-Congenital anomalies of the kidney and the urinary tract: a Murmansk County Birth Registry study

Running title: Congenital urinary anomalies in Murmansk County

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Abstract

Background

Congenital anomalies of the kidney and the urinary tract (CAKUTs) are relatively common birth defects. The combined prevalence in Europe was 3.3 per 1000 in 2012. The risk factors for these anomalies are not clearly identified. The aims of our study were to calculate the birth prevalences of urinary malformations in Murmansk County during 2006-2011 and to investigate related prenatal risk factors.

Methods

The Murmansk County Birth Registry was the primary source of information and our study included 50 936 singletons in the examination of structure, prevalence and proportional distribution of CAKUTs. The multivariate analyses of risk factors involved 39 322 newborns.

Results

The prevalence of CAKUTs was 4.0 per 1000 newborns [95%CI: 3.4-4.5] and did not change during the study period. The most prevalent malformation was congenital hydronephrosis (14.2% of all cases). Diabetes mellitus or gestational diabetes [OR = 4.77, 95%CI: 1.16-19.65], acute infections while pregnant [OR = 1.83, 95%CI: 1.14-2.94], the use of medication during pregnancy [OR = 2.03, 95%CI: 1.44-2.82], and conception during the summer [OR = 1.75, 95%CI 1.15-2.66] were significantly associated with higher risk of CAKUTs.

Conclusions

The overall four-fold enhancement of the occurrence of urinary malformations in Murmansk County for the 2006-2011 period showed little annual dependence. During pregnancy, use of medications, infections, pre-existing diabetes mellitus or gestational diabetes were associated with increased risk of these anomalies, as was conception during summer. Our findings have direct applications in improving prenatal care in Murmansk County and establishing targets for prenatal screening and women’s consultations.

Key words: Congenital anomalies of the kidney and the urinary tract, risk factors, Russia, the Murmansk County Birth Registry

Introduction

Congenital anomalies of the kidney and the urinary tract (CAKUTs) constitute one of the most common groups of birth defects. In 2012, the prevalence in Europe was 3.3 per 1000 births (EUROCAT, 2013). They represent a highly heterogeneous group, with a few being incompatible with life while minor abnormalities can be asymptomatic for long periods of time (Barakat and Drougas, 1991). Anomalies of the kidney are more common than those of the lower urinary tract and often lead to chronic renal failure (Barakat and Drougas, 1991). Collectively, CAKUTs account for 30–50% of cases of renal failure among children worldwide (dos Santos Junior et al., 2014).

The development of human kidneys is completed by weeks 34-36 of gestation (Hei and Yi, 2014), and thus are amenable to teratogens during the whole pregnancy. The role of maternal and environmental factors in development of CAKUTs is not well established. Previous studies have reported associations of CAKUTs with a number of maternal factors, including: pre-existing diabetes mellitus (DM) or gestational diabetes (GD) (Kalter, 2003; Sheffield et al., 2002; Shnorhavorian a et al., 2011); febrile illness during pregnancy (Abe a et al., 2003), advance age (Shnorhavorian et al., 2011); renal disease (Shnorhavorian et al., 2011); as well as medication use (especially non-steroid anti-inflammatory drugs and angiotensin converting enzyme inhibitors; Boubred et al., 2006). Studies of the effect on CAKUTs from tobacco use and alcohol consumption have yielded controversial results in that some show negative associations, while others do not (Kallen, 1997; Li et al., 1996; Shnorhavorian et al., 2011). The evidence for seasonal variation is also contradictory in that increased risk of CAKUTs has been reported for both newborns conceived (Luteijn et al., 2014) or delivered during the summer months (Feldman et al., 2009).

The prevalence of CAKUTs in Russia is estimated at the population and country level through mandatory reporting of birth defects of its three most severe forms, namely renal agenesis or dysgenesis, epispadias and bladder extrophy. The total prevalence of these three forms in Russia was 0.1 per 1000 newborns in 2011 (RIPCS, 2011). Studies of urinary birth defects in different regions of Russia report prevalences of all CAKUTs that vary from 1.1 per 1000 in Saratov to 5.7 per 1000 in Izhevsk (Andreeva, 2008). Moreover, CAKUTs represented 10-15% of all birth defects (Andreeva, 2008; Trefilov, 2006) and were responsible for 65% of cases of chronic renal failure (Molchanova, 2004). By contrast, we could not identify any Russian studies that explored risk factors for this group of congenital defects.

The population-based birth registry in Murmansk County recorded all anomalies diagnosed from 22 weeks of gestation until hospital discharge and thus provides unique opportunities for research. Previously we reported a high prevalence of musculoskeletal and urinary tract malformations in the town of Monchegorsk, which is located in Murmansk County (Postoev et al., 2015a). The overall perinatal prevalence of CAKUTs in Monchegorsk increased from 4.4 per 1000 in 1993-2002 (that of all BD was 38.7 per 1000) to 19.1 in 2003-2011 (46.3 per 1000 for all BD). Thus, the CAKUTs accounted for 41% of all registered birth defects. An increase in the prevalence of CAKUTs has also been reported by the European Surveillance of Congenital Anomalies (EUROCAT), but to a lesser extent (from 1.5/1000 in 1980 to 3.6/1000 in 2011) (EUROCAT, 2013). The cystic kidney prevalence reported by the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) for Norway increased from 0.1/1000 in 1974 to 0.6/1000 in 2010 (ICBDSR, 2013). This trend could partly be explained by implementation of prenatal diagnostics in 1990s in Western countries and in the early 2000s in Russia. Pertinent visualisation allowed 81.8% of CAKUTs to be detected prior to birth in Europe (Wiesel et al., 2005), while in the Murmansk region it was 42% (Postoev et al., 2015b). Nevertheless, the exact reasons that explain the observed increases remain unknown. Factors such as smoking and alcohol consumption during pregnancy and genital/urinary infection may have contributed, as their prevalences increased considerably in Russia during a period of transition.

The aims of this study were to calculate the birth prevalence of CAKUTs in Murmansk County and to investigate the perinatal risk factors for their occurrence.

Materials and Methods

SUBJECTS AND DATA SOURCES

The study population of this registry-based study included all newborns delivered in Murmansk County and registered in the MCBR in the period 2006-2011 (total N=52 086). The MCBR was also the primary source of information about associated risk factors.

Murmansk County is situated in the Kola Peninsula of Northwest Russia, of which a significant part is located above the Arctic Circle. The region has 766 300 inhabitants, of whom 92.6% are urbanites (Murmanskstat, 2015a). Its population has decreased by 30 000 during the last five years. There were 9017 newborns in the County in 2014 and corresponds to a birth rate of 11.7/1000, which is similar to that reported for the whole of Russia (Murmanskstat, 2015b).

The MCBR was established in 2005 and includes all births in Murmansk County as of January 1, 2006. The registered data were systematically collected in the county's 15 delivery departments and included the following specific sources: the medical histories of the mothers; delivery journals and records; birth records; and interviews with the mothers conducted by a physician or midwife. The MCBR database contains data about paternal age, ethnicity, residence, and occupation; maternal civil status, education, height and weight; data about previous pregnancies and diseases before pregnancy; course of the current pregnancy (including complications, intake of supplements, smoking habits, any abuse, diseases during pregnancy, and results of prenatal screening); delivery type and post-delivery maternal complications; and the status of the newborn, his/her gestational age and any medical conditions during the early neonatal period. These recorded sources have previously been described in detail (Anda et al., 2008; Anda et al., 2011), and their quality was determined to be satisfactory for epidemiological research.

STUDY VARIABLES

The diagnoses of congenital malformations were based on the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10), which includes birth defects in Chapter XVII. The CAKUTs fall under the codes Q60-Q64. In spite of their different clinical manifestations, CAKUTs have a common mesoderm origin, and manifest during similar critical periods of embryogenesis (Moore et al., 2003; dos Santos Junior et al, 2014). Consequently, investigation of common risk factors for this group of malformations seems pertinent and any malformation coded as a CAKUT was thus included in our analysis. Diagnoses were recorded up to the departure of the newborns from the birth clinics.

Prenatal ultrasound screening in Russia was established by national law in 2000, and includes ultrasonography at gestational ages of 10-14, 20-24 and 30-32 weeks and biochemical tests of blood alpha-fetoprotein and chorionic gonadotropin at gestational age 11-14 weeks (Ministry of Health of Russian Federation, 2000). It is offered by obstetricians to every pregnant woman in compliance with a national law, and is free of charge. Postnatal ultrasonography supplemented routine examinations and any prenatal suspicion of an anomaly of the urinary system was confirmed by examination after birth. Fetal deaths were followed up by autopsy examinations.

Potential risk factors were selected based on a detailed literature review and pertinent information was taken directly from the MCBR database. All continuous variables were recoded as categorical. Maternal age was divided into three groups, specifically less than 18, 18-35, and older than 35 years, while the father's age was dichotomized with a cut-off point at 35 years. The international classification for maternal body mass index (BMI) was adopted, with underweight defined as <18.5 kg/m^2, 18.5-24.9 kg/m^2 for normal weight, and ≥25 kg/m^2 as being overweight or obese. BMIs were calculated according to maternal anthropometry at the first antenatal visit. Yes/no dichotomization with the absence of a factor as the reference category was adopted for the following: occurrence or use during pregnancy of DM or GD, consumption of multivitamins or folic acid intake, cigarette smoking and infections; and evidence of alcohol abuse, chronic genital or urinary infections before pregnancy. The season of conception was calculated using the first day of the last menses.

Data analyses

We used the registered two- and three-digit level ICD-10 codes to analyse the classification of CAKUTs, their prevalences and proportional distributions. Newborns with multiple malformations were included in the numerator of these estimates when a CAKUT was present among the diagnoses. All prevalence estimates are presented with their 95% confidence intervals (CI). There were 52 806 pregnancy outcomes registered in the MCBR, of which 1 313 were excluded due to missing or incorrect information about gestational age and 99 due to missing information about birth defects. All cases of multiple pregnancy (n = 458) were also precluded from the analyses. Thus, 50 936 singletons were included in the investigation of structure, prevalence and proportional distribution of CAKUTs.

The prevalence of CAKUTs was estimated for newborns with and without a consideration of possible risk factors (or for maternal characteristics with multiple values), and compared statistically using the chi-square test. Adjusted malformation risks associated with the selected predictors were analysed by multiple logistic regression using CAKUTs as a binary outcome. Risk ratios were approximated by odds ratios extracted from the regression model. There were 39 322 newborns (185 cases) without any missing information for the variables of interest, and these were included in the logistic regression analysis. Detailed information about missing variables is presented in Figure 1. The final regression model was established by employing the backward stepwise regression model, using the likelihood ratio method for inclusion of all studied factors and probability criteria for removal of 0.1. All analyses were performed using IBM SPSS 21.0 software package.

Ethical considerations

The Committee for Research Ethics at the Northern State Medical University (Arkhangelsk, Russia) and the Regional Committee for medical and health research ethics (Tromsø, Norway) approved the current study.

Results

There were 203 registered newborns with CAKUTs in Murmansk County in 2006-2011. The prevalence at birth was 4.0 per 1000 newborns (95%CI 3.4-4.5) and it did not change over time (p for linear trend = 0.26). Nevertheless, there was some variation in the birth prevalence: from 2.4 per 1000 newborns (95% CI 1.3-3.4) in 2006 to 5.6 per 1000 newborns (95% CI 4.0-7.1) in 2008.

More than half of the malformations were diagnosed as "other congenital anomalies of kidney". Congenital hydronephrosis was the most prevalent malformation and represented 14.2% of all registered CAKUTs. Multiple anomalies of the kidney or urinary system affected every tenth newborn with CAKUTs (see Table 1).

Paternal age, maternal BMI, proportion of supplement intake (multivitamin, folic acid), as well as the fraction of mothers who smoked or consumed alcohol was not significantly different between newborns with and without malformations (Table 2).

The prevalence of CAKUTs at birth was significantly higher among newborns whose mothers had genitourinary infections before the pregnancy ($p = 0.02$), or any infection during the current pregnancy ($p < 0.001$) and mothers who took medications when being pregnant ($p = 0.001$). Similarly, the occurrence of CAKUTs was different between newborns conceived in different seasons ($p = 0.001$), with the highest prevalence for newborns conceived during the summer (Table 2).

The prevalence of CAKUTs among newborns whose mothers suffered from DM or GD was higher but not significantly so ($p = 0.09$). The latter likely reflects the low proportion (0.2%) of mothers with these conditions.

Based on the multivariate analysis results summarized in Table 3, diabetes mellitus or gestational diabetes (adjusted OR = 4.77), infections during pregnancy (adjusted OR = 2.03), the use of any medication during pregnancy (adjusted OR = 1.83) and conception during summer (adjusted OR = 1.75) were the only variables significantly associated with CAKUTs.

Discussion

Prevalence of CAKUTs

The estimated all-year birth prevalence of CAKUT at birth in Murmansk County was higher than that for the combined data for all EUROCAT member countries for the same period (Dolk et al., 2010). This difference reached statistical significance for 2008 (p=0.0008) and 2009 (p=0.003): 5.6 *versus* 3.4 and 5.4 *versus* 3.5, respectively (EUROCAT, 2013).

The most prevalent group was unspecified malformations. Since some of the latter were not confirmed after discharge from the maternity wards, our results could have been subject to overestimation. In addition, some minor anomalies might be revealed later in life even when the level of prenatal diagnosis of CAKUTs is high. For example, 73% of all congenital hydronephrosis cases were diagnosed prior to birth in Europe in 1995-2004 (Garne et al., 2009). In our previous study (Postoev et al., 2015b), the prenatal detection rate for CAKUTs in Monchegorsk was 42.1% for the 2000-2007 period. The possibility for underestimating the prevalence when using data at birth is illustrated by Caiulo et al., 2012, who showed that the prevalence of CAKUTs among children at the age of two months was close to 1 % based on mass ultrasound screening.

Our observed prevalences of renal agenesis and congenital hydronephrosis were lower and that of cystic kidney disease higher relative to the EUROCAT registry data. The latter indicate that the proportion of pregnancy terminations due to kidney malformation varied from 4.9% for congenital hydronephrosis to 68.2% for renal agenesis (EUROCAT, 2013). The lower prevalence of severe malformation in our data set might be explained by the exclusion of pregnancies under 22 weeks of gestation.

Diagnostic issues

The estimation of birth defect prevalences depend on the diagnostic quality and experience of the clinicians performing the ultrasound examination. There were no national guidelines for the influence of gestational age in assessments of urodynamic and parenchymal changes (Adamenko et al., 2008), nor strict ultrasound criteria for pyelectasis and hydronephrosis. Consequently, it is not surprising that diagnoses of CAKUTs may be done using different clinical norms. Our data supports this perspective, as the prevalence of CAKUTs in Murmansk County varied between districts and hospitals. Such inconsistency can lead to over diagnosis of some CAKUTs during perinatal screening, especially congenital hydronephrosis and non-specified malformations.

RISK FACTORS OF CAKUTS

The risk factors identified in the current study (see Table 3) have been reported previously, although they appear to differ in the duration and extent of their influence. The discussion that follows explores this.

Amri et al. (1999) demonstrated a potential harmful effect of hyperglycemia on kidney development in rats involving *in vivo* and *in vitro* experiments. Prospective cohort and case-control studies have also assessed this impact (Sheffield et al., 2002; Banhidy et al., 2010; Shnorhavorian et al., 2011; Dart et al., 2015). Relative to GD, the risk of CAKUTs was higher for DM (Shnorhavorian et al., 2011). Due to the small number of cases, it was not possible in our study to consider DM and GD separately. Nevertheless, the combined variable showed a strong association with CAKUTs The magnitude of the observed prevalence of newborns with CAKUTs among mothers with diabetes was 1.6%, which is four-fold lower than that reported in a Texas (USA) study conducted in 1991-2000 (Shnorhavorian et al., 2011).

The significant association of CAKUTs with maternal infections during pregnancy is supported by other studies (Abe et al., 2003; Lukomska et al., 2012). These studies differ from the current assessment by limiting the exposure to the first trimester of pregnancy rather than considering the whole pregnancy duration. We opted for this approach because nephrogenesis is not limited to the first 12 weeks of pregnancy. Explanations of the teratogenic effect of maternal infectious may include the associated hyperthermia. In a summary of their animal experiments, Edwards et al., (1995) document the occurrence of structural malformations of the kidney (e.g., hypoplasia and agenesis) in offspring of mothers with extensive exposure to hyperthermia during pregnancy. Based on the Atlanta Birth Defects Case-control Study, Erickson (1991) reports robust associations between all defects and maternal febrile illnesses (specifically, “any fever” or “flu” experienced by the study respondents during the 4 months prior to conception and the first trimester). Unfortunately, we could not separate infectious diseases by presence or absence of fever, because no such information was available in the registry database. Moreover, prevalence of non-febrile infections could have been underestimated due to underreporting by mothers. Thus, the effect of infections observed in the present work should be considered as a combined effect of infectious agents and hyperthermia. Even though the emphasis in birth defect risk-factor studies has been on febrile infections in the context of hyperthermia as the teratogen, there is good evidence that maternal non-febrile infections and chronic diseases do indeed pose potential risks of birth defects and susceptibility to disease after birth (e.g., Erickson, 1991; Dong et al., 2015; Lee et al., 2015).

Infections during pregnancy may be expected to be closely related with the intake of certain medications, and this is perhaps this is reflected in the nearly two-fold risk of CAKUTs among newborns of mothers reporting infections and use of medications during pregnancy. This risk is similar in magnitude to those reported for antibiotics and antipyretics medications (Abe et al., 2003; Lukomska et al., 2012). We refrained from dividing the drugs into pharmacological groups, because most women (12 452 or 31.8%) consumed more than one medication due to pregnancy complications or maternal illness that existed prior to pregnancy; the most frequently used were dipyridamolum, drotaverinum and dydrogesteronum. Higher risk of CAKUTs has also been identified for aspirin-containing drugs (Abe et al., 2003) and angiotensin-converting enzyme inhibitors (Ratnapalan and Koren, 2002), but these were not frequently administrated in our study and this obviated any further analysis.

We found that the highest prevalences of CAKUTs occurred for newborns conceived during the months March-August, and this is supported by our logistic regression analysis (see Table 3). Luteijn et al., (2014) reported that urinary defects among European newborns peaked in July and indicated that this seasonality was driven by congenital hydronephrosis; it made up roughly 40% of the urinary defects. While Carton (2012) found the same seasonal variation with a peak in July for renal agenesis or hypoplasia based on the data for 1 967 654 livebirths in New York State, USA. Since Murmansk County is within or near the Arctic Circle, the summer season is brief and relatively cold; moreover, this is an unique arctic daylight regimens during the year (long in summer and short in winter). A recent study from Norway (Hwang et al., 2013), which includes data for regions with similar climate features, did not show seasonal variation in the prevalence of CAKUTs. However, it did identify peaks in March and February, respectively for respiratory defects and Down syndrome. Generally speaking, there is some evidence (see Hwang et al., 2013 and references therein) that observed seasonal variation may reflect environmental factors (e.g., different concentrations of teratogenic pollutants in air or water), meteorological conditions (polar night and day), and variation in the frequency of acute maternal infections. In our data set, adjustment for infections during pregnancy indirectly identified potential influences of the first two factors, but this could not be quantified due to the absence of such information in the MCBR.

The impact of maternal chronic genital and urinary tract infections has not been routinely assessed in CAKUTs studies. However, Shnorhavorian et al. (2011) report a five-fold increase in CAKUTs in association with pre-existing maternal renal disease. Our own findings indicate a near significant association (see Table 3). We presume that this reflects insufficient statistical power because of a rather high proportion of missing data for this variable. Related issues are the misclassification of this risk factor due to different diagnostic practices and an inherent reluctance to report it (i.e., non-differential bias). Inclusion of missing values as non-exposure lead to increased risk ratios. Moreover, we also expect misclassification to have occurred between this pre-pregnancy variable and “acute infections during pregnancy”.

Strengths and weaknesses

The current study is the first population-based assessment of the epidemiology of CAKUTs and their risk factors in North-West of Russia that employs a register database shown to be of acceptable validity (Anda et al., 2008). The MCBR provides information not only on outcome, but also about exposure risk factors during pregnancy. It was established in accordance with international standards, and minimizes the possibility of selection bias. These attributes lead to good generalizability. Nevertheless, our study has some limitations.

The ascertainment of the CAKUT cases is possibly incomplete, because only those diagnosed during the stay in maternity houses were included. As indicated earlier, there were possibilities for misclassification due to the high proportion of non-specified malformations.

Missing values constituted an important issue in our multivariable analysis, as for some of the variables this exceeded than 10% (see Figure 1). These necessary exclusions from the logistic regression analysis might have biased our risk ratio estimates, which could have resulted in an underestimation of the risk ratios. As indicted above, a high proportion of missing data could have resulted in an underestimation of the risk ratios.

We sought to control confounding in estimating the influence of CAKUT risk factors by considering only well-established variables in the logistic regression analysis. We also avoided the inclusion in the model of all independent variables as categorical, as this could potentially lead to imperfect adjustment and bias due to residual confounding (Rothman et al., 2008). The breakdown into more than two categories of maternal age, body mass index and season are other cases in point.

The likelihood of underreporting of socially sensitive information such as maternal smoking also needs to be mentioned. Furthermore, data about the consumption of alcohol were not provided by the mothers, but was based on documented evidence of abuse provided by physicians. Although these factors were not significant predictors, they could have led to non-differential misclassification of exposure by attenuating the CAKUT risk estimates among smoking mothers.

Conclusions

The prevalence of CAKUTs in Murmansk County during 2006-2011 was 4.0 per 1000 newborns without significant changes over the observation period. The usage of medications during pregnancy, maternal diabetes mellitus or gestational diabetes, maternal infections during the pregnancy, and conception during June-August was associated with increased risk of CAKUTs. These findings have direct applications in improving prenatal care in Murmansk County and establishing targets for prenatal screening and consultations with affected women; they constitute a framework for future research on the teratogenic effects of medications and infections.

Acknowledgements

The authors thank the office staff of the Murmansk County Birth Registry and Rod Wolstenholme, executive officer, Section for Dissemination Services at Faculty of Health Sciences, The Arctic University of Norway.

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Table legend

TABLE 1. Diagnosis-specific Frequencies, Prevalences (per 1000 newborns) and Distribution (%) of CAKUTs Among Newborns in Murmansk County (2006-2011)

TABLE 2. Univariate Comparisons of the Prevalence of CAKUTs by Maternal Socio-demographic, Anthropometric and Lifestyle Characteristics in Murmansk County (2006-2011)

TABLE 3. Risk Factors Associated with CAKUTs (results of the multivariate analysis)

Figure legend

FIGURE 1. Number of Births Included in the Analyses and Information about Missing Variables

TABLE 1. *Diagnosis-specific Frequencies, Prevalences (per 1000 newborns) and Distribution (%) of CAKUTs Among Newborns in Murmansk County (2006-2011)*

ICD-10 code	**Birth defect**	**Distribution**		**Prevalence (95%CI) per 1000 newborns**
		n	**%**	
Q 60	Renal agenesis and other reduction defects of kidney	4	2.0	0.08 (0.03-0.20)
Q 61	Cystic kidney disease	21	10.3	0.41 (0.27-0.63)
Q 62	Congenital obstructive defects of renal pelvis and congenital malformations of ureter	39	19.2	0.77 (0.56-1.05)
Q62.0	Congenital hydronephrosis	29	14.3	0.57 (0.40-0.82)
Q 63	Other congenital malformations of kidney	108	53.2	2.13 (1.76-2.56)
Q 64	Other congenital malformations urinary system	7	3.5	0.14 (0.07-0.28)
	Multiple anomalies of kidney or urinary system	24	11.8	0.47 (0.32-0.70)
Total		203	100	4.00 (3.43-4.54)

TABLE 2. *Univariate Comparisons of the Prevalence of CAKUTs by Maternal Socio-demographic, Anthropometric and Lifestyle Characteristics in Murmansk County (2006-2011)*

Characteristics	N	%	Prevalence of CAKUTs		p-Value[1]
			n	Per 1000 newborns	
Age of mother:					0.39
less 18 years	721	1.4	5	6.9	
18-35 years	45706	89.7	178	3.9	
older 35 years	4508	8.9	20	4.4	
Age of father:					0.10
18-35 years	37092	79.6	143	3.9	
older 35 years	9477	20.4	48	5.1	
Maternal BMI:					0.42
less 18.5 kg/m2	3133	6.3	10	3.2	
18.5-24.9 kg/m2	32801	65.7	140	4.3	
more than 25kg/m2	13976	28.0	50	3.6	
Use of medications during pregnancy:					0.001
yes	39125	76.8	176	4.5	
no	11811	23.2	27	2.3	
Diabetes mellitus or gestational diabetes:					0.09
yes	124	0.2	2	16.1	
no	50812	99.8	201	4.0	
Multivitamin intake during the pregnancy:					0.34
yes	46900	92.5	191	4.1	
no	3824	7.5	11	2.9	
Folic acid intake during the pregnancy:					0.16
yes	12965	25.6	43	3.3	
no	37619	74.4	159	4.2	
Cigarette smoking during the pregnancy:					0.52
yes	9169	18.3	39	4.3	
no	40836	81.7	155	3.8	
Evidence of alcohol abuse:					0.17
yes	187	0.4	2	10.7	
no	50545	99.6	200	4.0	
Chronic sex tract or urinal infections before pregnancy:					0.02
yes	10992	25.2	61	5.5	
no	32564	74.8	124	3.8	
Infections during the pregnancy:					<0.001
yes	7345	14.4	56	7.6	
no	43591	85.6	147	3.4	
Season of conception[2]:					0.001
Winter	12671	24.9	37	2.9	
Spring	12383	24.3	56	4.5	
Summer	12734	25.1	71	5.6	
Autumn	13077	25.7	39	3.0	

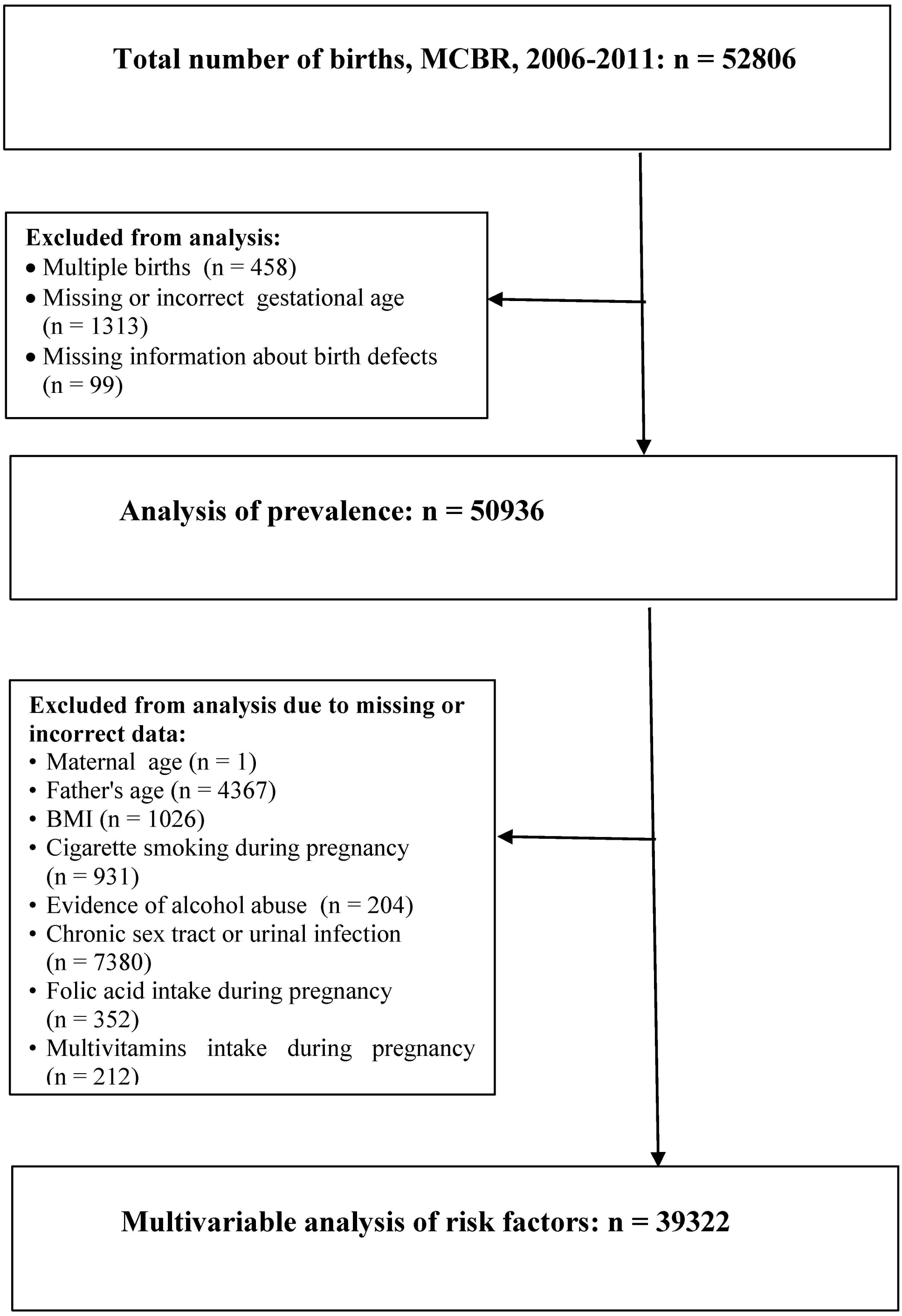
[1]- Significant p-values indicate that differences in prevalence exist between the categories of the indicated

characteristics.
[2]The months of the year are grouped by seasons as follows: December-February (Winter); March-May (Spring); June-August (Summer); and September-November (Autumn)

TABLE 3. *Risk Factors Associated with CAKUTs (results of the multivariate analysis)*

Characteristics[1]	Adjusted OR	95%CI
Use of medications during pregnancy	1.83	1.14-2.94
Diabetes mellitus or gestational diabetes	4.77	1.16-19.65
Chronic sex tract or urinal infections before pregnancy	1.34	0.97-1.84
Infections during the pregnancy	2.03	1.44-2.82
Season of conception		
Winter	1.00	-
Spring	1.45	0.94-2.25
Summer	1.75	1.15-2.66
Autumn	0.86	0.51-1.35

[1-] Only those variables that remained in the final regression model (backward stepwise regression) are presented.


Total number of births, MCBR, 2006-2011: n = 52806
Excluded from analysis:
• Multiple births (n = 458)
• Missing or incorrect gestational age (n = 1313)
• Missing information about birth defects (n = 99)
Analysis of prevalence: n = 50936
Excluded from analysis due to missing or incorrect data:
• Maternal age (n = 1)
• Father's age (n = 4367)
• BMI (n = 1026)
• Cigarette smoking during pregnancy (n = 931)
• Evidence of alcohol abuse (n = 204)
• Chronic sex tract or urinal infection (n = 7380)
• Folic acid intake during pregnancy (n = 352)
• Multivitamins intake during pregnancy (n = 212)
Multivariable analysis of risk factors: n = 39322