VALIDITY OF PERINATAL PHARMACOEPIDEMIOLOGIC STUDIES USING DATA FROM THE RAMQ ADMINISTRATIVE DATABASE

Anick Bérard[1,2], Anaïs Lacasse[1,2]

[1]Faculty of Pharmacy, University of Montreal, Montreal, Canada, [2]Research Center, CHU Sainte-Justine, Montreal, Canada

Corresponding Author: anick.berard@umontreal.ca

ABSTRACT

Background
The RAMQ prescription claims database (RAMQ-Rx) is increasingly being used in perinatal pharmacoepidemiologic studies; but, there are reasons to believe that results generated with the RAMQ-Rx might not be generalizable to all patient populations.

Objectives
Compare characteristics between pregnant women insured by the RAMQ-Rx and those insured by a private drug insurance plan.

Methods
A prospective study performed within the population of pregnant women receiving prenatal care at different obstetrics and gynecology clinics affiliated to the University of Montreal, Canada, was conducted from October 2004 to March 2006. Women were eligible if they were ≥18 years of age, ≤16 weeks of gestation at the time of their first prenatal visit, and able to read and understand French or English. Eligible women were asked to fill out a self-administered questionnaire.

Results
Three hundred and sixty-three women met inclusion criteria, of which 99 (27%) had RAMQ-Rx coverage, and 264 (73%) had a private drug insurance coverage. Compared to those who were covered by private drug insurance plans, those insured by the RAMQ-Rx were younger (30.7yrs vs. 32.1yrs; P=0.03), more likely to be immigrant (60% vs. 24%; P<0.01), and have a household income below poverty level (39% vs. 2%; P<0.01). They were also less likely to be Caucasian (69% vs. 86%; P<0.01), employed (51% vs. 87%; P<.01), and have a post-secondary education (76% vs. 95%; P<0.01). No differences were observed on smoking status and alcohol use during pregnancy.

Conclusions
There are substantial differences between pregnant women insured by the RAMQ-Rx and those insured by private drug insurance plans. However, these differences will most likely limit generalizability, but not internal validity, of studies using data from the RAMQ-Rx database.

Key words: *Database, drug insurance, pharmacoepidemiology, pregnancy, Régie de l'assurance maladie du Québec, validity*

Administrative databases are increasingly being used for epidemiologic, and more specifically pharmacoepidemiologic research.[1-12] In fact, these sources of data offer many advantages such as very large sample sizes, well defined study frames for drug utilization studies, lack of recall bias, and the possibility to analyse numerous exposures and outcomes at the same time. Moreover, studies using administrative databases are conducted more rapidly and are less

expensive than field studies. Despite the possible lack or incompleteness of data on potential socioeconomic risk factors, lifestyle, or clinical variables, pharmacoepidemiologic studies using administrative databases are important and yield valuable information, especially for pregnant women who are excluded from most drug trials. Indeed, because the Food and Drug Administration and Health Canada do not permit the inclusion of pregnant women in clinical trials, data on the safety of drug exposure during pregnancy before the medication is on the market are scarce. Since it is almost impossible from an ethical point of view to randomize healthy pregnant women to receive medications not known to be safe for the foetus, the collection and follow-up of observational data is the only ethical way to close the knowledge gap between the limited value of animal studies and human pregnancy exposure to medications.

Although several observational human studies on the risks and benefits of medication use during pregnancy have been published, their sample sizes are often insufficient to rule out low-to-moderate increased risks for even the more commonly occurring adverse perinatal outcomes such as heart defects, neural tube defects, and oral clefts.

To circumvent this limitation, large administrative databases, such as the Régie de l'Assurance Maladie du Québec (RAMQ), have been increasingly used in recent years for perinatal pharmacoepidemiologic studies. The RAMQ database contains information on medical services (diagnoses and procedures) received by all Quebec residents. Although RAMQ covers all residents for the cost of physician visits, hospitalisations, and procedures, it only covers a portion of them for the cost of medications.

The RAMQ prescription claims database (RAMQ-Rx) covers individuals 65 years and older, recipients of social assistance (welfare recipients), and workers and their families (adherents) who do not have access to a private drug insurance program, accounting for approximately 43% of the overall Quebec population[13] and 36% of women between 15-45 years of age.[13,14] The RAMQ-Rx over-represents individuals of lower socioeconomic status (SES), and as of now, no data exists on SES, lifestyle and comorbidity differences between those insured by the RAMQ-Rx for their medications and those insured by private drug insurance plans. Although several US studies have reported SES, lifestyle or comorbidity differences between privately insured and government insured patients, such as Medicaid beneficiaries,[15-19] these are likely to be different in a context of universal health care such as in Quebec. Furthermore, the particularity of the Quebec health insurance program (all residents are covered for medical care and hospitalisations, and a portion are also covered for medication use) will likely affect the characteristic differences between those insured by the RAMQ-Rx and those insured by private drug insurance plans.

To assess the external validity of pharmacoepidemiologic studies conducted within the population of pregnant women insured by the RAMQ-Rx, we sought to compare SES, lifestyle, comorbidity profile, and pregnancy history between pregnant women insured by the RAMQ-Rx and those insured by a private drug insurance plan. Further comparisons were made between employed women insured by the RAMQ-Rx and employed women who were covered by a private drug insurance plan.

METHODS

Study Design and Population

A prospective study performed within the population of pregnant women receiving prenatal care at the obstetrics and gynecology clinic of the Centre Hospitalier Universitaire Sainte-Justine (CHU Sainte-Justine) or René-Laennec clinic, both affiliated to the University of Montreal, Quebec, Canada, was conducted from October 2004 to March 2006. Women were eligible if they were:

1) at least 18 years of age,
2) at their first prenatal visit,
3) pregnant within 16 weeks of the first day of their last menses,
4) able to read and understand French or English,
5) giving written informed consent.

Ethics approval was obtained from CHU Sainte-Justine's ethics committee.

Data Collection

The present study design and data collection were previously described elsewhere.[20-22] However, for

ease of understanding it is summarized here. At the end of their first prenatal visit, eligible women who accepted to participate were asked to fill out a self-administered questionnaire at home. The women were asked to return the questionnaire within one week of their first prenatal visit to the coordinating office at CHU Ste-Justine in Montreal.

Women's drug insurance plan was self-reported and defined as RAMQ-Rx or private (there is no possible overlapping according to Quebec law). Demographic and socioeconomic data collected in the questionnaire included maternal and gestational age, employment status, living arrangement (living alone or in couple), education level, and household income. Racial/ethnic groups were defined based on country of birth, race/ethnicity of parents, and self-perceived membership in racial/ethnic groups. Immigrant status was defined according to country of birth (Canada or other). Information on lifestyle, comorbidities, pregnancy history, maternal height, and weight were collected. Women were also asked whether they used vitamins, prescribed and over-the-counter medications.

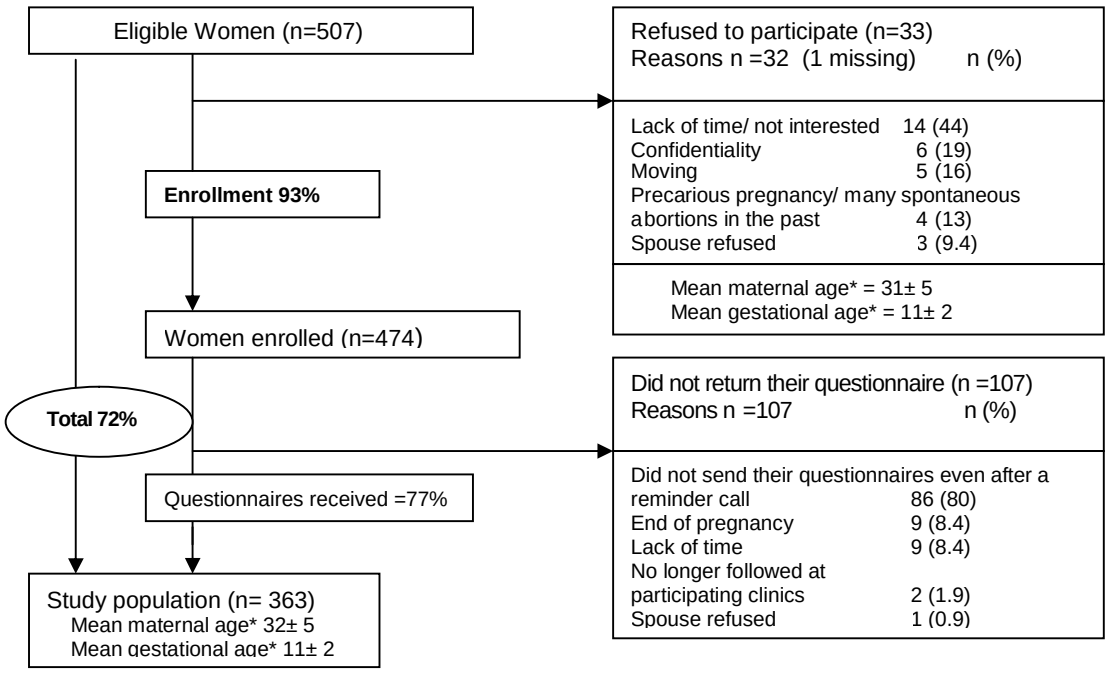
Statistical Analysis

Descriptive statistics were used to estimate the distribution of maternal characteristics in the two drug insurance plan groups. These characteristics were compared using Chi-squares, t-tests, and Fisher's exact tests when appropriate. The same was done to compare employed women insured by the RAMQ-Rx and employed women insured by a private drug insurance plan. All statistical analyses were performed using SAS Version 9.00 (SAS Institute, NC, USA).

RESULTS

A detailed flow-chart of the recruitment and refusals is presented in Figure 1. A total of 507 pregnant women were eligible to participate in the study. Among them, 474 (93%) gave informed consent, and 367 (77%) filled out and returned their questionnaire by mail. Responders were similar to non-responders regarding maternal and gestational age (Figure 1). Our study population consisted of 363 pregnant women recruited between 2004 and 2006 for which information on drug insurance plan was available.

FIG. 1 Study population recruitment and follow-up



*Maternal and gestational age at inclusion

A total of 99 women (27%) had RAMQ-Rx coverage and 264 (73%) a private drug insurance coverage. Maternal characteristics in the two drug insurance plan groups are presented in Table 1. Compared to those who were covered by a private drug insurance plan, those insured by the RAMQ-Rx were younger (30.7 years vs. 32.1 years; p= 0.03), more likely to be immigrant (60% vs. 24%; p<0.01), have a household income that is below poverty level (<20,000 CDN$/yr: 39% vs. 2%; p<0.01), be smokers before pregnancy (20% vs. 11%; p=0.03), be primigravida (woman who is pregnant for the first time; 26% vs. 14%; p<0.01), and be primipara (woman who has given birth once; 38% vs. 19%; p <0.01). They were also less likely to be Caucasian (69% vs. 86%; p<0.01), employed (51% vs. 87%; p<0.01), have a post-secondary education (76% vs. 95%; p<0.01), drink caffeine during pregnancy (47% vs. 62%; p=0.01), and drink alcohol before pregnancy (48% vs. 74%; p<0.01). Among pregnant women insured by the RAMQ-Rx, 50 (51%) were employed. Maternal characteristics of employed women insured by the RAMQ-Rx and women insured by a private drug insurance plan are presented in Table 2. The same differences as presented above were found except for maternal age and caffeine intake before pregnancy, which were no longer statistically different between pregnant workers insured by the RAMQ-Rx and those covered by a private drug insurance plan. Compared to employed women covered by a private drug insurance plan, employed women insured by the RAMQ-Rx were more likely to be immigrant (44% vs. 24%; p<0.01), have a household income that is below poverty level (<20,000 CDN$/yr: 23% vs. 2%; p<0.01), be smokers before pregnancy (30% vs. 11%; p<0.01), be primigravida (60% vs. 14%; p<0.01), and be primipara (50% vs. 19%; p<0.01). They were also less likely to be Caucasian (74% vs. 86%; p=0.03), have a post-secondary education (78% vs. 95%; p<0.01), and drink alcohol before pregnancy (52% vs. 74%; p<0.01).

TABLE 1 Maternal Characteristics in the two drug insurance plan groups.

Characteristics* n=363	**RAMQ-Rx* n= 99**		**Private drug insurance plan†** **n=264**		**p-value‡**
Socioeconomic Status					
Maternal age (yr) -mean (SD)	30.7	5.3	32.1	4.4	0.0252
Immigrant - n (%)	59	60	63	24	<0.0001
Race - n (%)					
Caucasian	68	69	227	86	
Asian	8	8.1	7	2.7	
Black	16	16	20	8	
Hispanic	7	7	10	4	0.0020
Work status - n (%)					
Student or not working	49	50	36	14	
Working	50	51	228	87	<0.0001
Living arrangement – n (%)					
With spouse or family or cotenant	94	96	260	99	
Living alone	4	4	4	1	0.2197
Education level – n (%)					
University completed	48	49	178	67	
College completed	16	16	55	21	
Professional certificate obtained	11	11	19	7	
Secondary school completed	24	24	12	5	<0.0001

Household income – CDN$/yr n (%)					
Less than 20 000$/yr	36	39	5	2	
Between 20 000 and 39 999$	32	35	30	12	
Between 39 000 and 59 999$	10	11	39	15	
Between 60 000 and 79 999$	9	10	41	16	
80 000 and over $	5	5	146	56	<0.0001
Lifestyle Habits					
Exercise during 1st trimester – n (%)	34	35	105	40	0.3995
Smoking before pregnancy – n (%)	20	20	30	11	0.0306
Smoking during 1st trimester – n (%)	3	3	12	5	0.5143
Caffeine intake before pregnancy– n (%)	76	77	220	83	0.1510
Caffeine intake during 1st trimester– n (%)	46	47	163	62	0.0113
Use of alcohol before pregnancy– n (%)	47	48	194	74	<0.0001
Use of alcohol during 1st trimester– n (%)	7	7	26	10	0.4068
Health Status and Medication					
Comorbidities before pregnancy § **–** n (%)					
0	70	71	193	73	
1	25	25	62	24	
2 or 3	4	4	9	3	0.8908
Vitamin use before pregnancy ‖ **–** n (%)	32	32	111	42	0.0913
Vitamin use during 1st trimester ‖ **–** n (%)	76	78	222	84	0.1267
Medication use during 1st trimester – n (%)	22	22	79	30	0.1447
Oral contraceptives use in the past 6 months – n (%)	15	15	48	18	0.5029
Pregnancy History					
Gravidity – n (%)					
Primigravida	26	26	37	14	
Multigravida	73	74	227	86	0.0061
Parity – n (%)					
0	37	38	50	19	
1	35	36	157	60	
2 or more (max: 4)	25	26	56	21	<0.0001
Pre-pregnancy weight ¶ **–** n (%)					
Normal (18.5≤ BMI <25 kg/m^2)	54	58	178	68	
Underweight (BMI <18.5 kg/m^2)	5	5	10	4	
Overweight (25≤ BMI <30 kg/m^2)	24	26	48	18	
Obese (BMI ≥30 kg/m^2)	10	11	25	10	0.3326

* Régie de l'assurance maladie du Québec drug insurance plan (RAMQ-Rx).
†Private drug insurance plan offered by the woman's employer, spouse's employer or parents' employer.
‡ Chi-squares, t-tests, and Fisher's exact tests when applicable.
§ Including asthma, anemia, depression, hypothyroidism, diabetes, epilepsy, hypertension and various problems like infections, eczema, migraines, etc.
‖ Including folic acid, multivitamins, prenatal vitamins and iron.
¶ Body mass index (BMI).

TABLE 2 Maternal characteristics of pregnant women who were employed and insured by the RAMQ-Rx and pregnant women who were employed and covered by a private drug insurance plan.

Characteristics* n=363	**Employed and insured by the RAMQ-Rx* n= 50**		**Insured by a private drug insurance plan† n=264**		**p-value‡**
Socioeconomic Status					
Maternal age (yr) - mean (SD)	31.1	5.4	32.07	4.4	0.2551
Immigrant – n (%)	22	44	63	24	0.0033
Race – n (%)					
Caucasian	37	74	227	86	
Asian	5	10	7	3	
Black	7	14	20	8	
Hispanic	1	2	10	4	0.0298
Living arrangement – n (%)					
With spouse or family or cotenant	47	96	260	99	
Living alone	2	4	4	1	0.2381
Education level – n (%)					
University completed	25	50	178	67	
College completed	8	16	55	21	
Professional certificate obtained	6	12	19	7	
Secondary school completed	11	22	12	5	<.0001
Household income – CDN$/yr - n (%)					
Less than 20 000$/yr	11	23	5	2	
Between 20 000 and 39 999$	20	42	30	12	
Between 39 000 and 59 999$	6	13	39	15	
Between 60 000 and 79 999$	8	17	41	16	
80 000 and over $	3	6	146	56	<.0001
Lifestyle Habits					
Exercise during 1st trimester – n (%)	17	34	105	40	0.4311
Smoking before pregnancy – n (%)	15	30	30	11	0.0006
Smoking during 1st trimester – n (%)	2	4	12	5	1.0000
Caffeine intake before pregnancy– n (%)	39	78	220	83	0.3630
Caffeine intake during 1st trimester– n (%)	26	53	163	62	0.2538
Use of alcohol before pregnancy– n (%)	26	52	194	74	0.0024
Use of alcohol during 1st trimester– n (%)	4	8	26	10	0.7988
Health Status and Medication					
Comorbidities before pregnancy § **–** n (%)					
0	38	76	193	73	
1	12	24	62	24	
2 or 3	0	0	9	3	0.5911
Vitamin use before pregnancy ‖ **–** n (%)	20	40	111	42	0.7880
Vitamin use during 1st trimester ‖ **–** n (%)	40	82	222	84	0.6265
Medication use during 1st trimester – n (%)	13	26	79	30	0.5761
Oral contraceptives use in the past 6 months – n (%)	6	12	48	18	0.3028

Pregnancy History					
Gravidity – n (%)					
Primigravida	30	60	37	14	
Multigravida	20	40	227	86	<.0001
Parity – n (%)					
0	25	50	50	19	
1	16	32	157	60	
2 or more (max: 4)	9	18	56	21	<.0001
Pre-pregnancy weight¶– n (%)					
Normal (18.5≤ BMI <25 kg/m^2)	30	64	178	68	
Underweight (BMI <18.5 kg/m^2)	3	6	10	4	
Overweight (25≤ BMI <30 kg/m^2)	8	17	48	18	
Obese (BMI ≥30 kg/m^2)	6	13	25	10	0.6598

* Régie de l'assurance maladie du Québec drug insurance plan (RAMQ-Rx).
†Private drug insurance plan offered by the woman's employer, spouse's employer or parents' employer.
‡ Chi-squares, t-tests, and Fisher's exact tests when applicable.
§ Including asthma, anemia, depression, hypothyroidism, diabetes, epilepsy, hypertension and various problems like infections, eczema, migraines, etc.
‖ Including folic acid, multivitamins, prenatal vitamins and iron.
¶ Body mass index (BMI).

DISCUSSION

Our study showed SES differences between pregnant women insured by the RAMQ-Rx and those covered by a private drug insurance plan such as maternal age, immigrant status, race/ethnicity, work status, education level, and household income; there were also lifestyle and pregnancy history differences. Similar differences were observed between pregnant workers insured by the RAMQ-Rx and those insured by private drug insurance plans.

Pregnant women insured by the RAMQ-Rx were younger than those covered by private drug insurance plans. This could be explained in part by the fact that young women might no longer be covered by a family private drug insurance plan but may not have an employment-based drug insurance plan yet. However, since the mean age difference is not clinically important (1.4 years), this should not limit generalizability of perinatal pharmacoepidemiologic studies conducted using data from the RAMQ-Rx administrative database. Consistent with our findings, other studies conducted in the US population reported that age,[23] race/ethnicity,[15,17,18,23] employment,[17,23] education,[18] and family income[18,23] differed according to health insurance coverage. Indeed, compared to those who were covered by a private insurance plan (medical and medications), it was reported that Medicaid beneficiaries in the U.S. population were more likely to have a household income that was below poverty level (<20,000 USD$/yr: 50% vs. 5%),[23] and less likely to be Caucasian (9-66% vs. 70-81%),[15,17,18,23] employed (23-44% vs. 75-88%),[17;23] and have a post-secondary education (62% vs. 94%).[18] Previous research also showed that employment can be considered the most important determinant of health insurance.[23] However, our study showed that similar differences can be observed between workers who are insured by a government drug insurance program (RAMQ-Rx) and workers insured by a private drug insurance plan, indicating that employment is not the only determinant explaining the differences even in the context of universal health care.

In our study, there was no difference in smoking and alcohol use during pregnancy between women covered by the RAMQ-Rx and those covered by a private drug insurance plan. However, women insured by the RAMQ-Rx were less likely to drink caffeine during pregnancy. Keeping in mind the important associations between pregnancy lifestyle and perinatal outcomes, this result highlights the value of the RAMQ database for perinatal pharmacoepidemiologic studies and enhances

interpretability when data on potential socioeconomic risk factors and lifestyle are missing. As for pre-pregnancy lifestyle, women insured by the RAMQ-Rx were more likely to be smokers but less likely to drink alcohol before pregnancy. However, pre-pregnancy lifestyle remains less of a concern for perinatal pharmacoepidemiologic studies. This result could partly be explained by the fact that risky lifestyles such as smoking and alcohol intake are associated with SES, which is itself a determinant of medication insurance status. Although the prevalence of alcohol and substance abuse were reported to be different according to drug insurance coverage,[17,18] it is difficult to compare our findings to others given that women in our study population were light drinkers (≤2 drinks/week),[24] and thus our results do not correspond to alcoholism or heavy drinking (defined as >7 drinks/week[25] or >14 drinks/week[26] in pregnant women). As for pregnancy history, our results suggest that women insured by the RAMQ-Rx were more likely to be primigravida (woman who is pregnant for the first time) or primipara (woman who has given birth once) than those who were covered by a private drug insurance plan. As of now, no one has ever studied pregnancy history differences between privately insured and government insured women. However, our findings could be partly explained by the fact that women insured by a private drug insurance plan were older. Indeed, increasing reproductive history has been associated with increasing maternal age.[27] Contrary to others,[18] our results do not support a comorbidity profile difference between women insured by the RAMQ-Rx and women who are insured by a private drug insurance plan. This could be partly explained by the fact that the Quebec health care system is universal, with the exception of the medication coverage, and thus there is no barrier in access to health care.

In our study, the participation rate was good and women who refused to participate were comparable to those enrolled in the study regarding maternal and gestational age, thus limiting selection bias. Furthermore, we feel confident that our study population is representative of pregnant women between 15-45 years of age in Quebec given that the proportion of those insured by the RAMQ-Rx is comparable to Quebec's annual statistics' data (ISQ data).[13,14] Furthermore, ISQ has never reported SES characteristic differences between those living in the urban Montreal area and those living in rural area[14] indicating that our study population of pregnant women is comparable to pregnant women living elsewhere in Quebec.

As previously stated, administrative databases are widely used for epidemiologic and pharmacoepidemiologic research.[1-12] Therefore, careful consideration has to be given to the internal and external validity of studies conducted within these databases. In fact, the evaluation of the generalizability of results is important in order to understand the medical context for which data are available.[28] Although literature presents differences between privately insured and publicly insured patients, such as Medicaid beneficiaries in the U.S. population,[15-19] no one has ever focused on differences between pregnant workers insured by the RAMQ-Rx and those insured by private drug insurance plans in the province of Quebec. Our data suggest substantial differences between pregnant women insured by the RAMQ-Rx and those covered by private drug insurance plans, regardless of whether they are working or not. However, in the case of the Medicaid database, it was suggested that the potential lack of generalizability was more problematic for descriptive than for analytic studies where comparisons are made between study and control groups from the same population that are theoretically subject to the same biases.[29] Overall, the results of our study have important implications for the interpretation and discussion of external validity of perinatal pharmacoepidemiologic studies conducted within the RAMQ-Rx database. Differences between pregnant women insured by the RAMQ-Rx and those insured by private drug insurance programs, regardless of their work status, will most likely limit generalizability but will not affect the internal validity of studies using data from the RAMQ-Rx administrative database. In fact, there was no difference in the distribution of important gestational exposure variables such as smoking, vitamin, and alcohol use during pregnancy. Moreover, the SES characteristics of pregnant women insured by the RAMQ-Rx, and more specifically household income, were not heavily skewed to one extreme or another, suggesting

sufficient numbers in either category to perform statistical adjustment for SES in perinatal pharmacoepidemiologic studies using the RAMQ database.

In conclusion, despite the lack of, or incompleteness of data on potential risk factors and clinical variables, pharmacoepidemiologic studies using administrative databases are important and yield valuable information. There are substantial differences between pregnant women insured by the RAMQ-Rx and those insured by private drug insurance plans regardless of their work status. However, these differences will most likely limit generalizability but not internal validity of perinatal pharmacoepidemiologic studies using data from the RAMQ-Rx administrative database.

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