 (23.6-27.9)	0.95 (0.86-1.04)[b]
≥2 prescriptions	7349	177	24.1 (20.6-27.6)	0.88 (0.75-1.03)[b]
Unexposed	113 698	3024	26.6 (25.7-27.5)	1 [Reference]
Spontaneous abortion				
Metoclopramide				
1 prescription	37 946	645	17.0 (15.7-18.3)	0.35 (0.32-0.38)[b]
≥2 prescriptions	7683	112	14.6 (11.9-17.3)	0.36 (0.30-0.44)[b]
Unexposed	151 661	9414	62.1 (60.9-63.3)	1 [Reference]
Stillbirth				
Metoclopramide				
1 prescription	40 306	116	2.9 (2.4-3.4)	0.93 (0.76-1.14)[b]
≥2 prescriptions	8154	26	3.2 (2.0-4.4)	0.76 (0.51-1.13)[b]
Unexposed	161 098	634	3.9 (3.6-4.2)	1 [Reference]
Preterm birth				
Metoclopramide				
1 prescription	28 446	1421	50.0 (47.4-52.5)	0.99 (0.93-1.05)[b]
≥2 prescriptions	8393	431	51.4 (46.6-56.1)	0.98 (0.89-1.09)[b]
Unexposed	146 908	7213	49.1 (48.0-50.2)	1 [Reference]
Low birth weight				
Metoclopramide				
1 prescription	28 479	966	33.9 (31.8-36.0)	0.97 (0.91-1.05)[b]
≥2 prescriptions	8385	304	36.3 (32.3-40.3)	1.01 (0.90-1.15)[b]
Unexposed	147 016	4985	33.9 (33.0-34.8)	1 [Reference]
Small for gestational age				
Metoclopramide				
1 prescription	28 479	2808	98.6 (95.1-102.1)	0.99 (0.94-1.03)[b]
≥2 prescriptions	8385	889	106.0 (99.4-112.6)	1.05 (0.98-1.13)[b]
Unexposed	147 016	14 452	98.3 (96.8-99.8)	1 [Reference]

(continued)

Table 3. Sensitivity Analyses of Metoclopramide Exposure in Pregnancy and Adverse Outcomes (continued)

Analysis	Participants No.	Events		Adjusted Measure of Association (95% CI)[a]
		No.	No. (95% CI) per 1000 Participants	
Metoclopramide exposure in gestational weeks 4 to 10				
Major congenital malformations overall				
Metoclopramide	23 352	584	25.0 (23.0-27.0)	0.93 (0.84-1.02)[b]
Unexposed	113 698	3024	26.6 (25.7-27.5)	1 [Reference]
Cases of congenital malformations from induced abortions and stillbirths included[c]				
Major congenital malformations overall				
Metoclopramide	12 187	356	29.2 (26.2-32.2)	1.00 (0.88-1.13)[b]
Unexposed	48 640	1421	29.2 (27.7-30.7)	1 [Reference]
Neural tube defects				
Metoclopramide	12 187	8	0.66 (0.20-1.11)	0.78 (0.35-1.73)[b]
Unexposed	48 640	38	0.78 (0.53-1.03)	1 [Reference]
Hydrocephalus				
Metoclopramide	12 187	5	0.41 (0.05-0.77)	0.78 (0.35-2.01)[b]
Unexposed	48 640	29	0.60 (0.38-0.81)	1 [Reference]
Anorectal atresia and stenosis				
Metoclopramide	12 187	4	0.33 (0.01-0.65)	1.00 (0.34-2.96)[b]
Unexposed	48 640	18	0.37 (0.20-0.54)	1 [Reference]
Limb reduction				
Metoclopramide	12 187	5	0.41 (0.05-0.77)	0.81 (0.29-2.21)[b]
Unexposed	48 640	24	0.49 (0.30-0.69)	1 [Reference]
Metoclopramide vs antiemetic antihistamine, outcome of spontaneous abortion				
Wk 7 to 11				
Metoclopramide	29 235	257	8.8 (7.7-9.9)	0.36 (0.26-0.51)[d,e]
Antihistamine	1367	39	28.5 (19.7-37.4)	1 [Reference]
Wk 12 to 16				
Metoclopramide	30 996	347	11.2 (10.0-12.4)	0.78 (0.51-1.20)[d,e]
Antihistamine	1639	22	13.4 (7.9-19.0)	1 [Reference]
Wk 17 to 22				
Metoclopramide	31 952	143	4.5 (3.7-5.2)	1.03 (0.48-2.20)[d,e]
Antihistamine	1885	7	3.7 (1.0-6.5)	1 [Reference]
Overall (wk 7 to 22)				
Metoclopramide	37 397	747	20.0 (18.6-21.4)	0.57 (0.44-0.73)[d,e]
Antihistamine	2054	68	33.1 (25.4-40.8)	1 [Reference]

[a] For the outcomes of spontaneous abortion and stillbirth, the reported measures of association are hazard ratios; for all other outcomes, prevalence odds ratios.

[b] Analysis of matched cohort with adjustment for hospitalization for hyperemesis gravidarum or nausea and vomiting and use of other antiemetics in pregnancy.

[c] Analysis in age-, calendar year-, and propensity score-matched subcohort of pregnancies with delivery dates or dates of pregnancy termination from April 2004 through March 2011. Characteristics of subcohort shown in eTable 6 in the Supplement.

[d] Analysis of unmatched cohort of metoclopramide vs antiemetic antihistamine (promethazine, cyclizine, and meclozine) users with adjustment for propensity score and for hospitalization for hyperemesis gravidarum or nausea and vomiting. Characteristics of cohort shown in eTable 7 in the Supplement.

[e] Wald tests for interaction between treatment status and gestational age as assessment of proportional hazards assumptions were: $P = .46$ for weeks 7 through 11, $P = .23$ for weeks 12 through 16, and $P = .43$ for weeks 17 through 22, and $P < .001$ for weeks 7 through 22.

with those exposed to antihistamine antiemetics. Overall (follow-up weeks 7-22), metoclopramide was inversely associated with spontaneous abortion; because the proportional hazards assumption was not fulfilled, the follow-up period was divided into 3 strata: metoclopramide was associated with significantly lower risk of spontaneous abortion in weeks 7 through 11 but not weeks 12 through 16 and 17 through 22.

Discussion

This register-based cohort study included more than 40 000 women exposed to metoclopramide in pregnancy and found that use of this drug was not associated with significantly increased risk of major congenital malformations overall, spon-

taneous abortion, and stillbirth. In analyses of 20 individual congenital malformation categories selected on the basis of power criteria, we found no evidence of significantly increased risks associated with metoclopramide use. Given the upper limit of the CIs, more than a 2-fold relative increase in risk for 17 of these 20 malformations could be ruled out with high degree of certainty.

Our findings confirm those from previous studies,[3,6-10] which have not identified increased risk of adverse fetal events associated with metoclopramide use in pregnancy, and expand substantially on the body of available safety data. Whereas previously published cohort studies total 4261 women exposed to metoclopramide in pregnancy, the number of included pregnancies in our study permitted analyses with precise estimation of risk for most outcomes and allowed analyses of serious adverse outcomes that are rare, ie, individual congenital malformations and stillbirth. One previous study had the specific aim of assessing individual malformations and, reporting case-control analyses of 3 specific entities, found no significant association with cleft lip, cleft palate, and hypospadias.[3] However, the OR for cleft palate indicated the possibility of increased risk (OR, 2.36 [95% CI, 0.85-6.55]; 5 metoclopramide-exposed cases). Our prevalence OR of 0.91 (95% CI, 0.51-1.62) argues against this possibility. The largest of the published studies (3458 women exposed in the first trimester) was primarily aimed at malformations overall, low birth weight, preterm birth, and perinatal death but also included explorative analyses of subclasses of malformations; although that study reported no significant associations, ORs for 7 of 18 subclasses were nonestimable because of small numbers.[6] We included 20 individual malformation categories selected according to prespecified power criteria; these required a minimally detectable relative risk of 2.5, corresponding to a background prevalence of 0.3 cases per 1000 liveborn infants. Although this strategy was applied in the interest of conclusive estimates, less prevalent defects were not studied individually; hence, results cannot be inferred to such defects. However, even if metoclopramide were associated with some rare malformation, it is worth noting that analyses of malformations overall were inconsistent with an increase in relative risk of more than 2%. Given the rate of 26.6 per 1000 among unexposed pregnancies, this rules out an absolute increase of more than 0.5 cases per 1000 exposed infants.

Although only 1 previous study assessed the probability of spontaneous abortion following metoclopramide exposure based on 6 cases,[7] our survival analyses of this outcome took gestational age into account and included 757 metoclopramide-exposed cases. The observed inverse association between metoclopramide use and spontaneous abortion is not unexpected and likely can be attributed to the well-described protective association between nausea and vomiting in pregnancy and spontaneous abortion; indeed, the strength of the association between nausea and vomiting and spontaneous abortion in previous studies was similar in magnitude to the association between metoclopramide exposure and spontaneous abortion observed in our study.[24,25] The notion that metoclopramide is unlikely to contribute protective effects is further supported by our observation that the protective association was attenuated when women using metoclopramide were compared with those using antiemetic antihistamines. Thus, we conclude that these data provide reassurance that metoclopramide was not associated with increased risk of spontaneous abortion.

We observed no significant associations between metoclopramide use and stillbirth, preterm birth, low birth weight, and SGA. This confirms and adds to previous results by providing data with a high precision of estimates and expands on these results by investigating the risk of fetal growth restriction, as assessed by the outcome of SGA.

Study strengths include the use of registers that provide complete coverage of Denmark, with linkage of data on the individual level; this permitted analyses of a large number of exposed pregnancies with detailed information regarding exposure, outcomes, and potential confounders. We assumed that filling a prescription was equivalent to use of the prescribed drug. Bias toward the null would be introduced if women did not take the drugs, a possible scenario for a drug such as metoclopramide (symptoms may have waned by the time women fill the prescription). However, sensitivity analyses according to the number of filled prescriptions, assuming that women who refilled prescriptions were more likely to have used the drug, gave results similar to those from the primary analyses. Although data on the specific indication for metoclopramide use were not available, it can be assumed that the vast majority of women used it for nausea and vomiting; further, as a proxy for severity, we adjusted for hospitalization for hyperemesis or nausea and vomiting.

Our primary analyses were of malformations among liveborn infants and did not include malformations among pregnancies terminated antenatally. We addressed this in a sensitivity analysis of a subcohort with available data on induced abortions for fetal anomaly and found no evidence for increased risk of malformations overall or of those individual malformation categories for which the proportion of termination is high. For variables with missing values, we used single-variable imputation; this simple form of imputation may lead to bias, especially when proportions of missing values are moderate to large and values "missing at random" cannot be assumed. In our study, only 6 variables had missing values, and the proportion of missing values was less than 5%. Furthermore, from our knowledge of the sampling mechanism of the data we believe that values "missing at random" can reasonably be assumed. Although we took several potential confounders into account through propensity score methods, data on smoking were not available for analyses of fetal death, and body mass index measurements were not available for any analyses.

Conclusion

This nationwide study in Denmark assessed the safety of metoclopramide use in pregnancy, comparing metoclopramide-exposed women with matched unexposed controls. With high precision of the estimates, we observed no significantly in-

creased risk of major malformations overall, 20 individual malformation categories, spontaneous abortion, stillbirth, preterm birth, low birth weight, and fetal growth restriction associated with metoclopramide use in pregnancy. As such, this study may help inform clinical decisions when treatment with metoclopramide is considered in pregnancy.

ARTICLE INFORMATION

Author Contributions: Dr Pasternak had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: All authors.
Acquisition of data: Svanström, Hviid.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Pasternak.
Critical revision of the manuscript for important intellectual content: Svanström, Mølgaard-Nielsen, Melbye, Hviid.
Statistical analysis: Svanström.
Obtained funding: Pasternak.
Administrative, technical, or material support: Melbye.
Study supervision: Melbye, Hviid.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Funding/Support: This study was supported by Danish Medical Research Council grant 11-115854 (Dr Pasternak).

Role of the Sponsor: The Danish Medical Research Council had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

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