

The Impact of Different Case Ascertainment Definitions on the Prevalence of Major Congenital Malformations and their Association with Asthma During Pregnancy

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Abstract *Objectives* To compare the prevalence of major malformations using different case ascertainment definitions and to evaluate their impact on maternal asthma-major malformations association. *Methods* A cohort of pregnancies with and without asthma between 1990 and 2010 was formed. We used two classification methods: the Two step Congenital Malformation Classification (TCMC) and the Canadian Congenital Anomalies Surveillance System (CCASS). Within each method, three case definitions were compared: (1) ≥ 1 diagnosis in the hospital database; (2) ≥ 1 diagnosis in the hospital database or ≥ 2 in the medical claims; and (3) ≥ 1 diagnosis in the hospital database or ≥ 1 in the medical claims. We calculated the prevalence of major malformations and adjusted odds ratios (aORs) for maternal asthma association. *Results* Of 467,946 pregnancies, 12.3 % were with active asthma. The prevalence estimates were: TCMC 5.10–7.08 % and CCASS 7.03–10.57 %. Asthma-major malformations association was weaker with the CCASS (aOR 1.14–1.20) versus TCMC (aOR 1.22–1.26). *Discussion* The case ascertainment definitions with ≥ 1 hospitalization are likely to be the most reliable in similar administrative databases. The case ascertainment definition had a considerable impact on the prevalence of major malformations, but

hardly influenced the aORs. Future studies should formally assess the validity of the case ascertainment definitions and allow generalizability to other maternal exposures.

Keywords Congenital malformations · Case definitions · Asthma · Pregnancy · Administrative databases

Significance

What is already known on this subject?

Several case ascertainment definitions of major congenital malformations are currently being used in perinatal epidemiology, but few studies compared their impacts.

What this study adds?

In this study, six different case ascertainment definitions were compared, resulting in a considerable impact on prevalence estimates, but little on the measures of association. The prevalence estimates ranged between 5.1 and 10.6 %, with medical claims playing a major role in the prevalence increase. The case ascertainment definitions using ≥ 1 diagnosis of major malformation recorded in hospital databases or discharge summary sheets are the most recommended since they have the least chance of including misclassified cases yet providing adequate results.

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Introduction

Computerized administrative databases have become an important source of data in perinatal epidemiology, with increasing number of studies evaluating the impact of

pregnancy exposures on perinatal outcomes including congenital malformations.(Correa and Kirby 2010) Major malformations are considered among the leading causes of infant, fetal, and post neonatal mortality in North America and Europe. (Khoshnood et al. 2011; *Public Health Agency of Canada. Perinatal Health Indicators for Canada 2013: a Report of the Canadian Perinatal Surveillance System. Ottawa, 2013.*) However, discrepancies are present in the estimated prevalence of major malformations in prior reports. These differences are attributed to several factors, including the source of data, the diagnostic codes validity, the classification method, and the period of assessment (e.g. at birth or during the 1st year of life).(Bedard et al. 2012; Hobbs et al. 2001; Rasmussen and Moore 2001) All these factors should be considered in specifying and developing the case ascertainment definitions in epidemiological studies. Typically, a case ascertainment definition for congenital malformations is pre-specified by the investigators and operated through applying an algorithm to the raw data in the databases (e.g. medical records with congenital malformations diagnoses) in order to capture the required cases.

Quebec is the second largest province in Canada and several health administrative databases were established and increasingly being used in epidemiological research. Among others, the *Régie de l'Assurance-Maladie du Québec* (RAMQ) Medical Claims database records data on medical services paid on a fee-for-service basis for all residents of Quebec and the *Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière* (MED-ECHO) database records data related to all acute care hospitalisations in the province. Both databases have been used previously for congenital malformations research.(Berard et al. 2007; De Wals et al. 2003; Eltonsy et al. 2014; Tairou et al. 2006) The accuracy of congenital malformations diagnoses recorded in MED-ECHO and RAMQ databases was reported in two studies.(Blais et al. 2013; Kulaga and Berard 2010) Kulaga et al. reported a 60 % relative agreement between MED-ECHO, RAMQ, Births and Deaths Registry records, and the mothers' reports.(Kulaga and Berard, 2010) Comparing the malformations diagnoses recorded in the linked MED-ECHO and RAMQ databases with the infants' medical charts (the gold standard), Blais et al. reported a positive predictive value (PPV) of 78.1 % for major malformations among asthmatic women and 69.0 % among non-asthmatic women.(Blais et al. 2013) However, the aforementioned studies did not investigate the accuracy of the diagnoses reported in each database separately. It is currently unknown whether one of these two databases has a higher accuracy of malformations diagnoses over the other. In Quebec, medical billing claims database is used mainly for billing and administrative purposes with the diagnoses information being

recorded by physicians and not mandatory. While in the hospitalizations database, the diagnoses recording is mandatory and performed by trained medical archivists.

Beside the variation in the prevalence estimates, the case ascertainment definitions might also influence the estimates for the associations between maternal exposures and congenital malformations. The two most likely common scenarios of deviations from the truth have different causes and effects. Incomplete and non-differential ascertainment of congenital malformations will hardly affect the effect estimates themselves but will affect the precision. On the other hand, over-ascertainment by inclusion of non-malformed newborns or newborns with minor malformations (i.e. false positives) could lead to underestimating of the true impact of the exposure and lower observed effect estimates. Therefore, the objective of the current study was to compare the prevalence of major malformations using different case ascertainment definitions that vary by the source of data and the classification method. We also evaluated the impact of these definitions on the association between maternal asthma and major malformations.

Methods

Data Sources

We used the Quebec Asthma and Pregnancy Database, including all pregnancies in all women with ≥ 1 asthma diagnosis (International Classification of Diseases [ICD] 9th Revision [ICD-9] code 493 or ICD-10 code J45) in the 2-year period preceding one of their deliveries and all pregnancies of a 4-times-larger random sample of other women who delivered between January 1, 1990 and March 31, 2010 in Quebec (see Fig. 1). The database includes 583,071 pregnancies, representing about 35 % of all births in the province in this period of time.(*Statistics Canada-Components of population growth, Canada, provinces and territories.* <http://www5.statcan.gc.ca/cansim/a26?lang=eng&retrLang=eng&id=0510004&paSer=&pattern=&stByVal=1&p1=1&p2=37&tabMode=dataTable&csid>) External validity was not assessed per se, but including all pregnancies from asthmatic women and a large random sample from non-asthmatic women should provide high external validity.

This database contains data extracted from the MED-ECHO and RAMQ databases. Since the RAMQ Medical Claims database records data on all medical visits, including diagnosis codes and procedures, for all residents of Quebec, we hypothesized that it contained valuable information on congenital malformations that could be missing from the MED-ECHO database. The diagnoses recorded in the MED-ECHO database are routinely

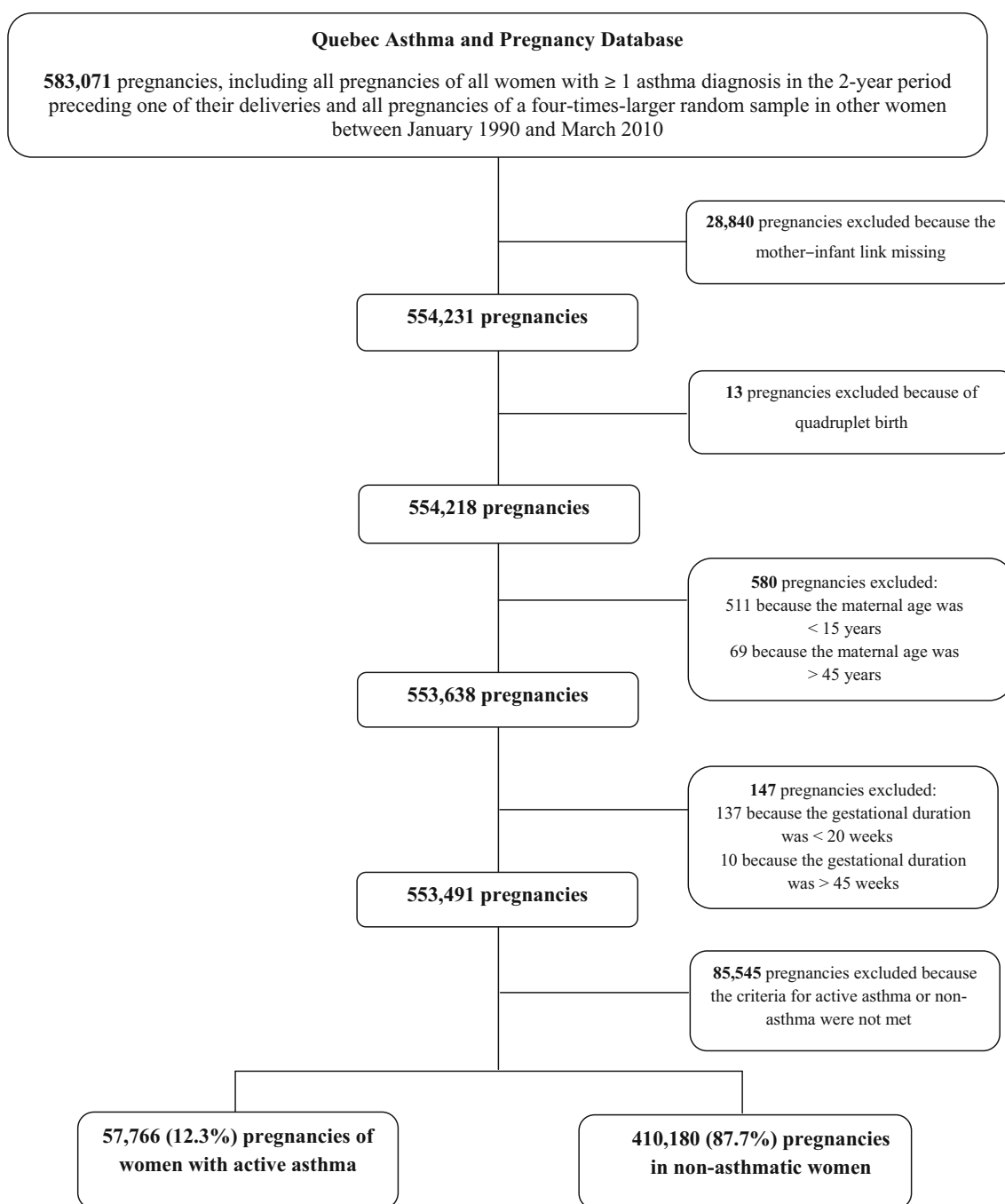


Fig. 1 Cohort selection flow-diagram

collected by trained medical archivists using the ICD-10 revised for Canada (ICD-10-CA) since 2006, and using the ICD-9 before 2006. The RAMQ Medical Claims database records diagnoses coded with ICD-9 codes. We obtained data from the RAMQ and MED-ECHO databases from January 1, 1988 to March 30, 2010 for the mothers, and from birth to March 30, 2010 for the offspring.

Study Cohort and Asthma Definition

A cohort of pregnancies in women with active asthma and women without asthma was selected. Asthma was defined as ≥ 1 asthma diagnosis (ICD-9 code 493, except 493.2, or ICD-10 code J45) recorded during a hospitalization, or ≥ 2 medical claims associated with an asthma diagnosis

within 2 consecutive years between 1988 and the delivery.(Gershon et al. 2009) This operational definition of asthma was previously validated and showed a sensitivity of 83.8 % and a specificity of 76.5 %.(Gershon et al. 2009) Asthma was considered to be present during pregnancy (i.e. active asthma) if there was at least one asthma diagnosis within 2 years before delivery.The pregnancy was considered as non-asthmatic if the woman had no diagnosis of asthma recorded in either database between 1988 and the delivery. The pregnancies inclusion criteria were: (1) a pregnancy with delivery between January 1, 1990 and March 31, 2009 (allowing 1 year of data available after birth to assess congenital malformations); (2) maternal age at the beginning of pregnancy of 15–45 years; (3) gestational duration of 20–45 weeks; and (4) fulfillment of the definitions for the presence/absence of active asthma during pregnancy. Quadruplet births from a single pregnancy were excluded to avoid zero cells and pregnancies missing the mother–infant link were excluded.

Classification of Congenital Malformations

Congenital malformations were identified using the ICD-9 and ICD-10 codes for congenital malformations recorded in MED-ECHO and RAMQ databases at birth and during the 1st year of life for live births (≥ 20 weeks gestation) and at birth for stillbirths. We compared two methods for the classification of congenital malformations. The first, the Two-step Congenital Malformation Classification (TCMC) method, which was developed specifically for research and used in previous perinatal epidemiological studies.(Blais et al. 2009, 2010; Eltonsy et al. 2014) Briefly, to facilitate the development of a complete and comprehensive list of congenital malformations, a system specific malformations list was primarily compared with a list provided by the Collaborative Perinatal Group.(Heinonen et al. 1977) The full list was then verified by a geneticist from the Centre Hospitalier Universitaire Sainte-Justine for exactness and completeness., The first step included classifying congenital malformations as major, minor, or major/minor. A malformation was defined as “major” if it was life-threatening or could cause major cosmetic defects. As judged by the geneticist, the “major/minor” category includes malformations that vary in their severity, depending on the condition of each case. The “minor” category includes malformations not classified in the major or major/minor categories. In the second step, the major/minor malformations were reclassified as major if the malformation was associated with at least one hospitalization with a primary or an admission diagnosis in the MED-ECHO database in the first year of life of the baby or as minor if not.

The second method was the national Canadian Congenital Anomalies Surveillance System (CCASS) method, which has been described in more detail in the CCASS periodic reports.(Public Health Agency of Canada. *Congenital Anomalies in Canada 2013: A Perinatal Health Surveillance Report*. Ottawa, 2013.) Briefly, the ICD-9 and ICD-10 codes for congenital malformations were classified into 14 categories of system-specific malformations. Then, preselected diagnostic codes for minor malformations were excluded from these categories. Notably, the CCASS method is the Canadian national method of ascertainment which is currently used with several provincial databases. The CCASS uses discharge abstract data (DAD) on newborns, collected from provincial and territorial hospitals via the Canadian Institute for Health Information (CIHI) and Québec’s MED-ÉCHO. The CCASS was originally developed for surveillance purposes. Online Resource 1 provides a complete description and comparison of the two classification methods. Congenital malformations were categorized into 16 system-specific categories, as presented in Online Resource 1. As presented in Table e1, the TCMC and the CCASS methods perfectly agree in the classification codes for nervous system, cardiac system, orofacial clefts, and Down syndrome. The rest of the system-specific malformations have codes that vary by the classification method.

Case Ascertainment Definitions of Congenital Malformations

We sought to compare case ascertainment definitions that differ by the source of data (i.e. diagnoses recorded in a hospital database [MED-ECHO] or in a medical billing claims database [RAMQ]) and the classification method (i.e. the TCMC or CCASS methods). We developed 3 case ascertainment definitions for each classification method, and they varied in the inclusion criteria from the strictest (i.e. using only hospital database) to the least strict (i.e. using ≥ 1 diagnosis from either the medical claims database or the hospital database). Using this methodology, we aimed at evaluating the separate effect of changing the classification method and changing the source of data.

We used six case ascertainment definitions: (1) TCMC: ≥ 1 major malformation diagnosis recorded in the hospital database; (2) TCMC: ≥ 2 major malformation diagnoses recorded in the medical claims database or ≥ 1 major malformation diagnosis recorded in the hospital database; (3) TCMC: ≥ 1 major malformation diagnosis recorded in the medical claims database or ≥ 1 major malformation diagnosis recorded in the hospital database; (4) CCASS: ≥ 1 major malformation diagnosis recorded in the hospital database; (5) CCASS: ≥ 2 major malformation diagnoses recorded in the medical claims database or ≥ 1 major

malformation diagnosis recorded in the hospital database; and (6) CCASS: ≥ 1 major malformation diagnosis recorded in the medical claims database or ≥ 1 major malformation diagnosis recorded in the hospital database. The six case ascertainment definitions are summarized in Table 1.

Statistical Analysis

The characteristics of the pregnancies were compared using descriptive statistics. We calculated the prevalence of major malformations using the six case ascertainment definitions. Next, we compared the prevalence of major malformations between pregnancies of women with active asthma and non-asthmatic women. We used generalized estimating equation (GEE) models with a logistic link and pregnancy as the unit of analysis to estimate crude and adjusted odds ratios (cOR, aOR) for major malformations with 95 % confidence intervals (CI). GEE models were used to account for the correlation between consecutive pregnancies in individual women. (Zeger et al. 1988) Adjusted models contained risk factors for congenital malformations, including maternal age at the start of pregnancy (18–34 and <18 or >35 years), (Gill et al. 2012) receipt of social assistance at the start of pregnancy (yes/no), (Yang et al. 2008) area of residence at delivery (rural/urban), (Langlois et al. 2009; Messer et al. 2010) multiple pregnancy (yes/no), and the following maternal co-morbidities identified from diagnoses recorded in the MED-ECHO or RAMQ databases up to 1 year before pregnancy: chronic hypertension (yes/no), (Liu et al., 2013) diabetes mellitus (yes/no), (Brent 2001; Liu et al. 2013) and epilepsy (yes/no). (Brent 2001) All statistical analyses were performed with SAS software, version 9.3 (SAS Institute Inc., Cary, NC).

Results

Of 467,946 pregnancies eligible for the study, 57,766 (12.3 %) were in women with active asthma and 410,180 (87.7 %) were in non-asthmatic women. The selection process is summarized in Fig. 1. The characteristics of the pregnancies in women with active asthma and non-asthmatic women are presented in Table 2. Most of the women in both groups were 18–34 years old and lived in urban areas. However, women with active asthma were more likely to receive social assistance and to suffer from other chronic diseases. Table 3 shows the prevalence of major malformations according to each case ascertainment definition. The prevalence of major malformations ranged from 5.1 to 7.1 % using the TCMC method and from 7.0 to 10.6 % using the CCASS method. The prevalence of major malformations increased when medical claims data were added to the hospitalization data. Additionally, the prevalence of major malformations was 37.8, 42.4, and 49.3 % higher with the CCASS method than with the TCMC classification method for the case ascertainment definitions ≥ 1 major malformation diagnosis recorded in the hospital database; ≥ 2 major malformation diagnoses recorded in the medical claims database or ≥ 1 major malformation diagnosis recorded in the hospital database; and ≥ 1 major malformation diagnosis recorded in the medical claims database or ≥ 1 major malformation diagnosis recorded in the hospital database, respectively.

Table 3 also shows the prevalence of system-specific major malformations. The most prevalent categories were cardiac malformations, and limb and musculoskeletal malformations, regardless of the case ascertainment definition. Only four categories (neural tube defects, urinary system malformations, orofacial clefts, and Down syndrome) had prevalence that were relatively not affected by

Table 1 Case ascertainment definitions for the major congenital malformations used in this study

Case ascertainment definition	Data source	
	Hospitalization database (MED-ECHO)	Medical claims database (RAMQ)
TCMC		
≥ 1 hospitalization	≥ 1 diagnostic code of major malformation	
≥ 1 hospitalization or ≥ 2 medical claims	≥ 1 diagnostic code of major malformation	or ≥ 2 diagnostic codes of major malformation
≥ 1 hospitalization or ≥ 1 medical claim	≥ 1 diagnostic code of major malformation	or ≥ 1 diagnostic code of major malformation
CCASS		
≥ 1 hospitalization	≥ 1 diagnostic code of major malformation	
≥ 1 hospitalization or ≥ 2 medical claims	≥ 1 diagnostic code of major malformation	or ≥ 2 diagnostic codes of major malformation
≥ 1 hospitalization or ≥ 1 medical claim	≥ 1 diagnostic code of major malformation	or ≥ 1 diagnostic code of major malformation

MED-ECHO Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière, *RAMQ* Régie de l'Assurance-Maladie du Québec, *TCMC* Two step Congenital Malformation Classification, *CCASS* Canadian Congenital Anomalies Surveillance System classification

Table 2 Characteristics of the pregnancies of women with active asthma and non-asthmatic women

	Pregnancies of women with active asthma (<i>n</i> = 57,766)		Pregnancies in non-asthmatic women (<i>n</i> = 410,180)	
	No.	%	No.	%
Maternal age at the start of pregnancy (years)				
<18	1827	3.2	6089	1.5
18–34	50,643	87.7	362,548	88.4
≥35	5296	9.2	41,543	10.1
Receipt of social assistance at the start of pregnancy	10,510	18.2	40,490	9.9
Urban area of residence at delivery	47,863	82.9	323,578	78.9
Multiple pregnancy	890	1.5	5152	1.3
Diagnoses before pregnancy				
Chronic hypertension	4862	8.4	20,634	5.0
Diabetes mellitus	5898	10.2	31,045	7.6
Epilepsy	342	0.6	1316	0.3

the different definitions. However, some categories were strongly affected by the data source (i.e. cardiac, central nervous system, eye, and other chromosomal malformations), other categories were affected by the classification method (i.e. limb and musculoskeletal, digestive system, integument, and ear, face and neck malformations), while others were affected by both (i.e. circulatory system, respiratory system, genital organ, and other and unspecified malformations).

Figure 2 shows the cORs and aORs for the association between maternal asthma and major malformations using all six case ascertainment definitions. The number and percentage of cases per group are presented in Online Resource 2. Using the TCMC method, maternal asthma was significantly associated with an increased prevalence of major malformations regardless of the definitions, with aORs ranging from 1.22 to 1.26. Using the CCASS method, maternal asthma was also significantly associated with an increased prevalence of major malformations regardless of the definitions, although the aORs were smaller and varied more, ranging from 1.14 to 1.20. Regardless of the classification method, adding medical claims data to the hospitalization data had little impact on the effect size of the aORs.

Discussion

In the current study, we compared six different case ascertainment definitions for major malformations that differ by the source of data and the classification method. Adding ≥ 1 or 2 medical claim diagnoses to hospital-based diagnoses increased the prevalence of major malformations

by 10.0 and 38.8 %, respectively, for the TCMC method and by 13.7 and 50.4 %, respectively, for the CCASS method. The classification method itself influenced the prevalence with increases from 37.8 % to 49.3 % with the CCASS as compared with the TCMC method. We also observed weaker estimates of the association with maternal asthma with the CCASS (aORs 1.14–1.20) versus the TCMC (aORs 1.22–1.26) method, even though the prevalence was always greater with the CCASS method.

Using hospital, vital statistics, and medical genetic departments databases, Bedard et al. reported congenital heart defects prevalence of 5.59 per 1000 births, that increased to 12.42 per 1000 births when outpatient pediatric cardiology database and terminations of pregnancy data were added.(Bedard, Lowry, Sibbald, et al., 2012) Others have evaluated the accuracy of diagnoses of congenital malformations recorded in administrative databases.(Bedard, Lowry, and Sibbald, 2012; Cooper et al., 2008; Metcalfe et al. 2014; Rasmussen and Moore 2001; Salemi et al. 2011) Metcalfe et al., using a provincial database from Canada, reported an accurate identification rate of 86.9 % for congenital malformations in the hospitalization database versus 51.1 % in outpatient database.(Metcalfe et al. 2014) In other prior reports, an estimated 5–20 % of cases of major malformations were false positives.(Bedard et al. 2012; Callif-Daley et al. 1995; Metcalfe et al. 2014; Salemi et al. 2011) Using linked data from Quebec, Kulaga et al. reported an agreement of 60 % with maternal reports of major malformations.(Kulaga and Berard 2010) Moreover, Blais et al. compared linked hospital and medical claims databases with data from the infants' medical charts, and reported a PPV of 78.1 % for major malformations in asthmatic women and 69.0 % in

Table 3 Prevalence of major congenital malformations according to the classification method and case ascertainment definition

	TCMC classification						CCASS classification					
	≥ 1 hospitalization		≥ 1 hospitalization or ≥ 2 medical claims		≥ 1 hospitalization or ≥ 1 medical claim		≥ 1 hospitalization		≥ 1 hospitalization or ≥ 2 medical claims		≥ 1 hospitalization or ≥ 1 medical claim	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Any major malformation ^a	23,868	5.1	26,273	5.6	33,142	7.1	32,894	7.0	37,396	8.0	49,439	10.6
System-specific malformations												
Neural tube defects	191	0.0	224	0.1	314	0.1	191	0.0	224	0.1	314	0.1
Central nervous system ^b	1252	0.3	1508	0.3	2287	0.5	1252	0.3	1508	0.3	2287	0.5
Cardiac	4792	1.0	5870	1.3	8191	1.8	4792	1.0	5870	1.3	8191	1.8
Circulatory system	1304	0.3	1572	0.3	2070	0.4	3145	0.7	3440	0.7	4059	0.9
Respiratory system	1206	0.3	1224	0.3	1330	0.3	580	0.1	723	0.2	1205	0.3
Eye	603	0.1	856	0.2	2416	0.5	304	0.1	566	0.1	2147	0.5
Ear, face, and neck	124	0.0	128	0.0	146	0.0	1684	0.4	1769	0.4	2163	0.5
Orofacial clefts	599	0.1	627	0.1	697	0.2	599	0.1	627	0.1	697	0.2
Digestive system	3591	0.8	3859	0.8	4772	1.0	1901	0.4	2119	0.5	2622	0.6
Genital organs	898	0.2	1100	0.2	1480	0.3	2577	0.6	3052	0.7	4255	0.9
Urinary system	3395	0.7	3463	0.7	3654	0.8	3367	0.7	3436	0.7	3622	0.8
Limb and musculoskeletal	5002	1.1	5279	1.1	5889	1.3	15,143	3.2	16,980	3.6	21,317	4.6
Integument	3210	0.7	3226	0.7	3316	0.7	1070	0.2	1104	0.2	1392	0.3
Down syndrome	494	0.1	513	0.1	560	0.1	494	0.1	513	0.1	560	0.1
Other chromosomal	269	0.1	601	0.1	1193	0.3	207	0.0	211	0.1	223	0.1
Other and unspecified	478	0.1	515	0.1	592	0.1	984	0.2	2366	0.5	4813	1.0

TCMC Two step Congenital Malformation Classification method, *CCASS* Canadian Congenital Anomalies Surveillance System classification method, ≥ 1 hospitalization: ≥ 1 major malformation diagnosis recorded in the hospital database; ≥ 1 hospitalization or ≥ 2 medical claims: ≥ 2 major malformation diagnoses recorded in the medical claims database or ≥ 1 major malformation diagnosis recorded in the hospital database; ≥ 1 hospitalization or ≥ 1 medical claim: ≥ 1 major malformation diagnoses recorded in the medical claims database or ≥ 1 major malformation diagnosis recorded in the hospital database

^a The sum of all system-specific malformations in each column exceeds the total number of cases with any major malformation because some infants had multiple malformations

^b Includes neural tube defects

non-asthmatics.(Blais et al. 2013) Of note, the above-mentioned studies have investigated the accuracy of the diagnoses per se, but did not compare the impact of different case ascertainment definitions on the prevalence and association estimates as in the current study.

We observed an increase of 10.0–13.7 % in the prevalence of major malformations for the case ascertainment definition of ≥ 1 hospitalization diagnosis or ≥ 2 medical claim diagnoses as compared to ≥ 1 hospitalization diagnosis. Meanwhile, the least strict definition of ≥ 1 hospitalization diagnosis or ≥ 1 medical claim diagnosis resulted in the greatest increase in the prevalence (by 38.8–50.4 %). It is possible that the medical claims included some suspected malformations that were never confirmed. For this reason, we believe that the definition based on ≥ 1 hospitalization diagnosis most probably includes the fewest false positives.

In terms of classification methods, the CCASS led to higher prevalence of major malformations than the TCMC, because some minor malformations were classified as major malformations. Indeed, the prevalence of some categories (e.g. limb and musculoskeletal, and ear, face and neck) were three times higher using the CCASS method. The number of misclassified cases is difficult to determine due to the lack of a gold standard, but we hypothesize that the specificity of the CCASS is lower than that of the TCMC method. This outcome misclassification increases the estimated prevalence and can lead to an information bias (non-differential misclassification) that would underestimate the impact of an exposure on the prevalence of major malformations. (Rothman et al. 2008) This phenomenon was indeed observed with the aORs being closer to the null with the CCASS than with the TCMC method. There is a well-documented association between asthma and major malformations, with an increased

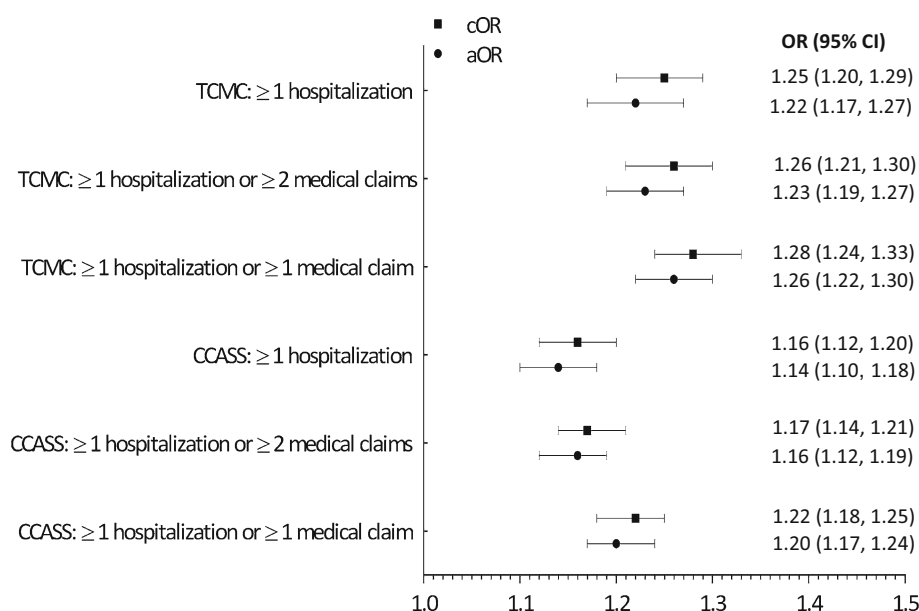


Fig. 2 Crude and adjusted odds ratios for major malformations in the pregnancies of women with active asthma versus pregnancies in non-asthmatic women using the specified case ascertainment definitions *TCMC* Two step Congenital Malformation Classification method; *CCASS* Canadian Congenital Anomalies Surveillance System classification method; ≥ 1 hospitalization: ≥ 1 major malformation diagnosis recorded in the hospital database; ≥ 1 hospitalization or ≥ 2

medical claims: ≥ 2 major malformation diagnoses recorded in the medical claims database or ≥ 1 major malformation diagnosis recorded in the hospital database; ≥ 1 hospitalization or ≥ 1 medical claim: ≥ 1 major malformation diagnoses recorded in the medical claims database or ≥ 1 major malformation diagnosis recorded in the hospital database; cOR: crude odds ratio; aOR: adjusted odds ratio; OR: odds ratio; CI: confidence interval

prevalence of about 20–30 % relative to pregnancies in non-asthmatic women.(Blais and Forget 2008; Blais et al. 2010; Murphy et al. 2013) The results obtained using the TCMC method were more consistent with these results. For these reasons, we believe that the TCMC method includes the fewest false positives.

The present study has some important strengths. It comprised one of the largest administrative-linked pregnancy databases including more than 500,000 pregnancies over 20 years. The study was the first to examine the number of additional cases of major malformations identified in outpatient medical claims database in Quebec, and the first to compare the CCASS classification method used for national surveillance to the TCMC method designed specifically for perinatal research. While we used Quebec databases, the results are generalizable and can straightforwardly reflect to different settings where similar health administrative databases are available.

The current study has some limitations. The lack of a gold standard means we were unable to estimate the PPV or the negative predictive value for the case ascertainment definitions. Although the accuracy of the diagnoses is expected to be greater in a hospital database (because of active and prospective data entry by trained medical archivists) than in a medical claims database maintained mainly for billing purposes, the recording of all diagnoses,

including suspected and confirmed cases, could lead to false-positive cases. However, there is no reason to believe that the recording was differential between asthmatic and non-asthmatic women, reducing this potential bias towards the null. Finally, it is unlikely that one maternal exposure (i.e. asthma) will result in the increase of all major malformations categories. We used all major malformations combined only as an empirical example that provided the largest number of cases and the capacity to compare with previous studies. Future research should explore the associations between maternal exposures and specific categories of malformations (e.g. maternal diabetes and cardiac defects).

In conclusion, our study showed that the case ascertainment definitions had a considerable impact on the prevalence of major malformations, but a small influence on the aORs. The case ascertainment definition based on ≥ 1 hospitalization diagnosis combined with the TCMC is the preferred method, since it has the least chance of including misclassified and false positive cases. These results could assist in guiding future research on congenital malformations and the comparative effectiveness and safety of drug therapies during pregnancy. Future studies are needed to formally assess the validity of the proposed case ascertainment definitions and to estimate their impact on other maternal exposures.

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Compliance with Ethical Standards

Conflict of interest All authors have indicated they have no potential conflicts of interest to disclose.

Ethical Statement This research project was approved by the Ethics Committee of the *Hôpital du Sacré-Cœur de Montréal*. Authorization was obtained from the *Commission d'Accès à l'Information du Québec* to access and link the RAMQ and MED-ECHO databases.

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