Clinical Kidney Journal, 2023, vol. 16, no. 12, 2652–2660

https://doi.org/10.1093/ckj/sfad217
Advance Access Publication Date: 6 September 2023
Original Article

ORIGINAL ARTICLE

Associations between maternal chronic diseases and congenital anomalies of the kidney and urinary tract in offspring: a population-based cohort study

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ABSTRACT

Background. The relationship between maternal chronic diseases and congenital anomalies of the kidneys and urinary tract (CAKUT) in offspring still needs elucidation. This study aimed to comprehensively evaluate the associations between maternal chronic disease and CAKUT in their offspring.

Methods. Data of mothers and children were extracted from the Taiwan Maternal and Child Health Database and National Health Insurance Research Database. The concept of developmental origins of health and disease (DOHaD) was used to select maternal chronic diseases.

Results. The study cohort included 1 196 175 mothers and 1 628 706 offspring. Analysis showed that maternal chronic diseases, especially type 1 diabetes, type 2 diabetes, gestational diabetes, connective tissue disorders and CAKUT were highly associated with CAKUT in the offspring. Higher maternal age, abnormal birthweight (>3500 g or <2500 g), gestational age <36 weeks and birth order <2 were all associated with a higher risk of CAKUT. Maternal chronic hypertension and taking angiotensin-related drugs increased the odds ratios of obstructive kidney disease in the offspring. Offspring tended to have the same type of CAKUT as their mothers.

Conclusion. Maternal chronic diseases, older maternal age and abnormal birthweight are risk factors for CAKUT. Also, a percentage of patients with CAKUT were not full-term newborns. Results support prenatal counselling and health management of pregnant women with chronic diseases and extra care for infants with a high risk of anomalies. It is strongly recommended that prevention of CAKUT in offspring should start with care of the mothers' prenatal chronic diseases.

Keywords: chronic disease, congenital anomaly of kidney and urinary tract disease (CAKUT), health characteristics, Maternal and Child Health Database, nationwide population-based cohort study

Received: 30.7.2022; Editorial decision: 9.8.2023

INTRODUCTION

Congenital anomalies of the kidney and urinary tract (CAKUT) is a group of abnormalities affecting the urinary system, representing ≈20–30% of all anomalies identified in the prenatal period [1–3]. The incidence rate ranges from 4 to 60 per 10 000 newborns [4, 5]. Although CAKUT is a congenital defect and is usually diagnosed before age 3 years, the outcomes of CAKUT patients vary. CAKUT may be unnoticed in early life and may also result in life-threatening kidney failure and end-stage renal disease.

Since CAKUT includes a group of conditions that affect the development of the urinary system before birth, the disease typically originates from defects in development. We suspect that the notion of developmental origins of health and disease (DOHaD) can be applied to CAKUT. The DOHaD concept connects stresses experienced by the foetus and diseases diagnosed after birth [6, 7]. Stressors may be insufficient nutrition availability, infection, exposure to chemicals or drugs or metabolism disorders induced by maternal chronic diseases [6, 8, 9]. These factors affect the pluripotent cells in the differentiation and formation of organs and tissues. Evidence shows that these changes are locked in human DNA in the form of epigenetic modifications [10]. Therefore, the association between CAKUT and DOHaD suggests that factors occurring during pregnancy may play a role in the development of CAKUT in the foetus.

Information regarding the association between maternal chronic disease and offspring CAKUT is limited. Several population-based studies have shown that maternal gestational or pregestational diabetes and maternal renal disease have been reported to be associated with higher risks of offspring CAKUT [5, 11–13]. However, the inclusion criteria for CAKUT offspring and the covariates analysed in the studies varied considerably. Tain *et al*. [5] reported the incidence and risks of CAKUT in newborns using the birth registry in Taiwan. Nonetheless, the incidence may be underestimated since, in the analysis, CAKUT was reported only within 7 days of birth. Information regarding maternal disease was recorded by medical staff in the birth registry, which may be inaccurate.

In this nationwide, population-based study, we hypothesized that specific maternal chronic diseases would increase the risk of CAKUT in offspring. The purpose of this study was to perform a comprehensive evaluation of the association between maternal chronic disease and CAKUT in their offspring. Several certified nationwide databases were used to provide accurate and complete records for evaluation by interlinkage of the databases.

MATERIALS AND METHODS

Data sources

The following datasets were used in this study: the Taiwan Maternal and Child Health Database (TMCHD), the Birth Certificate Application (BCA) and the National Health Insurance Research Database (NHIRD) of Taiwan.

The TMCHD provides encrypted personal identification numbers of all live newborns and their parents between 2003–2015, used to identify newborn babies and their parent pairs, enabling interlinkage between various datasets.

The BCA is maintained by the Health Promotion Administration of the Ministry of Health and Welfare in Taiwan and contains information on maternal characteristics (e.g. nationality, age at delivery, risk factors for pregnancy), perinatal care (e.g. specific management during perinatal period, method of delivery and complications of delivery) and the newborn's characteristics (e.g. sex, gestational age, birthweight, birth order, single/multiple births, congenital anomalies and Apgar scores).

The NHIRD provides medical claims and the histories of infants and mothers since 1998. Since the National Health Insurance program is a mandatory insurance plan provided by the government, the NHIRD covers >99% of the population, including both citizens and foreign nationals who have permission to work and study in Taiwan.

In Taiwan, it is legally required that all live births and deaths be registered within 10 days [14]. The above datasets are nationwide population-based databases that are established, updated and supervised by the Health and Welfare Data Science Center, Ministry of Health and Welfare, Taiwan [15]. Previous studies have shown that the databases are validated and have a high level of information integrity [16–18].

Study design and participants

This retrospective population-based cohort study extracted the data of newborns and their mothers from the aforementioned databases. All live births with a gestational age >22 weeks and a birthweight >500 g between 2004 and 2012 were enrolled in this study. All data on the characteristics of both mothers and their offspring were collected from the BCA dataset and clinical visits were collected from the medical claims in the NHIRD using encrypted personal identification numbers.

Exposure variables

Maternal chronic diseases that may generate stress or changes in blood flow and oxygenation to the foetus were identified based on the DOHaD concept and results of previous studies [5, 11–13, 19–22]. Codes from the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) were used to identify maternal chronic diseases diagnosed before giving birth from both inpatient and outpatient claims (Supplementary Table 1. Maternal chronic diseases included gestational diabetes, pregestational diabetes including types 1) and 2, hypertension, CAKUT, connective tissue disorders, thyroid disorders, iron deficiency anaemia, epilepsy or mood disorders, obesity and angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) administration during pregnancy. Data on mothers with the above-mentioned chronic diseases, except for gestational diabetes, were retrieved from the diagnostic records of women with at least one hospitalization or more than two outpatient visits within 1 year before and during pregnancy. Only mothers with gestational diabetes diagnosed after >20 weeks of gestation and those for whom ACEI or ARB medications were prescribed during pregnancy were included.

Outcome variables

The outcome variables include any form of CAKUT identified by ICD-9-CM codes. CAKUT was divided into four subgroups: renal anomaly, obstructive kidney disease, cystic kidney disease and other CAKUT. If more than one subtype of CAKUT was found in the same newborn, the earliest-appearing diagnosis was selected as the representative subtype of CAKUT. The numbers of infants found in the four groups were summarized into the overall infants' CAKUT group. To prevent the impact of clinically non-significant forms or spontaneously resolved defects, only those children with CAKUT diseases recorded at least once on hospital admission or during more than two outpatient clinic visits were

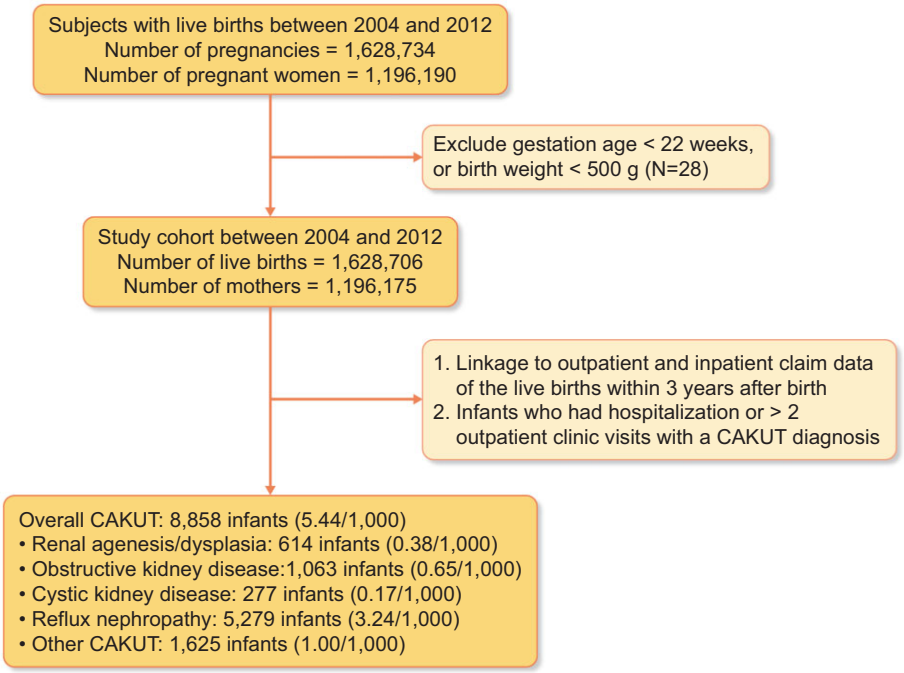

Figure 1: Flow chart of the study cohort selection.

included. Since most children with CAKUT are diagnosed before the age of 3 years [23], each infant in the present study was followed for 3 years after birth to ensure that each infant had the same follow-up period to avoid possible information bias.

Confounders

The potential confounders considered in this study were set as factors associated with the risk of CAKUT. The potential confounders were categorized into three fields: characteristics of the delivery, maternal sociodemographic and lifestyle factors and characteristics of the infant. The characteristics of delivery included parity, the type of delivery (single or multiple births) and the year of delivery. The maternal sociodemographic and lifestyle factors included nationality, age at delivery, smoking and urbanization level of residence at the time of birth. The characteristics of infants included sex, year of birth, birthweight, gestational age, birth order and geographic location of the birth site.

Statistical analysis

The prevalence of all and specific types of CAKUT between 2004 and 2012 was calculated and the Poisson regression model was used to test for trends in the prevalence of these diseases. The prevalence values for all and specific types of CAKUT of infants were assessed considering the association with maternal chronic diseases present before pregnancy. Potential confounders were adjusted using multiple logistic regression models with the generalized estimating equation and the results were presented as adjusted odds ratios (aORs) and 95% confidence intervals (CIs). To assess the potential effects of maternal chronic disease on the risk of CAKUT in the offspring, the percentage of the population with attributable risk was calculated (i.e. the proportion of cases that would have been avoided in the population if the selected maternal chronic disease had been eliminated). All statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NC, USA), and a two-tailed *P*-value $<.05$ was considered statistically significant.

Ethics approval

The study protocol was approved by the Institutional Review Board (IRB) of National Cheng Kung University Hospital (A-ER-108-245). Since this was a retrospective study and all patients' personal information was encrypted in the database and remained anonymous, the IRB waived signed informed consent.

RESULTS

A total of 1 196 190 pregnant women delivered and 1 628 734 infants were born between 2004 and 2012 in Taiwan. After excluding unqualified infants and their mothers, the remaining 1 196 175 women and 1 628 706 infants were incorporated into the study cohort. Among these, 4982 (3.06/1000) offspring were diagnosed with any form of CAKUT, including 1233 (0.76/1000) with obstructive kidney diseases, 731 (0.45/1000) with renal anomaly, 272 (0.17/1000) with cystic kidney diseases and 2746 (1.69/1000) with 'other CAKUT'. The flow chart of the study cohort selection is shown in Fig. 1.

Table 1 shows prevalence rates of CAKUT for infants and prevalence rates of maternal chronic diseases. Other CAKUT consistently ranked each year as the most prevalent subtype among infants with CAKUT, followed by obstructive kidney disease. Observing the year-to-year changes in prevalence, the trend test shows that the trend in overall infants' CAKUT did not reach statistical significance ($P = .6549$). Among specific types of CAKUT, an increasing trend was found in renal anomalies (from 0.26 to 0.55 per 1000 live births, $P < .0001$). Significant decreasing trends were found in obstructive kidney disease (from 0.87 to 0.63 per 1000 live births, $P = .0042$) and a slight decreasing

Table 1: Prevalence rates of overall and specific types of CAKUT among live births in Taiwan, 2004–2012.

Variables	Number (prevalence) per 1000 live births									Overall	P for trend
	2004	2005	2006	2007	2008	2009	2010	2011	2012		
Live births, *n*	192 949	185 594	184 867	186 354	181 727	179 114	145 260	175 389	197 452	1 628 706	
Overall infant CAKUT	538 (2.79)	533 (2.98)	608 (3.29)	617 (3.31)	563 (3.10)	580 (3.24)	464 (3.19)	522 (2.98)	537 (2.72)	4982 (3.06)	.6549
Renal anomaly	50 (0.26)	76 (0.41)	66 (0.36)	81 (0.43)	88 (0.48)	83 (0.46)	76 (0.52)	102 (0.58)	109 (0.55)	731 (0.45)	<.0001
Obstructive kidney disease	168 (0.87)	146 (0.79)	164 (0.89)	142 (0.76)	118 (0.65)	131 (0.73)	106 (0.73)	133 (0.76)	125 (0.63)	1233 (0.76)	.0042
Cystic kidney disease	21 (0.11)	26 (0.14)	35 (0.19)	33 (0.18)	37 (0.20)	30 (0.17)	30 (0.21)	25 (0.14)	35 (0.18)	272 (0.17)	.1906
Other CAKUT	299 (1.55)	305 (1.64)	343 (1.86)	361 (1.94)	320 (1.76)	336 (1.88)	252 (1.73)	262 (1.49)	268 (1.36)	2746 (1.69)	.0606
Maternal chronic diseases											
Gestational diabetes	2047 (10.61)	2114 (11.39)	2063 (11.16)	2588 (13.89)	3134 (17.25)	3327 (18.57)	2696 (18.56)	3192 (18.20)	3785 (19.17)	24 946 (15.32)	<.0001
Type 1 diabetes	57 (0.30)	89 (0.48)	94 (0.51)	92 (0.49)	78 (0.43)	97 (0.54)	89 (0.61)	121 (0.69)	131 (0.66)	848 (0.52)	<.0001
Type 2 diabetes	775 (4.02)	873 (4.70)	977 (5.28)	1053 (5.65)	1110 (6.11)	1215 (6.78)	1133 (7.80)	1356 (7.73)	1516 (7.68)	10 008 (6.14)	<.0001
Hypertension	792 (4.10)	925 (4.98)	1003 (5.43)	1111 (5.96)	1225 (6.74)	1297 (7.24)	1204 (8.29)	1459 (8.32)	1772 (8.97)	10 788 (6.62)	<.0001
CAKUT	112 (0.58)	136 (0.73)	156 (0.84)	192 (1.03)	226 (1.24)	246 (1.37)	195 (1.34)	263 (1.50)	342 (1.73)	1868 (1.15)	<.0001
Connective tissue disorders	638 (3.31)	737 (3.97)	958 (5.18)	1142 (6.13)	1393 (7.67)	1595 (8.90)	1495 (10.29)	1965 (11.20)	2551 (12.92)	12 474 (7.66)	<.0001

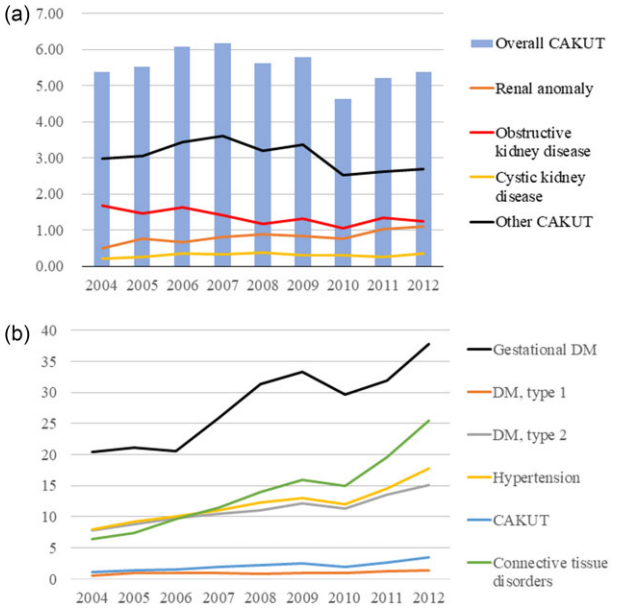

Figure 2: Prevalence rates of **(a)** various types of offspring CAKUT and **(b)** selected maternal chronic diseases in Taiwan between 2004 and 2012.

trend in other CAKUT (from 1.55 to 1.36 per 1000 live births, $P = .0606$). No significant trend was observed in cystic kidney disease ($P = .1906$). The same patterns are observed in Fig. 2a. In addition, the prevalence rates of maternal chronic diseases increased significantly. The prevalence rate of gestational diabetes, hypertension, type 2 diabetes, connective tissue diseases, CAKUT and type 1 diabetes increased from 10.61 to 19.17, 4.10 to 8.97, 4.02 to 7.68, 3.31 to 12.92, 0.58 to 1.73 and 0.30 to 0.66, respectively (Fig. 2b; all $P < .001$).

Supplementary Table 2 shows the prevalence rate and ORs stratified by the characteristics of mothers and infants. The results show a clear increasing trend in infants with CAKUT in association with maternal age. The aOR increased from 0.72 (95% CI 0.55–0.93) at maternal ages <20 years to 1.28 (95% CI 1.14–1.44) at maternal ages >35 years. The offspring gestational ages were also important. Lower gestational age increased the risk of CAKUT. The aOR for 22–36 weeks was 1.45 (95% CI 1.31–1.61) compared with full-term (37–41 weeks) infants. Also, sex, body weight and birth order of offspring also showed significance. Comparing with references, aOR for male, lower weight (<2500 g) and higher weight (≥3500 g) were 1.58 (95% CI 1.49–1.68), 1.34 (95% CI 1.19–1.51) and 1.15 (95% CI 1.07–1.24), respectively. The aORs for first offspring birth and second offspring birth were 1.33 (95% CI 1.07–1.67) and 1.29 (95% CI 1.02–1.61), respectively, compared with third offspring birth. Thus a birth order <2 was associated with the risk of CAKUT. Family income showed an interesting trend for infant CAKUT. Higher income was associated with a higher risk of infant CAKUT. Compared with family income <40 000 new Taiwan dollars (NT$)/month, the aORs were 1.16 (95% CI 1.08–1.25) and 1.34 (95% CI 1.24–1.45) when the family income was NT$40 000–80 000/month and >NT$80 000/month, respectively.

Table 2 shows the prevalence rates and ORs for overall CAKUT in offspring stratified by maternal chronic diseases from 2004 to 2012. Mothers with gestational diabetes, type 1 and type 2 diabetes and CAKUT were significantly associated with CAKUT infants. The most robust association was observed

Table 2: Prevalence rates and ORs of overall CAKUT in offspring by maternal chronic diseases, 2004–2012.

Maternal chronic diseases	Total, *n*	CAKUT, *n*	Prevalence per 1000 live births	OR (95% CI) Unadjusted	OR (95% CI) Adjusted	PAR1, %	PAR2, %
Gestational diabetes	24 946	133	5.33	1.77 (1.48–2.1)	**1.63 (1.37–1.95)**	1.30	0.21
Type 1 and 2 diabetes	10 856	65	5.99	1.97 (1.54–2.52)	**1.9 (1.48–2.43)**	0.81	0.76
Hypertension	10 788	35	3.24	1.06 (0.76–1.48)	1.03 (0.74–1.43)	0.03	0.27
Thyroid disorders	41 195	145	3.52	1.16 (0.98–1.36)	1.10 (0.93–1.30)	0.34	0.08
CAKUT	1913	25	13.07	4.07 (2.65–6.26)	**4.07 (2.65–6.26)**	0.49	1.17
Iron deficiency anaemia	33 268	108	3.25	1.06 (0.88–1.29)	1.09 (0.9–1.31)	0.25	0.15
Connective tissue disorders	12 474	51	4.09	1.34 (1.02–1.77)	1.27 (0.96–1.67)	0.28	0.05
Epilepsy or mood disorder	10 224	36	3.52	1.15 (0.83–1.6)	1.18 (0.85–1.64)	0.15	0.03
Obesity	4496	15	3.34	1.09 (0.66–1.81)	1.07 (0.64–1.78)	0.03	0.07
ACEI or ARB use during pregnancy	1487	8	5.38	1.76 (0.87–3.53)	1.74 (0.87–3.49)	0.09	0.11

PAR: population attributable risk; PAR1 was calculated by prevalence of disease, PAR2 was calculated with the total prevalence of 0.005439.
Adjusted ORs for CAKUT were calculated using a logistic regression model with the generalized estimating equation by adjusting for all of the variables listed in Table 2 plus maternal nationality, maternal age, birth order, sex, year of birth and urbanization level of birthplace. The OR is significant and shown in bold when the 95% CI does not overlap with the null value (OR = 1).

Table 3: Adjusted ORs of specific CAKUT in offspring by maternal chronic diseases, 2004–2012.

Maternal chronic diseases	aOR (95% CI) Renal anomaly (*n* = 731)	Obstructive kidney disease (*n* = 1233)	Cystic kidney disease (*n* = 272)	Other CAKUT (*n* = 2746)
Gestational diabetes	1.17 (0.69–1.99)	**2.38 (1.76–3.22)**	**2.26 (1.2–4.28)**	**1.38 (1.07–1.77)**
Type 1 and 2 diabetes	**2.56 (1.47–4.45)**	1.57 (0.91–2.71)	**2.59 (1.06–6.35)**	**1.79 (1.27–2.52)**
Hypertension	0.59 (0.19–1.83)	1.44 (0.81–2.54)	1.01 (0.25–4.06)	0.97 (0.61–1.54)
Thyroid disorders	1.11 (0.73–1.71)	1.28 (0.93–1.75)	1.54 (0.84–2.82)	0.98 (0.77–1.24)
CAKUT	**10.08 (5.22–19.47)**	1.36 (0.31–5.92)	**22.7 (10.61–48.55)**	2.09 (0.94–4.67)
Iron deficiency anaemia	1.21 (0.77–1.91)	0.91 (0.6–1.38)	0.53 (0.17–1.65)	1.19 (0.93–1.53)
Connective tissue disorders	0.63 (0.24–1.69)	1.07 (0.57–1.99)	2.27 (0.94–5.52)	**1.43 (1.01–2.02)**
Epilepsy or mood disorder	1.48 (0.7–3.13)	0.92 (0.44–1.94)	**2.89 (1.19–7.01)**	1.03 (0.64–1.65)
Obesity	1.39 (0.45–4.3)	1.48 (0.61–3.57)	1.24 (0.17–8.88)	0.79 (0.35–1.75)
ACEI or ARB use during pregnancy	1.51 (0.21–10.78)	**3.45 (1.29–9.25)**	NA	1.19 (0.38–3.72)

Adjusted ORs for CAKUT were calculated using a logistic regression model with the generalized estimating equation by adjusting for all of the variables listed in Table 2 plus maternal nationality, maternal age, birth order, sex, year of birth and urbanization level of birthplace. The OR is significant and shown in bold when the 95% CI does not overlap with the null value (OR = 1).

between maternal CAKUT and offspring CAKUT [aOR 4.07 (95% CI 2.65–6.26)]. Additionally, mothers with type 1 and 2 diabetes exhibited the second-strongest association with CAKUT in their infants [aOR 1.9 (95% CI 1.48–2.43)].

Table 3 shows the aORs of specific CAKUT in offspring stratified by maternal chronic diseases between 2004 and 2012. Mothers with gestational diabetes have higher risks of having infants with obstructive kidney disease [aOR 2.38 (95% CI 1.76–3.22)], cystic kidney disease [aOR 2.26 (95% CI 1.20–4.28)] and other CAKUT [aOR 1.38 (95% CI 1.07–1.77)]. A significant association was observed between mothers with type 1 and 2 diabetes and the risk of cystic kidney disease [aOR 2.59 (95% CI 1.06–6.35)], renal anomaly [aOR 2.56 (95% CI 1.47–4.45)] and other CAKUT [aOR 1.79 (95% CI 1.27–2.52)]. Similar patterns were observed between maternal CAKUT and the risk of infants having cystic kidney disease [aOR 22.7 (95% CI 10.61–48.55)] and renal anomaly [aOR 10.08 (95% CI 5.22–19.47)]. The use of ACEI or ARB medication during pregnancy was associated with higher risks of mothers having infants with obstructive renal disease [aOR 3.45 (95% CI 1.29–9.25)].

Table 4 shows the aORs of specific CAKUT in offspring by maternal specific CAKUT from 2004 to 2012. Mothers with cystic kidney disease [aOR 68.54 (95% CI 30.49–154.05)] had 68.54 times the risk of having infants with cystic kidney disease. The same patterns were also observed in renal anomalies [aOR 41.15 (95% CI 15.48–109.4)] but not in obstructive kidney disease and other CAKUT. Moreover, mothers with renal anomalies had a higher risk of having infants with cystic kidney disease and mothers with cystic kidney disease or other CAKUT had a significantly higher risk of having infants with renal anomalies than mothers without cystic kidney disease or other CAKUT [aOR 28.1 (95% CI 3.95–199.72) and aOR 12.78 (95% CI 3.17–51.54), respectively].

DISCUSSION

This population-based cohort study evaluated the associations between maternal chronic disease and offspring CAKUT. Results showed that the prevalence of overall CAKUT remains largely unchanged, but an increasing trend is observed in

Table 4: Adjusted ORs of specific CAKUT in offspring by CAKUT, 2004–2012.

	aOR (95% CI)			
Maternal chronic diseases	Renal anomaly ($n = 731$)	Obstructive kidney disease ($n = 1233$)	Cystic kidney disease ($n = 272$)	Other CAKUT ($n = 2746$)
Renal anomaly	**41.15 (15.48–109.4)**	NA	**28.1 (3.95–199.72)**	2.65 (0.35–19.84)
Obstructive kidney disease	2.5 (0.35–17.72)	3.15 (0.7–14.07)	NA	1.42 (0.31–6.51)
Cystic kidney disease	**7.96 (2–31.72)**	NA	**68.54 (30.49–154.05)**	2.14 (0.52–8.91)
Other CAKUT	**12.78 (3.17–51.54)**	NA	NA	3.19 (0.64–16.02)

Adjusted ORs for CAKUT were calculated using a logistic regression model with the generalized estimating equation by adjusting for all of the variables listed in Table 2 plus maternal nationality, maternal age, birth order, sex, year of birth and urbanization level of birthplace. The OR is significant and shown in bold when the 95% CI does not overlap with the null value (OR = 1).

renal anomalies and a declining trend is observed in obstructive kidney disease and other CAKUT. Maternal diabetes (types 1 and 2), gestational diabetes and maternal CAKUT are associated with CAKUT in the offspring. Statistical analysis showed that each maternal chronic disease was associated with different types of CAKUT. Diabetes (both type 1 and type 2) and maternal CAKUT were associated with renal anomalies in the offspring. Gestational diabetes and ACEI or ARB are associated with obstructive kidney disease. Specific maternal CAKUT types are highly associated with the same CAKUT type in offspring.

The prevalence of overall infants' CAKUT in the present study was 3.06/1000 live births between 2004 and 2012, which is within the lower range reported previously [5, 10, 24–26]. The variations between different reports may be associated with the criteria of CAKUT diagnosis, the database used for information retrieval, variations in sample size and ethnic differences. Of note, Tain *et al.* [5] reported a prevalence of 0.42/1000 live births of CAKUT in Taiwan between 2004 and 2011. Their study extracted information from the BCA system in Taiwan, but CAKUT may not be diagnosed at birth. In the present study, comprehensive definitions were used for both kidney and urinary tract defects. We extracted information for both birth registrations and medical claims from the NHIRD within the first 3 years of each newborn. Considering the time period of most CAKUT detection and the wider coverage rate of the nationwide databases used, the present study represents a more comprehensive analysis of CAKUT.

Meta-analyses showed that maternal diabetes, both pregestational and gestational, was linked to CAKUT [27, 28]. However, individual population-based cohort studies showed inconsistent results [5, 11–13, 29–31]. Some reports suggest that gestational diabetes accounts for 5–6.1% of malformation in newborns, which is much higher than the 1.3–2.8% in pregnant women without gestational diabetes [27–29, 31]. Dart *et al.* [11] suggested that gestational diabetes has a small impact on newborn CAKUT and that pregestational diabetes in the first 20 weeks is more significant [11]. In contrast, Hsu *et al.* [12] found that renal aplasia/dysplasia and obstructive uropathy were linked to gestational diabetes but not pregestational diabetes. In this study, significant associations were found between gestational diabetes or types 1 and 2 diabetes and the occurrence of CAKUT in offspring. This shows that although gestational diabetes has a smaller effect on CAKUT than other chronic diseases, its effect is still significant. Pregnant women with any form of diabetes should receive prenatal counselling and additional care should be taken for childbearing.

Although the mechanism regarding CAKUT and diabetes is still missing, animal studies may provide some hints. Studies in pregnant murine models indicate that offspring, when exposed to hyperglycaemia during pregnancy, can experience a reduction of up to 35% in nephron endowment at birth [32]. They suggested nephron deficits were the effects on the nuclear factor κB pathway, a major intracellular target of hyperglycaemia and oxidative stress, as well as the expression of genes of the intrarenal renin–angiotensin system during embryogenesis. Alternatively, it was suggested that changes in extracellular matrix components, such as proteoglycan and laminin, may also contribute to dysmorphogenesis of the embryonic kidney [33]. In the human foetus, kidney development occurs at 5–34 weeks of gestation [34]. It is biologically plausible therefore that exposure to a teratogen, such as hyperglycaemia, during this process may lead to CAKUT. Further studies examining the effects of maternal diabetes should include rigorous evaluation of both types of diabetes to better understand the discrepancy between type 1 and type 2 diabetes and gestational diabetes.

ACEI and ARB medications are first-line therapy for children with CAKUT, providing a protective effect to prevent or slow the development of chronic kidney disease [35]. They are also commonly used for cardiovascular patients to reduce the risk of myocardial infarction and stroke [36]. Although they are usually contraindicated during pregnancy due to the teratogenic risks, one study from the UK indicated that ACEI or ARB medication is more frequently prescribed in women of childbearing age, but pre-pregnancy advice and contraception advice were suboptimal in these women [37]. The results of the present study indicate that these two drug types are significantly associated with obstructive kidney diseases after stratification into CAKUT subgroups [38–40]. Thus we suggest that ACEI and ARB medication should be stopped in pregnant women. Also, due to the small number of women [1.2% (1487/1 196 175)] using ACEI or ARB medication in the cohort, it appears clinicians in Taiwan are already trying to avoid the impact of ACEI and ARB in pregnant women.

The results of the present study indicated that mothers with a specific type of CAKUT tended to have newborns with the same type of CAKUT. Since the study did not identify and exclude patients with kidney-related inherited diseases such as autosomal dominant kidney disease, this observation may be attributed to inherited diseases. Pregnant females with these inherited diseases logically have a high risk of passing the diseases to their offspring. Due to this limitation, it is unclear whether factors other than inheritance contribute to the observed results. Researchers in the field of CAKUT have been investigating potential responsible genes, nucleotide polymorphisms and

epigenetic modifications for many years, but no definitive conclusions have been reached [10, 41–43]. Further studies are needed to continue exploring genetic factors in order to gain a better understanding of CAKUT.

Strengths and limitations

The present study was strengthened by its substantial sample size from reliable databases and reliable assessment of associations between maternal chronic illness and specific types of CAKUT. However, with the retrospective study design, selection bias cannot be ruled out entirely, although it would be minimal. Since National Health Insurance is mandatory in Taiwan, significant resources are allocated towards providing frequent prenatal care and neonatal check-ups [44], which suggests that the present study is complete and valid.

Nevertheless, several limitations must be noted. First, the retrospective study design and the inclusion of only Taiwanese mothers and newborns may limit generalization of results to other populations. Second, we restricted the detection period to the first 3 years of life, which may ignore cases of CAKUT that developed in later years and may also lead to underestimating CAKUT incidence. However, such underestimation should be trivial, since a previous study showed that most CAKUT patients in Taiwan are diagnosed before the age of 3 years [23]. Third, patients with inherited kidney diseases were not excluded. This solidified the CAKUT linkage between moms and their children. Also, ICD-9-CM codes were used to identify CAKUT cases, which may lead to misclassification due to a lack of image evaluation, such as renal ultrasonography for confirmation of CAKUT. To minimize such misclassification, we only enrolled study subjects with ICD-9-CM codes for at least two outpatient visits or one hospital admission, as reported in previous studies [45]. Also, only live births were studied and newborns with gestation <22 weeks and a birthweight <500 g were excluded. Since the urinary system is not fully developed in those infants and serious defects in the urinary system usually leads to stillbirth, the prevalence of CAKUT would likely be higher than reported if these subjects had been included. Finally, although the prevalence of CAKUT is low in Taiwan, some maternal lifestyle factors, such as smoking and alcohol consumption [46], were not included in our analysis.

CONCLUSIONS

Maternal chronic diseases, especially diabetes, including gestational, type 1 and type 2, and CAKUT are highly associated with CAKUT in the offspring and specific maternal diseases are associated with specific subtypes of CAKUT in the offspring. These results may facilitate early identification of women at highest risk of having children with CAKUT and the provision of more specific preconception counselling and more frequent prenatal screening. Early detection of high-risk infants with CAKUT may also help to reduce the complications of CAKUT and comorbidities of future chronic kidney disease.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

ACKNOWLEDGEMENTS

The study was supported by the Cheng Chen Foundation, Taiwan.

FUNDING

The study received grant support from the National Science and Technology Council (NSTC), Taiwan. (112-2321-B-006-008).

AUTHORS' CONTRIBUTIONS

H.-H.C. and Y.-Y.C. were responsible for the study concepts, study design, data acquisition, data analysis, statistical analysis and manuscript preparation, editing and review. C.-C.C. and P.-L.K. were responsible for manuscript editing and review. C.-F.T. was responsible for data acquisition, data analysis, statistical analysis and manuscript review. H.-H.C., P.-L.K. and Y.-Y.C. are guarantors of the integrity of the study.

DATA AVAILABILITY STATEMENT

Data are available for bona fide researchers who request it from the authors.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Melo BF, Aguiar MB, Bouzada MCF *et al*. Early risk factors for neonatal mortality in CAKUT: analysis of 524 affected newborns. *Pediatr Nephrol* 2012;**27**:965–72. https://doi.org/10.1007/s00467-012-2107-y
2. Mizuno R. Increase in male fetal deaths in Japan and congenital anomalies of the kidney and urinary tract. *Reprod Toxicol* 2010;**30**:405–8. https://doi.org/10.1016/j.reprotox.2010.05.004
3. Queisser-Luft A, Stolz G, Wiesel A *et al*. Malformations in newborn: results based on 30,940 infants and fetuses from the Mainz congenital birth defect monitoring system (1990–1998). *Arch Gynecol Obstet* 2002;**266**:163–7. https://doi.org/10.1007/s00404-001-0265-4
4. Murugapoopathy V, Gupta IR. A primer on congenital anomalies of the kidneys and urinary tracts (CAKUT). *Clin J Am Soc Nephrol* 2020;**15**:723–31. https://doi.org/10.2215/CJN.12581019
5. Tain YL, Luh H, Lin CY. Incidence and risks of congenital anomalies of kidney and urinary tract in newborns. A population-based case-control study in Taiwan. *Medicine (Baltimore)* 2016;**95**:e2659. https://doi.org/10.1097/MD.0000000000002659
6. Heindel JJ, Vandenberg LN. Developmental origins of health and disease: a paradigm for understanding disease etiology and prevention. *Curr Opin Pediatr* 2015;**27**:248–53. https://doi.org/10.1097/MOP.0000000000000191
7. Mandy M, Nyirenda M. Developmental origins of health and disease: the relevance to developing nations. *Int Health* 2018;**10**:66–70. https://doi.org/10.1093/inthealth/ihy006
8. Arima Y, Fukuoka H. Developmental origins of health and disease theory in cardiology. *J Cardiol* 2020;**76**:14–7. https://doi.org/10.1016/j.jjcc.2020.02.003
9. Nobile S, Di Sipio Morgia C, Vento G. Perinatal origins of adult disease and opportunities for health promotion: a narrative review. *J Pers Med* 2022;**12**:157. https://doi.org/10.3390/jpm12020157

10. Nicolaou N, Renkema KY, Bongers EMHF *et al*. Genetic, environmental, and epigenetic factors involved in CAKUT. *Nat Rev Nephrol* 2015;**11**:720–31. https://doi.org/10.1038/nrneph.2015.140
11. Dart AB, Ruth CA, Sellers EA *et al*. Maternal diabetes mellitus and congenital anomalies of the kidney and urinary tract (CAKUT) in the child. *Am J Kidney Dis* 2015;**65**:684–91. https://doi.org/10.1053/j.ajkd.2014.11.017
12. Hsu CW, Yamamoto KT, Henry RK *et al*. Prenatal risk factors for childhood CKD. *J Am Soc Nephrol* 2014;**25**:2105–11. https://doi.org/10.1681/ASN.2013060582
13. Shnorhavorian M, Bittner R, Wright JL *et al*. Maternal risk factors for congenital urinary anomalies: results of a population-based case-control study. *Urology* 2011;**78**:1156–61. https://doi.org/10.1016/j.urology.2011.04.022
14. Health Promotion Administration. Birth reporting. http://www.hpa.gov.tw/English/ClassPrint.aspx?No1/4201502020008. (accessed 17 January 2023) .
15. Ministry of Health and Welfare. National Center for Health and Welfare Data Analysis and Application. https://dep.mohw.gov.tw/DOS/lp-2503-113-xCat-DOS_dc002.html (accessed 17 January 2023).
16. Chen BY, Hwang BF, Guo YL. Epidemiology of congenital anomalies in a population-based birth registry in Taiwan, 2002. *J Formos Med Assoc* 2009;**108**:460–8. https://doi.org/10.1016/S0929-6646(09)60093-0
17. Li CY, Chen LH, Chiou MJ *et al*. Set-up and future applications of the Taiwan Maternal and Child Health Database (TMCHD). *Taiwan Gong Gong Wei Sheng Za Zhi* 2016;**35**:209.
18. Lin CM, Lee PC, Teng SW *et al*. Validation of the Taiwan Birth Registry using obstetric records. *J Formos Med Assoc* 2004;**103**:297–301.
19. Alwan NA, Hamamy H. Maternal iron status in pregnancy and long-term health outcomes in the offspring. *J Pediatr Genet* 2015;**4**:111–23.
20. Andersen SL, Laurberg P. Managing hyperthyroidism in pregnancy: current perspectives. *Int J Womens Health* 2016;**8**:497–504. https://doi.org/10.2147/IJWH.S100987
21. Carta M, Cimador M, Giuffrè M *et al*. Unilateral multicystic dysplastic kidney in infants exposed to antiepileptic drugs during pregnancy. *Pediatr Nephrol* 2007;**22**:1054–7. https://doi.org/10.1007/s00467-007-0446-x
22. Parikh CR, McCall D, Engelman C *et al*. Congenital renal agenesis: case-control analysis of birth characteristics. *Am J Kidney Dis* 2002;**39**:689–94. https://doi.org/10.1053/ajkd.2002.31982
23. Chou HH, Lin CY, Chiou YH *et al*. Clinical characteristics and prevalence of complications of chronic kidney disease in children: the Taiwan Pediatric Renal Collaborative study. *Pediatr Nephrol* 2016;**31**:1113–20. https://doi.org/10.1007/s00467-016-3325-5
24. Li ZY, Chen YM, Qiu LQ *et al*. Prevalence, types, and malformations in congenital anomalies of the kidney and urinary tract in newborns: a retrospective hospital-based study. *Ital J Pediatr* 2019;**45**:50. https://doi.org/10.1186/s13052-019-0635-9
25. Loane M, Dolk H, Kelly A *et al*. Paper 4: EUROCAT statistical monitoring: identification and investigation of ten year trends of congenital anomalies in Europe. *Birth Defects Res A Clin Mol Teratol* 2011;**91**(Suppl 1):S31–43. https://doi.org/10.1002/bdra.20778
26. Yosypiv IV. Congenital anomalies of the kidney and urinary tract: a genetic disorder? *Int J Nephrol* 2012;**2012**:909083. https://doi.org/10.1155/2012/909083
27. Parimi M, Nitsch D. A systematic review and meta-analysis of diabetes during pregnancy and congenital genitourinary abnormalities. *Kidney Int Rep* 2020;**5**:678–93. https://doi.org/10.1016/j.ekir.2020.02.1027
28. Zhang TN, Huang XM, Zhao XY *et al*. Risks of specific congenital anomalies in offspring of women with diabetes: a systematic review and meta-analysis of population-based studies including over 80 million births. *PLoS Med* 2022;**19**:e1003900. https://doi.org/10.1371/journal.pmed.1003900
29. Feig DS, Hwee J, Shah BR *et al*. Trends in incidence of diabetes in pregnancy and serious perinatal outcomes: a large, population-based study in Ontario, Canada. *Diabetes Care* 2014;**37**:1590–6. https://doi.org/10.2337/dc13-2717
30. Jensen DM, Damm P, Moelsted-Pedersen L *et al*. Outcomes in type 1 diabetic pregnancies: a nationwide, population-based study. *Diabetes Care* 2004;**27**:2819–23. https://doi.org/10.2337/diacare.27.12.2819
31. Moore LL, Singer MR, Bradlee ML *et al*. A prospective study of the risk of congenital defects associated with maternal obesity and diabetes mellitus. *Epidemiology* 2000;**11**:689–94. https://doi.org/10.1097/00001648-200011000-00013
32. Amri K, Freund N, Vilar J *et al*. Adverse effects of hyperglycemia on kidney development in rats: in vivo and in vitro studies. *Diabetes* 1999;**48**:2240–5. https://doi.org/10.2337/diabetes.48.11.2240
33. Kanwar YS, Liu ZZ, Kumar A *et al*. D-glucose-induced dysmorphogenesis of embryonic kidney. *J Clin Invest* 1996;**98**:2478–88. https://doi.org/10.1172/JCI119066
34. Woolf AS. Multiple causes of human kidney malformations. *Arch Dis Child* 1997;**77**:471–4. https://doi.org/10.1136/adc.77.6.471
35. Gabriele MM, Nogueira PCK. Management of hypertension in CAKUT: protective factor for CKD. *Front Pediatr* 2019;**7**:222. https://doi.org/10.3389/fped.2019.00222
36. Yusuf S, Sleight P, Pogue J *et al*. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;**342**:145–53.
37. Lovegrove E, Robson J, McGettigan P. Pregnancy protection and pregnancies in women prescribed ACE inhibitors or ARBs: a cross-sectional study in primary care. *Br J Gen Pract* 2020;**70**:e778–84. https://doi.org/10.3399/bjgp20X712997
38. Johansen-Bibby A. Prescribing for pregnancy: chronic hypertension. *Drug Ther Bull* 2022;**60**:60–3. https://doi.org/10.1136/dtb.2021.000051
39. Liu Y, Li Y, Zhang J *et al*. Pregnancy complications and outcomes among women with congenital heart disease in Beijing, China. *Front Cardiovasc Med* 2022;**8**:765004. https://doi.org/10.3389/fcvm.2021.765004
40. Siegmund AS, Pieper PG, Bilardo CM *et al*. Cardiovascular determinants of impaired placental function in women with cardiac dysfunction. *Am Heart J* 2022;**245**:126–35. https://doi.org/10.1016/j.ahj.2021.11.020
41. Khan K, Ahram DF, Liu YF *et al*. Multidisciplinary approaches for elucidating genetics and molecular pathogenesis of urinary tract malformations. *Kidney Int* 2022;**101**:473–84. https://doi.org/10.1016/j.kint.2021.09.034
42. Kohl S, Habbig S, Weber LT *et al*. Molecular causes of congenital anomalies of the kidney and urinary tract

(CAKUT). *Mol Cell Pediatr* 2021;**8**:2. https://doi.org/10.1186/s40348-021-00112-0

43. Li S, Ye ZF, Mather KA *et al*. Early life affects late-life health through determining DNA methylation across the lifespan: a twin study. *EBioMedicine* 2022;**77**:103927. https://doi.org/10.1016/j.ebiom.2022.103927
44. Lin HC, Lin YJ, Hsiao FH *et al*. Prenatal care visits and associated costs for treatment-seeking women with depressive disorders. *Psychiatr Serv* 2009;**60**:1261–4. https://doi.org/10.1176/ps.2009.60.9.1261
45. Chou HH, Chiou MJ, Liang FW *et al*. Association of maternal chronic disease with risk of congenital heart disease in offspring. *CMAJ* 2016;**188**:E438–46. https://doi.org/10.1503/cmaj.160061
46. Ko TJ, Tsai LY, Chu LC *et al*. Parental smoking during pregnancy and its association with low birth weight, small for gestational age, and preterm birth offspring: a birth cohort study. *Pediatr Neonatol* 2014;**55**:20–7. https://doi.org/10.1016/j.pedneo.2013.05.005

Received: 30.7.2022; Editorial decision: 9.8.2023