Maternal Chronic Disease and Congenital Anomalies of the Kidney and Urinary Tract in Offspring: A Japanese Cohort Study

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Maternal Chronic Disease and Congenital Anomalies of the Kidney and Urinary Tract in Offspring: A Japanese Cohort Study

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Rationale & Objective: Several maternal chronic diseases have been reported as risk factors for congenital anomalies of the kidney and urinary tract (CAKUT) in offspring. However, these investigations used case-control designs, and cases with isolated genitourinary CAKUT were not distinguished from cases in which CAKUT were present with extrarenal congenital anomalies (complicated CAKUT). We examined the association of maternal diseases with isolated and complicated CAKUT in offspring using data from a prospective cohort study.

Study Design: A nationwide prospective birth cohort study.

Setting & Participants: 100,239 children enrolled in the Japan Environment and Children's Study between January 2011 and March 2014 at 15 research centers. Physicians' diagnoses in mothers and children were collected from medical record transcripts and questionnaires.

Exposures: Medical histories of maternal noncommunicable diseases, including obesity, hypertension, diabetes mellitus, kidney disease, hyperthyroidism, hypothyroidism, psychiatric disease, epilepsy, cancer, and autoimmune disease.

Outcomes: CAKUT diagnosed during the first 3 years of life, classified as isolated or complicated.

Analytical Approach: Multivariable Poisson regression with generalized estimating equations accounting for clustering by clinical center.

Results: Among the 100,239 children, 560 (0.6%) had CAKUT, comprising 454 (81%) isolated and 106 (19%) complicated forms. The risk of isolated CAKUT was increased in children of mothers who experienced kidney disease (adjusted risk ratio [RR], 1.80 [95% CI, 1.12-2.91]) or cancer (RR, 2.11 [95% CI, 1.15-3.86]). Furthermore, the risk of complicated CAKUT was increased in children of mothers with diabetes mellitus (RR, 3.04 [95% CI, 1.64-5.61]).

Limitations: Lack of standardization or prespecification of clinical definitions, diagnostic criteria, measurements, and testing. Genetic testing was not performed.

Conclusions: Isolated CAKUTs and complicated CAKUTs were associated with different maternal diseases. The results may inform clinical management of pregnancy and highlight potential differences in the genesis of isolated and complicated forms of CAKUT.

Visual Abstract online

Complete author and article information (including a list of the members of the Japan Environment and Children's Study Group) provided before references.

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Congenital anomalies of the kidney and urinary tract (CAKUT) are heterogeneous congenital defects in the urinary system. These include malformations of the kidney and urinary tract as well as abnormalities of the shape or anatomic position of the kidney,[1,2] accounting for 20%-30% of all congenital malformations.[3,4] CAKUT occur as an isolated form limited to the genitourinary system (termed isolated CAKUT) or together with extrarenal congenital anomalies (referred to as complicated CAKUT). The diverse manifestations and severity of CAKUT are considered to result from different spatial and temporal events in renal morphogenesis of the fetus, which continues until 36 gestational weeks.[5,6] Neonates with severe cases with no kidney formation do not survive, whereas those with less severe cases can survive with CAKUT, which are usually found during the fetal period or childhood, or with reduced nephron endowment, which may be first recognized as chronic kidney disease (CKD) in adulthood.[7,8]

The pathogenesis of CAKUT has been investigated in genetic, epigenetic, and epidemiologic studies.[1,7] Although a number of candidate genes have been reported,[9] causative genetic variants are not identified in the majority of cases. Even when carrying a mutation in CAKUT genes, an individual may exhibit a phenotype distinct from that of other individuals with the same mutation or may not show a CAKUT phenotype at all.[2,9] These observations indicate the possible effects of environmental factors on renal morphogenesis in a direct way or via epigenetic modifications.[1,7] Among several environmental factors, chronic noncommunicable diseases in mothers, such as diabetes mellitus and obesity, have been reported as important risk factors in epidemiological studies.[10,11] However, virtually all of these investigations used case-control designs and did not distinguish between isolated CAKUT and complicated CAKUT, although the underlying pathogenic mechanisms have been suggested to differ between the 2 forms.[1,2,12]

The present study investigated the association between maternal noncommunicable disease and CAKUT in offspring using data from a nationwide prospective birth cohort study, the Japan Environment and Children's Study

PLAIN-LANGUAGE SUMMARY

Prior studies reported that several maternal chronic diseases are associated with congenital anomalies of the kidney and urinary tract (CAKUT) in offspring without distinguishing isolated cases of CAKUT from those complicated by extrarenal anomalies. By studying the prospective cohort of the Japan Environment and Children's Study, we were able to examine the association of maternal diseases with isolated and complicated CAKUT. We found that the risk of isolated CAKUT was increased in children of mothers who experienced kidney disease or cancer, whereas complicated CAKUT was more common in children of mothers with diabetes mellitus. These findings provide insights that may inform the management of pregnancy and highlight potential differences in the genesis of isolated and complicated forms of CAKUT.

(JECS). In the current dataset of JECS, information on congenital malformations of any organ system (eg, central nervous, cardiovascular, and renal systems) was collected consecutively until children were 3 years old. Accordingly, this dataset enabled us to include the patients identified as having congenital malformations pre- and postnatally and to distinguish between isolated and complicated CAKUT. Determining the possible risks associated with maternal illness is important for providing better care for women who may wish to bear children.

Methods

Study Design

This study was conducted as a part of JECS, which aims to evaluate the effects of environmental factors on a variety of children's health issues. The details of the study design were reported previously.[13,14] In brief, pregnant participants and their partners were registered between January 2011 and March 2014 at 15 research centers covering a wide geographical area of Japan. The coverage of the participating children was estimated to be approximately 45%, corresponding to approximately 3% of Japanese newborns at that time.[14] The data of mothers and children used in this study were obtained from medical-record transcripts in the first trimester of pregnancy, at delivery (birth record), and when the child was 1 month old (clinic/hospital record of outpatient check-up). The data were also collected from self-administered questionnaires in the first trimester and second/third trimesters of pregnancy and when the child was 6, 12, 24, and 36 months old. The JECS did not provide definitions of maternal diseases and offspring congenital anomalies, a specific designation to use a diagnostic reference system, or any policies to determine the extent or frequency of clinical investigations. Therefore, the diagnoses were made at the community physicians' discretion based on the diagnostic criteria or the definition determined by relevant academic medical societies in Japan. The JECS was conducted in accordance with the Helsinki Declaration. The protocol was approved by the Ministry of Environment's Institutional Review Board for Epidemiological Studies and by the ethics committees of all the participating institutions (no. 100910001). Written informed consent was obtained from all participants.

Participants

In this study, we used the "jecs-ta-20190930" fixed dataset, which was released in October 2019. The dataset contains all of the available data extracted from medical-record transcripts and questionnaires until children reached 36 months of age. The data of 104,062 fetuses from 103,060 pregnancies were linked to the respective maternal data. After excluding 3,376 fetuses because of miscarriage or unknown birth status and 447 children with missing information on sex or birth weight, we analyzed a total of 100,239 children, including 99,932 live births and 307 stillbirths.

Exposures

The main exposure factors were medical histories of maternal noncommunicable diseases until the mother delivered the child. A mother was judged as having a disease when her diagnosis was reported from the first-trimester questionnaire and/or birth record, although the details of the diagnosis were not specified. The targeted diseases included obesity, hypertension, diabetes mellitus, kidney disease, hyperthyroidism, hypothyroidism, psychiatric disease, epilepsy, cancer, and autoimmune disease.

The first-trimester questionnaire asked pregnant women to "Please make marks on the checkboxes of any diseases with which you have ever been diagnosed by physicians" with regard to all targeted diseases except obesity. A disease was practically treated as preexisting when the diagnosis was based on the first-trimester questionnaire. The birth record also recorded which diseases existed during the index pregnancy, further including "gestational hypertension" and "gestational diabetes." However, in several cases, "hypertension" and "gestational hypertension" were concurrently checked, probably because of difficulty in distinguishing them without a specific definition of the illnesses. Thus, these 2 were not distinguished from each other and were combined as "hypertension." "Diabetes" and "gestational diabetes" were similarly combined as "diabetes." Ultimately, a mother was regarded as having a disease when it was reported in the first-trimester questionnaire and/or birth record.

Obesity was defined by a prepregnancy body mass index (calculated as weight divided by height squared) of $\geq 25\ kg/m^2$, which is optimal for the detection of obesity-related disorders in the Japanese population as determined by the Japan Society for the Study of Obesity.[15] The anthropometric data were obtained from the first-

trimester medical record and birth record in virtually all (99.5%) of the mothers eligible for the analysis and from the first-trimester questionnaire in the remaining mothers.

Outcomes

The primary outcome was CAKUT in offspring diagnosed during the first 3 years of life. The diagnosis of congenital extrarenal anomalies was also determined to discriminate between isolated and complicated forms of CAKUT. The physicians' diagnoses were collected consecutively from multiple sources: 2 medical record transcripts (birth record and check-up at child age 1 month) and 4 questionnaires (at child ages 6, 12, 24, and 36 months). The transcripts checked for congenital anomalies that had been detected until that point. The questionnaires asked caregivers to "Please fill in the names of any diseases with which your child has ever been diagnosed by physicians." A child was judged as having an anomaly when it was reported from at least one source. Therefore, for example, if an extrarenal anomaly was identified at birth and a subtype of CAKUT was discovered thereafter, the case was eventually classified as complicated CAKUT. The clinical practice of antenatal and postnatal ultrasonography in Japan is described in Item S1.

CAKUT comprised the following renal malformations and were grouped into 6 subtypes: (i) lower urinary tract obstruction (eg, posterior urethral valve, Potter sequence, omphalocele-exstrophy-imperforate anus complex and cloaca), (ii) vesicoureteral reflex, (iii) ureteral obstruction (eg, ureteropelvic and ureterovesical junction obstruction), (iv) hypoplasia or dysplasia (eg, kidney agenesis/hypoplasia/dysplasia and multicystic dysplastic kidney), (v) ectopia (eg, horseshoe and ectopic kidney), and (vi) complex/others (eg, 2 or more subtypes of CAKUT or other uncategorized renal malformations such as renal cyst or duplicated collecting system).

The participants were classified into 4 groups (Table S1): (i) "no anomalies" for those without any congenital anomalies, (ii) "isolated CAKUT" for those with renal malformation without extrarenal anomalies, (iii) "complicated CAKUT" for those with renal malformations and extrarenal anomalies, and (iv) "other anomalies" for those with extrarenal anomalies without renal malformations. The details of the extrarenal anomalies are provided in Item S1.

Statistical Analyses

To determine the age at which isolated or complicated CAKUT was identified, the cumulative incidence of each CAKUT was calculated when the child was 0, 1, 6, 12, 24, and 36 months of age. The prevalence corresponded to the cumulative incidence at 36 months, ie, whether the offspring had CAKUT identified during the first 3 years of life. To assess the association between maternal illness and the prevalence of CAKUT among offspring, we used a multivariable Poisson regression model with a generalized estimating equation accounting for the clustering effect of centers.

To estimate the risk of isolated CAKUT versus no malformations in association with each maternal disease, we created regression models that included each individual maternal disease and all covariates as independent variables (single-disease model). Because obesity, hypertension, diabetes mellitus, and kidney disease are reported to be highly comorbid,[16,17] as was indeed the case in our study (Table S2), the single-disease models were unable to determine which of the 4 diseases most directly influenced the occurrence of CAKUTs. Therefore, to determine this, we built another regression model that included the 4 diseases together as well as all covariates (multiple-disease model).

The covariates included were (i) sex, (ii) gestational age, (iii) birth weight, (iv) mother's age, (v) highest level of maternal education (junior high school, high school, university, or graduate school), (vi) annual household income (<4,000,000, 4,000,000-5,999,999, or ≥6,000,000 Japanese yen), (vii) smoking during gestation (confirmed via first-trimester questionnaire), (viii) alcohol use during gestation (via second-/third-trimester questionnaire), and (ix) folic acid supplementation by 12 weeks of gestational age (via first- and second-/third-trimester questionnaires).

Statistical analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing). To employ the generalized estimating equation after multilevel multiple imputation for missing data concerning exposures and covariates, we used the R packages geepack, mice, and miceadds. The results are reported with an adjusted risk ratio (RR) and 95% CI.

Results

Among the 100,239 participants, 560 (0.6%) received a diagnosis of CAKUT and 4,170 (4.2%) presented with other anomalies during the first 3 years of life (Table S1). In those with CAKUT, 454 (81.1%) had the isolated form and 106 (18.9%) had the complicated form. Of the 454 with isolated CAKUT, 160 (35.2%) were identified by birth and the others were identified with an increasing frequency thereafter, mostly during the first year of life (Fig 1A). In contrast, the majority of those with complicated CAKUT (75 of 106 [70.8%]) received a perinatal diagnosis, including 4 stillborn infants. The prevalences might have been underestimated because the dropout rate of the cohort was 18.0% at 36 months of child age (Fig S1).

The subtypes of CAKUT differed significantly between isolated and complicated forms ($P < 0.001$, χ^2 test; Fig 1B). Isolated CAKUT mainly comprised ureteral obstruction (66.3%) and vesicoureteral reflex (15.9%) and less frequently hypoplasia or dysplasia (7.9%). Conversely, complicated CAKUT had a variety of subtypes, including

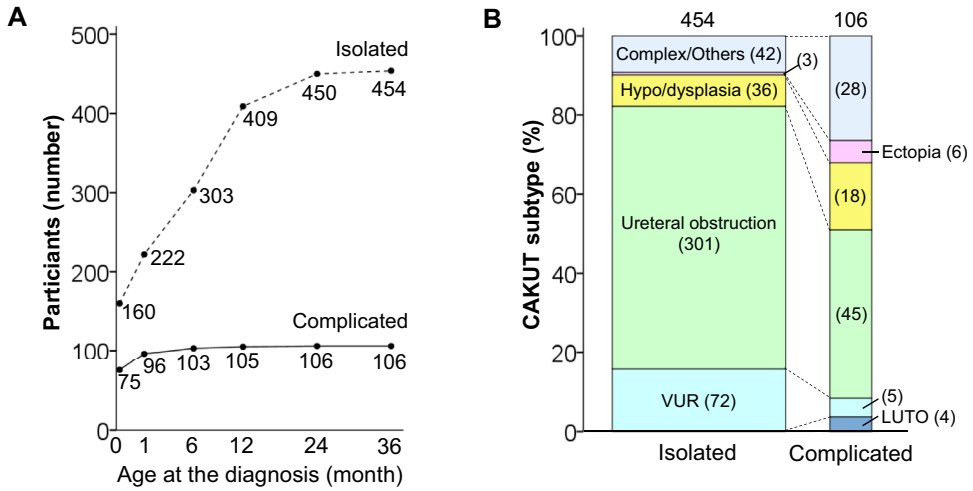

Figure 1. (A) The cumulative numbers of cases with isolated and complicated congenital anomalies of the kidney and urinary tract (CAKUT) with respect to the age of the patient at the time of diagnosis. (B) The percentages of each subtype of isolated and complicated CAKUT. The numbers in parentheses indicate the count of the subtype, which is represented as the area size. Abbreviations: LUTO, lower urinary tract obstruction; VUR, vesicoureteral reflex.

ureteral obstruction (42.5%), hypo-/dysplasia (17.0%), ectopia (5.7%), vesicoureteral reflex (4.7%), and lower urinary tract obstruction (3.8%).

Table 1 shows the baseline characteristics of the children who had no congenital anomalies, isolated or complicated CAKUT, and other anomalies. Among the 100,239 mothers with a mean maternal age of 31.2 years, the prevalence of noncommunicable illness was relatively high for obesity (10.7%), hypertension (3.8%), diabetes mellitus (3.2%), kidney disease (2.1%), and psychiatric disease (5.3%). With regard to hypertension and diabetes, the prevalences of preexisting disorders (0.5% and 0.2%, respectively) were much lower than those of overall disorders (Table S3). Offspring with isolated and complicated CAKUT tended to show a male predominance, birth at a younger gestational age, and a lower birth weight than in those with no anomalies.

In single-disease regression models, an increased risk of isolated CAKUT was observed in children from mothers with kidney disease (adjusted RR, 1.80 [95% CI, 1.12-2.91]) or cancer (adjusted RR, 2.11 [95% CI, 1.15-3.86]; Fig 2A; Table 2A). The multiple-disease model confirmed the significance of kidney disease (adjusted RR, 1.80 [95% CI, 1.12-2.88]) among the 4 highly comorbid diseases (Fig 2B; Table 2B). Regarding complicated CAKUT, the single-disease models indicated that the risk was significantly associated with diabetes mellitus (adjusted RR, 3.04 [95% CI, 1.64-5.61]) and marginally associated with hyperthyroidism (adjusted RR, 3.24 [95% CI, 1.00-10.57]). When the diagnoses were based only on the first-trimester questionnaire, preexisting diabetes exhibited a very strong association (adjusted RR, 7.35 [95% CI, 1.70-31.89]; Fig S2; Table S4). In the multiple-disease model, the association between maternal diabetes and complicated CAKUT persisted (adjusted RR, 2.71 [95% CI, 1.48-4.94]). The risks of other anomalies were modestly increased in children of mothers with obesity (adjusted RR, 1.14 [95% CI, 1.04-1.26]), hypertension (adjusted RR, 1.23 [95% CI, 1.10-1.38]), or diabetes (adjusted RR, 1.39 [95% CI, 1.17-1.63]). The multiple-disease model also demonstrated a significant association with diabetes mellitus (adjusted RR, 1.34 [95% CI, 1.13-1.58]), although the effect size of the association was smaller than that for complicated CAKUT.

To gain further insight into the contribution of maternal hyperglycemia to the pathogenesis of complicated CAKUTs, we examined the levels of glycosylated hemoglobin A (ie, hemoglobin A_{1c}), a marker of glycemic control, in the early stages of pregnancy (Item S1). The mean hemoglobin A_{1c} level was significantly higher in mothers with diabetes (5.47%), especially preexisting diabetes (6.32%), than in nondiabetic mothers (5.18%; $P < 0.001$). Compared with the levels in diabetic mothers of children with no congenital anomalies (5.47%), those in children with complicated CAKUT (5.83%) were nominally higher ($P = 0.07$), but those in children with isolated CAKUT (5.46%) and other anomalies (5.51%) were comparable (Fig 3). However, we were unable to draw definitive conclusions based on these findings because of the small sample sizes for isolated CAKUT (n = 18) and complicated CAKUT (n = 8).

Discussion

This large prospective cohort study investigated the associations between various maternal noncommunicable diseases and CAKUT in offspring. The associations showed differing patterns between patients with isolated versus

Table 1. Baseline Characteristics of Participants (N = 100,239)

Characteristic	No anomalies (n = 95,509)		Isolated CAKUT (n = 454)		Complicated CAKUT (n = 106)		Other anomalies (n = 4,170)	
	Value	Missing[a]	Value	Missing	Value	Missing	Value	Missing
Offspring factors								
Male sex	48,919 (51.2%)	0	342 (75.3%)	0	62 (58.5%)	0	2,047 (49.1%)	0
Gestational age, wk	39.2 ± 1.7	0	38.8 ± 2.5	0	37.9 ± 2.8	0	38.5 ± 2.7	0
Birth weight, g	3,010 ± 438	0	2,979 ± 534	0	2,711 ± 699	0	2,856 ± 597	0
Maternal factors								
Age, y	31.2 ± 5.1	7	31.5 ± 5.1	0	31.2 ± 5.2	0	31.6 ± 5.1	0
Education	–	2,267	–	17	–	2	–	129
Junior high school	4,521 (4.8%)	–	14 (3.2%)	–	6 (5.8%)	–	190 (4.7%)	–
High school	68,556 (73.5%)	–	316 (72.3%)	–	81 (77.9%)	–	2,967 (73.4%)	–
University/ graduate school	20,165 (21.6%)	–	107 (24.5%)	–	17 (16.3%)	–	884 (21.9%)	–
Family income	–	8,458	–	50	–	6	–	371
Low: <4,000,000 JPY	35,034 (40.2%)	–	156 (38.6%)	–	41 (41.0%)	–	1,502 (39.5%)	–
Middle: 4,000,000-5,999,999 JPY	28,777 (33.1%)	–	131 (32.4%)	–	33 (33.0%)	–	1,247 (32.8%)	–
High: ≥6,000,000 JPY	23,240 (26.7%)	–	117 (29.0%)	–	26 (26.0%)	–	1,050 (27.6%)	–
Smoking during pregnancy	16,959 (18.1%)	1,929	57 (12.8%)	10	22 (21.0%)	1	701 (17.1%)	69
Alcohol during pregnancy	45,855 (49.3%)	2,502	236 (53.8%)	15	51 (49.5%)	3	1,874 (46.6%)	150
Folate use during pregnancy	29,824 (31.7%)	1,435	149 (33.6%)	10	32 (30.8%)	2	1,315 (32.0%)	58
Maternal disease								
Obesity	10,142 (10.6%)	127	59 (13.0%)	1	17 (16.0%)	0	494 (11.9%)	5
Hypertension	3,572 (3.7%)	0	20 (4.4%)	0	10 (9.4%)	0	242 (5.8%)	0
Diabetes mellitus	2,978 (3.1%)	0	21 (4.6%)	0	10 (9.4%)	0	197 (4.7%)	0
Kidney disease	1,973 (2.1%)	0	17 (3.7%)	0	3 (2.8%)	0	91 (2.2%)	0
Hyperthyroidism	1,128 (1.2%)	0	5 (1.1%)	0	4 (3.8%)	0	62 (1.5%)	0
Hypothyroidism	1,153 (1.2%)	0	2 (0.4%)	0	2 (1.9%)	0	59 (1.4%)	0
Psychiatric disease	5,010 (5.2%)	0	17 (3.7%)	0	8 (7.5%)	0	241 (5.8%)	0
Epilepsy	569 (0.6%)	0	5 (1.1%)	0	2 (1.9%)	0	32 (0.8%)	0
Cancer	1,060 (1.1%)	0	11 (2.4%)	0	1 (0.9%)	0	53 (1.3%)	0
Autoimmune disease	886 (0.9%)	0	5 (1.1%)	0	2 (1.9%)	0	50 (1.2%)	0

Values for continuous variables given as mean ± standard deviation. Abbreviations: CAKUT, congenital anomalies of the kidney and urinary tract; JPY, Japanese yen.
[a]"Missing" indicates the number of participants with missing data.

complicated CAKUT. The risk of isolated CAKUT was increased in children of mothers with a history of kidney disease or cancer. In contrast, the risk of complicated CAKUT was increased in children whose mothers had diabetes mellitus. This study suggests that the risk of CAKUT in relation to maternal disease may depend on whether the CAKUT is accompanied by extrarenal anomalies.

In this study, isolated and complicated CAKUT showed differential clinical presentations. The majority of those with the complicated form had already been identified by birth, whereas those with the isolated form were identified with an increasing frequency after birth. CAKUT can be detected antenatally by obstetric ultrasonography. Postnatally, when an infant is born with apparent external malformations or symptoms of internal major anomalies such as congenital heart diseases, the entire body, including the renal system, is aggressively investigated in the neonatal period. This appears to explain the early identification of complicated CAKUT in our study. Conversely, many CAKUT cases are discovered for the first time at the presentation of overt symptoms, such as

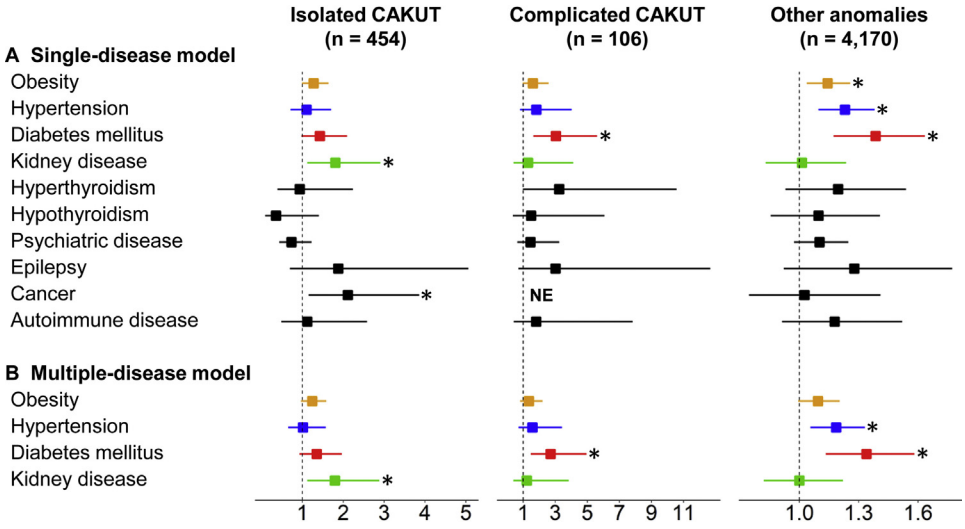

Figure 2. Forest plots showing the adjusted risk ratios for the outcomes versus no defects in association with maternal diseases using (A) single-disease and (B) multiple-disease models. The horizontal lines indicate 95% CIs. Asterisk: $P < 0.05$. Abbreviations: CAKUT, congenital anomalies of the kidney and urinary tract; NE, not estimated from regression model.

urinary tract infection, during childhood. This manner of discovery may account for the relatively later diagnosis of isolated CAKUT. We also found that the subtypes of CAKUT differed between isolated and complicated forms, with the isolated form related mainly to ureteral obstruction and vesicoureteral reflex, whereas the complicated form was more strongly related to the malformations of hypo-/dysplasia, ectopia, and lower urinary tract obstruction. These differing relationships seem consistent with the finding that the pathogenesis of CAKUT is suggested to differ among subtypes[1,9] and between isolated and complicated forms.[2,12]

The risk of isolated CAKUT was increased in children of mothers with kidney disease in our study. The detailed diagnosis of kidney disease was uncertain but presumed to include CAKUT and CKD. Individuals with reduced nephron endowment, which is a manifestation of CAKUT, can be identified as having CKD in adulthood.[7] Because 10%-15% of cases with CAKUT show familial aggregation,[18,19] common genetic predispositions may produce the combination of a mother with CAKUT or CKD and a child with CAKUT. It is unclear why maternal kidney disease was associated with isolated, but not complicated, CAKUT. A variety of mutations and copy number variations of disease-causing genes are detected in approximately one fourth of CAKUT cases.[1,20] Because such established genetic abnormalities are less frequently identified in isolated forms than complicated forms of CAKUT,[1,12,20] other unknown genetic predispositions may make larger contributions to the occurrence of isolated CAKUT. Another possibility is the use of renin angiotensin system blockers, which are associated with major malformations of the offspring's organs, including the renal system.[21] The drugs are contraindicated for pregnant women but might be used if the pregnancy was unplanned or suboptimally managed. The marginal association between maternal hyperthyroidism and complicated CAKUT in this study might also be explained by such teratogenic drug effects.[22-24]

The risk of isolated CAKUT was also increased in the children of mothers who had a history of cancer. Radiation therapy and chemotherapy for cancer are well known to increase the risk of adverse outcomes, including congenital malformations when used during the first trimester,[25-27] and would therefore be very unlikely to be administered to pregnant women. Accordingly, most of the mothers with a history of cancer were found to be cancer survivors who probably had received these therapies before pregnancy. Although several case-control or retrospective studies have reported that the risk of congenital malformations including the renal system[28-30] is not increased in children of female cancer survivors, the potential teratogenicity is suggested to persist after cancer therapies.[30] The reason for our significant result is unclear but might be attributable to the advantages of the prospective design, the discrimination between isolated and complicated cases, and the longitudinally collected information on the malformations.

In our study, the risk of complicated CAKUT, as well as other malformations, was increased in children of mothers with diabetes mellitus. A number of epidemiological studies have demonstrated the association of maternal diabetes with not only congenital malformations overall[31,32] but also renal malformations.[10,11,33,34] These associations may be due mainly to maternal hyperglycemia. In animal models of diabetes, maternal hyperglycemia adversely affects the development of the fetal kidney, including ureteric bud branching morphogenesis and

Table 2. Association of Maternal Diseases With Offspring Outcomes

	Adjusted Risk Ratio (95% CI)		
	Isolated CAKUT (n = 454)	Complicated CAKUT (n = 106)	Other Anomalies (n = 4,170)
Single-disease model			
Obesity	1.27 (0.99-1.64)	1.60 (0.98-2.59)	1.14 (1.04-1.26)[a]
Hypertension	1.10 (0.71-1.70)	1.82 (0.82-4.03)	1.23 (1.10-1.38)[a]
Diabetes mellitus	1.43 (0.97-2.09)	3.04 (1.64-5.61)[a]	1.39 (1.17-1.63)[a]
Kidney disease	1.80 (1.12-2.91)[a]	1.29 (0.41-4.12)	1.01 (0.83-1.24)
Hyperthyroidism	0.93 (0.39-2.24)	3.24 (1.00-10.57)	1.20 (0.93-1.54)
Hypothyroidism	0.35 (0.09-1.40)	1.49 (0.36-6.08)	1.10 (0.86-1.41)
Psychiatric disease	0.73 (0.43-1.22)	1.46 (0.65-3.25)	1.10 (0.97-1.25)
Epilepsy	1.88 (0.69-5.06)	3.01 (0.72-12.67)	1.28 (0.92-1.77)
Cancer	2.11 (1.15-3.86)[a]	NE	1.03 (0.75-1.41)
Autoimmune disease	1.12 (0.48-2.58)	1.81 (0.42-7.83)	1.18 (0.91-1.52)
Multiple-disease model			
Obesity	1.24 (0.97-1.58)	1.35 (0.83-2.21)	1.09 (0.99-1.20)
Hypertension	1.01 (0.66-1.57)	1.57 (0.72-3.42)	1.19 (1.06-1.33)[a]
Diabetes mellitus	1.35 (0.93-1.96)	2.71 (1.48-4.94)[a]	1.34 (1.13-1.58)[a]
Kidney disease	1.80 (1.12-2.88)[a]	1.22 (0.39-3.85)	1.00 (0.82-1.22)

The single-disease models include each disease and all of the following covariates: sex, gestational age, birth weight, maternal age, education, family income, and maternal smoking, alcohol, and folate use during pregnancy. The multiple-disease models include the 4 diseases and all covariates together. Abbreviations: CAKUT, congenital anomalies of the kidney and urinary tract; NE, not estimated from the regression model because only one case was observed in the children from the exposed mothers.
[a]Statistically significant difference ($P < 0.05$) for the outcome versus no anomalies.

nephron endowment.[35,36] In diabetic women, congenital malformations in offspring are preventable when the maternal blood glucose is well controlled before and during early pregnancy.[31,32] The importance of hyperglycemia in early pregnancy, when active nephrogenesis occurs, may be supported by the very high risk of complicated CAKUT (adjusted RR of 7.35) in children of mothers with preexisting diabetes.

Intriguingly, our study further revealed that the risk of complicated CAKUT in relation to maternal diabetes (adjusted RR of 3.04) was stronger than that of other anomalies (adjusted RR of 1.39). This stronger association appears to be in agreement with our findings for hemoglobin A_{1c}. Compared with the mean levels of hemoglobin A_{1c} in diabetic mothers whose children had no malformations (5.47%), the values were higher in diabetic mothers who delivered children with complicated CAKUT (5.83%) but not in diabetic mothers of children with other anomalies (5.51%). All these values were much lower than the diagnostic threshold of diabetes mellitus in the general population (6.5%).[37] However, the levels during early pregnancy could be lower, even with gestational diabetes, than in the nonpregnant state,[38] and such levels could be sufficient to increase the risk of adverse pregnancy outcomes.[39] Maternal hyperglycemia in the early stage of pregnancy may have a greater impact on the renal system than on other organs. Alternatively, the association might be produced by a genetic disorder involving the gene *HNF1B*, which causes, in an autosomal dominant manner, renal cysts and diabetes syndrome (RCAD; Online Mendelian Inheritance in Man #137920).[40] This syndrome shows a wide spectrum of clinical phenotypes; a given patient may present with complicated CAKUT without diabetes whereas another may have diabetes alone even if they share the same mutation.[41] Therefore, in families with RCAD, it is possible for a mother to have diabetes and her children to have complicated CAKUT.

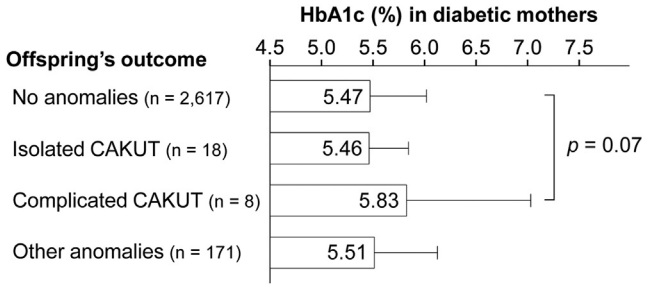

Figure 3. Mean and standard deviation (error bars) of hemoglobin A_{1c} (HbA_{1c}) in diabetic mothers with respect to the 4 outcomes in offspring. The 2-tailed *t* test demonstrates a marginally significant difference between cases with no anomalies and those with complicated congenital anomalies of the kidney and urinary tract (CAKUT).

Several limitations of the present study warrant mention. First, there was a risk of sampling bias because the coverage of the voluntary participation was estimated to be less than half, and the rates of participation might have differed among the 15 centers. However, our study population seems representative of the general Japanese population because the basic characteristics of the mothers and children in JECS were comparable to those obtained in national surveys.[14] Second, because the diagnoses of mothers and children were partially obtained from a self-reported questionnaire, and the JECS did not specifically designate

diagnostic criteria, procedures, or data collection policies, the diagnosis might have been missed, biased, or inconsistent across participating centers. In particular, there may have been some information bias because clinicians might have sought to detect fetal congenital anomalies in mothers with diseases more aggressively than in mothers without diseases. Third, detailed information was not obtained from the questionnaires concerning the onset of the maternal disease, its severity, or medications taken. Furthermore, the diagnosis of each maternal disease was not specified (eg, CAKUT, CKD, chronic nephritis, and diabetic nephropathy were possible for "kidney disease"). Finally, although CAKUT is considered to result from the interplay between genetic and environmental factors,[1,7] genetic analyses were not performed in the present study. Without genetic testing, we cannot confirm the validity of grouping all the isolated CAKUT events together.

In conclusion, the present study distinguished between the isolated and complicated forms of CAKUT and showed that each form was associated with different maternal noncommunicable diseases. Our results provide insights to better manage women of childbearing age and highlight potential differences in the genesis of isolated and complicated forms of CAKUT. Analysis of genomic data collected in the JECS is warranted to determine the relative contributions of genetic and environmental factors to the pathogenesis of isolated and complicated CAKUT.

Supplementary Material

Supplementary File (PDF)

Item S1: Supplemental methods.

Figure S1: Availability of the questionnaires and medical-record transcripts.

Figure S2: Forest plots showing adjusted RRs for the outcomes versus no anomalies in association with maternal preexisting diseases.

Table S1: Classification of congenital anomalies.

Table S2: Comorbidity of obesity, hypertension, diabetes, and kidney disease in mothers.

Table S3: The incidences of maternal preexisting diseases with respect to offspring outcomes.

Table S4: The association of maternal preexisting diseases with offspring outcomes.

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Maternal Chronic Disease and Congenital Anomalies of the Kidney and Urinary Tract in Offspring

Setting & Participants

Japan Environment and Children's Study (JECS)

Among 100,239 children of multicenter prospective cohort:

Isolated CAKUT (N = 454)
(CAKUT with no extrarenal anomalies)

Complicated CAKUT (N = 106)
(CAKUT with extrarenal anomalies)

Findings

Exposure

Maternal Diseases

- Obesity
- Hypertension
- Diabetes mellitus
- Renal disease
- Hyperthyroidism
- Hypothyroidism
- Psychiatric disease
- Epilepsy
- Cancer
- Autoimmune disease

Adjusted Risk Ratio (95% CI)

- ↑1.80 (1.12-2.91) → Isolated CAKUT
- ↑2.11 (1.15-3.86) → Isolated CAKUT
- ↑3.04 (1.64-5.61) → Complicated CAKUT

Outcome

Offspring's CAKUT

CONCLUSION: Isolated and complicated forms of CAKUT were associated with different maternal diseases.

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