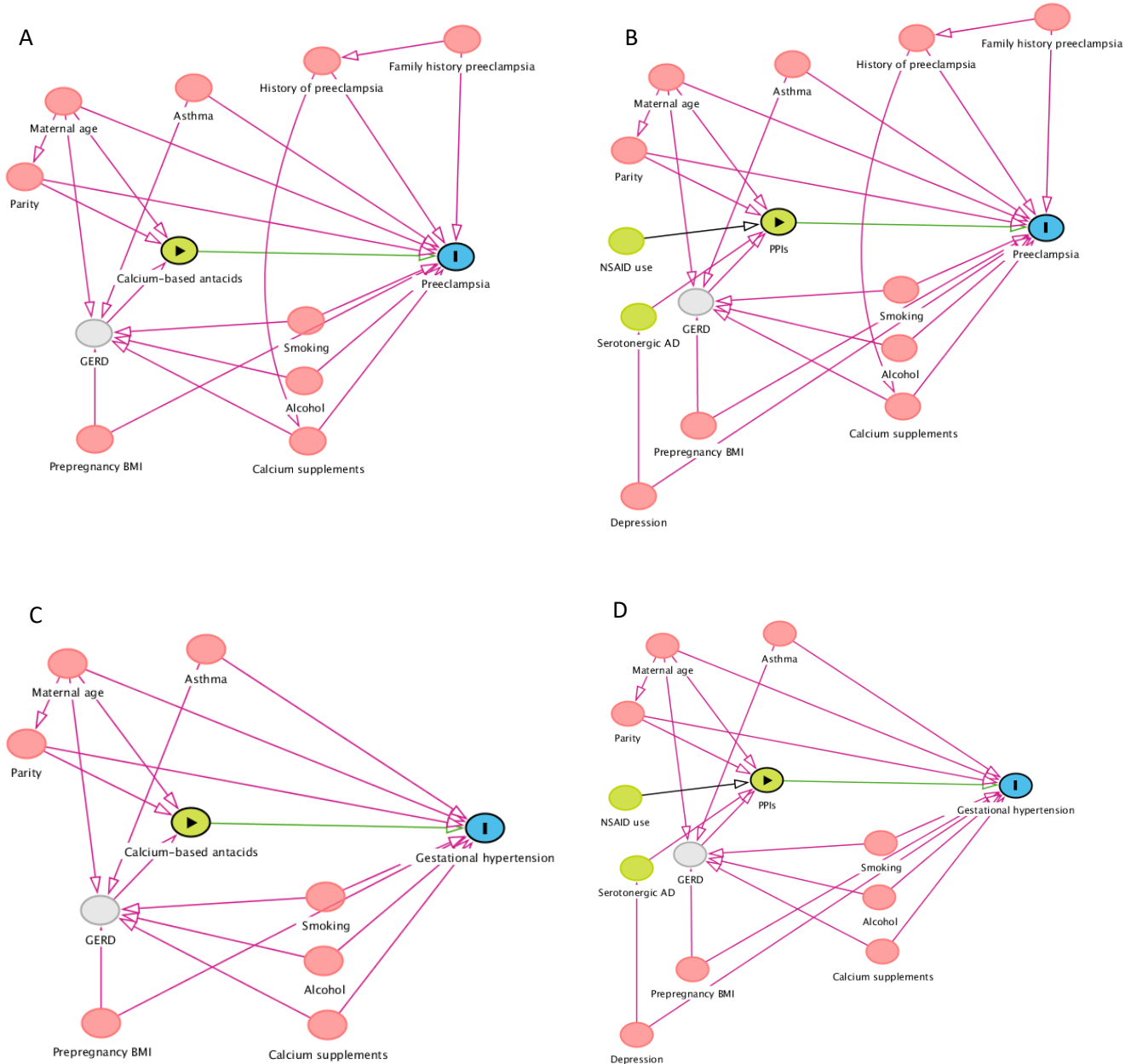**Supplementary Table 1. Supplementary description of methods.**

Diagnostic criteria for hypertensive disorders of pregnancy in The Netherlands[a]		Missing confounder data
Gestational hypertension	A diastolic blood pressure ≥90 mmHg and/or a systolic blood pressure ≥140 mmHg after gestational week 20. The elevated blood pressure needs to be measures twice, with a sphygmomanometer, and with an interval of at least 4 hours.	Missing values on the sufficient set of confounders were 0.3% for parity, 0.9% for pre-pregnancy BMI, 1.3% for asthma, 1.4% for depression, 2.1% for alcohol consumption, 2.3% for smoking, and 24.2% for use of calcium-containing supplements. Overall, 27% of pregnancies had missing data in at least one confounder. We imputed missing values through multiple imputation using chained equations (25 imputations) under the assumptions that data were missing at random. We included exposure and outcome variables, as well as auxiliary variables (maternal age, country of birth, level of education, use of multivitamin supplements, and cohort) in the imputation procedure. Imputed data were used in all models.
Preeclampsia	Hypertension in combination with proteinuria of ≥300 mg/24 h	

[a] Source: De Boer J, Zeeman K, Verhoeven C. KNOV-standaard: Hypertensieve aandoeningen tijdens de zwangerschap, bevalling en kraamperiode. Koninklijke Nederlandse Organisatie van Verloskundigen; Utrecht, 2011. Available at: https://assets.knov.nl/p/557056/none/PDF%20Vakkennis/KNOV_Standaard_Hypertensie_versie2012.pdf. Accessed September 7, 2022.

Supplementary Figure 1. Directed Acyclic Graphs (DAGs) for the identification of sufficient sets of confounders. Separate DAGs were compiled for the association between (panel A) calcium-based antacids and pre-eclampsia, (B) proton pump inhibitors (PPIs) and preeclampsia, (C) calcium-based antacids and gestational hypertension, and (D) PPIs and gestational hypertension.

AD, antidepressant; BMI, Body Mass Index; GERD, gastro-esophageal reflux disease; NSAID, non-steroidal anti-inflammatory drug

Supplementary Table 2. Characteristics of pregnancies included in the current study and pregnancies lost-to-follow-up.

Characteristic	Included (N=9,058)		Lost-to-follow-up (N=1,044)	
	n	(%)	n	(%)
Maternal age, mean (SD)	31.3	(3.7)	31.3	(4.0)
Country of birth				
The Netherlands	8,625	(96.2)	983	(95.9)
Other	341	(3.8)	42	(4.1)
Missing	92		19	
Level of education				
Low/intermediate	2,095	(23.3)	333	(32.8)
High	6,887	(76.7)	681	(67.2)
Missing	76		30	
Chronic conditions				
Asthma	566	(6.3)	73	(7.2)
Chronic hypertension	28	(0.3)	4	(0.4)
Depression	142	(1.6)	37	(3.7)
Pre-existing diabetes	22	(0.2)	4	(0.4)
Pre-pregnancy BMI, mean (SD)	23.7	(4.1)	24.2	(4.7)
Parity				
0 previous deliveries	4,947	(54.8)	537	(51.7)
≥1 previous delivery	4,083	(45.2)	501	(48.3)
Missing	28		6	
History of preeclampsia				
Yes	171	(1.9)	21	(2.1)
No	8,784	(98.1)	1,005	(98.0)
Missing	103		18	
Smoking during pregnancy				
Yes	458	(5.2)	78	(8.0)
No	8,369	(94.8)	894	(92.0)
Missing	231		72	
Alcohol during pregnancy				
Yes	1,418	(16.0)	144	(15.0)
No	7,431	(84.0)	819	(85.1)
Missing	209		81	
Calcium-containing supplements				
Yes	5,386	(78.4)	563	(85.2)
No	1,482	(21.6)	98	(14.8)
Missing	2,190		383	
Exposed				
Calcium-based antacids GW 0-33	1,860	(21.1)	263	(31.8)
Calcium-based antacids GW 0-16	726	(8.1)	118	(11.5)
Calcium-based antacids GW 17-33	1,602	(18.2)	181	(23.2)
Proton pump inhibitors GW 0-33	333	(3.8)	39	(5.0)
Proton pump inhibitors GW 0-16	171	(1.9)	23	(2.3)
Proton pump inhibitors GW 17-33	291	(3.3)	31	(4.0)

BMI, Body Mass Index; GW, gestational week; SD, standard deviation

Supplementary Table 3. Maternal and pregnancy characteristics by cohort.

Characteristic	PRIDE Study (N=6,741)		The Dutch Pregnancy Drug Register (N=2,317)	
	n	(%)	n	(%)
Maternal age, mean (SD)	31.3	(3.7)	31.6	(3.8)
Country of birth				
The Netherlands	6,425	(95.3)	2,200	(95.0)
Other	237	(3.5)	104	(4.5)
Missing	79	(1.2)	13	(0.6)
Level of education				
Low/intermediate	1,533	(22.7)	562	(24.3)
High	5,135	(76.2)	1,752	(75.6)
Missing	73	(1.1)	3	(0.1)
Chronic conditions				
Asthma	445	(6.6)	121	(5.2)
Chronic hypertension	11	(0.2)	17	(0.7)
Depression	93	(1.4)	49	(2.1)
Pre-existing diabetes	8	(0.1)	14	(0.6)
Pre-pregnancy BMI				
Underweight	203	(3.0)	65	(2.8)
Normal weight	4,637	(68.8)	1,581	(68.2)
Overweight	1,318	(19.6)	442	(19.1)
Obese	524	(7.8)	207	(8.9)
Missing	59	(0.9)	22	(0.9)
Parity				
0 previous deliveries	3,683	(54.6)	1,264	(54.6)
≥1 previous delivery	3,058	(45.4)	1,025	(44.2)
Missing	0	(0.0)	28	(1.2)
History of preeclampsia				
Yes	124	(1.8)	47	(2.0)
No	6,559	(97.3)	2,225	(96.0)
Missing	58	(0.9)	45	(1.9)
Smoking during pregnancy				
Yes	316	(4.7)	142	(6.1)
No	6,217	(92.2)	2,152	(92.9)
Missing	208	(3.1)	23	(1.0)
Alcohol during pregnancy				
Yes	897	(13.3)	521	(22.5)
No	5,650	(83.8)	1,781	(76.9)
Missing	194	(2.9)	15	(0.6)
Calcium-containing supplements				
Yes	5,304	(78.7)	82	(3.5)
No	1,153	(17.1)	329	(14.2)
Missing	284	(4.2)	1,906	(82.3)
Exposure status				
Calcium-based antacids GW 0-33	1,368	(20.3)	495	(21.4)
Calcium-based antacids GW 0-16	577	(8.6)	151	(6.5)
Calcium-based antacids GW 17-33	1,193	(17.7)	411	(17.7)
Proton pump inhibitors GW 0-33	220	(3.3)	112	(4.8)
Proton pump inhibitors GW 0-16	114	(1.7)	56	(2.4)
Proton pump inhibitors GW 17-33	200	(3.0)	89	(3.8)

BMI, Body Mass Index; GW, gestational week; SD, standard deviation

Supplementary Table 4. Maternal and pregnancy characteristics by trajectory group of calcium-based antacid use in gestational weeks 0-33.

Characteristic	Calcium-based antacid trajectory group[a]					
	No use (N=6,964)		Low use (N=992)		High use (N=123)	
Maternal age, mean (SD)	31.4	(3.7)	31.5	(3.7)	31.7	(3.4)
Maternal country of birth, n (%)						
The Netherlands	6,629	(95.2)	958	(96.6)	116	(94.3)
Other	264	(3.8)	29	(2.9)	5	(4.1)
Level of education, n (%)						
Low/intermediate	1,629	(23.4)	168	(16.9)	27	(22.0)
High	5,278	(75.8)	818	(82.5)	93	(75.6)
Chronic conditions, n (%)						
Asthma	398	(5.7)	72	(7.3)	11	(8.9)
Chronic hypertension	19	(0.3)	7	(0.7)	0	(0.0)
Depression	113	(1.6)	9	(0.9)	4	(3.3)
Pre-existing diabetes	16	(0.2)	2	(0.2)	1	(0.8)
Pre-pregnancy BMI, mean (SD)	23.6	(4.0)	23.7	(4.0)	24.6	(5.2)
Parity, n (%)						
0 previous deliveries	3,764	(54.0)	572	(57.7)	68	(55.3)
≥1 previous delivery	3,179	(45.6)	417	(42.0)	55	(44.7)
History of preeclampsia, n (%)						
Yes	131	(1.9)	16	(1.6)	6	(4.9)
No	6,746	(96.9)	968	(97.6)	116	(94.3)
Smoking during pregnancy, n (%)						
Yes	330	(4.7)	47	(4.7)	8	(6.5)
No	6,470	(92.9)	932	(94.0)	112	(91.1)
Alcohol during pregnancy, n (%)						
Yes	1,095	(15.7)	165	(16.6)	22	(17.9)
No	5,722	(82.2)	819	(82.6)	97	(78.9)
Calcium-containing supplements, n (%)						
Yes	4,073	(58.5)	608	(61.3)	77	(62.6)
No	1,211	(17.4)	156	(15.7)	16	(13.0)

BMI, Body Mass Index; SD, standard deviation

[a]Numbers may not add up to totals due to missing values, ranging from 0.3% to 0.9% (level of education, chronic hypertension, pre-existing diabetes, pre-pregnancy BMI, and parity), 1.0% to 1.4% (country of birth, asthma, depression, and history of preeclampsia), and 2.1% to 2.3% (smoking and alcohol during pregnancy. For calcium-containing supplement use, missing value was 24.2%, because details on multivitamin use were unavailable in The Dutch Pregnancy Drug Register.

Supplementary Table 5. Associations between calcium-based antacid and proton pump inhibitor use in gestational weeks 0-19 and gestational hypertension. Data from the PRIDE Study (2012-2019) and The Dutch Pregnancy Drug Register (2014-2019).

Exposure group	Total	N (%) with GH		Crude RR (95% CI)	Adjusted RR (95% CI)[a]
Calcium-based antacids					
No use	7,612	526	(6.9)	Reference	Reference
Any use	843	79	(9.4)	1.4 (1.1-1.7)	1.2 (1.0-1.5)
Low dose (<1 g/day)	399	22	(5.5)	0.8 (0.5-1.2)	0.7 (0.5-1.1)
High dose (≥1 g/day)	444	57	(12.8)	1.9 (1.4-2.4)	1.6 (1.2-2.1)
Proton pump inhibitors					
No use	8,553	614	(7.2)	Reference	Reference
Any use	183	14	(7.7)	1.1 (0.6-1.8)	0.8 (0.5-1.4)
Low dose (≤1 DDD/day)	121	9	(7.4)	1.0 (0.6-2.0)	0.8 (0.4-1.6)
High dose (>1 DDD per day)	59	5	(8.5)	1.2 (0.5-2.7)	0.9 (0.4-2.3)

CI, confidence interval; DDD, Defined Daily Dose; GH, gestational hypertension; RR, relative risk
[a] Inverse probability of censoring weights; all models are adjusted for maternal age, asthma, pre-pregnancy BMI, parity, smoking during pregnancy, alcohol use during pregnancy, and use of calcium-containing supplements. Models for proton pump inhibitors are additionally adjusted for depression.

Supplementary Table 6. Associations between calcium-based antacid and proton pump inhibitor use after gestational week 19 and gestational hypertension. Data from the PRIDE Study (2012-2019) and The Dutch Pregnancy Drug Register (2014-2019).

Time-dependent exposure after GW19	N	GH	Person weeks	Rate (per 1000/week)	Crude HR (95% CI)	Adjusted HR (95% CI)[a]
Calcium-based antacids						
No use	8,070	617	138,143	4.5	Reference	Reference
Any use	1,260	90	14,176	6.3	1.3 (1.0-1.6)	1.2 (1.0-1.5)
Low dose (<1 g/day)	698	40	7,255	5.5	1.2 (0.9-1.7)	1.2 (0.9-1.6)
High dose (≥1 g/day)	680	50	6,921	7.2	1.3 (1.0-1.8)	1.2 (0.9-1.7)
Proton pump inhibitors						
No use	8,674	743	163,147	4.6	Reference	Reference
Any use	279	21	3,354	6.3	1.2 (0.8-1.9)	1.1 (0.7-1.7)
Low dose (≤1 DDD/day)	230	16	2,602	6.1	1.2 (0.7-2.0)	1.1 (0.7-1.8)
High dose (>1 DDD /day)	63	5	752	6.6	1.3 (0.6-3.2)	1.1 (0.4-2.7)

CI, confidence interval; DDD, Defined Daily Dose; GH, gestational hypertension; GW, gestational week; HR, hazard ratio.

[a] Inverse probability of censoring weights; all models are adjusted for maternal age, asthma, pre-pregnancy BMI, parity, smoking during pregnancy, alcohol use during pregnancy, and use of calcium-containing supplements. Models for proton pump inhibitors are additionally adjusted for depression.

Supplementary Table 7. Associations between calcium-based antacid and proton pump inhibitor use in gestational weeks 0-33 and late-onset preeclampsia among women at high risk of developing preeclampsia. Data from the PRIDE Study (2012-2019).

Exposure group	Total	N (%) with PE		Crude RR (95% CI)	Adjusted RR (95% CI)[a]
Calcium-based antacids in GW 0-33					
No use	1,563	75	(4.8)	Reference	Reference
Any use	493	31	(6.3)	1.3 (0.9-2.0)	1.2 (0.8-1.9)
Low dose (<1 g/day)	257	16	(6.2)	1.3 (0.8-2.2)	1.2 (0.7-2.1)
High dose (≥1 g/day)	231	15	(6.5)	1.4 (0.8-2.3)	1.3 (0.7-2.2)
Low use trajectory	262	16	(6.1)	1.3 (0.8-2.1)	1.3 (0.8-2.1)
High use trajectory	35	2	(5.7)	1.2 (0.3-4.7)	N/A
Calcium-based antacids in GW 0-16					
No use	1,859	90	(4.8)	Reference	Reference
Any use	203	14	(6.9)	1.4 (0.8-2.5)	1.3 (0.8-2.3)
Low dose (<1 g/day)	82	10	(12.2)	2.5 (1.4-4.7)	2.3 (1.2-4.4)
High dose (≥1 g/day)	56	1	(1.8)	N/A	N/A
Calcium-based antacids in GW 17-33					
No use	1,623	83	(5.1)	Reference	Reference
Any use	427	23	(5.4)	1.1 (0.7-1.6)	1.0 (0.6-1.6)
Low dose (<1 g/day)	232	8	(3.5)	0.7 (0.3-1.4)	0.7 (0.3-1.3)
High dose (≥1 g/day)	172	13	(7.6)	1.5 (0.8-2.6)	1.3 (0.8-2.4)
Proton pump inhibitors in GW 0-33					
No use	1,986	97	(4.9)	Reference	Reference
Any use	74	9	(12.2)	2.5 (1.3-4.7)	2.2 (1.2-4.3)
Low dose (≤1 DDD/day)	56	7	(12.5)	2.6 (1.2-5.3)	2.3 (1.1-4.8)
High dose (>1 DDD per day)	18	2	(11.1)	2.3 (0.6-8.5)	N/A
Proton pump inhibitors in GW 0-16					
No use	2,039	103	(5.1)	Reference	Reference
Any use	35	3	(8.6)	1.7 (0.6-5.1)	1.4 (0.5-4.3)
Low dose (≤1 DDD/day)	15	2	(13.3)	2.6 (0.7-9.7)	N/A
High dose (>1 DDD/day)	13	0	(0.0)	N/A	N/A
Proton pump inhibitors in GW 17-33					
No use	1,991	97	(4.9)	Reference	Reference
Any use	69	9	(13.0)	2.7 (1.4-5.1)	2.4 (1.2-4.7)
Low dose (≤1 DDD/day)	48	6	(12.5)	2.6 (1.2-5.6)	2.4 (1.1-5.1)
High dose (>1 DDD/day)	13	2	(15.4)	3.2 (0.9-11.4)	N/A

CI, confidence interval; DDD, Defined Daily Dose; GW, gestational week; PE, preeclampsia; RR, relative risk
[a] Inverse probability of censoring weights; all models are adjusted for maternal age, asthma, pre-pregnancy BMI, parity, smoking during pregnancy, alcohol use during pregnancy, and use of calcium-containing supplements. Models for proton pump inhibitors are additionally adjusted for depression.

Supplementary Table 8. Associations between calcium-based antacid and proton pump inhibitor use after gestational week 33 and late-onset preeclampsia among women at high risk of developing preeclampsia. Data from the PRIDE Study (2012-2019).

Time-dependent exposure after GW33	N	PE	Person weeks	Rate (per 1000/week)	Crude HR (95% CI)	Adjusted HR (95% CI)[a]
Calcium-based antacids						
No use	1,810	88	9,224	9.5	Reference	Reference
Any use	292	9	1,343	6.7	0.7 (0.4-1.4)	0.7 (0.3-1.3)
Low dose (<1 g/day)	136	3	602	5.0	0.5 (0.2-1.6)	N/A
High dose (≥1 g/day)	169	6	741	8.1	0.8 (0.4-1.9)	0.8 (0.3-1.8)
Proton pump inhibitors						
No use	2,045	97	10,789	9.0	Reference	Reference
Any use	62	5	263	19.0	2.2 (0.9-5.4)	2.1 (0.8-5.2)
Low dose (≤1 DDD/day)	49	3	204	14.7	1.7 (0.5-5.4)	N/A
High dose (>1 DDD/day)	16	2	59	33.9	4.1 (1.0-15.8)	N/A

CI, confidence interval; DDD, Defined Daily Dose; GW, gestational week; HR, hazard ratio; PE, preeclampsia.
[a] Inverse probability of censoring weights; all models are adjusted for maternal age, asthma, pre-pregnancy BMI, parity, smoking during pregnancy, alcohol use during pregnancy, and use of calcium-containing supplements. Models for proton pump inhibitors are additionally adjusted for depression.

Supplementary Table 9. Associations between calcium-based antacid and proton pump inhibitor use in gestational weeks 0-33 and late-onset preeclampsia, restricted to women who did not use calcium-containing supplements. Data from the PRIDE Study (2012-2019) and The Dutch Pregnancy Drug Register (2014-2019).

Exposure group	Total	N (%) with PE		Crude RR (95% CI)	Adjusted RR (95% CI)[a]
Calcium-based antacids in GW 0-33					
No use	1,211	30	(2.5)	Reference	Reference
Any use	266	10	(3.8)	1.5 (0.8-3.1)	1.3 (0.6-2.6)
Low dose (<1 g/day)	138	3	(2.2)	0.9 (0.3-2.8)	N/A
High dose (≥1 g/day)	125	7	(5.6)	2.3 (1.0-5.0)	1.9 (0.9-4.4)
Low use trajectory	156	4	(2.6)	1.0 (0.4-2.9)	N/A
High use trajectory	16	1	(6.3)	N/A	N/A
Calcium-based antacids in GW 0-16					
No use	1,379	36	(2.6)	Reference	Reference
Any use	101	3	(3.0)	1.1 (0.4-3.6)	N/A
Low dose (<1 g/day)	48	2	(4.2)	1.6 (0.4-6.4)	N/A
High dose (≥1 g/day)	29	1	(3.5)	N/A	N/A
Calcium-based antacids in GW 17-33					
No use	1,240	32	(2.6)	Reference	Reference
Any use	237	8	(3.4)	1.3 (0.6-2.8)	1.2 (0.6-2.5)
Low dose (<1 g/day)	124	2	(1.6)	0.6 (0.2-2.6)	N/A
High dose (≥1 g/day)	102	6	(5.9)	2.3 (1.0-5.3)	2.1 (0.9-4.9)
Proton pump inhibitors in GW 0-33					
No use	1,433	39	(2.7)	Reference	Reference
Any use	48	1	(2.1)	N/A	N/A
Low dose (≤1 DDD/day)	31	1	(3.2)	N/A	N/A
High dose (>1 DDD per day)	17	0	(0.0)	N/A	N/A
Proton pump inhibitors in GW 0-16					
No use	1,455	40	(2.8)	Reference	Reference
Any use	26	0	(0.0)	N/A	N/A
Low dose (≤1 DDD/day)	13	0	(0.0)	N/A	N/A
High dose (>1 DDD/day)	11	0	(0.0)	N/A	N/A
Proton pump inhibitors in GW 17-33					
No use	1,441	39	(2.7)	Reference	Reference
Any use	40	1	(2.5)	N/A	N/A
Low dose (≤1 DDD/day)	24	0	(0.0)	N/A	N/A
High dose (>1 DDD/day)	13	0	(0,0)	N/A	N/A

CI, confidence interval; DDD, Defined Daily Dose; GW, gestational week; PE, preeclampsia; RR, relative risk
[a] Inverse probability of censoring weights; all models are adjusted for maternal age, asthma, pre-pregnancy BMI, parity, smoking during pregnancy, and alcohol use during pregnancy.

Supplementary Table 10. Associations between calcium-based antacid and proton pump inhibitor use after gestational week 33 and late-onset preeclampsia, restricted to women who did not use calcium-containing supplements. Data from the PRIDE Study (2012-2019) and The Dutch Pregnancy Drug Register (2014-2019).

Time-dependent exposure after GW19	N	PE	Person weeks	Rate (per 1000/week)	Crude HR (95% CI)	Adjusted HR (95% CI)
Calcium-based antacids						
No use	1,358	36	7,218	5.0	Reference	Reference
Any use	170	3	789	3.8	0.7 (0.2-2.3)	N/A
Low dose (<1 g/day)	79	2	350	5.7	1.1 (0.3-4.4)	N/A
High dose (≥1 g/day)	97	1	439	2.3	N/A	N/A
Proton pump inhibitors						
No use	1,484	39	8,048	4.8	Reference	Reference
Any use	40	0	172	0.0	N/A	N/A
Low dose (≤1 DDD/day)	28	0	117	0.0	N/A	N/A
High dose (>1 DDD /day)	13	0	55	0.0	N/A	N/A

CI, confidence interval; DDD, Defined Daily Dose; GW, gestational week; HR, hazard ratio; PE, preeclampsia.