15.3.27. Genital, other (Custom RG11)

The custom RG11 code group has been defined as any reported al58 code except for Q54.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	1168	2.37 *
Excluding single outpatient reports (S3-S5)	520	1.05 *
Excluding all outpatient reports (S6-S8)	427	0.87 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		0.32 **

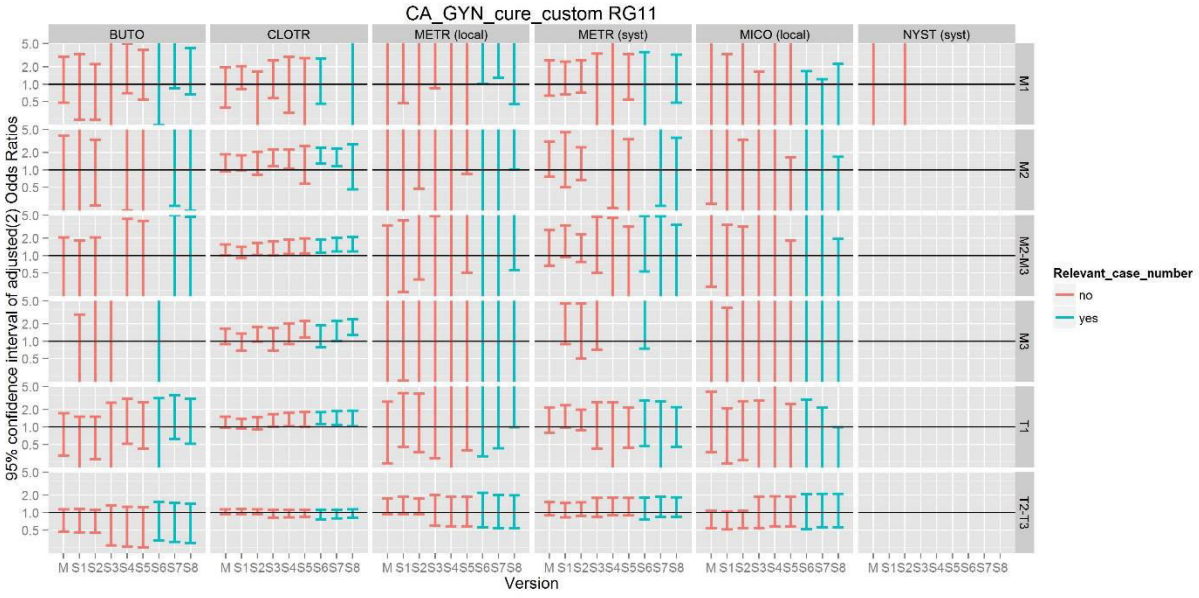
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

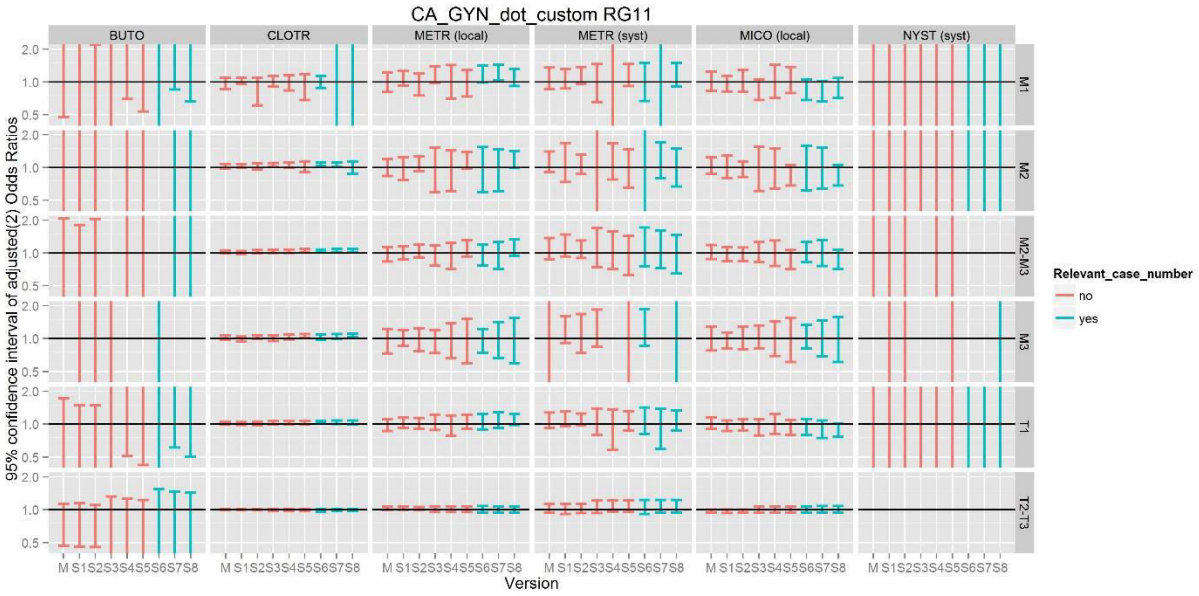
Based on the above numbers, single outpatient reports may be unreliable for the analysis of this anomaly category. Hence, sensitivity analyses S6-S8 are the most relevant ones for the analysis of this code group.

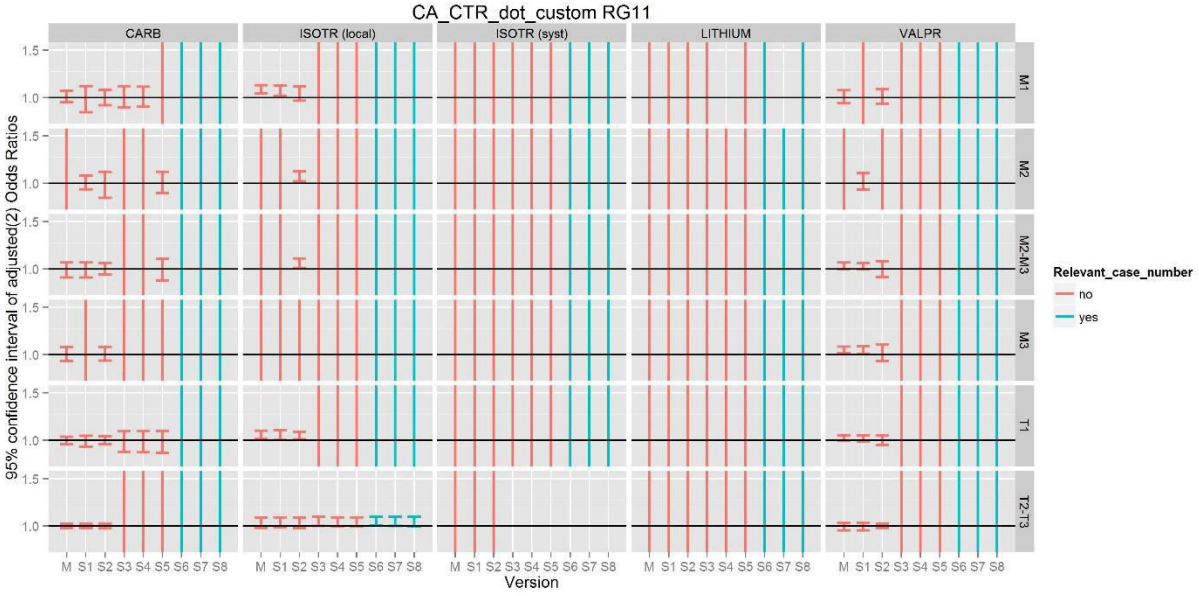
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.Z. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.Z. 95% confidence intervals of odds ratios of drug exposure in the RG11 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_custom RG11
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
M S1 S2 S3 S4 S5 S6 S7 S8
Relevant_case_number
no
yes


CA_CTR_dot_custom RG11
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
M S1 S2 S3 S4 S5 S6 S7 S8
Relevant_case_number
no
yes

15.3.28. Limb (EUROCAT al61)

The EUROCAT al61 code group has been defined as any reported ICD code in the Q65-Q74 range.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	91,070	184.53 *
Excluding single outpatient reports (S3-S5)	21,422	43.41 *
Excluding all outpatient reports (S6-S8)	4663	9.45 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		5.50 **

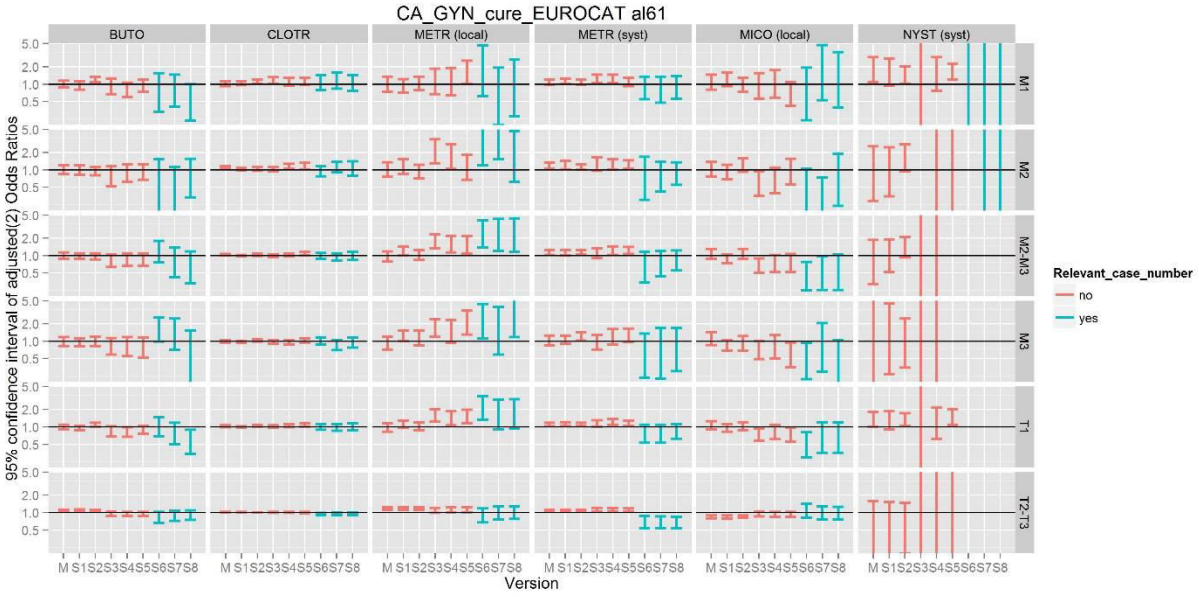
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

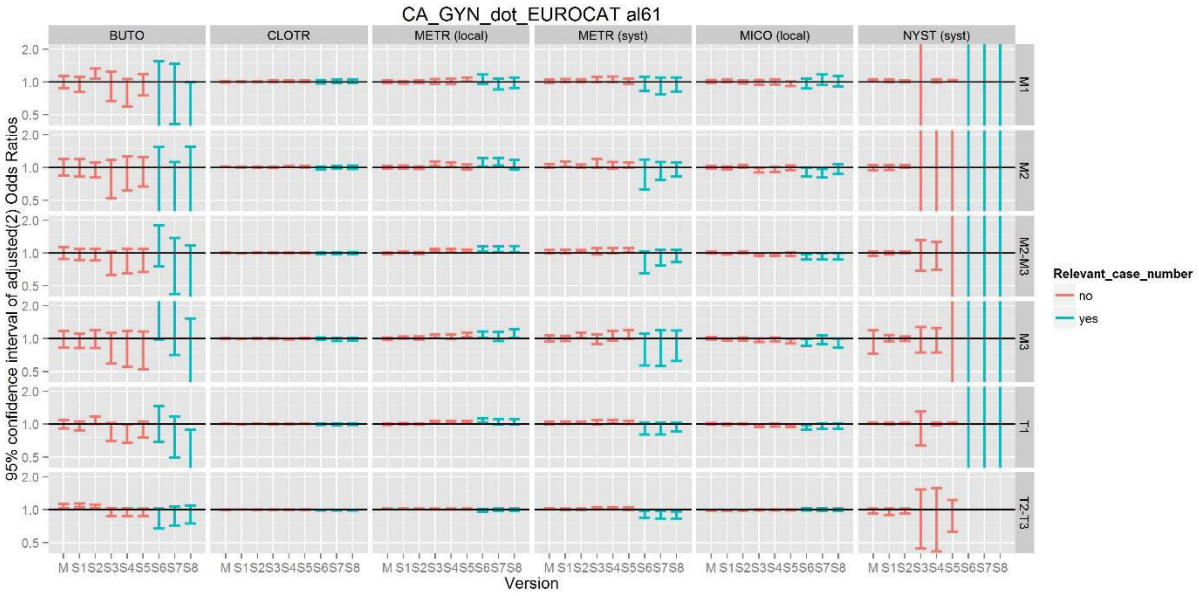
Based on the above numbers, outpatient reports may be unreliable for the analysis of this category; hence, sensitivity analyses S6-S8 are the most relevant ones for the analysis of this code group.

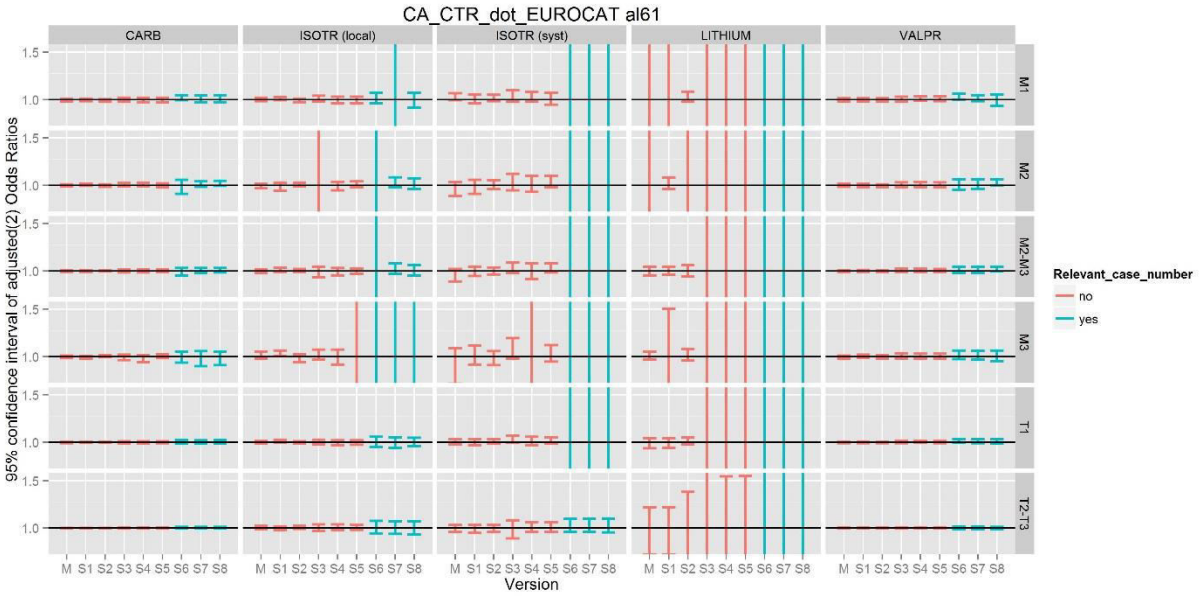
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.AA. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.AA. 95% confidence intervals of odds ratios of drug exposure in the al61 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_EUROCAT al61
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1S2S3S4S5S6S7S8
Version
Relevant_case_number
no
yes


CA_CTR_dot_EUROCAT al61
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1 S2 S3 S4 S5 S6 S7 S8
Version
Relevant_case_number
no
yes

15.3.29. Club foot – talipes equinovarus (EUROCAT al66)

The EUROCAT al66 code group has been defined as any reported ICD code in the Q660 range.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	1571	3.18 *
Excluding single outpatient reports (S3-S5)	748	1.52 *
Excluding all outpatient reports (S6-S8)	663	1.34 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		0.76 **

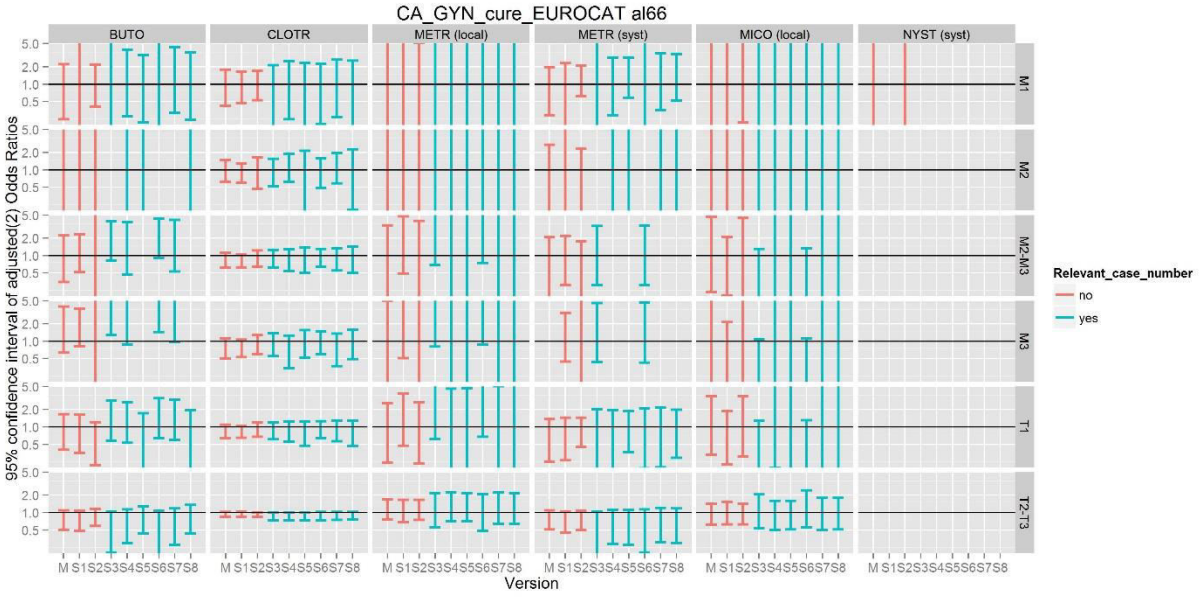
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

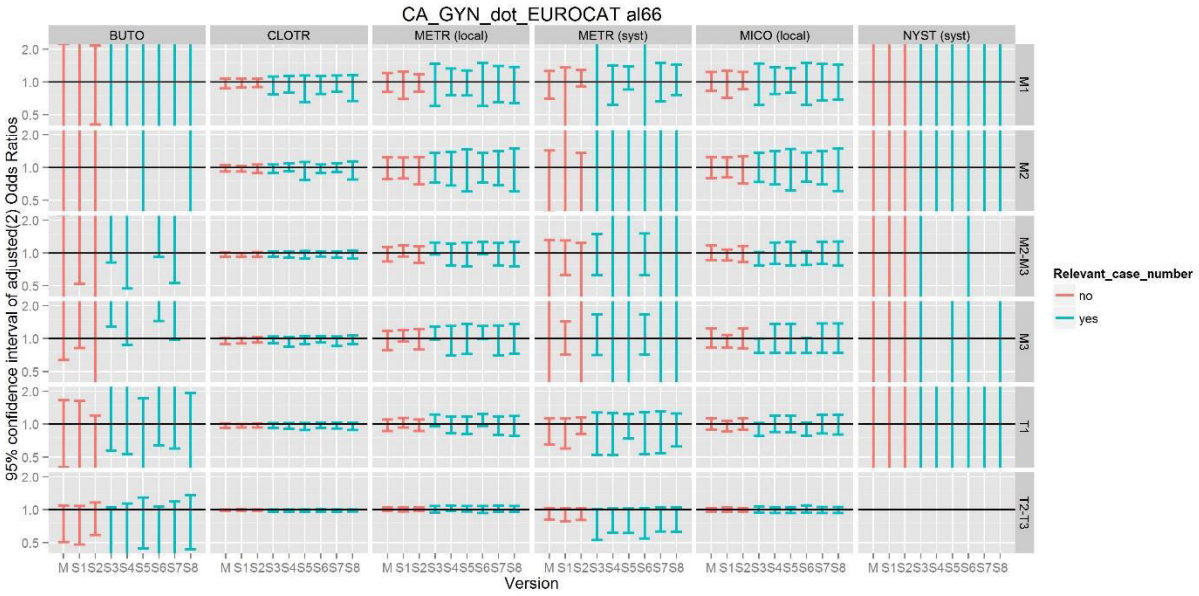
Based on the above numbers, single outpatient reports may be unreliable for the analysis of this category; hence, sensitivity analyses S3-S8 are the most relevant ones for the analysis of this code group.

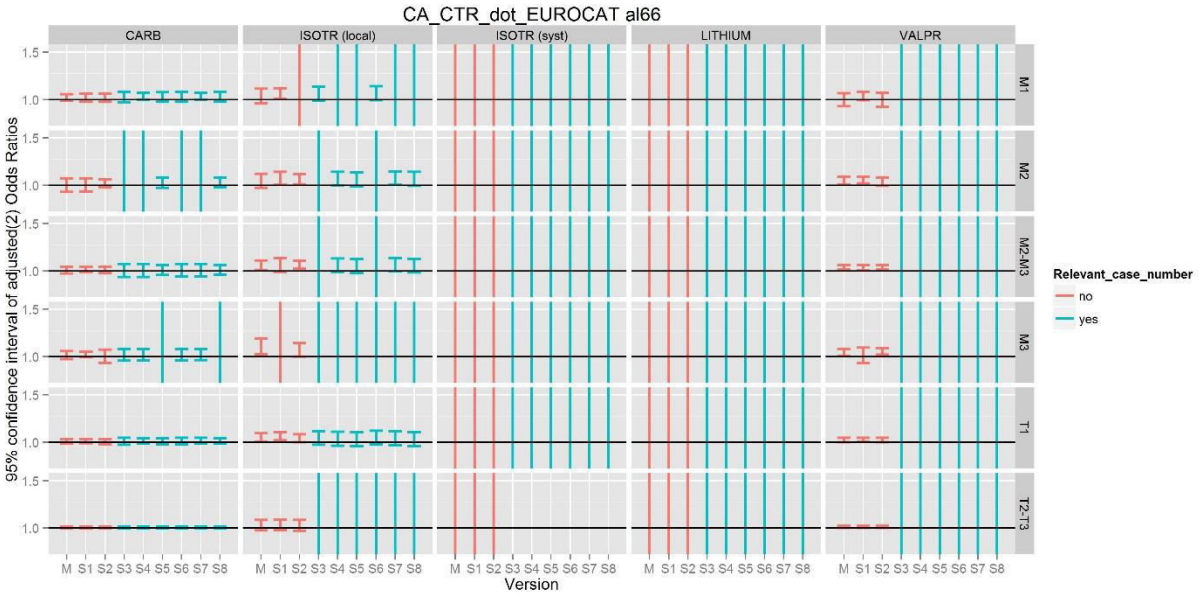
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.BB. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.BB. 95% confidence intervals of odds ratios of drug exposure in the al66 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_EUROCAT al66
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes


CA_CTR_dot_EUROCAT al66
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes

15.3.30. Hip dislocation and/or dyspasia (EUROCAT al67)

The EUROCAT al67 code group has been defined as any reported Q650-Q652, Q6580, Q6581 ICD code.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	65,778	133.28 *
Excluding single outpatient reports (S3-S5)	15,919	32.26 *
Excluding all outpatient reports (S6-S8)	2213	4.48 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		0.81 **

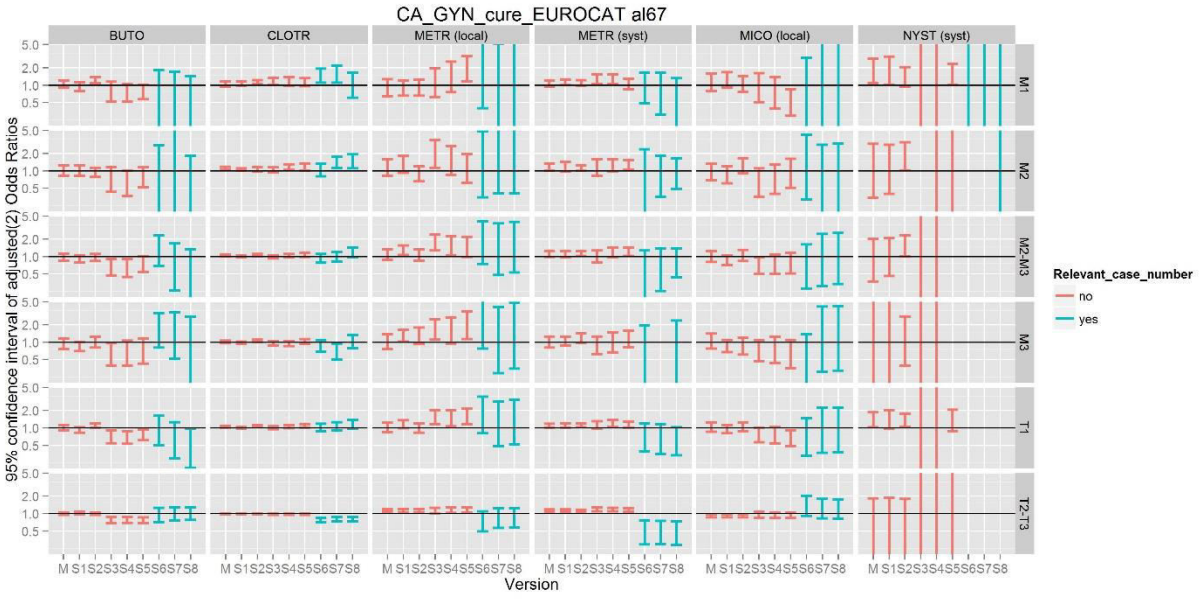
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

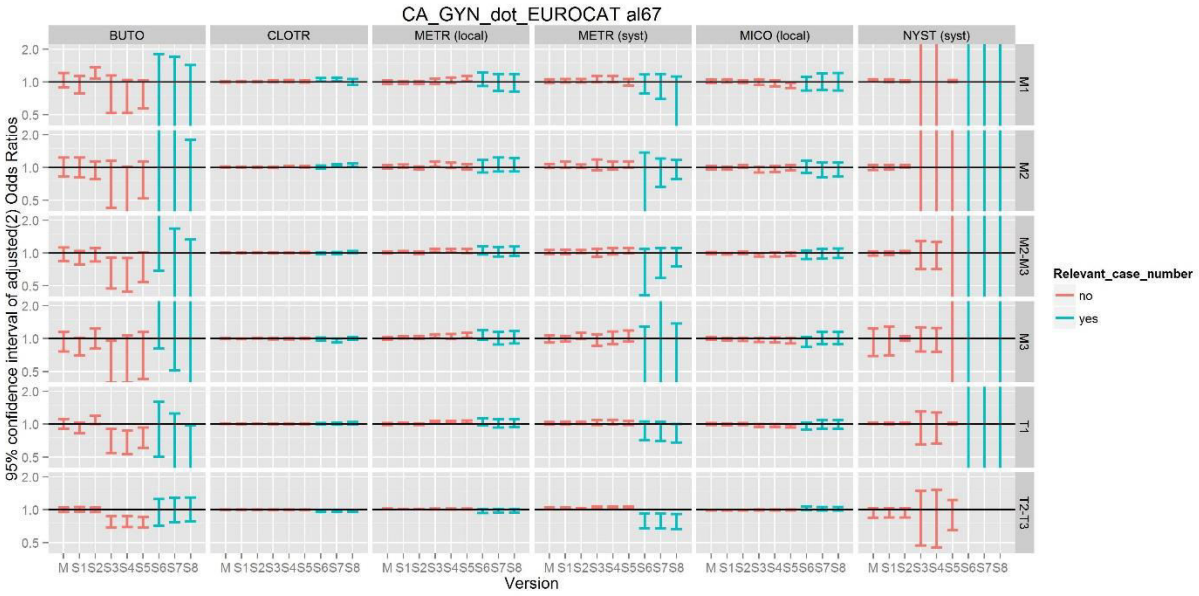
Based on the above numbers, outpatient reports may be unreliable for the analysis of this category; hence, sensitivity analyses S6-S8 are the most relevant ones for the analysis of this code group. Note the substantial over-reporting of cases to the OEP database – due to the liberal use of these codes in the clinical practice, part of the OEP reported cases may not represent severe/true congenital anomalies.

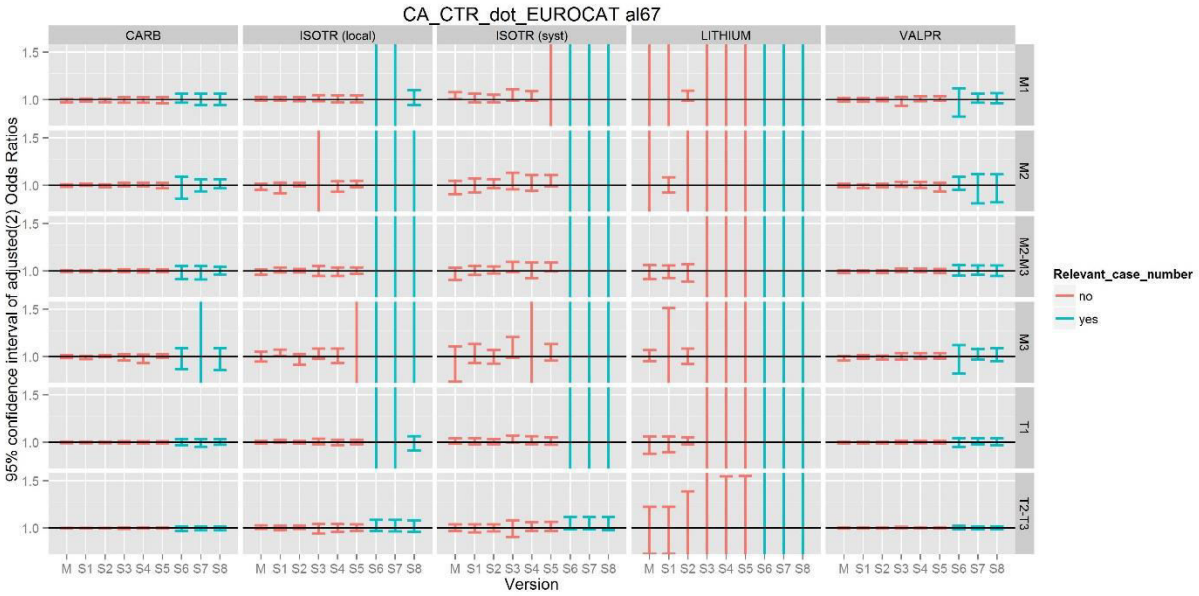
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.CC. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.CC. 95% confidence intervals of odds ratios of drug exposure in the al67 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_EUROCAT al67
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes


CA_CTR_dot_EUROCAT al67
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes

15.3.31. Hip dislocation and/or dyspasia, including "congenital deformity of hip, unspecified" (Custom RG12)

The custom RG12 code group has been defined as any reported al67 code and/or Q659 ICD code.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	88,378	179.07 *
Excluding single outpatient reports (S3-S5)	19,595	39.70 *
Excluding all outpatient reports (S6-S8)	3103	6.29 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		1.14 **

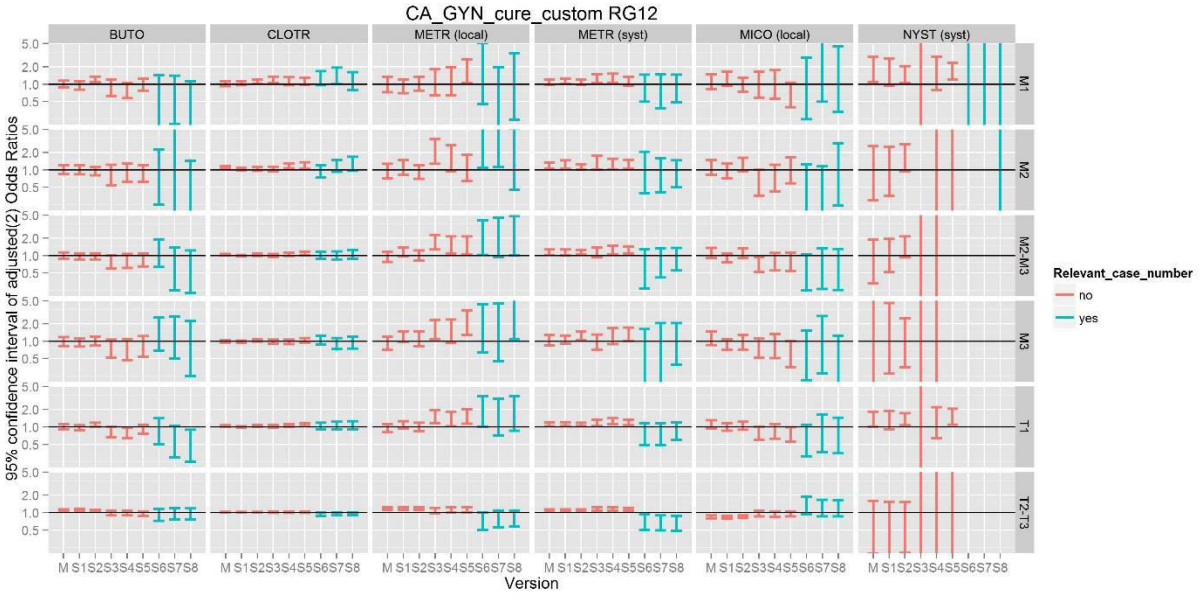
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

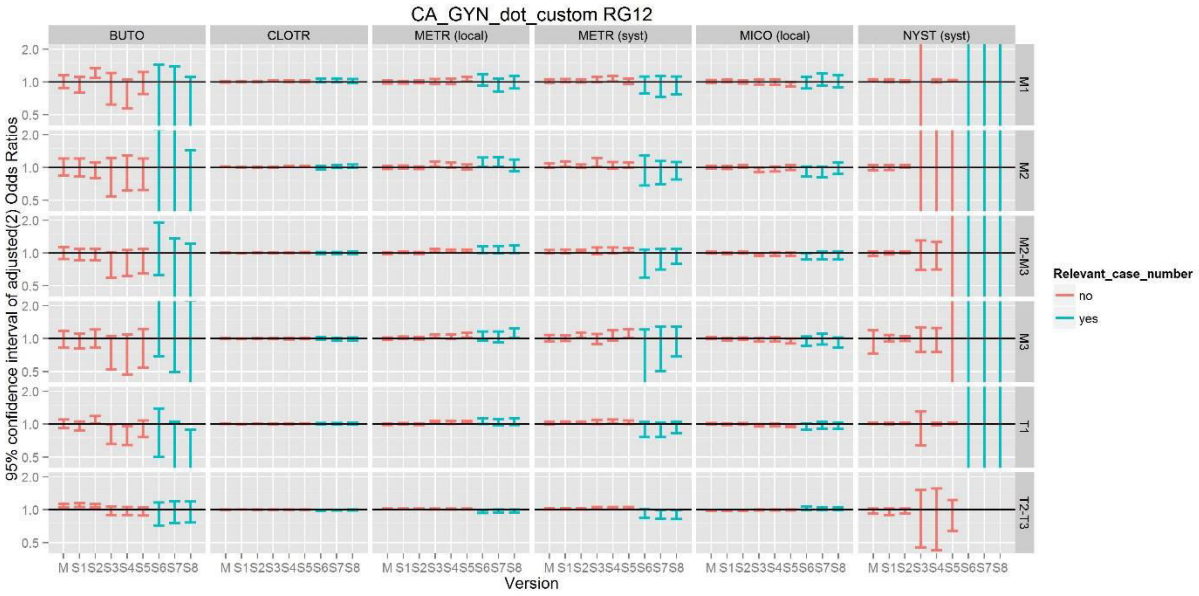
Based on the above numbers, outpatient reports may be unreliable for the analysis of this category; hence, sensitivity analyses S6-S8 are the most relevant ones for the analysis of this code group. Note the substantial over-reporting of cases to the OEP database – due to the liberal use of the relevant codes in the clinical practice, part of the OEP reported cases may not represent severe/true congenital anomalies.

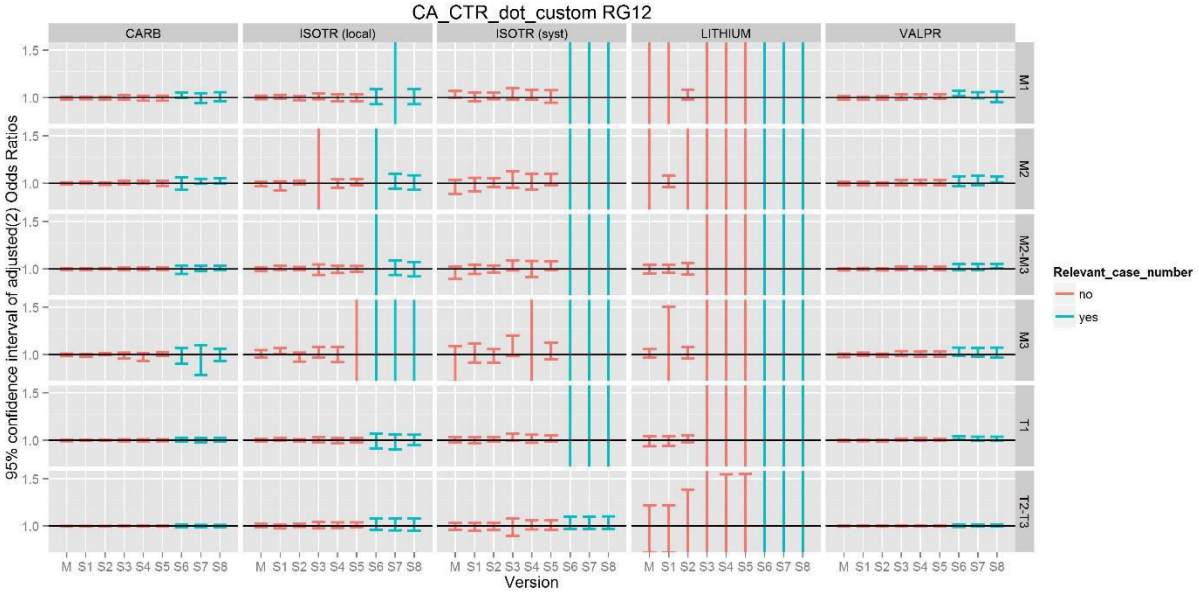
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.DD. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.DD. 95% confidence intervals of odds ratios of drug exposure in the RG12 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_custom RG12
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes


CA_CTR_dot_custom RG12
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes

15.3.32. Limb, other (Custom RG13)

The custom RG13 code group has been defined as any reported al61 code excluding ICD codes Q660, Q650-652, Q6580, Q6581, Q659.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	2315	4.69 *
Excluding single outpatient reports (S3-S5)	1358	2.75 *
Excluding all outpatient reports (S6-S8)	970	1.97 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		2.79 **

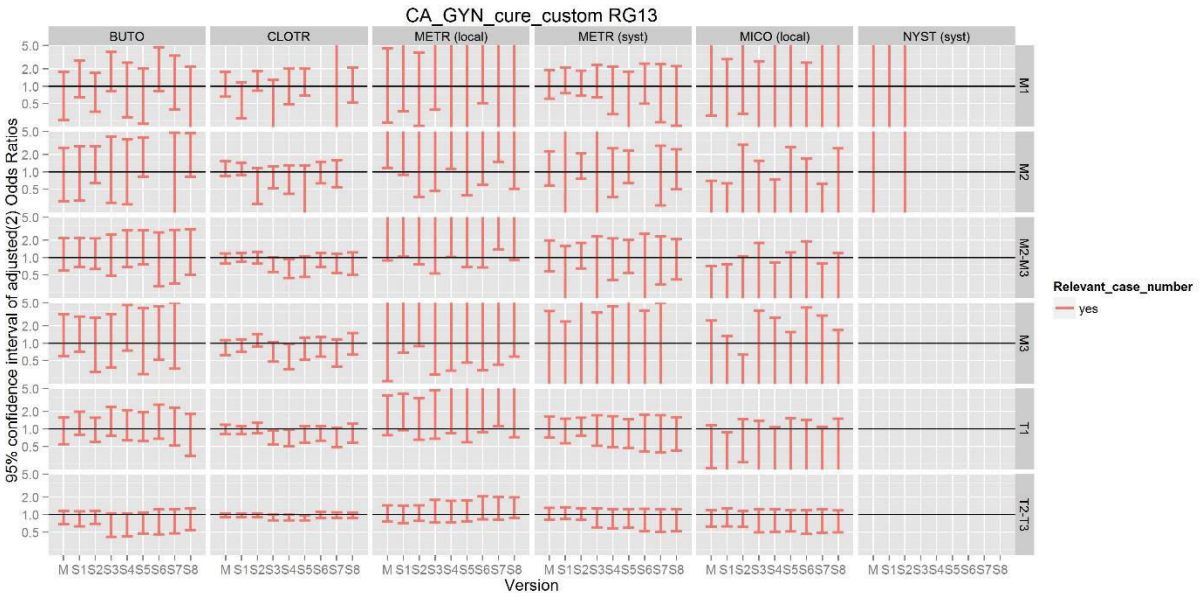
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

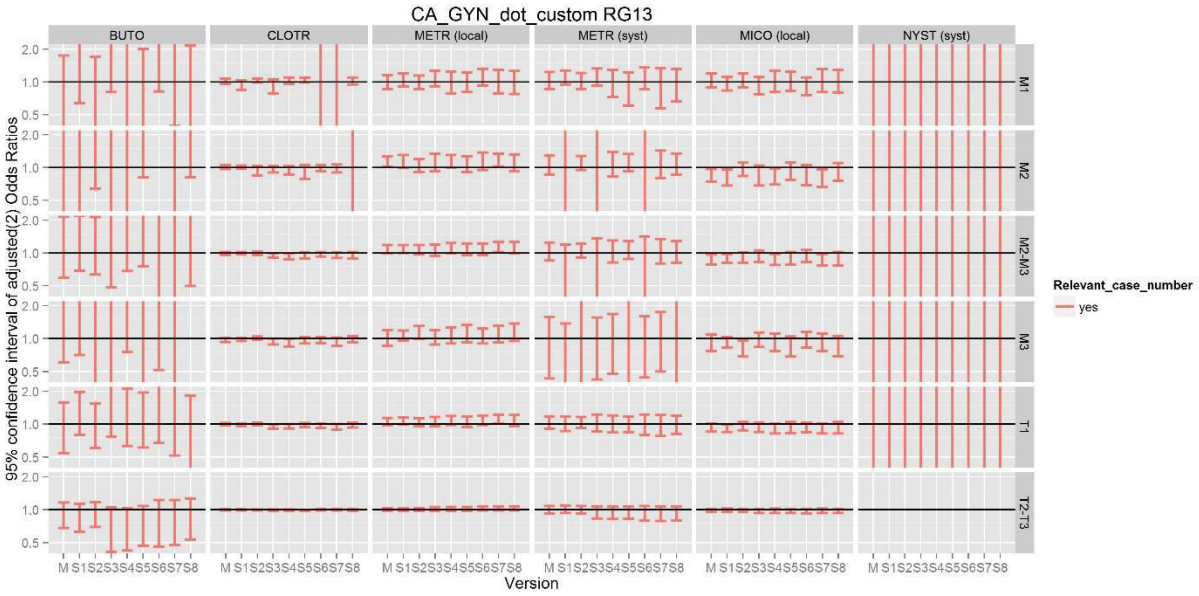
Based on the above numbers, single outpatient reports may be unreliable for the analysis of this category, while the restriction to inpatient cases could exclude a substantial fraction of true cases. Hence, all analyses are relevant for the analysis of this code group.

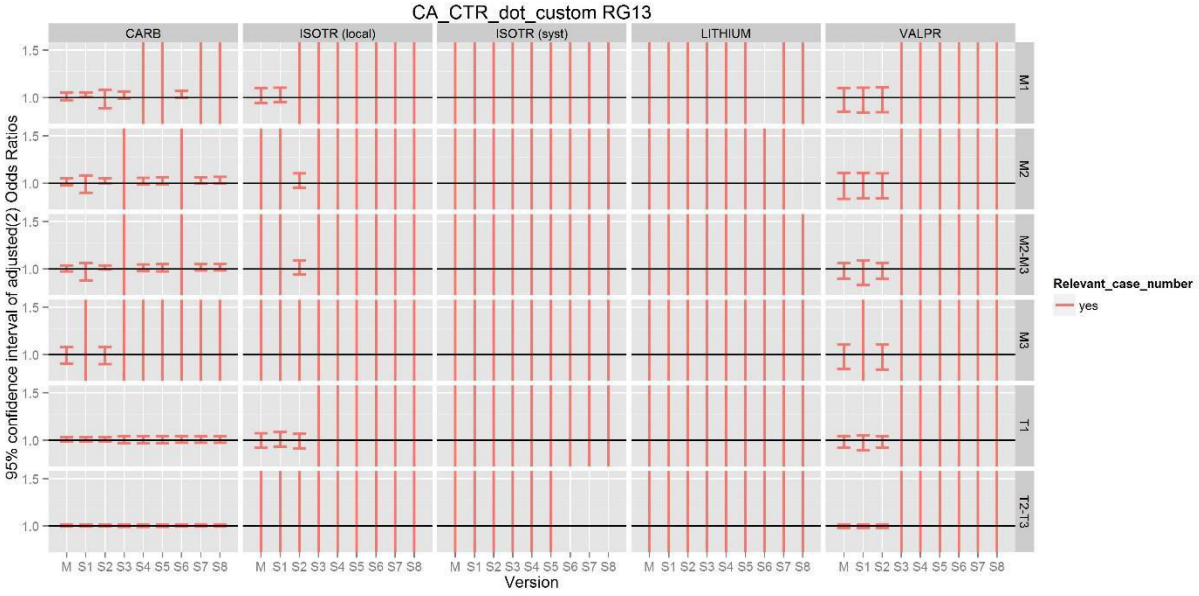
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.EE. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.EE. 95% confidence intervals of odds ratios of drug exposure in the RG13 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_custom RG13
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
yes


CA_CTR_dot_custom RG13
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
yes

15.3.33. Congenital skin disorders (EUROCAT al 81)

The EUROCAT al81 code group has been defined as any reported ICD code in the Q80-Q82 range.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	1233	2.50 *
Excluding single outpatient reports (S3-S5)	759	1.54 *
Excluding all outpatient reports (S6-S8)	730	1.48 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		2.14 **

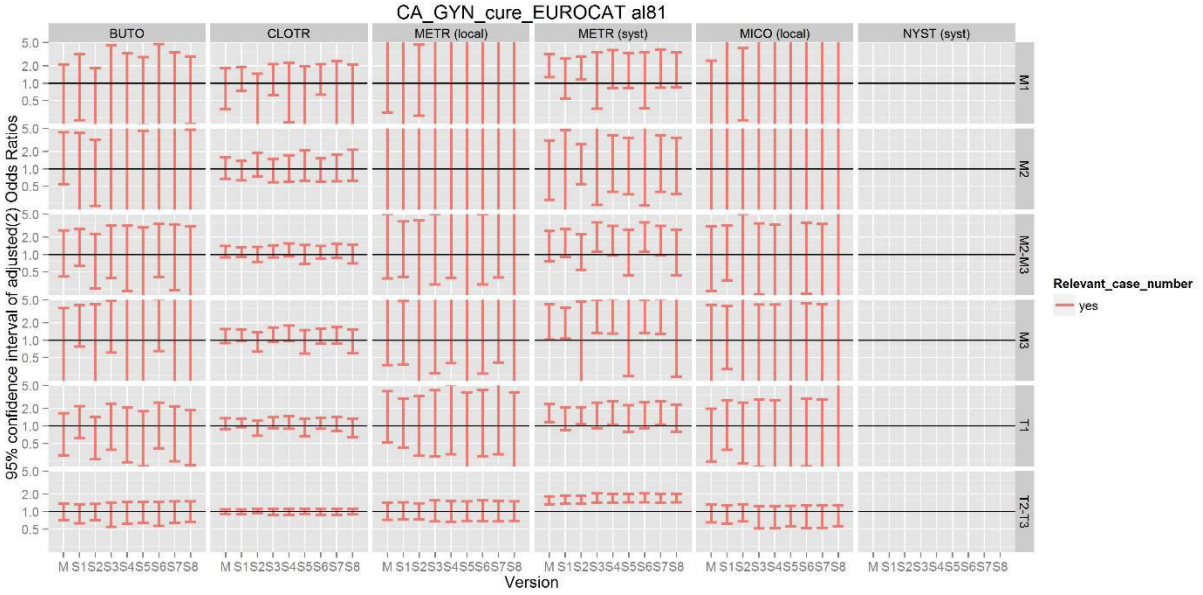
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

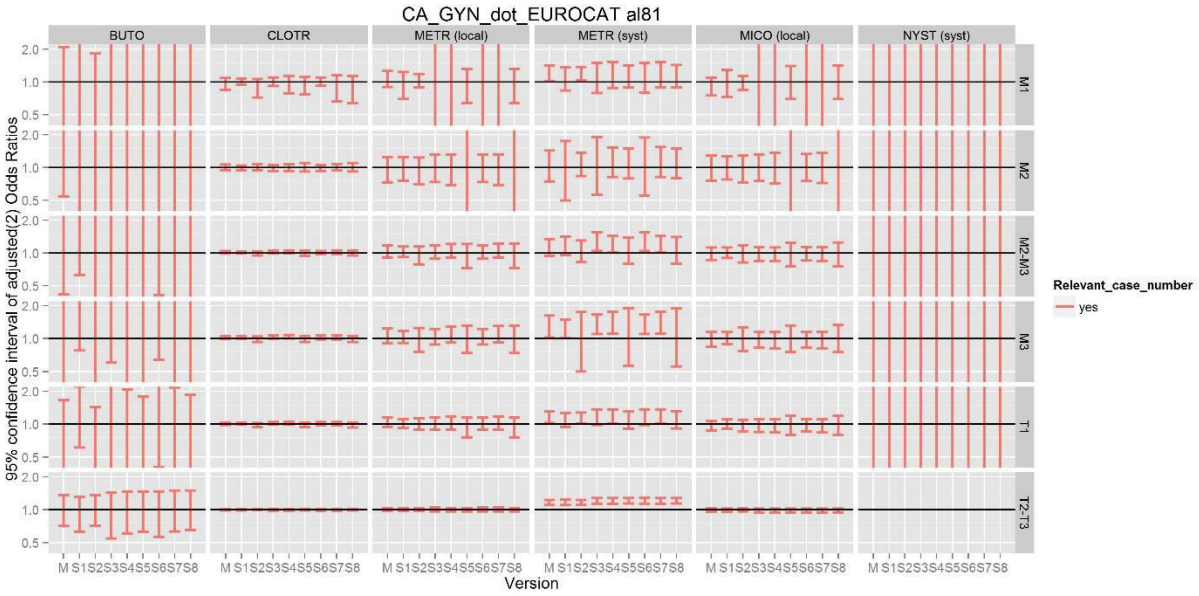
Based on the above numbers, outpatient reports may be reliable for the analysis of this category; hence, the main analysis and all sensitivity analyses are relevant for the analysis of this code group.

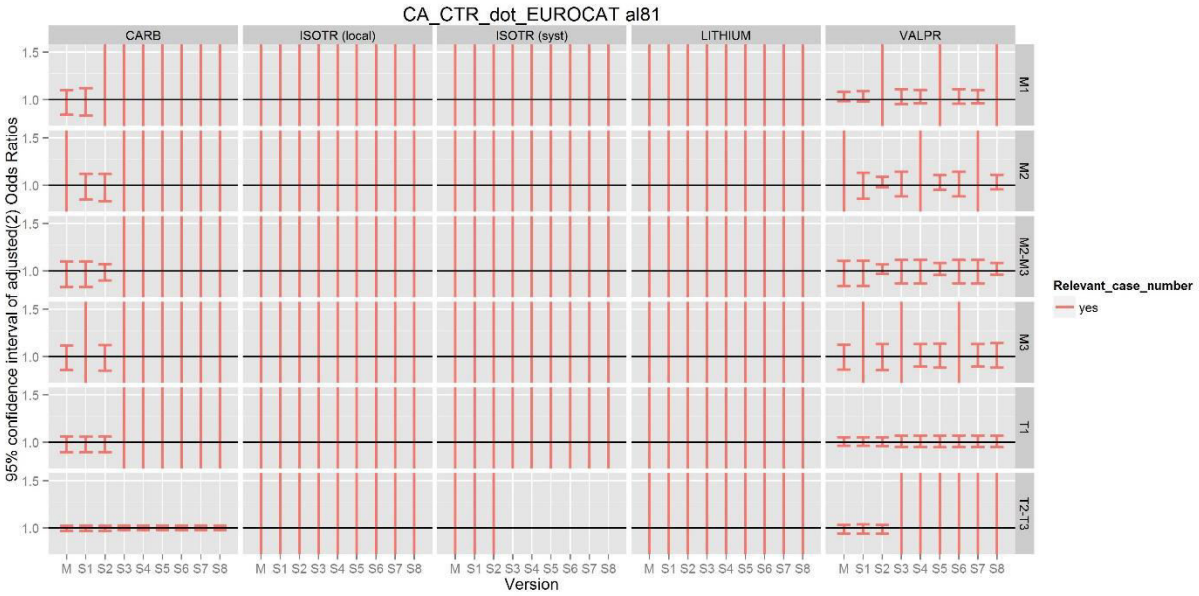
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.FF. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.FF. 95% confidence intervals of odds ratios of drug exposure in the al81 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_EUROCAT al81
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
yes


CA_CTR_dot_EUROCAT al81
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
yes

15.3.34. Other anomalies/syndromes, other (Custom RG14)

The custom RG14 code group has been defined as any reported ICD code belonging to the al75-76, al79-80, al82-84, al86, al104-105, al108 subgroups.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	2047	4.15 *
Excluding single outpatient reports (S3-S5)	1051	2.13 *
Excluding all outpatient reports (S6-S8)	767	1.55 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		0.74 **

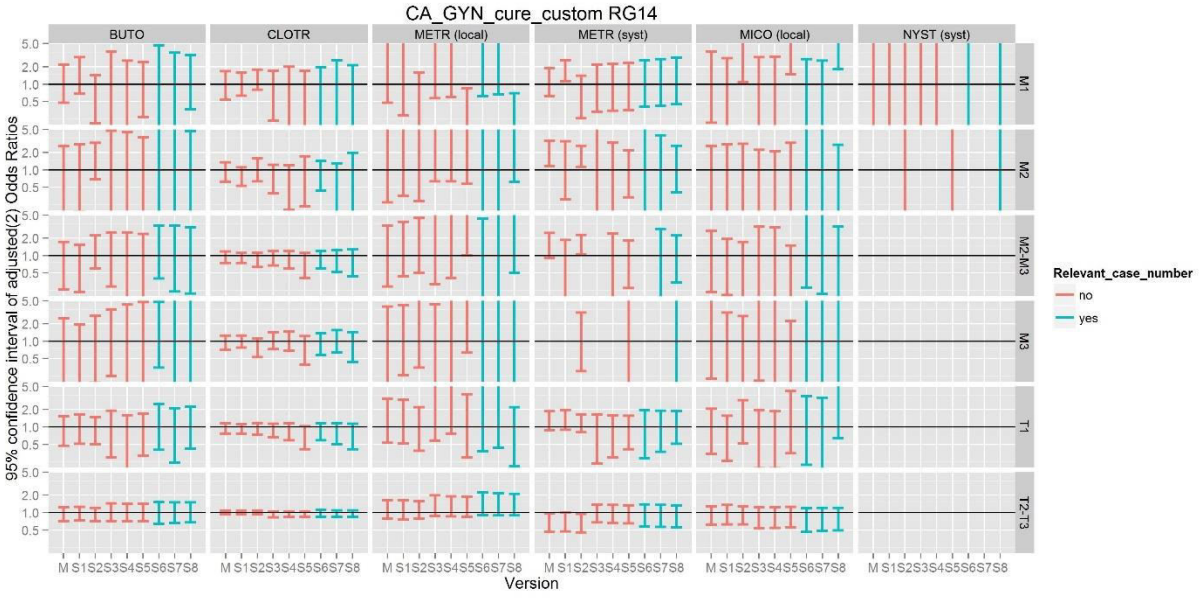
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

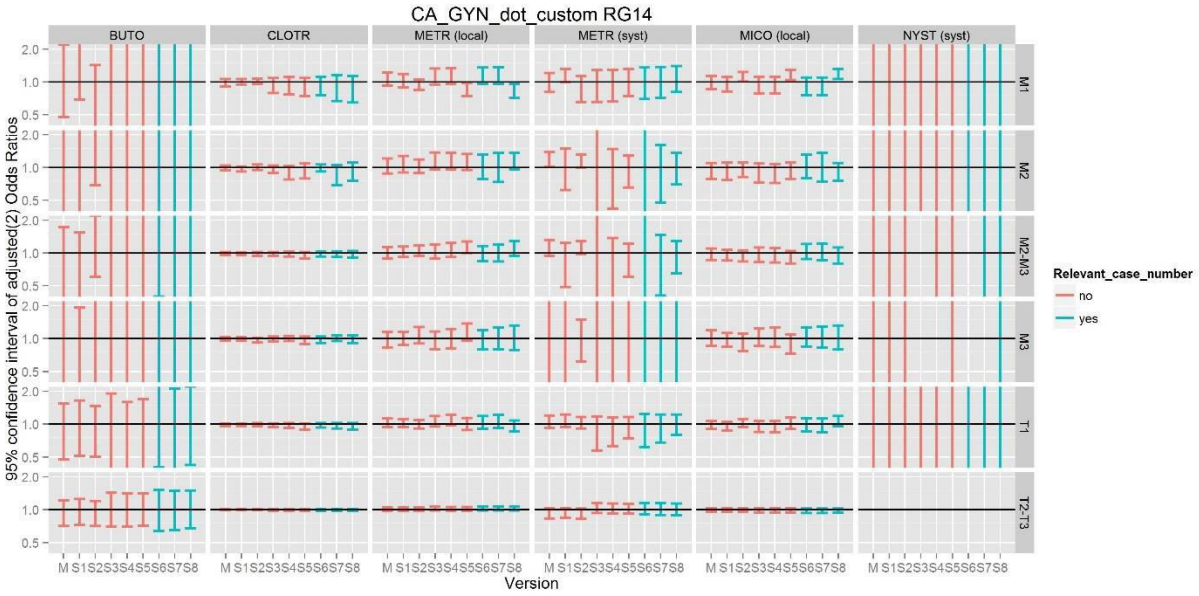
Based on the above numbers, outpatient reports may be unreliable for the analysis of this category; hence, sensitivity analyses S6-S8 are the most relevant ones for the analysis of this code group.

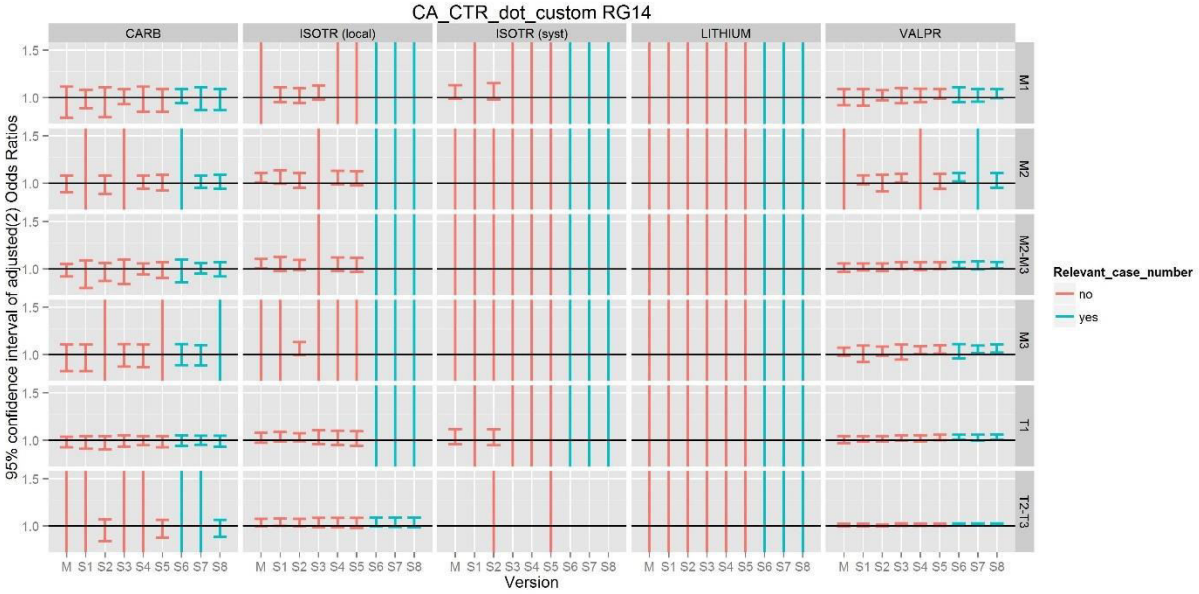
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.GG. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.GG. 95% confidence intervals of odds ratios of drug exposure in the RG14 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_custom RG14
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes


CA_CTR_dot_custom RG14
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes

15.3.35. All anomalies (EUROCAT al1)

The EUROCAT al1 code group has been defined as any reported ICD code belonging to the Q-chapter or to the D215, D821, D1810, P350, P351, P371 ranges; excluding minor anomalies listed in Protocol amendment 2, Table 3.1.4.1.A.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	140,653	284.99 *
Excluding single outpatient reports (S3-S5)	50,378	102.08 *
Excluding all outpatient reports (S6-S8)	27,315	55.34 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		53.1 #

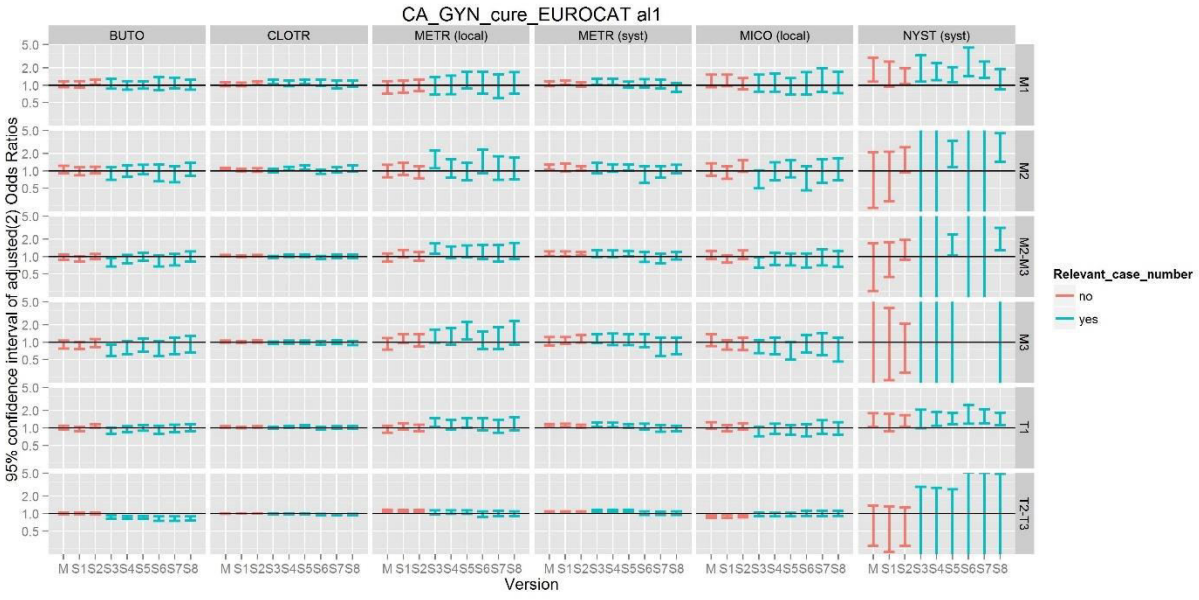
*Number of cases divided by 493,535 live births in the study; #reported overall rate per 1,000 live births and late fetal deaths {OEFI, 2013 #60}.

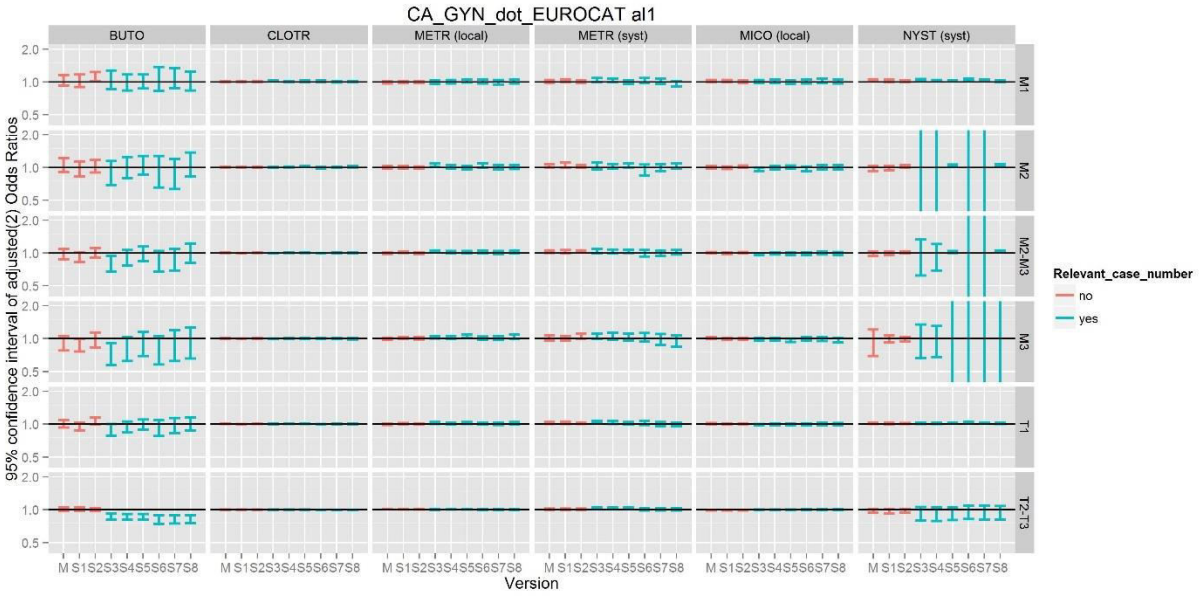
Based on the above numbers, the overall rate of all anomalies can be best approximated in the OEP database when all outpatient records are neglected. Accordingly, sensitivity analyses S3-S8 are the most relevant ones for the analysis of this overall code group.

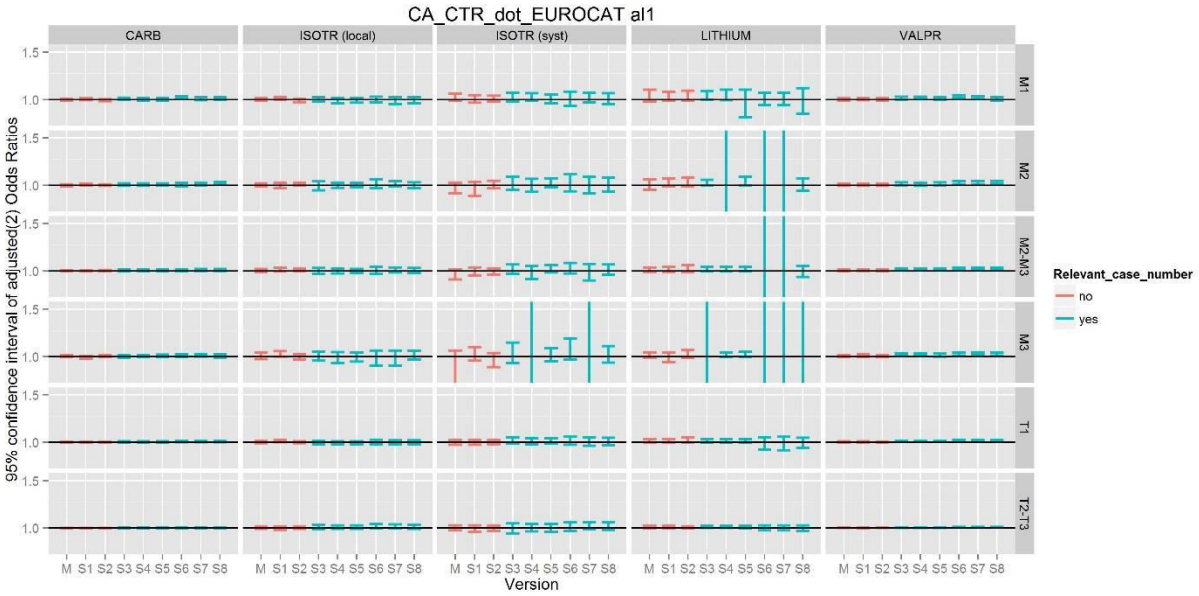
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.HH. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.HH. 95% confidence intervals of odds ratios of drug exposure in the al1 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_EUROCAT al1
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1S2S3S4S5S6S7S8
Version
Relevant_case_number
no
yes

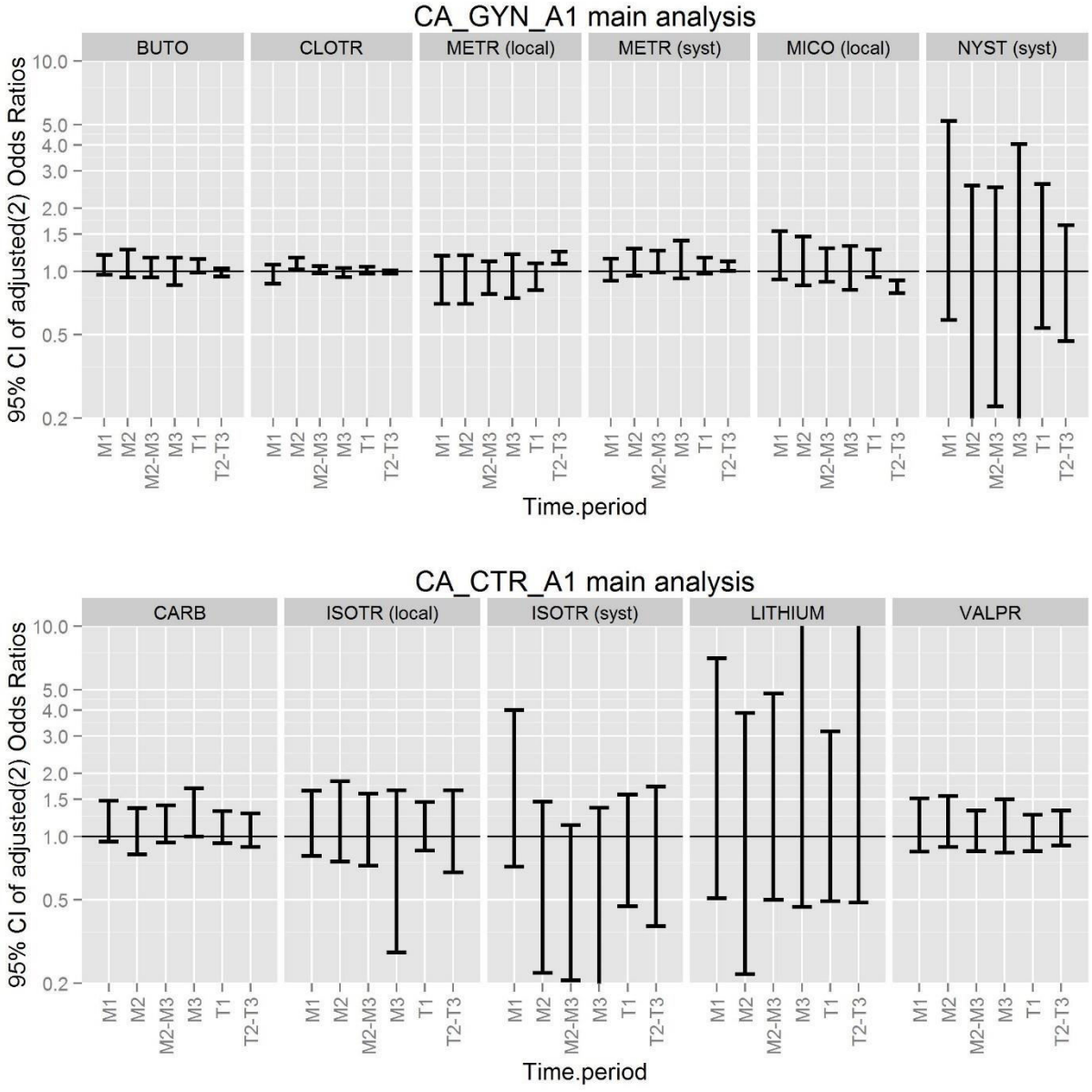

CA_CTR_dot_EUROCAT al1
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1 S2 S3 S4 S5 S6 S7 S8
Version
Relevant_case_number
no
yes

15.3.36. Protocol Amendment 1, main analysis

In the main analysis of Protocol Amendment 1, congenital anomalies were defined as any elective termination with foetal defects, stillbirth with foetal defects, or live births with congenital anomalies, where the list of codes indicative for foetal defects / congenital anomalies was defined in Annex 3.1.2. of Protocol Amendment 1. This analysis found 389.6 cases for 1,000 live births, in contrast to the official rate of 53.1 cases per 1,000 live births and late fetal deaths ({OEFI, 2013 #60}. Accordingly, the Amendment 1 main analysis is considered to be not relevant. However, confidence intervals of the fully adjusted odds ratios are shown in Figure 15.II. For a full tabular summary of all Amendment 1 congenital anomaly study results, please see Section 15.1.

Figure 15.II. 95% confidence intervals of odds ratios of drug exposure in the Amendment 1 main analysis, adjusted to all confounders.

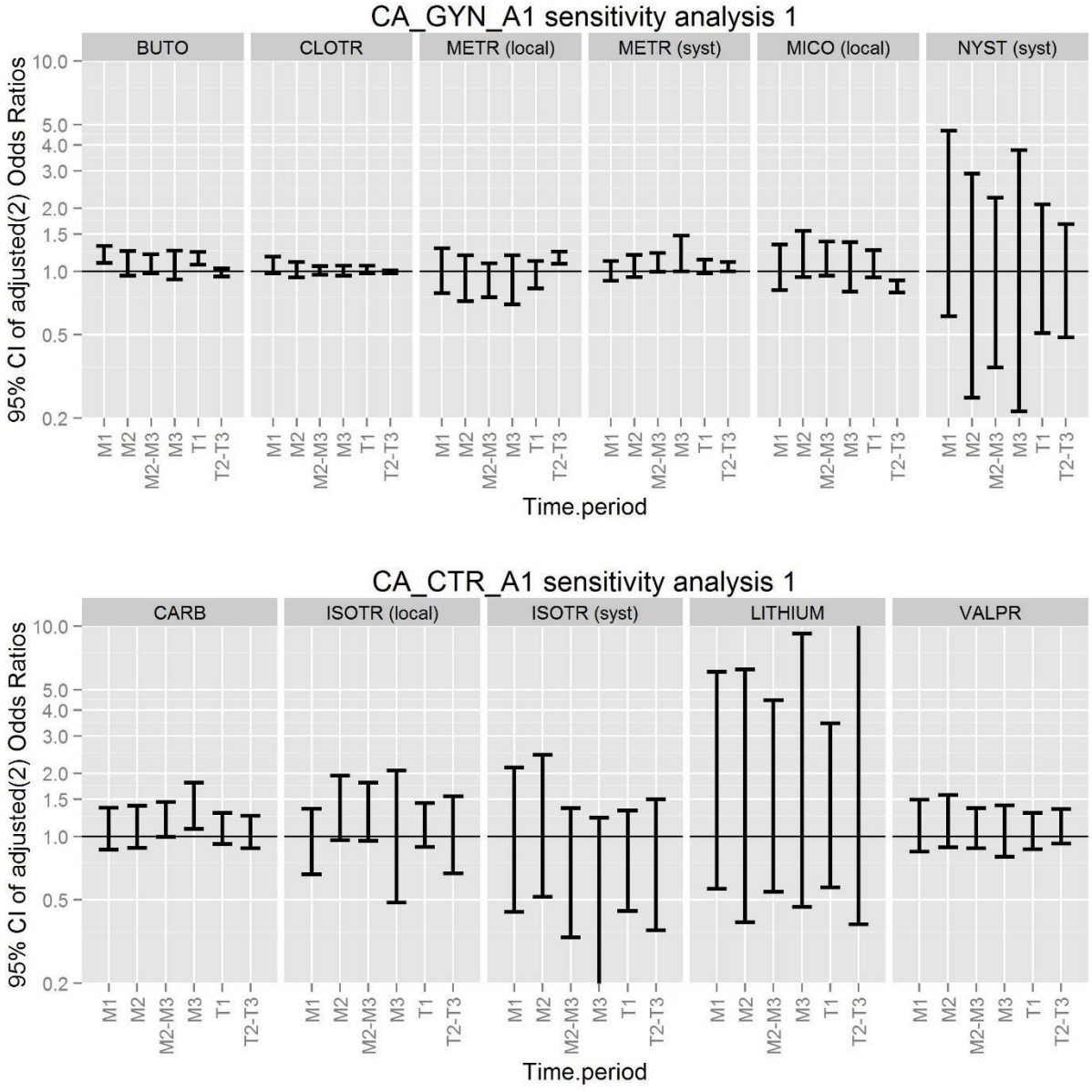
First panel: gynecology drug exposure; second panel: active controls. BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M{i} and T{i}, i-th month or trimester. Missing error bars indicate the lack of model results (insufficient exposure).



15.3.37. Protocol Amendment 1, sensitivity analysis 1

In Amendment 1 sensitivity analysis 1, Day 1 of pregnancy was estimated as {AFP reported date} minus 135 days. The rate of false positive cases was the same as in the main analysis, therefore sensitivity analysis 1 is not considered to be relevant. However, confidence intervals of the fully adjusted odds ratios are shown in Figure 15.JJ. For a full tabular summary of all Amendment 1 congenital anomaly study results, please see Section 15.1.

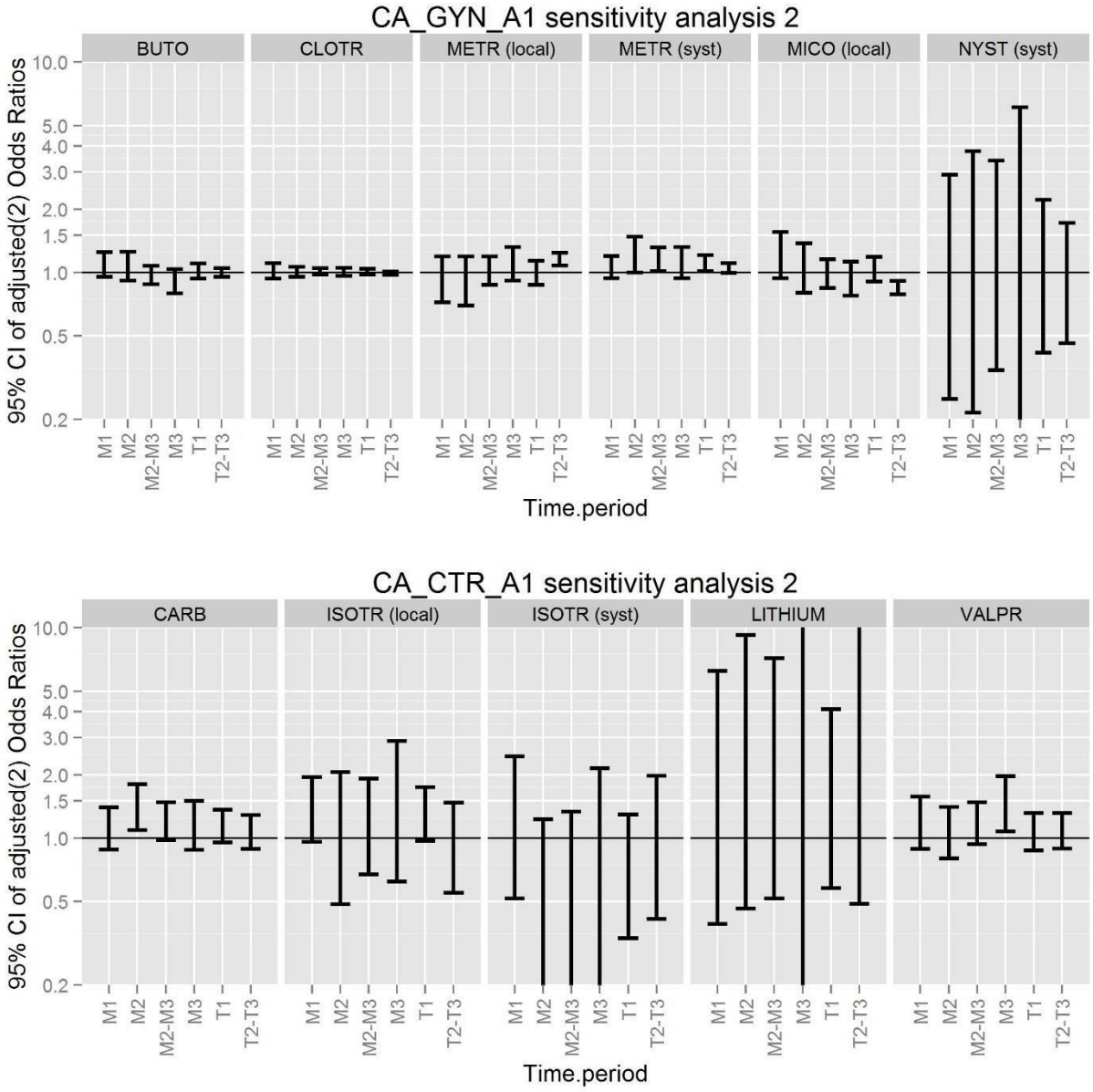
Figure 15.JJ. 95% confidence intervals of odds ratios of drug exposure in Amendment 1 sensitivity analysis 1, adjusted to all confounders.
First panel: gynecology drug exposure; second panel: active controls. BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M{i} and T{i}, i-th month or trimester. Missing error bars indicate the lack of model results (insufficient exposure).



15.3.38. Protocol Amendment 1, sensitivity analysis 2

In Amendment 1 sensitivity analysis 2, Day 1 of pregnancy was estimated as {AFP reported date} minus 107 days. The rate of false positive cases was the same as in the main analysis, therefore sensitivity analysis 2 is not considered to be relevant. However, confidence intervals of the fully adjusted odds ratios are shown in Figure 15.KK. For a full tabular summary of all Amendment 1 congenital anomaly study results, please see Section 15.1.

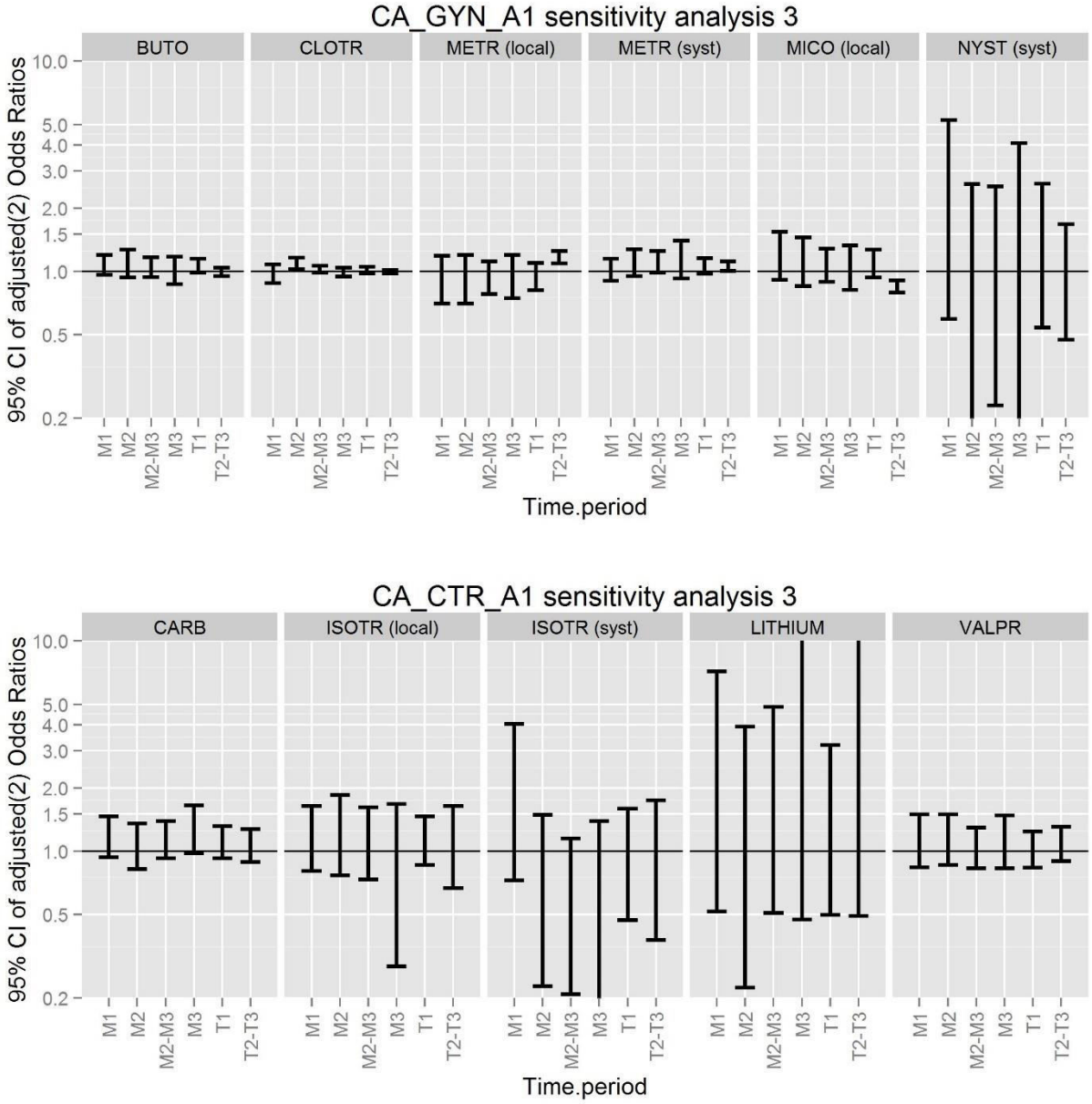
Figure 15.KK. 95% confidence intervals of odds ratios of drug exposure in Amendment 1 sensitivity analysis 2, adjusted to all confounders.
First panel: gynecology drug exposure; second panel: active controls. BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M{i} and T{i}, i-th month or trimester. Missing error bars indicate the lack of model results (insufficient exposure).



15.3.39. Protocol Amendment 1, sensitivity analysis 3

In Amendment 1 sensitivity analysis 3, stillbirths without foetal defect were included in the control group. The rate of false positive cases was the same as in the main analysis (Table 10.R in Section 10.3.3), therefore sensitivity analysis 3 is not considered to be relevant. However, confidence intervals of the fully adjusted odds ratios are shown in Figure 15.LL. For a full tabular summary of all Amendment 1 congenital anomaly study results, please see Section 15.1.

Figure 15.LL. 95% confidence intervals of odds ratios of drug exposure in Amendment 1 sensitivity analysis 3, adjusted to all confounders.
First panel: gynecology drug exposure; second panel: active controls. BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M{i} and T{i}, i-th month or trimester. Missing error bars indicate the lack of model results (insufficient exposure).

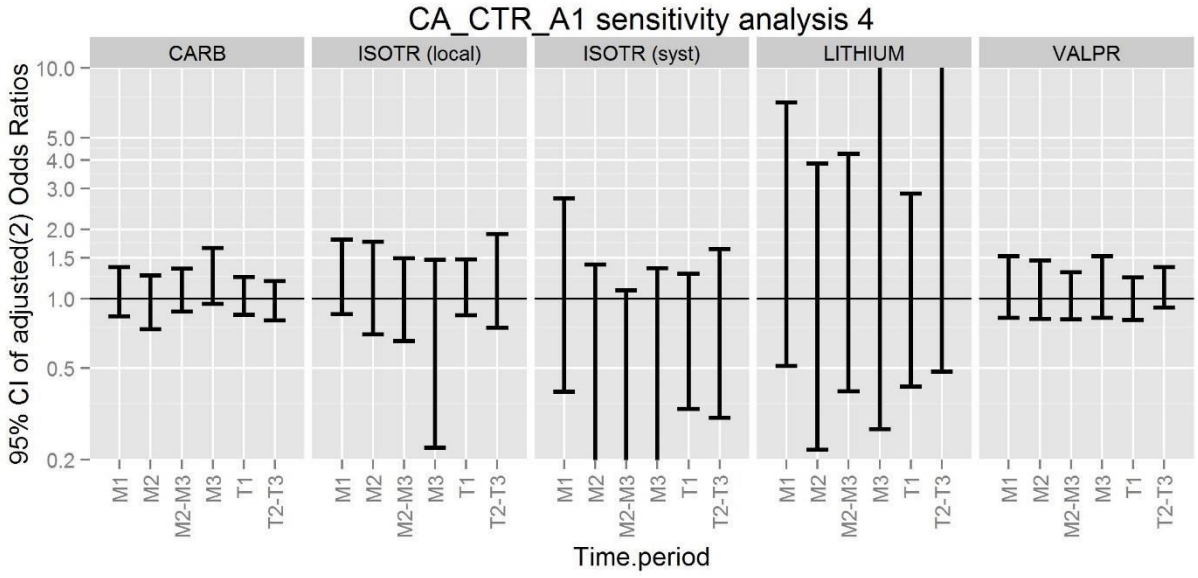


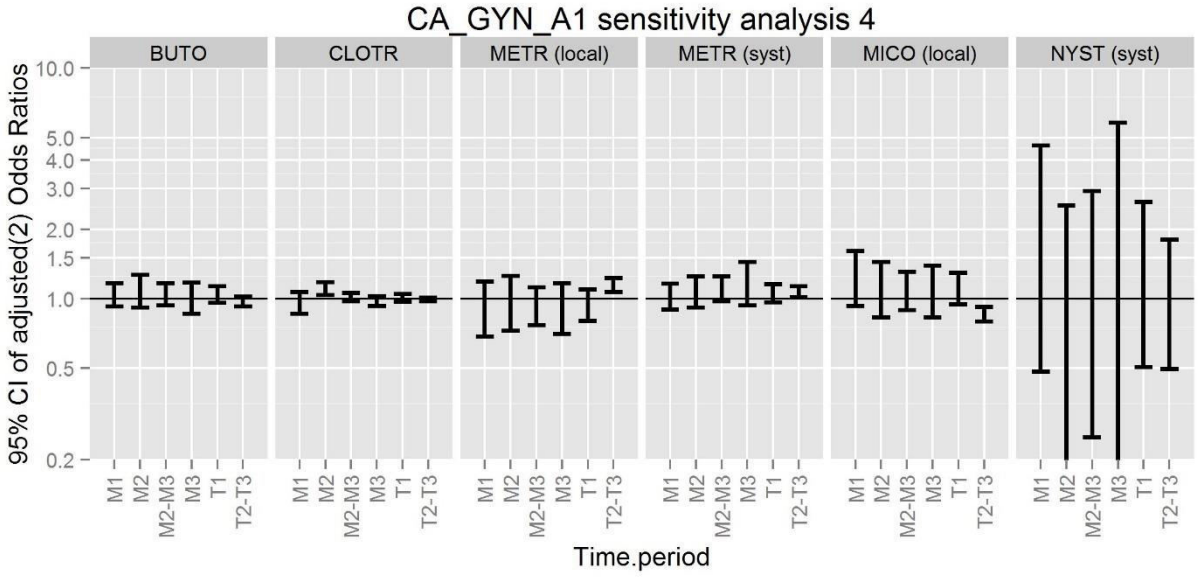
15.3.40. Protocol Amendment 1, sensitivity analysis 4

In Amendment 1 sensitivity analysis 4, cases and controls without reported AFP screening test in the last 26 weeks before pregnancy outcome are excluded from the analysis. Since the same extensive list of codes was used for outcome identification as in the main analysis, sensitivity analysis 4 is not considered to be relevant (see Table 10.R in Section 10.3.3). However, confidence intervals of the fully adjusted odds ratios are shown in Figure 15.MM. For a full tabular summary of all Amendment 1 congenital anomaly study results, please see Section 15.1.

Figure 15.MM. 95% confidence intervals of odds ratios of drug exposure in Amendment 1 sensitivity analysis 4, adjusted to all confounders.

First panel: gynecology drug exposure; second panel: active controls. BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M{i} and T{i}, i-th month or trimester. Missing error bars indicate the lack of model results (insufficient exposure).



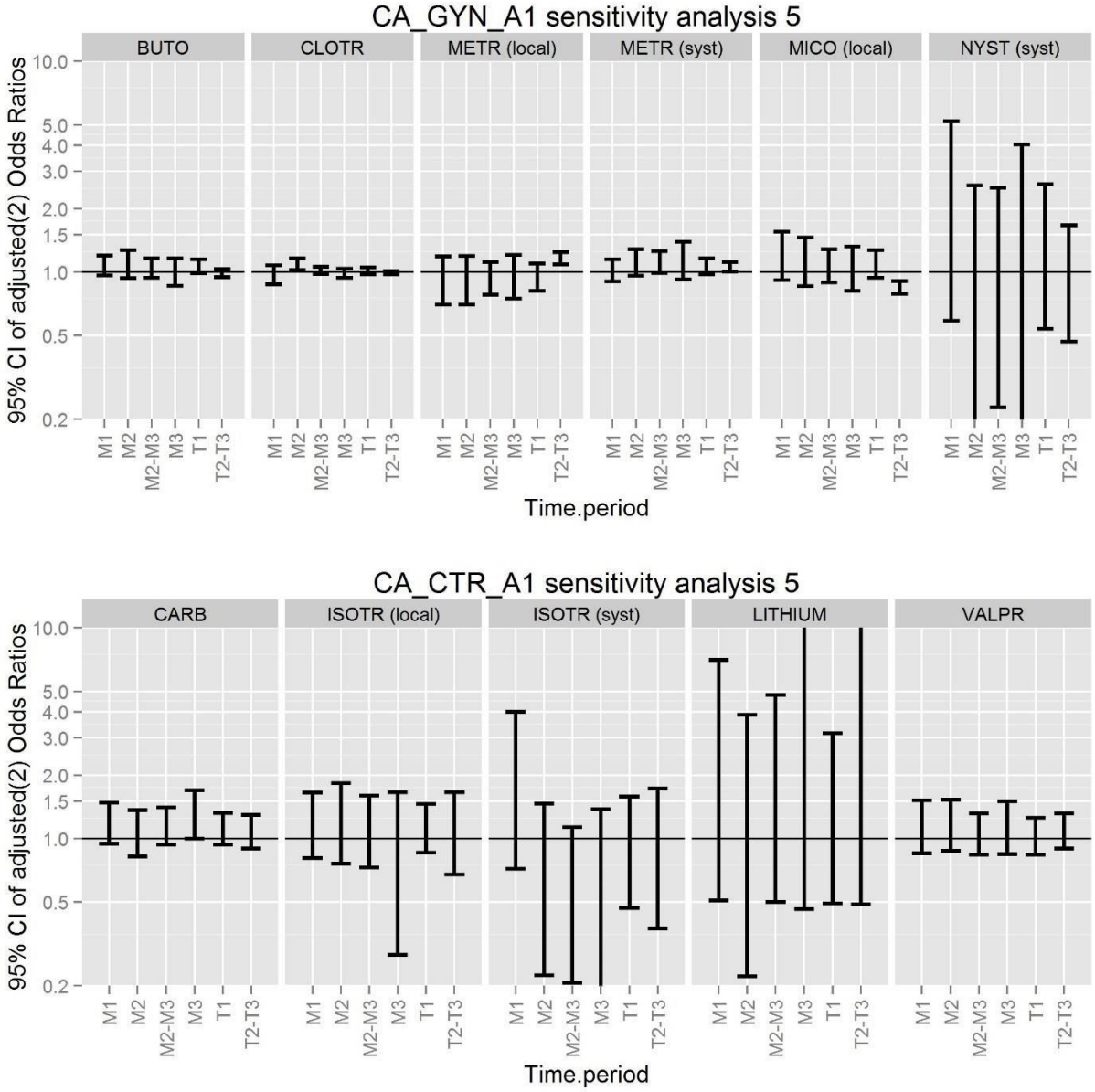


15.3.41. Protocol Amendment 1, sensitivity analysis 5

In Amendment 1 sensitivity analysis 5, elective terminaltions with foetal defects were excluded from the cases. However, since the same extensive list of codes was used for outcome identification in live births as in the main analysis, sensitivity analysis 5 is not considered to be relevant (see Table 10.R in Section 10.3.3). Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.NN. For a full tabular summary of all Amendment 1 congenital anomaly study results, please see Section 15.1.

Figure 15.NN. 95% confidence intervals of odds ratios of drug exposure in the Amendment 1 sensitivity analysis 5, adjusted to all confounders.

First panel: gynecology drug exposure; second panel: active controls. BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M{i} and T{i}, i-th month or trimester. Missing error bars indicate the lack of model results (insufficient exposure).

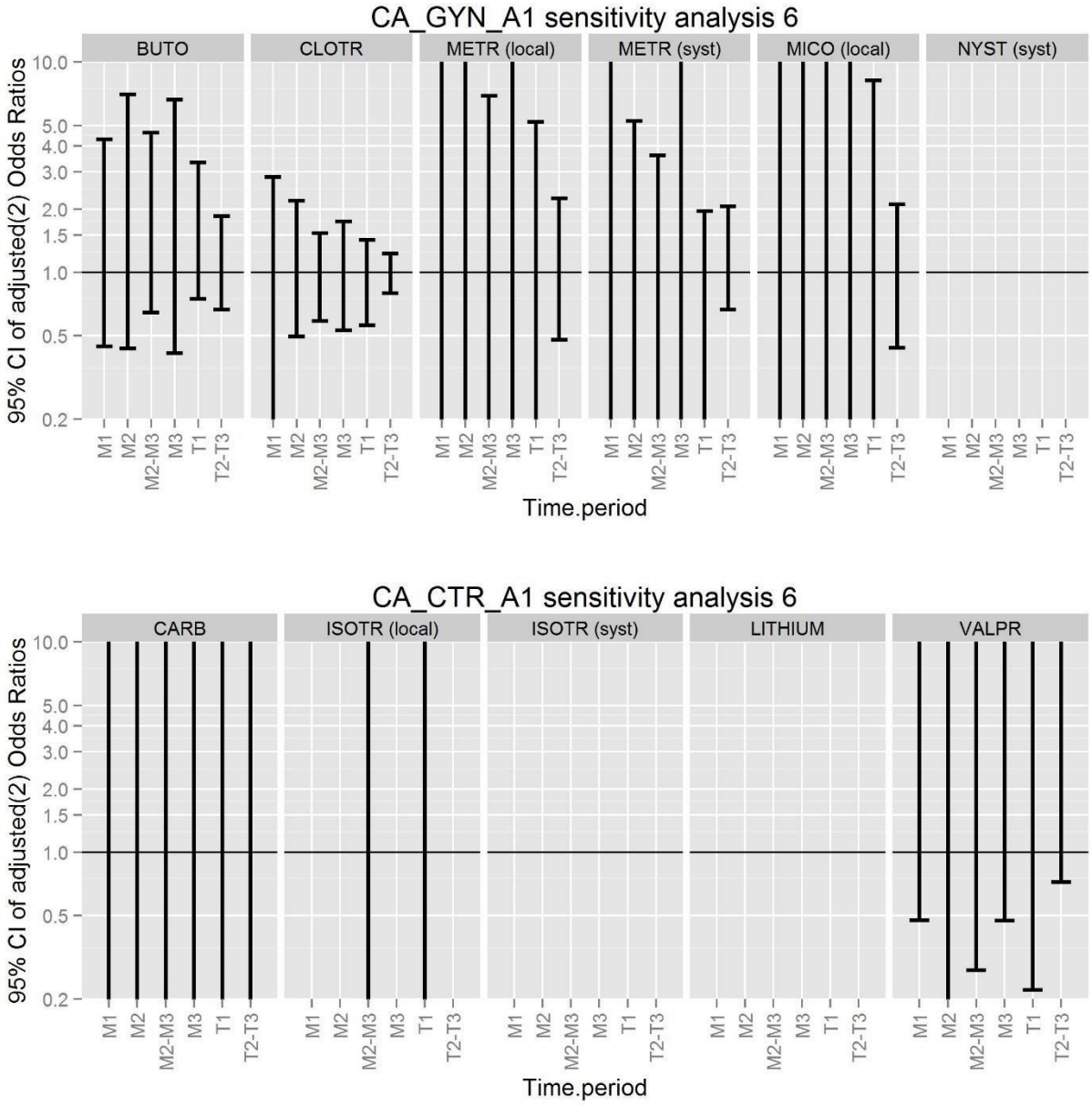


15.3.42. Protocol Amendment 1, sensitivity analysis 6

In Amendment 1 sensitivity analysis 6, dedicated analyses on the risk of cleft lip/palate associated to drug exposure were conducted. Cleft lip/palate was defined as any reported code a from a specific code group (see Section 9.1.2). Due to the use of specific codes, this analysis is considered to be not biased by the general high rate of false positive cases in Amendment 1 analyses. Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.OO. For a full tabular summary of all Amendment 1 congenital anomaly study results, please see Section 15.1.

Figure 15.OO. 95% confidence intervals of odds ratios of drug exposure in the Amendment 1 sensitivity analysis 6, adjusted to all confounders.

First panel: gynecology drug exposure; second panel: active controls. BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M{i} and T{i}, i-th month or trimester. Missing error bars indicate the lack of model results (insufficient exposure).

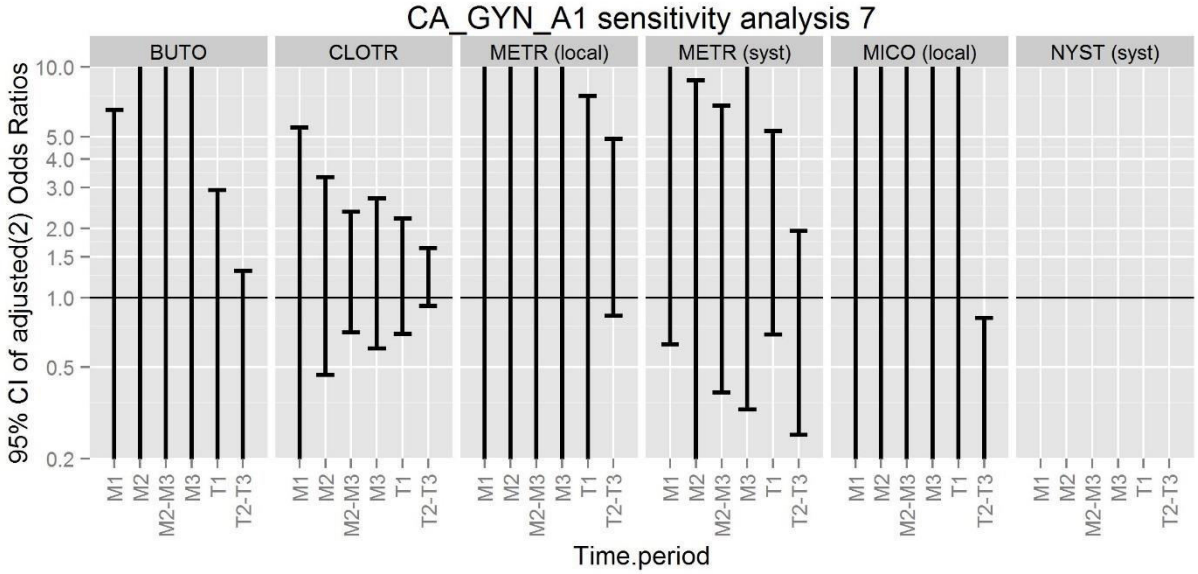


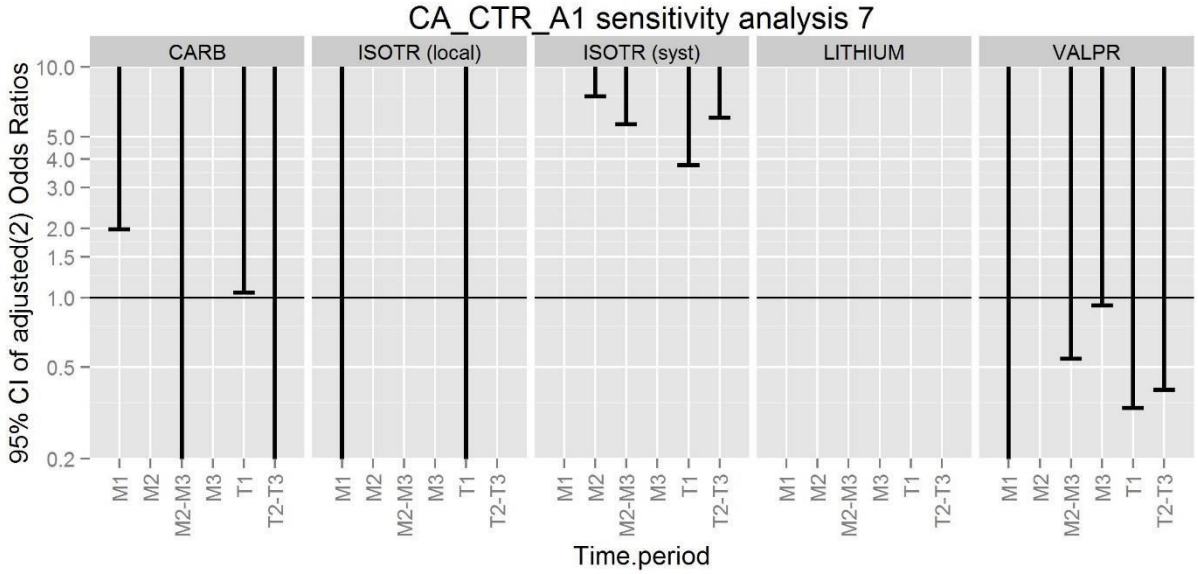
15.3.43. Protocol Amendment 1, sensitivity analysis 7

In Amendment 1 sensitivity analysis 7, dedicated analyses on the risk of abdominal wall defects associated to drug exposure were conducted. Abdominal wall defect was defined as any reported code a from a specific code group (see Section 9.1.2). Due to the use of specific codes, this analysis is considered to be not biased by the general high rate of false positive cases in Amendment 1 analyses. Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.PP. For a full tabular summary of all Amendment 1 congenital anomaly study results, please see Section 15.1.

Figure 15.PP. 95% confidence intervals of odds ratios of drug exposure in the Amendment 1 sensitivity analysis 7, adjusted to all confounders.

First panel: gynecology drug exposure; second panel: active controls. BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M{i} and T{i}, i-th month or trimester. Missing error bars indicate the lack of model results (insufficient exposure).



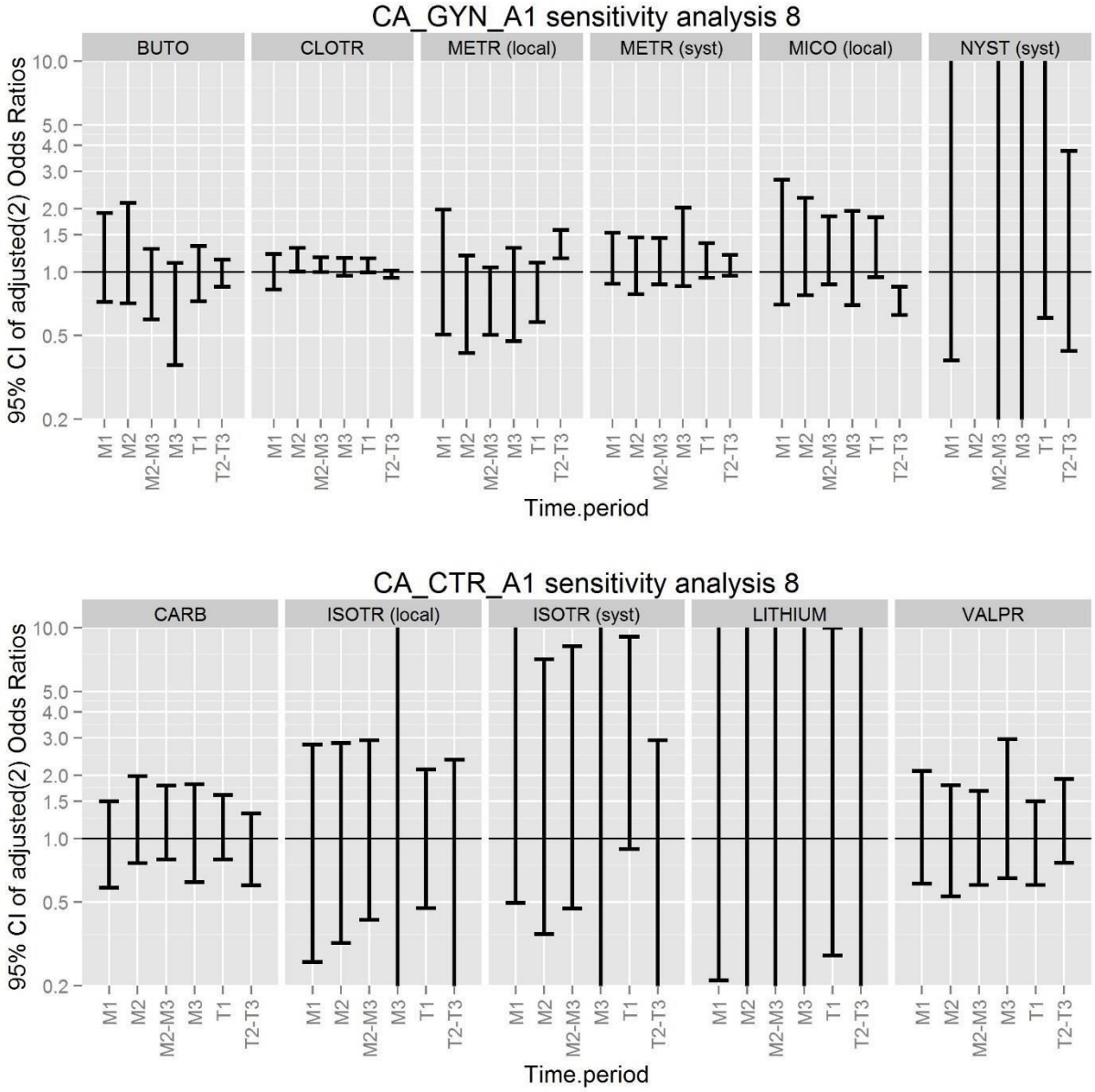


15.3.44. Protocol Amendment 1, sensitivity analysis 8

In Amendment 1 sensitivity analysis 8, the same extensive list of codes was used for outcome identification as in the main analysis, but for a smaller cohort with longer follow-up. Accordingly, sensitivity analysis 8 is not considered to be relevant (see Table 10.R in Section 10.3.3). However, confidence intervals of the fully adjusted odds ratios are shown in Figure 15.3.44.A. For a full tabular summary of all Amendment 1 congenital anomaly study results, please see Section 15.1.

Figure 15.QQ. 95% confidence intervals of odds ratios of drug exposure in the Amendment 1 sensitivity analysis 8, adjusted to all confounders.

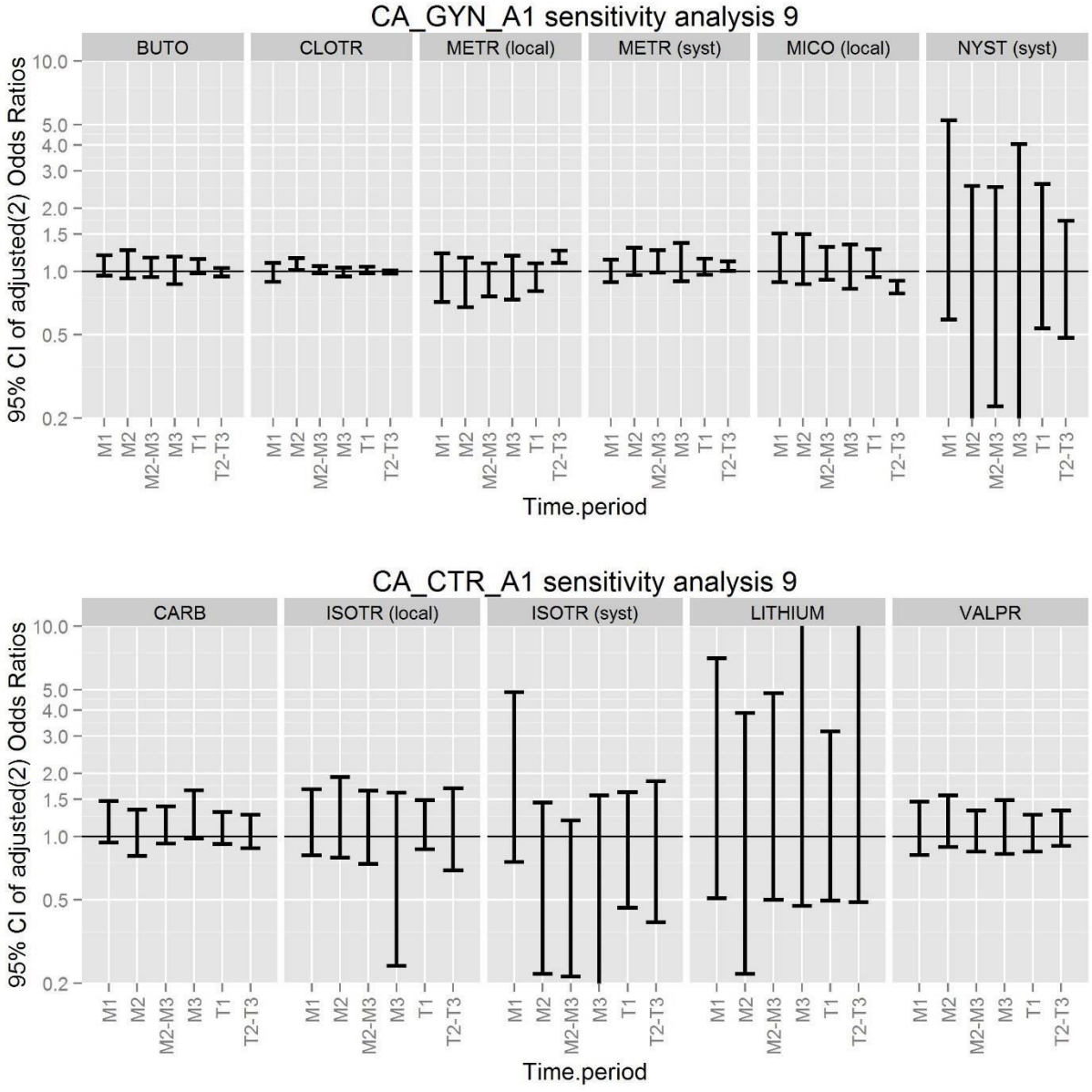
First panel: gynecology drug exposure; second panel: active controls. BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M{i} and T{i}, i-th month or trimester. Missing error bars indicate the lack of model results (insufficient exposure).



15.3.45. Protocol Amendment 1, sensitivity analysis 9

In Amendment 1 sensitivity analysis 9, the same extensive list of codes was used for outcome identification as in the main analysis, but for a smaller cohort with available AFP screening tests. Accordingly, sensitivity analysis 9 is not considered to be relevant. However, confidence intervals of the fully adjusted odds ratios are shown in Figure 15.RR. For a full tabular summary of all Amendment 1 congenital anomaly study results, please see Section 15.1.

Figure 15.RR. 95% confidence intervals of odds ratios of drug exposure in the Amendment 1 sensitivity analysis 9, adjusted to all confounders.
First panel: gynecology drug exposure; second panel: active controls. BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M{i} and T{i}, i-th month or trimester. Missing error bars indicate the lack of model results (insufficient exposure).



15.4. Detailed results on low birthweight

Table 15.V. Main analysis, low birthweight threshold 2,500 g

Variable	Value	N (%)	OR (95% CI)*		
			crude	adjusted (1)	adjusted (2)
Butoconazole and clotrimazole exposure variables					
B11	no	439031 (99.9%)	1 (reference)	1 (reference)	1 (reference)
	yes	559 (0.1%)	1.2 (0.88-1.62)	1.27 (0.94-1.72)	1.35 (0.997-1.83)
B12	no	439558 (100%)	1 (reference)	1 (reference)	1 (reference)
	yes	29 (0%)	1.38 (0.42-4.53)	1.44 (0.44-4.73)	1.52 (0.46-5)
B13+	no	439587 (100%)	1 (reference)	1 (reference)	1 (reference)
	yes	0 (0%)	0 (0-1000+)	0 (0-1000+)	0 (0-1000+)
B21	no	438388 (99.7%)	1 (reference)	1 (reference)	1 (reference)
	yes	1202 (0.3%)	0.71 (0.55-0.92)	0.77 (0.59-0.99)	0.8 (0.62-1.04)
B22	no	439446 (100%)	1 (reference)	1 (reference)	1 (reference)
	yes	139 (0%)	0.48 (0.2-1.17)	0.55 (0.23-1.36)	0.57 (0.23-1.4)
B23+	no	439561 (100%)	1 (reference)	1 (reference)	1 (reference)
	yes	28 (0%)	0.48 (0.06-3.5)	0.62 (0.08-4.61)	0.64 (0.09-4.78)
B31	no	438602 (99.8%)	1 (reference)	1 (reference)	1 (reference)
	yes	988 (0.2%)	0.42 (0.29-0.6)	0.43 (0.3-0.62)	0.45 (0.31-0.65)
B32	no	439458 (100%)	1 (reference)	1 (reference)	1 (reference)
	yes	130 (0%)	0.21 (0.05-0.83)	0.22 (0.05-0.89)	0.22 (0.06-0.9)
B33+	no	439573 (100%)	1 (reference)	1 (reference)	1 (reference)
	yes	17 (0%)	0 (0-1000+)	0 (0-1000+)	0 (0-1000+)
C11	no	438107 (99.7%)	1 (reference)	1 (reference)	1 (reference)
	yes	1483 (0.3%)	0.67 (0.53-0.85)	0.72 (0.56-0.91)	0.73 (0.57-0.93)
C12	no	439244 (99.9%)	1 (reference)	1 (reference)	1 (reference)
	yes	346 (0.1%)	0.78 (0.49-1.23)	0.87 (0.54-1.38)	0.89 (0.56-1.42)
C13+	no	439545 (100%)	1 (reference)	1 (reference)	1 (reference)
	yes	42 (0%)	0.95 (0.3-3.07)	1.36 (0.41-4.46)	1.39 (0.42-4.57)
C21	no	435044 (99%)	1 (reference)	1 (reference)	1 (reference)
	yes	4546 (1%)	0.92 (0.82-1.03)	0.99 (0.88-1.11)	1.02 (0.9-1.15)
C22	no	438038 (99.6%)	1 (reference)	1 (reference)	1 (reference)
	yes	1552 (0.4%)	0.82 (0.66-1.02)	0.89 (0.72-1.1)	0.92 (0.74-1.14)
C23+	no	439315 (99.9%)	1 (reference)	1 (reference)	1 (reference)
	yes	267 (0.1%)	0.4 (0.2-0.81)	0.47 (0.23-0.96)	0.49 (0.24-1)
C31	no	435785 (99.1%)	1 (reference)	1 (reference)	1 (reference)
	yes	3805 (0.9%)	0.58 (0.49-0.68)	0.59 (0.5-0.69)	0.61 (0.52-0.71)
C32	no	438549 (99.8%)	1 (reference)	1 (reference)	1 (reference)
	yes	1041 (0.2%)	0.56 (0.41-0.76)	0.58 (0.42-0.79)	0.6 (0.44-0.82)
C33+	no	439450 (100%)	1 (reference)	1 (reference)	1 (reference)
	yes	135 (0%)	0.49 (0.2-1.21)	0.57 (0.23-1.41)	0.59 (0.24-1.45)
Socio-economic status indicators					
URBAN	no	150615 (34.3%)	1 (reference)	1 (reference)	1 (reference)
	yes	288975 (65.7%)	0.8 (0.78-0.81)	0.89 (0.86-0.91)	0.89 (0.87-0.91)
SHH	no	376459 (85.6%)	1 (reference)	1 (reference)	1 (reference)
	yes	63131 (14.4%)	1.18 (1.15-1.22)	1.28 (1.24-1.32)	1.28 (1.23-1.32)
SLHH	no	418256 (95.1%)	1 (reference)	1 (reference)	1 (reference)
	yes	21334 (4.9%)	1.57 (1.5-1.64)	1.7 (1.63-1.79)	1.7 (1.62-1.78)
SLHHK	no	403935 (91.9%)	1 (reference)	1 (reference)	1 (reference)
	yes	35655 (8.1%)	1.64 (1.58-1.7)	1.69 (1.63-1.76)	1.69 (1.62-1.75)

Table 15.W. Sensitivity analysis 1, low birthweight threshold 2,500 g

Variable	Value	N (%)	OR (95% CI)		
			crude	adjusted (1)	adjusted (2)
Butoconazole and clotrimazole exposure variables					
B11+	no	438996 (99.9%)	1 (reference)	1 (reference)	1 (reference)
	yes	594 (0.1%)	1.2 (0.9-1.61)	1.2 (0.9-1.61)	1.28 (0.95-1.71)
C11+	no	437716 (99.6%)	1 (reference)	1 (reference)	1 (reference)
	yes	1874 (0.4%)	0.7 (0.56-0.86)	0.7 (0.56-0.86)	0.72 (0.58-0.88)
Socio-economic status indicators					
URBAN	no	150615 (34.3%)	1 (reference)	1 (reference)	1 (reference)
	yes	288975 (65.7%)	0.8 (0.78-0.81)	0.89 (0.86-0.91)	0.89 (0.87-0.91)
SHH	no	376459 (85.6%)	1 (reference)	1 (reference)	1 (reference)
	yes	63131 (14.4%)	1.18 (1.15-1.22)	1.28 (1.24-1.32)	1.28 (1.24-1.32)
SLHH	no	418256 (95.1%)	1 (reference)	1 (reference)	1 (reference)
	yes	21334 (4.9%)	1.57 (1.5-1.64)	1.7 (1.63-1.79)	1.7 (1.63-1.79)
SLHHK	no	403935 (91.9%)	1 (reference)	1 (reference)	1 (reference)
	yes	35655 (8.1%)	1.64 (1.58-1.7)	1.69 (1.63-1.76)	1.69 (1.63-1.76)

Table 15.X. Sensitivity analysis 2, low birthweight threshold 2,500 g

Variable	Value	N (%)	OR (95% CI)*		
			crude	adjusted (1)	adjusted (2)
Butoconazole and clotrimazole exposure variables					
B11	no	439031 (99.9%)	1 (reference)	1 (reference)	1 (reference)
	yes	559 (0.1%)	1.2 (0.88-1.62)	1.2 (0.88-1.62)	1.27 (0.94-1.72)
B12	no	439558 (100%)	1 (reference)	1 (reference)	1 (reference)
	yes	29 (0%)	1.38 (0.42-4.53)	1.39 (0.42-4.58)	1.48 (0.45-4.85)
B13+	no	439587 (100%)	1 (reference)	1 (reference)	1 (reference)
	yes	0 (0%)	0 (0-1000+)	0 (0-1000+)	0 (0-1000+)
C11	no	438107 (99.7%)	1 (reference)	1 (reference)	1 (reference)
	yes	1483 (0.3%)	0.67 (0.53-0.85)	0.67 (0.53-0.85)	0.69 (0.54-0.87)
C12	no	439244 (99.9%)	1 (reference)	1 (reference)	1 (reference)
	yes	346 (0.1%)	0.78 (0.49-1.23)	0.77 (0.49-1.23)	0.81 (0.51-1.28)
C13+	no	439545 (100%)	1 (reference)	1 (reference)	1 (reference)
	yes	42 (0%)	0.95 (0.3-3.07)	0.95 (0.3-3.07)	1.01 (0.31-3.26)
Socio-economic status indicators					
URBAN	no	150615 (34.3%)	1 (reference)	1 (reference)	1 (reference)
	yes	288975 (65.7%)	0.8 (0.78-0.81)	0.89 (0.86-0.91)	0.89 (0.87-0.91)
SHH	no	376459 (85.6%)	1 (reference)	1 (reference)	1 (reference)
	yes	63131 (14.4%)	1.18 (1.15-1.22)	1.28 (1.24-1.32)	1.28 (1.24-1.32)
SLHH	no	418256 (95.1%)	1 (reference)	1 (reference)	1 (reference)
	yes	21334 (4.9%)	1.57 (1.5-1.64)	1.7 (1.63-1.79)	1.7 (1.63-1.79)
SLHHK	no	403935 (91.9%)	1 (reference)	1 (reference)	1 (reference)
	yes	35655 (8.1%)	1.64 (1.58-1.7)	1.69 (1.63-1.76)	1.69 (1.63-1.76)

Table 15.Y. Sensitivity analysis 3, low birthweight threshold 2,500 g

Variable	Value	N (%)	OR (95% CI)*		
			crude	adjusted (1)	adjusted (2)
Butoconazole and clotrimazole exposure variables					
BD1	no	437314 (99.5%)	1 (reference)	1 (reference)	1 (reference)
	yes	2276 (0.5%)	0.74 (0.62-0.89)	0.74 (0.61-0.89)	0.78 (0.65-0.94)
BD2	no	439177 (99.9%)	1 (reference)	1 (reference)	1 (reference)
	yes	413 (0.1%)	0.61 (0.38-0.97)	0.6 (0.38-0.97)	0.63 (0.39-1.02)
BD3+	no	439469 (100%)	1 (reference)	1 (reference)	1 (reference)
	yes	120 (0%)	0.11 (0.02-0.79)	0.11 (0.02-0.78)	0.11 (0.02-0.79)
CD1	no	431831 (98.2%)	1 (reference)	1 (reference)	1 (reference)
	yes	7759 (1.8%)	0.8 (0.73-0.88)	0.8 (0.73-0.88)	0.82 (0.75-0.91)
CD2	no	436630 (99.3%)	1 (reference)	1 (reference)	1 (reference)
	yes	2960 (0.7%)	0.73 (0.62-0.86)	0.73 (0.62-0.85)	0.76 (0.64-0.89)
CD3+	no	438655 (99.8%)	1 (reference)	1 (reference)	1 (reference)
	yes	935 (0.2%)	0.52 (0.37-0.73)	0.51 (0.37-0.72)	0.55 (0.39-0.77)
Socio-economic status indicators					
URBAN	no	150615 (34.3%)	1 (reference)	1 (reference)	1 (reference)
	yes	288975 (65.7%)	0.8 (0.78-0.81)	0.89 (0.86-0.91)	0.89 (0.87-0.91)
SHH	no	376459 (85.6%)	1 (reference)	1 (reference)	1 (reference)
	yes	63131 (14.4%)	1.18 (1.15-1.22)	1.28 (1.24-1.32)	1.28 (1.23-1.32)
SLHH	no	418256 (95.1%)	1 (reference)	1 (reference)	1 (reference)
	yes	21334 (4.9%)	1.57 (1.5-1.64)	1.7 (1.63-1.79)	1.7 (1.62-1.78)
SLHHK	no	403935 (91.9%)	1 (reference)	1 (reference)	1 (reference)
	yes	35655 (8.1%)	1.64 (1.58-1.7)	1.69 (1.63-1.76)	1.69 (1.62-1.75)

Table 15.Z. Sensitivity analysis 4, low birthweight threshold 2,000 g

Variable	Value	N (%)	OR (95% CI)*		
			crude	adjusted (1)	adjusted (2)
Butoconazole and clotrimazole exposure variables					
B11	no	439 031 (99.87%)	1 (reference)	1 (reference)	1 (reference)
	yes	559 (0.13%)	1.18 (0.73-1.92)	1.25 (0.77-2.03)	1.32 (0.81-2.14)
B12	no	439 558 (99.99%)	1 (reference)	1	1
	yes	32 (0.01%)	2.51 (0.6-10.52)	2.59 (0.62-10.85)	2.74 (0.65-11.48)
B13	no	439 587 (100%)	1 (reference)	1 (reference)	1 (reference)
	yes	0 (0%)	0 (0-1000+)	0 (0-1000+)	0 (0-1000+)
B21	no	438 388 (99.73%)	1 (reference)	1 (reference)	1 (reference)
	yes	1 202 (0.27%)	0.74 (0.49-1.11)	0.81 (0.53-1.22)	0.84 (0.55-1.27)
B22	no	439 446 (99.97%)	1 (reference)	1 (reference)	1 (reference)
	yes	144 (0.03%)	0.8 (0.26-2.52)	0.96 (0.3-3.01)	0.99 (0.31-3.11)
B23	no	439 561 (99.99%)	1 (reference)	1 (reference)	1 (reference)
	yes	29 (0.01%)	1.35 (0.18-9.9)	1.85 (0.25-13.82)	1.94 (0.26-14.45)
B31	no	438 602 (99.78%)	1 (reference)	1 (reference)	1 (reference)
	yes	988 (0.22%)	0.31 (0.15-0.62)	0.31 (0.15-0.62)	0.32 (0.16-0.65)
B32	no	439 458 (99.97%)	1 (reference)	1 (reference)	1 (reference)
	yes	132 (0.03%)	0 (0-1000+)	0 (0-1000+)	0 (0-1000+)
B33	no	439 573 (100%)	1 (reference)	1 (reference)	1 (reference)
	yes	17 (0%)	0 (0-1000+)	0 (0-1000+)	0 (0-1000+)
C11	no	438 107 (99.66%)	1 (reference)	1 (reference)	1 (reference)
	yes	1 483 (0.34%)	0.7 (0.48-1.02)	0.75 (0.51-1.1)	0.76 (0.52-1.12)
C12	no	439 244 (99.92%)	1 (reference)	1 (reference)	1 (reference)
	yes	346 (0.08%)	0.89 (0.44-1.8)	0.95 (0.47-1.92)	0.97 (0.48-1.97)
C13	no	439 545 (99.99%)	1 (reference)	1 (reference)	1 (reference)
	yes	45 (0.01%)	0 (0-1000+)	0 (0-1000+)	0 (0-1000+)
C21	no	435 044 (98.97%)	1 (reference)	1 (reference)	1 (reference)
	yes	4 546 (1.03%)	0.92 (0.76-1.11)	1 (0.82-1.21)	1.03 (0.85-1.25)
C22	no	438 038 (99.65%)	1 (reference)	1 (reference)	1 (reference)
	yes	1 552 (0.35%)	0.77 (0.54-1.1)	0.83 (0.58-1.19)	0.86 (0.6-1.23)
C23	no	439 315 (99.94%)	1 (reference)	1 (reference)	1 (reference)
	yes	275 (0.06%)	0.84 (0.37-1.89)	1.07 (0.47-2.43)	1.12 (0.49-2.54)
C31	no	435 785 (99.13%)	1 (reference)	1 (reference)	1 (reference)
	yes	3 805 (0.87%)	0.42 (0.31-0.57)	0.42 (0.31-0.58)	0.44 (0.32-0.6)
C32	no	438 549 (99.76%)	1 (reference)	1 (reference)	1 (reference)
	yes	1 041 (0.24%)	0.66 (0.42-1.06)	0.68 (0.42-1.08)	0.7 (0.44-1.12)
C33	no	439 450 (99.97%)	1 (reference)	1 (reference)	1 (reference)
	yes	140 (0.03%)	0.55 (0.14-2.21)	0.59 (0.14-2.41)	0.6 (0.15-2.47)
Socio-economic status indicators					
URBAN	no	150 615 (34.26%)	1 (reference)	1 (reference)	1 (reference)
	yes	288 975 (65.74%)	0.82 (0.79-0.85)	0.91 (0.88-0.95)	0.91 (0.88-0.95)
SHH	no	376 459 (85.64%)	1 (reference)	1 (reference)	1 (reference)
	yes	63 131 (14.36%)	1.17 (1.12-1.23)	1.27 (1.21-1.34)	1.27 (1.2-1.34)
SLHH	no	418 256 (95.15%)	1 (reference)	1 (reference)	1 (reference)
	yes	21 334 (4.85%)	1.63 (1.52-1.75)	1.77 (1.65-1.9)	1.77 (1.64-1.9)
SLHHK	no	403 935 (91.89%)	1 (reference)	1 (reference)	1 (reference)
	yes	35 655 (8.11%)	1.55 (1.47-1.65)	1.63 (1.53-1.73)	1.62 (1.53-1.72)

Table 15.AA. Sensitivity analysis 5, low birthweight threshold 2,000 g

Variable	Value	N (%)	OR (95% CI)*		
			crude	adjusted (1)	adjusted (2)
Butoconazole and clotrimazole exposure variables					
B1p	no	438 996 (99.86%)	1 (reference)	1 (reference)	1 (reference)
	yes	594 (0.14%)	1.25 (0.79-1.97)	1.25 (0.79-1.97)	1.32 (0.84-2.09)
C1p	no	437 716 (99.57%)	1 (reference)	1 (reference)	1 (reference)
	yes	1 874 (0.43%)	0.72 (0.51-1)	0.72 (0.51-1)	0.74 (0.53-1.03)
Socio-economic status indicators					
URBAN	no	150 615 (34.26%)	1 (reference)	1 (reference)	1 (reference)
	yes	288 975 (65.74%)	0.82 (0.79-0.85)	0.91 (0.88-0.95)	0.91 (0.88-0.95)
SHH	no	376 459 (85.64%)	1 (reference)	1 (reference)	1 (reference)
	yes	63 131 (14.36%)	1.17 (1.12-1.23)	1.27 (1.21-1.34)	1.27 (1.21-1.34)
SLHH	no	418 256 (95.15%)	1 (reference)	1 (reference)	1 (reference)
	yes	21 334 (4.85%)	1.63 (1.52-1.75)	1.77 (1.65-1.9)	1.77 (1.65-1.9)
SLHHK	no	403 935 (91.89%)	1 (reference)	1 (reference)	1 (reference)
	yes	35 655 (8.11%)	1.55 (1.47-1.65)	1.63 (1.53-1.73)	1.63 (1.53-1.73)

Table 15.BB. Sensitivity analysis 6, low birthweight threshold 2,000 g

Variable	Value	N (%)	OR (95% CI)*		
			crude	adjusted (1)	adjusted (2)
Butoconazole and clotrimazole exposure variables					
B11	no	439 031 (99.87%)	1 (reference)	1 (reference)	1 (reference)
	yes	559 (0.13%)	1.18 (0.73-1.92)	1.18 (0.73-1.92)	1.25 (0.77-2.03)
B12	no	439 558 (99.99%)	1 (reference)	1 (reference)	1 (reference)
	yes	32 (0.01%)	2.51 (0.6-10.52)	2.54 (0.61-10.62)	2.69 (0.64-11.26)
B13	no	439 587 (100%)	1 (reference)	1 (reference)	1 (reference)
	yes	0 (0%)	0 (0-1000+)	0 (0-1000+)	0 (0-1000+)
C11	no	438 107 (99.66%)	1 (reference)	1 (reference)	1 (reference)
	yes	1 483 (0.34%)	0.7 (0.48-1.02)	0.7 (0.48-1.02)	0.72 (0.49-1.05)
C12	no	439 244 (99.92%)	1 (reference)	1 (reference)	1 (reference)
	yes	346 (0.08%)	0.89 (0.44-1.8)	0.89 (0.44-1.8)	0.93 (0.46-1.87)
C13	no	439 545 (99.99%)	1 (reference)	1 (reference)	1 (reference)
	yes	45 (0.01%)	0 (0-1000+)	0 (0-1000+)	0 (0-1000+)
Socio-economic status indicators					
URBAN	no	150 615 (34.26%)	1 (reference)	1 (reference)	1 (reference)
	yes	288 975 (65.74%)	0.82 (0.79-0.85)	0.91 (0.88-0.95)	0.91 (0.88-0.95)
SHH	no	376 459 (85.64%)	1 (reference)	1 (reference)	1 (reference)
	yes	63 131 (14.36%)	1.17 (1.12-1.23)	1.27 (1.21-1.34)	1.27 (1.21-1.34)
SLHH	no	418 256 (95.15%)	1 (reference)	1 (reference)	1 (reference)
	yes	21 334 (4.85%)	1.63 (1.52-1.75)	1.77 (1.65-1.9)	1.77 (1.65-1.9)
SLHHK	no	403 935 (91.89%)	1 (reference)	1 (reference)	1 (reference)
	yes	35 655 (8.11%)	1.55 (1.47-1.65)	1.63 (1.53-1.73)	1.63 (1.53-1.73)

Table 15.CC. Sensitivity analysis 7, low birthweight threshold 2,000 g

Variable	Value	N (%)	OR (95% CI)*		
			crude	adjusted (1)	adjusted (2)
Butoconazole and clotrimazole exposure variables					

BD1	no	437 314 (99.5%)	1 (reference)	1 (reference)	1 (reference)
	yes	2 276 (0.5%)	0.73 (0.54-0.98)	0.72 (0.53-0.98)	0.76 (0.56-1.03)
BD2	no	439 177 (99.91%)	1 (reference)	1 (reference)	1 (reference)
	yes	413 (0.09%)	0.65 (0.31-1.37)	0.65 (0.31-1.36)	0.67 (0.32-1.42)
BD3	no	439 469 (99.97%)	1 (reference)	1 (reference)	1 (reference)
	yes	121 (0.03%)	0.31 (0.04-2.22)	0.31 (0.04-2.2)	0.32 (0.04-2.23)
CD1	no	431 831 (98.2%)	1 (reference)	1 (reference)	1 (reference)
	yes	7 759 (1.8%)	0.73 (0.62-0.86)	0.73 (0.62-0.86)	0.75 (0.63-0.88)
CD2	no	436 630 (99.3%)	1 (reference)	1 (reference)	1 (reference)
	yes	2 960 (0.7%)	0.67 (0.51-0.89)	0.67 (0.51-0.88)	0.7 (0.53-0.92)
CD3	no	438 655 (99.8%)	1 (reference)	1 (reference)	1 (reference)
	yes	935 (0.2%)	0.74 (0.46-1.18)	0.73 (0.46-1.17)	0.78 (0.49-1.24)
Socio-economic status indicators					
URBAN	no	150 615 (34.3%)	1 (reference)	1 (reference)	1 (reference)
	yes	288 975 (65.7%)	0.82 (0.79-0.85)	0.91 (0.88-0.95)	0.91 (0.88-0.95)
SHH	no	376 459 (85.6%)	1 (reference)	1 (reference)	1 (reference)
	yes	63 131 (14.4%)	1.17 (1.12-1.23)	1.27 (1.21-1.34)	1.27 (1.2-1.34)
SLHH	no	418 256 (95.1%)	1 (reference)	1 (reference)	1 (reference)
	yes	21 334 (4.9%)	1.63 (1.52-1.75)	1.77 (1.65-1.9)	1.77 (1.64-1.9)
SLHHK	no	403 935 (91.9%)	1 (reference)	1 (reference)	1 (reference)
	yes	35 655 (8.1%)	1.55 (1.47-1.65)	1.63 (1.53-1.73)	1.62 (1.53-1.72)

Table 15.DD. Sensitivity analysis 8, linear regression models on birthweight (in grams)

Var.	Value	N (%)	Coefficient (95% CI)*		
			crude	adjusted (1)	adjusted (2)
Butoconazole and clotrimazole exposure variables					
B11	no	439 379 (99.87%)	0 (reference)	0 (reference)	0 (reference)
	yes	562 (0.13%)	-19.99 (-67.55-27.58)	-28.82 (-76.53-18.89)	-40.23 (-87.77-7.31)
B12	no	439 909 (99.99%)	0 (reference)	0 (reference)	0 (reference)
	yes	32 (0.01%)	-70.03 (-269.24-129.18)	-76.18 (-275.38-123.03)	-85.17 (-283.66-113.33)
B13	no	439 938 (100%)	0 (reference)	0 (reference)	0 (reference)
	yes	0 (0%)	202.48 (-448.11-853.07)	173.13 (-477.47-823.74)	152.51 (-495.77-800.79)
B21	no	438 737 (99.73%)	0 (reference)	0 (reference)	0 (reference)
	yes	1 204 (0.27%)	39.21 (6.69-71.73)	28.26 (-4.65-61.16)	19.52 (-13.27-52.31)
B22	no	439 797 (99.97%)	0 (reference)	0 (reference)	0 (reference)
	yes	144 (0.03%)	106.26 (12.34-200.18)	85.27 (-9.14-179.67)	80.16 (-13.91-174.23)
B23	no	439 912 (99.99%)	0 (reference)	0 (reference)	0 (reference)
	yes	29 (0.01%)	5.93 (-203.33-215.18)	-27.59 (-239.02-183.84)	-33.9 (-244.58-176.77)
B31	no	438 953 (99.78%)	0 (reference)	0 (reference)	0 (reference)
	yes	988 (0.22%)	96.22 (60.33-132.1)	92.28 (56.03-128.53)	82.09 (45.97-118.21)
B32	no	439 809 (99.97%)	0 (reference)	0 (reference)	0 (reference)
	yes	132 (0.03%)	136.53 (38.44-234.63)	127.35 (28.75-225.95)	126.17 (27.92-224.42)
B33	no	439 924 (100%)	0 (reference)	0 (reference)	0 (reference)
	yes	17 (0%)	134.83 (-138.47-408.14)	127.79 (-148.32-403.9)	125.39 (-149.73-400.52)
C11	no	438 456 (99.66%)	0 (reference)	0 (reference)	0 (reference)
	yes	1 485 (0.34%)	47.78 (18.49-77.07)	36.42 (6.96-65.87)	32.64 (3.29-61.99)
C12	no	439 595 (99.92%)	0 (reference)	0 (reference)	0 (reference)
	yes	346 (0.08%)	33.83 (-26.77-94.44)	16.51 (-44.56-77.58)	11.15 (-49.7-72.01)
C13	no	439 896 (99.99%)	0 (reference)	0 (reference)	0 (reference)
	yes	45 (0.01%)	158.05 (-9.94-326.04)	112.33 (-58.16-282.82)	106.05 (-63.83-275.93)
C21	no	435 387 (98.96%)	0 (reference)	0 (reference)	0 (reference)
	yes	4 554 (1.04%)	15.66 (-1.13-32.44)	4.71 (-12.27-21.69)	-2.26 (-19.19-14.66)
C22	no	438 387 (99.65%)	0 (reference)	0 (reference)	0 (reference)
	yes	1 554 (0.35%)	42.16 (13.53-70.8)	28.31 (-0.54-57.16)	21.22 (-7.52-49.97)

C23	no	439 666 (99.94%)	0 (reference)	0 (reference)	0 (reference)
	yes	275 (0.06%)	74.91 (6.93-142.88)	30.24 (-39.82-100.3)	20.75 (-49.06-90.56)
C31	no	436 135 (99.13%)	0 (reference)	0 (reference)	0 (reference)
	yes	3 806 (0.87%)	65.59 (47.25-83.94)	62.84 (44.3-81.38)	55.39 (36.91-73.87)
C32	no	438 900 (99.76%)	0 (reference)	0 (reference)	0 (reference)
	yes	1 041 (0.24%)	85.3 (50.34-120.27)	79.93 (44.71-115.14)	72.91 (37.82-108)
C33	no	439 801 (99.97%)	0 (reference)	0 (reference)	0 (reference)
	yes	140 (0.03%)	188.89 (93.64-284.14)	169.79 (73.17-266.4)	163.11 (66.84-259.38)
Socio-economic status indicators					
URBAN	no	150 713 (34.26%)	0 (reference)	0 (reference)	0 (reference)
	yes	289 228 (65.74%)	49.8 (46.22-53.37)	25.41 (21.69-29.13)	25.16 (21.44-28.88)
SHH	no	376 812 (85.65%)	0 (reference)	0 (reference)	0 (reference)
	yes	63 129 (14.35%)	-33.46 (-38.3--28.61)	-47.92 (-52.9--42.95)	-47.72 (-52.7--42.74)
SLHH	no	418 591 (95.15%)	0 (reference)	0 (reference)	0 (reference)
	yes	21 350 (4.85%)	-93.98 (-101.88--86.07)	-110.71 (-118.67--102.75)	-110.35 (-118.32--102.39)
SLHHK	no	404 267 (91.89%)	1	1	1
	yes	35 674 (8.11%)	-136.04 (-142.25--129.83)	-140.05 (-146.5--133.59)	-139.55 (-146.01--133.1)

Table 15.EE. Sensitivity analysis 9, linear regression models on birthweight (in grams)

Var.	**Value**	**N (%)**	**Coefficient (95% CI)***		
			crude	**adjusted (1)**	**adjusted (2)**
Butoconazole and clotrimazole exposure variables					
B1p	no	439 344 (99.86%)	0 (reference)	0 (reference)	0 (reference)
	yes	597 (0.14%)	-21.56 (-67.71-24.59)	-21.51 (-67.66-24.64)	-34.14 (-80.13-11.84)
C1p	no	438 065 (99.57%)	0 (reference)	0 (reference)	0 (reference)
	yes	1 876 (0.43%)	47.92 (21.85-73.99)	47.91 (21.84-73.99)	41.33 (15.35-67.31)
Socio-economic status indicators					
URBAN	no	150 713 (34.26%)	0 (reference)	0 (reference)	0 (reference)
	yes	289 228 (65.74%)	49.8 (46.22-53.37)	25.41 (21.69-29.13)	25.38 (21.66-29.1)
SHH	no	376 812 (85.65%)	0 (reference)	0 (reference)	0 (reference)
	yes	63 129 (14.35%)	-33.46 (-38.3--28.61)	-47.92 (-52.9--42.95)	-47.88 (-52.86--42.9)
SLHH	no	418 591 (95.15%)	0 (reference)	0 (reference)	0 (reference)
	yes	21 350 (4.85%)	-93.98 (-101.88--86.07)	-110.71 (-118.67--102.75)	-110.72 (-118.68--102.75)
SLHHK	no	404 267 (91.89%)	0 (reference)	0 (reference)	0 (reference)
	yes	35 674 (8.11%)	-136.04 (-142.25--129.83)	-140.05 (-146.5--133.59)	-140.03 (-146.49--133.58)

Table 15.FF. Sensitivity analysis 10, linear regression models on birthweight (in grams)

Var.	Value	N (%)	Coefficient (95% CI)*		
			crude	adjusted (1)	adjusted (2)
Butoconazole and clotrimazole exposure variables					
B11	no	439 379 (99.87%)	0 (reference)	0 (reference)	0 (reference)
	yes	562 (0.13%)	-19.99 (-67.55-27.58)	-19.87 (-67.43-27.69)	-32.62 (-80.02-14.77)
B12	no	439 909 (99.99%)	0 (reference)	0 (reference)	0 (reference)
	yes	32 (0.01%)	-70.03 (-269.24-129.18)	-71.34 (-270.55-127.86)	-80.83 (-279.31-117.66)
B13	no	439 938 (100%)	0 (reference)	0 (reference)	0 (reference)
	yes	0 (0%)	202.48 (-448.11-853.07)	202.65 (-447.93-853.23)	178.77 (-469.46-827.01)
C11	no	438 456 (99.66%)	0 (reference)	0 (reference)	0 (reference)
	yes	1 485 (0.34%)	47.78 (18.49-77.07)	47.85 (18.56-77.14)	41.83 (12.65-71.02)
C12	no	439 595 (99.92%)	0 (reference)	0 (reference)	0 (reference)
	yes	346 (0.08%)	33.83 (-26.77-94.44)	33.98 (-26.62-94.58)	25.75 (-34.64-86.13)
C13	no	439 896 (99.99%)	0 (reference)	0 (reference)	0 (reference)
	yes	45 (0.01%)	158.05 (-9.94-326.04)	158.21 (-9.78-326.19)	145.66 (-21.72-313.04)
Socio-economic status indicators					
URBAN	no	150 713 (34.26%)	0 (reference)	0 (reference)	0 (reference)
	yes	289 228 (65.74%)	49.8 (46.22-53.37)	25.41 (21.69-29.13)	25.38 (21.66-29.1)
SHH	no	376 812 (85.65%)	0 (reference)	0 (reference)	0 (reference)
	yes	63 129 (14.35%)	-33.46 (-38.3--28.61)	-47.92 (-52.9--42.95)	-47.88 (-52.86--42.91)
SLHH	no	418 591 (95.15%)	0 (reference)	0 (reference)	0 (reference)
	yes	21 350 (4.85%)	-93.98 (-101.88--86.07)	-110.71 (-118.67--102.75)	-110.71 (-118.68--102.75)
SLHHK	no	404 267 (91.89%)	0 (reference)	0 (reference)	0 (reference)
	yes	35 674 (8.11%)	-136.04 (-142.25--129.83)	-140.05 (-146.5--133.59)	-140.03 (-146.48--133.57)

Table 15.GG. Sensitivity analysis 11, linear regression models on birthweight (in grams)

Variable	Value	N (%)	Coefficient (95% CI)*		
			Crude	adjusted (1)	adjusted (2)
Butoconazole and clotrimazole exposure variables					
BD1	no	437 664 (99.48%)	0 (reference)	0 (reference)	0 (reference)
	yes	2 277 (0.52%)	48.09 (24.42-71.77)	48.98 (25.31-72.66)	37.16 (13.56-60.75)
BD2	no	439 526 (99.91%)	0 (reference)	0 (reference)	0 (reference)
	yes	415 (0.09%)	68.93 (13.59-124.27)	70.06 (14.73-125.4)	59.86 (4.72-115)
BD3	no	439 820 (99.97%)	0 (reference)	0 (reference)	0 (reference)
	yes	121 (0.03%)	88.86 (-13.59-191.32)	90.25 (-12.19-192.7)	86.61 (-15.47-188.69)
CD1	no	432 171 (98.23%)	0 (reference)	0 (reference)	0 (reference)
	yes	7 770 (1.77%)	28.41 (15.52-41.31)	29.23 (16.33-42.13)	22.62 (9.77-35.48)
CD2	no	436 979 (99.33%)	0 (reference)	0 (reference)	0 (reference)
	yes	2 962 (0.67%)	46.02 (25.25-66.8)	47.06 (26.29-67.84)	38.42 (17.72-59.12)
CD3	no	439 006 (99.79%)	0 (reference)	0 (reference)	0 (reference)
	yes	935 (0.21%)	110.05 (73.16-146.94)	111.18 (74.29-148.07)	97.75 (60.99-134.51)
Socio-economic status indicators					
URB	no	150 713 (34.26%)	0 (reference)	0 (reference)	0 (reference)
	yes	289 228 (65.74%)	49.8 (46.22-53.37)	25.41 (21.69-29.13)	25.18 (21.46-28.9)
SHH	no	376 812 (85.65%)	0 (reference)	0 (reference)	0 (reference)
	yes	63 129 (14.35%)	-33.46 (-38.3--28.61)	-47.92 (-52.9--42.95)	-47.67 (-52.65--42.69)
SLHH	no	418 591 (95.15%)	0 (reference)	0 (reference)	0 (reference)
	yes	21 350 (4.85%)	-93.98 (-101.88--86.07)	-110.71 (-118.67--102.75)	-110.39 (-118.35--102.43)
SLHHK	no	404 267 (91.89%)	0 (reference)	0 (reference)	0 (reference)
	yes	35 674 (8.11%)	-136.04 (-142.25--129.83)	-140.05 (-146.5--133.59)	-139.52 (-145.97--133.06)