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A Systematic Review and Meta-Analysis of Diabetes During Pregnancy and Congenital Genitourinary Abnormalities

Mounika Parimi[1] and Dorothea Nitsch[1]

[1]Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

Introduction: This study aimed to assess available epidemiological evidence of the relationship between diabetes during pregnancy and congenital abnormalities of the kidney and the urinary tract (CAKUT).

Methods: POPLINE, MEDLINE, EMBASE, Global Health, CINAHL, and Cochrane Library were searched to retrieve 6962 articles of which 15 case-control and 11 cohort studies met the inclusion criteria. Random-effects meta-analysis was performed to estimate the association between CAKUT and diabetes during pregnancy.

Results: Offspring born to mothers with any form of diabetes in pregnancy had a 50% increased risk of CAKUT compared with offspring of mothers without diabetes (relative risk [RR], 1.51; 95% confidence interval [CI], 1.36–1.67). Compared with offspring with nondiabetic mothers, offspring of mothers with pre-existing diabetes had an almost 2-fold rate of CAKUT (RR, 1.97; 95% CI, 1.52–2.54). Offspring of mothers with gestational diabetes had a 39% increased risk of CAKUT (RR, 1.39; 95% CI, 1.26–1.55) compared with offspring of mothers with no diabetes. The subset of studies that adjusted for body mass index (BMI) before pregnancy showed similar associations. Population attributable risks for gestational diabetes were estimated to be 3.7% of cases of CAKUT in the United States, 4% of CAKUT cases in the United Kingdom, with up to 14.4% CAKUT cases in the South Asian population in the United Kingdom.

Conclusion: This study suggests that 2.0% to 3.7% of cases of CAKUT in the United States, and up to 14% of CAKUT in some populations could be eliminated if gestational diabetes was prevented or eliminated.

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CAKUT refers to a range of structural and functional anomalies of the kidney, collecting system, bladder, and urethra. The specific cause of CAKUT remains unknown; however, maternal factors, genetics, and environmental factors are thought to contribute to CAKUT.[1–4]

The incidence of CAKUT was estimated at 4.2 per 10,000 births in Taiwan[5] and prevalence of CAKUT is reported between 0.1% and 0.7%.[6,7] Only the most severe forms are diagnosed during the first year after birth and less severe cases of CAKUT can be identified later on during development. CAKUT has severe implications for the health system, as they can be responsible for up to 50% of pediatric chronic kidney disease cases.[8,9] CAKUT is one of the major underlying diseases in the young adult population on renal replacement therapy.[9,10] Many patients with CAKUT, even if they are undiagnosed and remain healthy in adolescence, have an increased risk of end-stage renal disease during adulthood.[11] Therefore, effective interventions to prevent CAKUT in newborns may have the potential to prevent substantive morbidity. Hence, it is important to understand whether there are modifiable maternal factors associated with CAKUT.

Diabetes is accepted as one of the risk factors for congenital anomalies generally, but evidence of diabetes as a risk factor specifically for CAKUT is sparse.[12,13] Diabetes during pregnancy poses health threats for mother and baby alike, and can be classified into type 1 diabetes, type 2 diabetes, and gestational diabetes.[14] Uncontrolled diabetes in pregnancy creates a diabetogenic environment for the fetus, increasing the risk of adverse pregnancy results including

Correspondence: Dorothea Nitsch, Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK. E-mail: Dorothea.Nitsch@lshtm.ac.uk

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macrosomia, neonatal hypoglycemia, congenital abnormality, and perinatal mortality.[14,15]

Worldwide, there has been a reported increase in women with diabetes mellitus in the childbearing age.[16] Diabetes does not only affect high-income countries, but its burden is spread across low- and middle-income countries as well.[17] An increase of diabetic pregnancies can increase the incidence of adverse pregnancy outcomes, both for mother and infant.[15] It is therefore important to understand if diabetes in pregnancy is associated specifically with CAKUT.

This systematic review aimed to understand the association between diabetes during pregnancy and CAKUT, including an estimate of the number of cases of CAKUT in the general population that may be attributed to diabetic pregnancies.

METHODS

Literature Search Strategy

One reviewer (MP) searched CINAHL Plus, EMBASE, MEDLINE, PubMed, POPLINE databases, and the Cochrane Library, from inception until April 12, 2017. An updated search in May 2019 identified no additional studies that could be included in this systematic review. All hits were considered without a limitation by year. Each domain of interest (diabetes during pregnancy, including pre-existing, type 1, type 2 diabetes, and gestational diabetes, and congenital abnormalities) was searched for with a MeSH term, and a free-text search. Hits within the domain were combined first, followed by a combination search between the 2 domains. CAKUT was not specifically used within the search strategy, as several relevant articles with results on renal and urogenital abnormalities were eliminated by a CAKUT-specific narrow search. Rather, all articles that investigated the role of diabetes on any form of congenital abnormalities were broadly screened so that any reported categorical division of abnormality (i.e., listing numbers on genitourinary abnormalities or CAKUT) by presence and/or absence of diabetes was not missed by a narrow search strategy. The search strategy was slightly modified for the POPLINE database.

One reviewer (MP) screened titles and abstracts of articles resulting from the database searches and isolated potentially relevant articles. DN served as a second reviewer who screened 100 random abstracts, and a k statistic was generated to calculate agreement between the 2 reviewers. The full texts of relevant articles were examined against the inclusion and exclusion criteria, and the decision about eligibility was made by MP. Borderline cases were discussed between DN and MP.

Inclusion and Exclusion Criteria

Articles from peer-reviewed journals were considered for the review. Only human studies were included. Included articles had to refer to some form of diabetes during pregnancy as a risk factor. All articles referring to any congenital abnormalities were inspected to check for a breakdown with specific types of congenital abnormalities, with congenital renal, urogenital, genital, urinary and/or kidney malformation or abnormality or defect as a category. Any type of CAKUT and chronic kidney disease as outcomes were included. Observational and intervention studies with a clear, specified comparison offspring group with CAKUT, compared within mothers with and without diabetes were included.

Articles were excluded if they were not published in a peer-reviewed journal, including conference posters, abstracts, and letters. Grey literature was not considered. Studies were excluded if they did not have a comparison group. Last, studies were excluded if they were in a language other than English. Animal studies were excluded.

Data Extraction

Data were extracted using a prespecified extraction form adapted from PRISMA data extraction tool kits.[18] The tool kit was adapted to this systematic review to include setting, year, study design, study population, definition of exposure and outcome, ascertainment, and main results. Data were extracted for pre-existing diabetes only, for gestational diabetes only, and combined diabetes types (pre-existing and gestational together).

Quality Assessment

The quality assessment tool was adapted for observational studies from the Cochrane Collaboration's tool for assessing risk of bias in randomized trials.[19] Case-control studies and cohort studies had a slightly different assessment tool. Studies were evaluated on participation bias, loss to follow-up (for cohorts), recall bias (for case-control studies), nondifferential classification of exposure and outcomes, observer bias, ascertainment bias of exposure, and confounding for relevant maternal characteristics. All categories of bias in all studies were analyzed and classified as low risk (green), uncertain or medium risk (yellow), or high risk (red) of bias with predefined explanations for high and low risk of bias for each category.

Meta-Analysis

Meta-analysis was performed if the articles contained an effect estimate (odds ratio [OR] or risk ratio) comparing occurrence of genitourinary abnormality in

the nondiabetic control group compared with the maternal diabetes group. Quantitative information for meta-analysis (RR and 95% CI) was either reported directly in the study or had to be calculated.

To manually calculate RR and 95% CI, raw numbers of genitourinary abnormality in nondiabetic control and exposed diabetic groups were used. When articles reported individual renal and genital abnormalities, all relevant abnormalities that fit into the genitourinary abnormality umbrella were grouped together. The raw numbers were extracted from the articles and calculations were made with the risk ratio calculator using the MEDCALC software online.[20] The calculator computes RR and 95% CI according to Altman.[21] The number of genitourinary abnormalities in the exposed group (i.e., the maternal diabetes group) was divided by the total number of diabetic mothers, and compared with the number of genitourinary abnormalities in the control group (i.e., nondiabetic mother group was divided by the total number in the control group).

If articles reported an RR, then this was used for meta-analysis, otherwise the manually calculated RR was used. If an adjusted RR was presented, then this was used. ORs and risk ratios were combined because genitourinary abnormalities are rare, and the number of these abnormalities is small. Therefore, there is no drastic difference between OR calculation and a risk ratio calculation.

The RR and the 95% CI were exported to STATA 14 (StataCorp, College Station, TX) and the log of the RR and the 95% CI were used for random-effects meta-analysis. A random-effect meta-analysis was performed, as the studies have slight variations in definitions of outcome, and therefore the assumption of a single population giving rise to the separate studies is not met.

Sensitivity Analysis for Confounding

In this review, some estimates were crude, others were adjusted, raising the possibility of residual confounding affecting the final summary measure of association. From evaluating all studies, maternal age and BMI were determined to be important confounders in the study. Therefore, all studies were accessed for the likelihood for confounding when comparing genitourinary abnormalities in the case group and the control group.

Studies were classified to have minimal confounding when:

(i) Studies at least adjusted for maternal age. In addition, studies needed to adjust for all variables in multivariate analysis that were different between cases and controls in the univariate analysis (but not on the causal pathway).

(ii) For studies that adjusted the estimate for the association of all congenital abnormalities with diabetes for confounders, and for which there was no difference found between the crude and adjusted ratios or rates. This situation arose for studies with small counts that did not allow adjustment for associations seen for specific subgroups. Here we assumed that any confounding structure in the data would apply for the rate ratio for genitourinary anomalies as seen for the total sample.

All articles that fulfilled 1 of the 2 preceding criteria were used for a random-effects meta- analysis, considering only articles with minimal confounding.

In addition, articles that adjusted for BMI were combined in a meta-analysis.

Population Attributable Risk

Population attributable risk (PAR) of gestational diabetes for CAKUT was calculated based on prevalence estimated for diabetes during pregnancies and the most conservative estimate of RR from the meta-analysis (RR, 1.42). Because meta-analysis and sensitivity analysis indicated strong evidence for an association between gestational diabetes and congenital genitourinary abnormalities, PAR was calculated for gestational diabetes only. In addition, the RR used for calculations of PAR was from the meta-analysis conducted with studies that attempted to adjust for confounding, as this was the most conservative estimate.

Because there is no clear report on the true global prevalence of gestational diabetes and because rates of gestational diabetes differ according to population factors and diagnostic factors, PAR was calculated for specific countries.[22,23] Based on available prevalence data, PAR was calculated for the United States, United Kingdom/Ireland (stratified by white population and South Asian population), and India.

RESULTS

After a rigorous systematic search, 15 case controls studies and 11 cohort studies met the inclusion/exclusion criteria and were included in the systematic review (Figure 1). Comparison of inclusion/exclusion of 100 random articles by the second reviewer (DN) compared with the first reviewer resulted in Cohen's $\kappa = 1$ representing 100% consensus between both reviewers.

Assessment of Included Studies

A detailed breakdown of the case-control and cohort studies is presented in Tables 1[5,24–37] and 2.[13,15,38–47]

All included cohort studies were from high-income country settings and covered the period between 1984 and 2010 and included the total sample size of 6,053,931 mothers with and without diabetes among 9

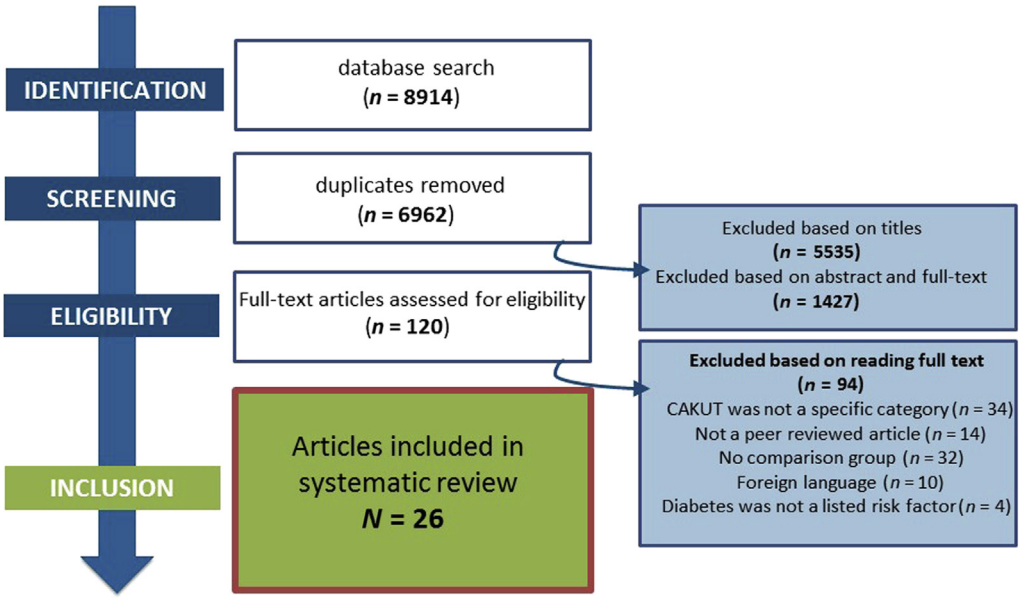

Figure 1. Flow diagram for selection of articles included in the systematic review. The initial database searches identified 8914 articles, of which 26 articles were included in the systematic review (15 case controls and 11 cohort studies). CAKUT, congenital abnormalities of the kidney and the urinary tract.

studies that were included in the meta-analysis. Eight studies were regionally based, 2 were hospital based,[13,40] and 1 study was based nationally.[43] Ten comparative cohort studies compared pregnancy outcomes in cohort of diabetic mothers with a cohort of nondiabetic mothers. The comparison of interest was the frequency of CAKUT in offspring of mothers with diabetes compared with the frequency of CAKUT in offspring of mothers with no diabetes during pregnancy.[13,15,32,39,42–44] One study compared the infants born to women with diabetes with infants in the general (source) population and compared the frequency of renal abnormalities between these cohorts.[45] One study was not included in meta-analysis, as a comparative nondiabetic population was not defined.[40]

The settings of the case-control studies were from a mixture of high-income countries (Europe, Canada, and the United States) and middle-income countries (Turkey and Taiwan). Eleven studies were population based and 4 were hospital based. Studies covered the period between 1980 and 2011. Twelve case-control studies first sampled cases (i.e., children, newborns, or in some cases fetuses with CAKUT). These cases were then compared with controls (children, newborns, or fetuses without CAKUT) with regard to the frequency of maternal diabetes in pregnancy. There was 1 study that sampled based on exposure status among a population of CAKUT patients. Mothers of CAKUT patients with diabetes were cases, and mothers of CAKUT patients without diabetes were the controls. This study was not included in the meta-analysis.[30] There were 2 population-based case-control studies that included all newborns with CAKUT from the population, and the frequency of mothers with and without diabetes was calculated among children with CAKUT.[32,33] Because these were population based, these 2 studies were included in the meta-analysis. The total number of cases was 17,013 across 13 case-control studies. This calculation does not include 2 studies: 1 that was excluded from meta-analysis and 1 study did not report on the specific *n* for case and control groups for the all abnormality subgroup, but rather reported the OR only. More information on specific counts among case and control groups among diabetic and nondiabetic mothers is included in Table 1.

Qualitative Assessment of All Included Studies

The quality of the studies was variable: Figure 2 summarizes the qualitative assessment of case-control and cohort studies according a colour scheme: red to indicate a high risk of bias, yellow for uncertain risk, and green for low risk of bias. An explanation of the reasoning for specific ratings and the scale for assessment is included in the supplementary materials (Supplementary Table S1A–C).

Almost all studies had no evidence of recall or observer bias. Nondifferential misclassification of exposure (i.e., either missing diagnosis of diabetes or wrong categorization of the type of diabetes) was a problem in some studies. Nondifferential misclassification of the outcome (i.e., wrongly diagnosed congenital genitourinary abnormality) was a problem in studies with no strict diagnostic criteria. Differential ascertainment bias arises if pregnant women with diabetes

Table 1. Study characteristics of case-control studies

Study details					Exposure			Outcome		
Study/ paper	Date	Setting	Case definition	Control definition	Exposure definition	Type of diabetes	Ascertainment	Definition	Abnormality specification	Ascertainment
Banhidy[24]	2010	Hungary	Cases were children diagnosed with CAs from birth until 1 postnatal yr (including deaths and termination) from the HCAR (1980–1996) $n = 3555$	Controls were newborn infants without any CA selected by National Birth Registry matched 2 controls per case (sex, birth wk, district of residence) $n = 38,151$	International Consensus, glucose serum test high serum glucose level + diagnostic glucose tolerance test	T1D, T2D, and GDM	Medically recorded data obtained from logbooks	CA were differentiated into groups lethal, severe, and mild; single or multiple	Renal agenesis/ dysgenesis; obstructive urinary CA, hypospadias	Mandatory notification by physicians to HCAR of CA from birth until end of first postnatal yr or autopsy reports of infant deaths
Correa[25]	2008	United States: 10 states covered under the NBDPS	Live births, stillbirths, or terminations with CA from NBDPS between 1997 and 2003; only known-cause abnormalities were excluded[a] $n = 51$	Live-born infants without birth defects randomly selected from birth certificates or hospitals $n = 4895$	Physician-diagnosed diabetes but reported by the mother	PGDM, GDM	Self-reported diabetes status	Isolated or multiple defects classified by clinical geneticists based on reviews of clinical information	Bilateral renal agenesis/ hypoplasia	Obtained from NBDPS data based on clinical geneticists' diagnosis (cases) controls randomly selected from birth certificates or hospitals
Dart[26]	2015	Manitoba, Canada	Infants older than 20 weeks' gestational age born in Manitoba with at least 1 ICD code for CAKUT (stillborn infants included); infants were both between fiscal yr 1996/ 1997 and 2009/ 2010 $n = 945$	Infants without ICD code for CAKUT or other CA in first yr of life, matched 5 controls:1 case (gestational age, sex and birth year); excluded if 2 yr of follow-up not available $n = 4725$	ICD codes, PGDM: ICD code for DM over 2-yr period before pregnancy	GDM, PGDM (T1D+ T2D)	ICD codes; forms and Diabetes Education Resource for Children and Adolescents, drug data	CAKUT from ICD-9 and -10 codes	CAKUT	Hospital records for first 2 yr of life
Davis[27]	2010	Texas (Houston/ Galveston area) Texas Health Service Region 6	Deliveries with renal agenesis/ dysgenesis identified from the Texas Birth Defects Registry within first postnatal yr (from births after 20 weeks' gestation) from 2000–2002 $n = 89$	Controls were frequency matched using cumulative incidence sampling 4 controls:1 case (delivery yr, and vital status at delivery) $n = 356$	DM not specified	No distinction between types of GDM or PGDM	Birth certificates and fetal death records	Deliveries with renal agenesis/dysgenesis	Renal agenesis/ dysgenesis	Texas birth defect registry (surveillance system through 1 yr of life)
Frías[28]	2007	Spain (80 hospitals included in study) 1976–2005	Cases are identified by pediatrician examination of all newborns in participating hospitals as those with major or minor CA $n = 1057$	Children born between 1976 and 2005; were included in the study only if data on maternal glucose tolerance were available $n = 30,009$	Maternal Glucose Tolerance Status	PGDM and GDM	Glucose challenge test performed between 24 and 28 wks of gestation	Coding according 2 levels and 3 sublevels, modified ICD-8 codes along with additional specifications	MDK	Examination by pediatrician: CA (cases) identified using modified version of ICD-8; next child born nonmalformed of same sex in same hospital was classified as control
Groen in 't Woud[29]	2016	Nijmegen, Netherlands	Patients diagnosed with renal agenesis, renal dysplasia, ureteropelvic junction obstruction, duplex collecting system, multicystic dysplastic kidney, PUV, and/or VUR treated at Radboud Medical Center from 1981 onward, genetic and chromosomal anomalies excluded $n = 553$	Controls born between 1990 and 2011 were randomly sampled from 39 municipalities throughout the Netherlands and controls with major CA excluded $n = 2116$	Assumed to be physician-diagnosed diabetes but reported by mother	Pre-existing (diagnosed up until 10th wk of pregnancy) or diabetes during pregnancy (diagnosed after 10th wk)	Questionnaire filled out by parents of patients in AGORA data bank	CAKUT (from 2004) + other renal abnormalities until 2004 as part of AGORA	CAKUT	Medical review of cases from AGORA by pediatric nephrologist, urologist, and/or clinical geneticist

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Table 1. (Continued) Study characteristics of case-control studies

Study details					Exposure			Outcome		
Study/ paper	Date	Setting	Case definition	Control definition	Exposure definition	Type of diabetes	Ascertainment	Definition	Abnormality specification	Ascertainment
Garne[30,b]	2011	18 regions in Europe	EUROCAT registry was used; cases are CA with mother who has PGDM; live births, fetal deaths and terminations were included $n =$ unknown	Malformed infants or fetuses from EUROCAT whose mothers were nondiabetic $n =$ unknown	ICD-10 codes and other written text associated with maternal diabetes	PGDM	As recoded in the EUROCAT database, the registry was based on multiple sources of information (birth, death certificates, terminations of pregnancy, hospital records, etc.)	ICD-9 or ICD-10 with BPA extensions; subgroups of anomalies are based on ICD BPA codes	Isolated renal anomalies	As recoded in the EUROCAT database based on multiple sources of information (birth, death certificates, terminations of pregnancy, hospital records, etc.)
Nielsen[31]	2005	Hungary- from HCAR	CA including malformed fetuses after termination of pregnancy in second and third trimesters, stillborn fetuses, live-born infants diagnosed with CA until first yr of life between 1980 and 1996. Some mild CA and syndromes of known origins were excluded $n = 2657$	2 newborns per case without CA were chosen as controls (matched for sex, birth week, district of parents' residence) $n = 38,151$	Pre-gestational insulin-treated DM if insulin use was recorded in the log book before or during 1st trimester	PGDM	Questionnaire and antenatal logbooks (written record of disease and drugs given by obstetrician)	Classification made by HCAR	Renal agenesis/ dysgenesis and obstructive CA of the urinary tract	Physician-reported stillborn, infant deaths, termination, included
Newham[32,c]	2013	North of England	All singleton births, stillbirths, miscarriages, or terminations from 1996–2008 with CA, chromosomal anomalies excluded $n = 986$	No control for this study, as this was a population-based case-control study $n = 6162$	Pre-gestational diabetes	From NorDIP records	ICD-10 classification and categorized according to EUROCAT criteria	From NorCAS	Urinary abnormalities	Examination by physician after birth
Postoev[33]	2016	Murmansk County, Russia	Newborns (more than 22 wks of gestation) with CAKUT recorded in the MCBR from 2006 to 2011 $n = 203$	Newborns without CAKUT from the birth registry (2006–2011) $n = 50,723$	DM and GDM as diagnosed by physicians	DM and GDM	From the MCBR database	According to ICD-10	CAKUT	From the MCBR database
Ramos-Arroyo[34]	1992	Spain	CA in live births identified by physician diagnoses at participating hospitals within 3 days of life between 1976 and 1985 $n =$ N/A	One control per case, next nonmalformed live birth of the same sex born in same hospital $n =$ N/A	Insulin-dependent or non–insulin-dependent- chronic, or GDM when first diagnosed during pregnancy	Insulin-dependent and non–insulin-dependent DM and GDM	From interview with mother	CA diagnosed by experienced physician	Genitourinary	Examination by physician after birth
Shnorhavorian[35]	2011	Washington State, USA	Children with urinary anomalies (ICD-9) at birth through 5 yr of age diagnosed between 1987 and 2007, chromosomal anomalies were excluded $n = 4248$	Infants without urinary tract anomalies selected from birth records and frequency matched 4 controls:1 case (matched for birth yr) $n = 17,258$	DM recorded in WSBR as pre-existing medical condition so physician diagnosis	PGDM and GDM	As recorded in WSBR	Urinary anomalies from ICD-9	CUTA; but in meta-analysis kidney anomalies is used	From the WSBR and linked with Washington CHARS database
Soylu[36]	2017	Turkey	Children 0–18 yr with prenatal or postnatal CAKUT diagnosis, chromosomal renal anomalies excluded $n = 140$	Children 0–18 yr having a urinary tract infection, without CAKUT, matched 1:1 $n = 140$	Gestational diabetes recorded by medical professional	GDM	Hospital files of all cases examined retrospectively (antenatal data from routine questionnaire during clinic visit)	Uncertain— not reported	CAKUT	Uncertain

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Table 1. (Continued) Study characteristics of case-control studies

Study details					Exposure			Outcome		
Study/ paper	Date	Setting	Case definition	Control definition	Exposure definition	Type of diabetes	Ascertainment	Definition	Abnormality specification	Ascertainment
Tain[5]	2016	Taiwan	Newborn with renal hypoplasia, polycystic kidney disease, ureteropelvic junction obstruction, and other kidney disorders in Taiwan between 2004 and 2011 $n = 668$	Newborns selected randomly from birth without any CA, matched 1 case:5 controls (matched by birth yr and Apgar score) $n = 3340$	Diabetes before and during pregnancy as listed in BCA	GDM, PGDM	As recorded in BCA dataset	Recorded by birth delivery doctor in form and classified into 9 types, 1 of which is genitourinary	CAKUT (included kidney disorders and anomalies but not genital anomalies)	As recorded in BCA dataset
Hsu[37]	2014	Washington State, USA	Childhood CKD from birth certificates between 1987 and 2008 in Washington State $n = 1861$	Randomly selected from births with no history of CKD recorded in discharge data and were frequency matched by birth yr, 1 case:10 controls $n = 18,677$	Uncertain	GDM, PGDM	From WA birth records and linked to discharge data	ICD-9 codes renal dysplasia/aplasia and obstructive uropathy	Renal dysplasia/ aplasia, obstructive uropathy	From WA birth records and linked to discharge data

AGORA, Aetiologic research into Genetic and Occupational/environmental Risk factors for Anomalies in children; BCA, birth certificate application; BPA, British Paediatric Association; CA, congenital abnormalities; CHARS, comprehensive hospital admission reporting system; CKD, chronic kidney disease; CUTA, congenital urinary tract anomalies; DM, diabetes mellitus; EUROCAT, European network of population-based registries for the epidemiological surveillance of congenital anomalies; GDM, gestational diabetes mellitus; HCAR, Hungarian Congenital Abnormality Registry; ICD, International Classification of Diseases; MCBR, Murmansk County Birth Registry; MDK, multicystic dysplastic kidneys; N/A, not available; NBDPS, national birth defects prevention; NorCAS, Northern Congenital Abnormality Survey; NorDIP, Northern Diabetes in Pregnancy Survey; PGDM, pre-gestational diabetes mellitus; PUV, posterior urethral valves; T1D, type 1 diabetes; T2D, type 2 diabetes; VUR, vesicoureteral reflux; WSBR, Washington Stage Birth Registry.

[a]Final study population was narrowed due to response rate among mothers, and study criteria that only mothers with known diabetes status and estimated delivery between 1997 and 2003 were included. Study population consisted of 4895 controls and 13,030 cases.

[b]This study is an anomaly, as controls are sampled based on exposure rather than a traditional case-control where sampling is based on the outcome. Therefore, this study is not included in the meta-analysis.

[c]This study is a population-based case-control study. All cases in a population were identified (pregnancies with abnormalities) and rate of abnormalities were compared based on maternal diabetes status.

may be monitored closely for presence of abnormalities in their offspring in some settings. This was also a concern in studies in which terminations of pregnancy and miscarriages were not considered in analysis and where there was no follow-up of children after birth; CAKUT can be diagnosed after birth in the first few years of life.

Adjustment for confounding was variable among studies. Because of the small numbers of CAKUT in the studies, adjusting for confounding was difficult. Some studies adjusted for confounding factors in analyses of risk factors for overall congenital abnormalities but only reported crude data for CAKUT specifically. Maternal age and obesity can all be considered potential confounders because of their association with both diabetes and congenital abnormalities.[45] These were accounted for in studies with larger study populations.

Association Between Diabetes and Congenital Genitourinary Abnormalities

Figure 3[5,24–29,33,35,37,41,44–46] shows the relative risk (RR) and 95% CIs from the combination of cohort studies and case-control studies investigating the relationship among all diabetes during pregnancy and CAKUT and their pooled random-effects estimates. The estimated values indicate an increased risk of CAKUT associated with any form of diabetes in pregnancy (i.e., pre-existing diabetes or/and gestational diabetes). Compared with nondiabetic pregnancies, women with diabetes have a higher risk of giving birth to infants with CAKUT. The pooled RR of CAKUT among mothers with any form of diabetes (pre-existing and gestational) was 1.51 (1.36–1.67), and the I^2 value (measure of variation across studies) was 25.3% ($P = 0.182$), indicating low heterogeneity of findings. The funnel plot suggested minimal evidence of publication bias (Supplementary Figure S1A).

Some studies specifically investigated the type of diabetes (pre-existing or gestational) in pregnancy, allowing stratified meta-analysis is this systematic review. Analysis restricted to mothers with pre-existing diabetes (i.e., diabetes known before pregnancy) resulted in a pooled RR of 1.97 (1.52–2.54) (Figure 4b[13,15,38,40–46]). However, there was evidence of high heterogeneity in the meta-analysis and pooling of results for pre-existing diabetes only and CAKUT ($I^2 = 70.2\%$, $P < 0.001$), and evidence of publication bias in the corresponding funnel plot (Supplementary Figure S1B). In contrast, when restricting analyses to studies that investigated the link between mothers with gestational diabetes and CAKUT, the pooled RR was 1.39 (1.26–1.55) (Figure 4a[5,24–37]), with low heterogeneity of results in the meta-analysis ($I^2 = 0.0\%$, $P = 0.884$) and only minimal/no evidence of

Table 2. Study characteristics of cohort studies

Study details				Exposure			Outcome		
Study/ paper	Date	Setting	Population (no., age, inclusion/exclusion)	Exposure definition	Type of diabetes	Ascertainment	Definition	Abnormality specification	Ascertainment
Agha[38]	2016	Ontario, Canada	All children born in hospital in Ontario, Canada between 1994 and 2009 $n = 2,058,755$	According to physician diagnosis	PGDM	Ontario Diabetes Database collection from physician claims and hospital discharge abstracts	ICD-9 and -10 codes	Renal defects	Discharge Abstract Database
Bell[39]	2012	North of England	All singleton pregnancies in northern UK resulting in live birth, stillbirth, late fetal loss, or termination of pregnancy following prenatal diagnosis of a fetal abnormality (1996–2008) who are also covered by registry data from CA register and diabetes in pregnancy register $n = 401,149$	According to the NorDIP survey- HbA1c levels	PGDM (at least 6 mo before conception)	NorDIP, which records details of all known diabetic pregnancies irrespective of outcomes	According to the ICD-10 and categorized using EUROCAT criteria by group, subtype, or syndrome	Urinary	NorCAS collecting information on all cases of CA, fetal loss, termination of pregnancy until 12 yrs of age
Garcia-Patterson[40,a]	2004	Barcelona, Spain	Infants born between 1/1986 and 7/2002 at 22 complete gestation wks or later of mothers with documented diagnosis of GDM $n =$ NA	Third workshop conference on GDM criteria	GDM	Hospital records	Major CA: life-limiting, caused cosmetic or functional impairment, or needed surgery	Renal/ urinary	Examination by neonatologist followed by image studies if CA was suspected
Janssen[41]	1996	Washington State, USA	All certificates indicating diabetes in mothers from 1984–1991 in Washington State; comparative cohort consisted of women with no diabetes; Down syndrome was excluded, live births only were considered $n = 19,314$	Physician diagnosis as indicated in certificate of live births	GDM, PGDM	From Washington State certificates of live births	Physician-diagnosed: no criteria indicated	Malformed genitalia, renal agenesis, and other urogenital anomalies	From Washington State certificates of live births
Liu[42]	2015	Canada	Live births in Canada (excluding Quebec) for fiscal yr 2002/03– 2012/13, stillbirths were excluded, inclusion criteria included >22 weeks' gestation and >500 g birth weight $n = 2,839,680$	Pre-pregnancy DM according to ICD-10	Pre-pregnancy DM: T1D and T2D	From the Discharge Abstract Database	Medical record of CA according to ICD-10	Genitourinary	From Discharge Abstract Database
Moore[43]	2000	USA	10/1984–06/1987: women from 100 obstetric practices who underwent 2nd trimester amniocentesis or alpha-fetoprotein screening studies $n = 22,951$	National standards for diabetes classification T1D, T2D, GDM	For urogenital CA, only GDM information available	Telephone interview between 15th and 20th mo of gestation, specific time of onset and other detailed questions about diabetes control and medication	6-Digit code list from Centers for Disease Control and Prevention and exclusion of nonchromosomal abnormalities	Urogenital	Outcome questionnaire mailed to delivering physicians (77% response rate) and the rest completed by mother with clarification when necessary
Peticca[44]	2009	Ontario	All obstetric deliveries in Ontario province between 04/2005 and 05/2006, with voluntary participation in database $n = 120,604$	Diabetes was recorded as part of database by medical professionals	GDM, T1D, T2D	From Ontario Niday Perinatal Database, voluntary participation from sites; data acquired by nurse or staff and put into database	Recorded in the database by professional/midwife using hospital codes	Genitourinary	From the database

(Continued on next page)

Table 2. (Continued) Study characteristics of cohort studies

Study details				Exposure			Outcome		
Study/ paper	Date	Setting	Population (no., age, inclusion/exclusion)	Exposure definition	Type of diabetes	Ascertainment	Definition	Abnormality specification	Ascertainment
Sharpe[45]	2005	South Australia	All singleton births (alive and stillbirths) in south Australia between 1986 and 2000 >400 g or >20 weeks' gestation, terminations not included $n = 282,260$	Blood glucose levels and diagnostic criteria in the hospitals	GDM, PGDM	Department of Health's POSU	Coded according to ICD-9 with British Pediatric Association Perinatal Supplement	Urogenital	From the SABDR collecting until age 5 yr
Sheffield[13]	2002	Texas, USA	All women delivering at Parkland hospital in Texas for the study period were included $n = 145,196$	From 1991–1996 some at-risk women were systematically screened for GDM; between 1996 and 2001 all women were screened	PGDM	Glucose tolerance test interpreted according to National Diabetes Data Group	Diagnosed by neonatal faculty and confirmed by geneticist	Renal	Newborn nursery hospital records at time of discharge or stillborn records
Vinceti[46]	2014	Italy	Deliveries (still and live births) recorded in the National Health service for the Emilia-Romagnia region between 01/1997 and 12/2010 (only those included in the Region Birth Defects Registry) $n = 12,917$	GDM and PGDM as diagnosed by physician listed in the registries	PGDM (T1D, T2D) and GDM	First ascertainment from hospital discharge record from National Health Service, Birth Certificate Archives of PGDM; ascertainment was validated with drug records to confirm classification	ICD-9	Genitourinary	Emilia-Romagna Region Birth Defects registry
Yang[15]	2006	Nova Scotia, Canada	All diabetic and nondiabetic mothers between 01/1988 and 12/2002; pregnancies reaching 20 weeks of gestation and 500 g were considered; terminations were not included $n = 151,105$	Defined according to White's classification[b]	PGDM	Abstracted from standardized antenatal record collected at first antenatal visit: Nova Scotia Perinatal Database	Major CA defined as lethal, life-shortening, life-threatening, requiring major surgery, or affecting quality of life	Genito-urinary	From the Nova Scotia Atlee Perinatal Database

CA, congenital abnormalities; DM, diabetes mellitus; EUROCAT, European network of population-based registries for the epidemiological surveillance of congenital anomalies; GDM, gestational diabetes mellitus; HbA1c , hemoglobin A1C; ICD, International Classification of Diseases; NorCAS, Northern Congenital Abnormality Survey; NorDIP, Northern Diabetes in Pregnancy Survey; PGDM, pre-gestational diabetes mellitus; POSU, pregnancy outcome statistics unit; SABDR, South Australian Births Defect Register; T1D, type 1 diabetes; T2D, type 2 diabetes.

[a]This study was not included in the systematic review, as a control group of women without diabetes was not clearly defined and the rate of congenital abnormalities among the diabetic group was not compared with congenital abnormalities in the nondiabetic group.

[b]Widely used to assess maternal and fetal risk and differentiates between GDM and pre-existing diabetes; named after Priscila White.[47]

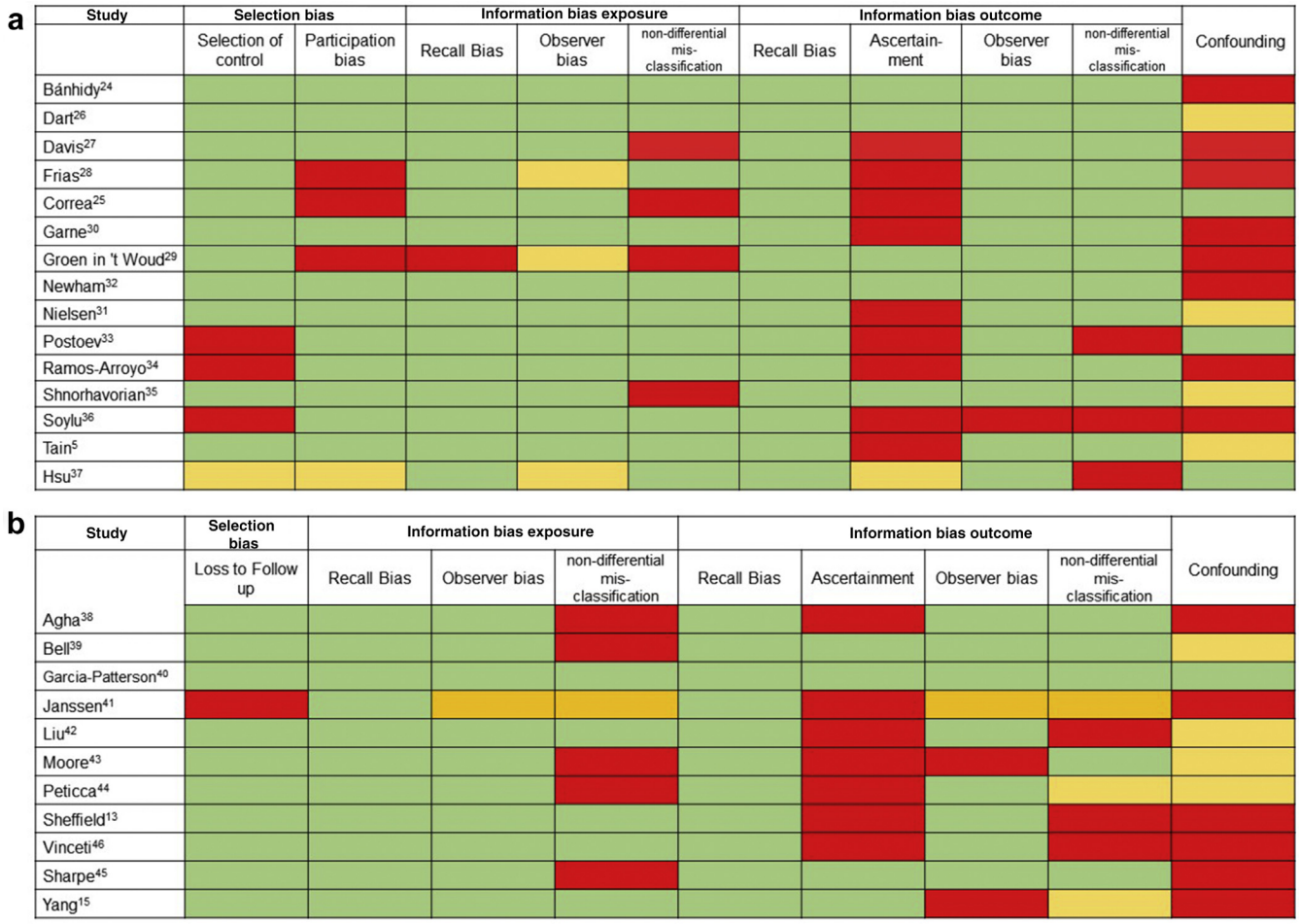

Figure 2. Quality assessment of all included (a) case-control studies and (b) cohort studies. Fifteen case-control studies (a) and 11 cohort studies (b) were qualitatively assessed for their risk of bias and confounding and ranked as red for high risk, yellow for uncertain risk, and green for low risk.

publication bias according to the funnel plot (Supplementary Figure S1C).

Sensitivity Analysis: Adjustment for Confounding

Two sensitivity analyses were performed to investigate the role of confounding on results. An in-depth analysis of confounders from each study, including comparison of crude and adjusted ORs (where available), is indicated in the supplementary materials (Supplementary Table S2, Supplementary Figure S2A–C and Supplementary Figure S3A,B).

First, we restricted the analyses to studies that adjusted for locally determined confounding variables. Depending on context, every study had a different set of possible confounders that investigators choose to adjust for. Maternal age was the only variable that was constantly adjusted among all studies. Restricting the analysis to studies that attempted to adjust for confounding slightly increased the summary measures of the association of any diabetes, pre-existing diabetes, and gestational diabetes with CAKUT compared with the summary measure when all the studies were included (Table 3).

A second analysis was restricted to studies that specifically adjusted for BMI as a confounding variable. Three studies evaluated the difference in rates of CAKUT in normal and high maternal BMI groups and found little to no evidence of difference in rates of abnormalities between the groups.[29,41,44] Hsu *et al.*[37] reported a difference between crude and adjusted ratio after adjustment for maternal BMI in pregestational diabetic women, and a small difference in gestational diabetic women. A positive association between chronic kidney disease in infants and maternal BMI, after adjusting for diabetes and hypertension is also reported.[37] One study found a difference in OR of CAKUT in gestational diabetic women in the second and third tertile of BMI compared with reference first tertile of BMI, concluding that prepregnancy BMI is a predictive variable of renal/urinary abnormalities.[21] There were only 2 studies that reported specific ORs of CAKUT after adjustment for maternal BMI that could be combined in meta-analysis

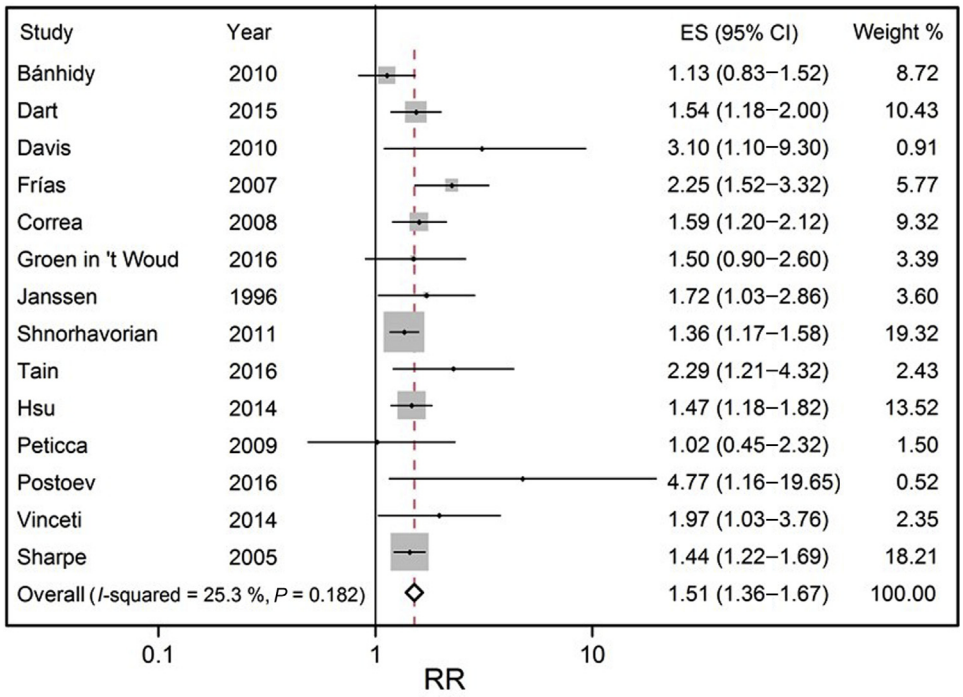

Figure 3. Forest plot of relative risk (RR) of congenital abnormalities of the kidney and the urinary tract (CAKUT) with all maternal diabetes. Fourteen studies[5,24–29,33,35,37,41,44–46] that compare CAKUT in offspring of mothers with any diabetes type and CAKUT in mothers with no diabetes are summarized here. The summary measure of association is RR, 1.51 (95% confidence interval [CI], 1.36–1.67). ES, effect estimate.

(OR 2.71 [0.77–9.59]) (Table 3).[25,37] Adjusting for BMI did not attenuate the association between gestational diabetes and CAKUT.

Population Attributable Risk

PAR was calculated based on the most conservative estimate of association between gestational diabetes and CAKUT, after attempting adjustment for known confounders (RR, 1.42). Table 4[23,48–50] indicates PAR of gestational diabetes for CAKUT based or prevalence estimates in the United States, the United Kingdom (white and South Asian population), and in India.

Assuming that gestational diabetes is causal for CAKUT, estimates suggest that approximately 2.0% to 3.7% of cases of CAKUT in the United States, and 3.3% to 4.0% of cases of CAKUT in the United Kingdom could be prevented if gestational diabetes was eliminated. In the South Asian population in the United Kingdom, this estimate can be as high as 14.4% (according to the Atlantic Diabetes in Pregnancy [ADIP] database). Using 2 estimates of reported prevalence of gestational diabetes in India, between 6.5% and 12.5% of CAKUT cases could be prevented if gestational diabetes was eliminated.

DISCUSSION

This systematic review and meta-analysis, combining case-control and cohort studies worldwide, provides evidence of a potential link between and diabetes during pregnancy and CAKUT: compared with nondiabetic mothers, women with any type of diabetes during pregnancy are 50% more likely to give birth to infants with congenital genitourinary abnormalities, the risk is 2-fold in women with pregestational diabetes and increased by 40% in women with gestational diabetes. Analyses restricted to studies that control for confounders did not change the results drastically.

These results are worrisome, especially as there has been an increase in diabetes incidence throughout the world, affecting low-, middle-, and high-income countries. The link between diabetes and congenital abnormalities overall has been investigated and is well established, and therefore finding an association between maternal diabetes and CAKUT in the offspring is plausible.[12,13] Calculating attributable fractions assuming that diabetes causes a 40% increase in the incidence of CAKUT concludes that approximately 1.9% to 3.7% of CAKUT in the United States and 4.1% of CAKUT in the United Kingdom/Ireland may be associated with gestational diabetes. This estimate is much higher in the South Asian population in the United Kingdom, estimating 14.4% of CAKUT associated with gestational diabetes. There is a potential that PAR is much higher, given that the RR for the association between any diabetes type in the mother and CAKUT is estimated to be at least 50% higher and the prevalence of women with any diabetes at pregnancy will automatically be higher than the prevalence of gestational diabetes only.

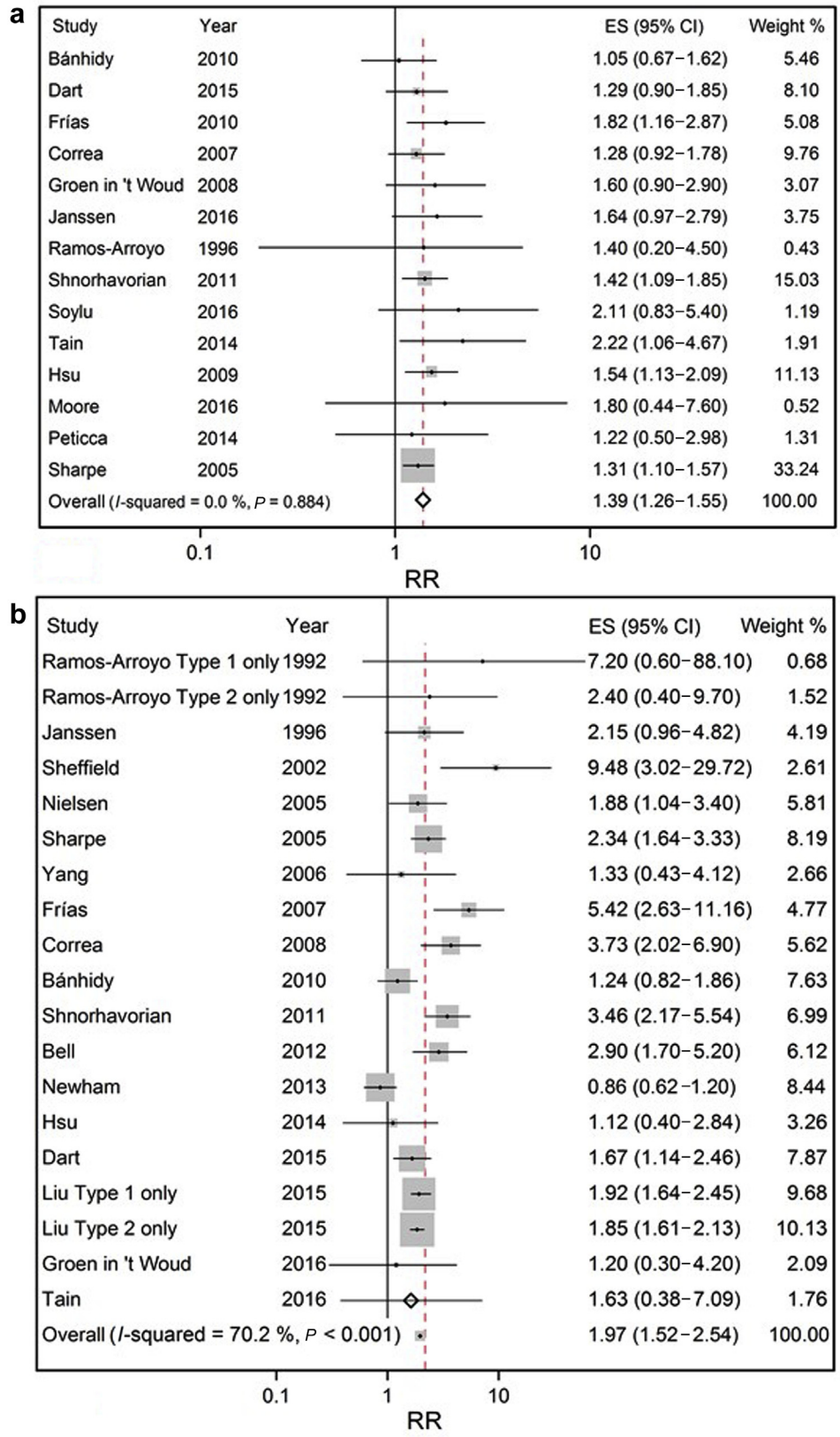

Figure 4. Forest plot of relative risk (RR) of congenital abnormalities of the kidney and the urinary tract (CAKUT) among (a) gestational diabetes and (b) pre-existing diabetes. Fourteen studies[5,24–37] that compare CAKUT in offspring of mothers with gestational diabetes (a) and 17 studies[5,13,15,38,40–46] of mothers with pre-existing diabetes (b), to CAKUT in mothers with no diabetes are summarized here. The summary measure of association is RR, 1.39 (95% confidence interval [CI], 1.26–1.55) for gestational diabetes and RR 1.97 (95% CI 1.52–2.54) for pre-existing diabetes. ES, effect estimate.

Table 3. Summary RR of association of diabetes and CAKUT in all studies and studies considered in sensitivity analysis

	All studies		Studies that attempted to control for confounding		Studies that adjusted for BMI	
	RR (95% CI)	I^2 (P value)	RR (95% CI)	I^2 (P value)	RR (95% CI)	I^2 (P value)
Any diabetes	1.51 (1.36–1.67)	25.3% (0.182)	1.56 (1.26–1.94)	13.1% (0.327)	—	
Pre-existing diabetes only	1.97 (1.52–2.54)	70.2% (0.000)	2.10 (1.75–2.52)	44.6% (0.071)	2.71 (0.77–9.59)	74.9% (0.019)
Gestational diabetes	1.39 (1.26–1.55)	0.0% (0.884)	1.42 (1.22–1.64)	0.0% (0.867)	1.50 (1.16–1.93)	74.9% (0.019)

BMI, body mass index; CAKUT, congenital abnormalities of the kidney and the urinary tract; CI, confidence interval; RR, relative risk.

This study supports the pathophysiology of CAKUT in the context of hyperglycaemia studied in animal models, which suggests that maternal hyperglycaemia adversely effects kidney development of the fetus. In rats, number of nephrons formed during kidney development in pups of diabetic female rats was significantly reduced due to hyperglycemia.[51] The 2 key events in kidney development, ureteric branching morphogenesis and nephrogenesis, both are adversely affected by hyperglycemia in diabetic mouse models.[52] Maternal diabetes during pregnancy can cause changes in gene expression levels in the mouse embryo, disrupting the epithelial layers and mesenchymal cell interactions during kidney development, which can cause CAKUT.[53–55]

A strength of this study includes an inclusive and wide search. A systematic search of reported literature including studies that did not specifically focus on renal abnormalities but reported congenital abnormalities for a range of organ systems was conducted. These studies would have been missed by a narrower search. Other study strengths include the inclusion of both case-control studies and cohort studies. Estimates of RR were presented for all diabetes and further stratified by gestational and pre-gestational diabetes. A thorough assessment of bias and confounding is included, with sensitivity analysis considering only those that adjusted for BMI (an important confounder).

A limitation of the study is that studies that were published in languages other than English were excluded. Of 6962 unique studies considered for this study, only 9 articles (0.1%) were published in a language other than English. Translated abstracts of these articles revealed that CAKUT was not identified as an outcome. Therefore, it is likely that the studies published in a language other than English would have been excluded from the meta-analysis anyway.

A concern is that studies were of variable quality. First, there remains a concern of ascertainment bias, that in some settings, women who have diabetes in pregnancy undergo more thorough screening for abnormalities in their offspring. However, Newham *et al.*[32] showed no difference in antenatal detection of CAKUT between women with and without pre-gestational diabetes. In addition, when scrutinizing the outcome definitions for the included studies, the clear majority are from large birth registries with thorough outcome ascertainment for severe and symptomatic forms of renal and urological abnormalities in early life. The case-control studies included CAKUT diagnosed after the first year of birth and therefore addressed this issue somewhat. The outcomes included are a heterogeneous mix including severe forms of CAKUT, including renal agenesis. However, considering the patho-mechanism of elevated glucose levels leading to organ abnormality, it would not be surprising to find a heterogeneous mix of outcomes, as has been reported for the effect of diabetes on congenital abnormalities overall.

Voluntary terminations of pregnancy were included in 6 studies among the 26 studies in the systematic review, as information on terminations were not

Table 4. PAR % of CAKUT due to gestational diabetes in the United Kingdom, United States, and India

Country	Prevalence of GDM (%)	PAR (%)
United States[a]		
CDC (national study)	4.6–9.2	1.9–3.7
United Kingdom/Ireland (all)[b]		
ADIP	10.19 (9.43–10.95)	4.1 (3.8–4.4)
BiB	8.15 (7.62–8.67)	3.3 (3.1–3.5)
Warwick	8.68 (8.0–9.36)	3.5 (3.3–3.8)
United Kingdom/Ireland (white)		
ADIP	8.6 (6.1–11.1)	3.5 (2.5–4.5)
BiB	4.9 (1.9–7.9)	2.0 (0.8–3.2)
Warwick	8.1 (5.2–11.0)	3.3 (2.1–4.4)
United Kingdom/Ireland (South Asian)		
ADIP	39.1 (28–50)	14.41 (10.5–17.4)
BiB	10.8 (8.1–13.4)	4.3 (3.3–5.3)
Warwick	10.8 (5.1–16.5)	4.3 (21.0–6.5)
India		
Chennai[c]	16.6	6.5
North India[d]	35	12.8

ADIP, Atlantic Diabetes in Pregnancy study; BiB, Born in Bradford Study; CAKUT, congenital abnormalities of the kidney and the urinary tract; CDC, Centers for Disease Control and Prevention; GDM, gestational diabetes mellitus; PAR, population attributable risk; Warwick, Warwick/Coventry Cohort Study.

[a]Mixed diagnostic criteria from 3 primary criteria used in the United States are by the National Diabetes Data Group, Carpenter and Coustan, and the International Association of Diabetes and Pregnancy Study Groups (IADPSG).[48]

[b]Prevalence data from systematic review; diagnostic criteria used for GDM: World Health Organization (WHO) 1999.[23]

[c]Study based on one government hospital in Chennai; diagnostic criteria for GDM: WHO 1999.[49]

[d]Population-based screening study in North India; diagnostic criteria for GDM: WHO 2013.[50]

accessible in most of the data sources. Therefore, it is likely that our systematic review underestimates the rate of CAKUT, especially in more recent years during which improved screening and detection methods may have led to greater number of voluntary terminations.

The likelihood of detecting CAKUT in diabetic pregnancies is probably higher compared with the nondiabetic population, as the likelihood for screening might be greater among the diabetic population. Therefore, the likelihood of detecting and terminating pregnancies with CAKUT could be higher among diabetic mothers in comparison with nondiabetic mothers, and the exclusion of still births most likely leads to an underestimation of the effect of diabetic pregnancies on CAKUT. However, the literature suggests that antenatal detection of CAKUT among women with and without pre-gestational diabetes is similar.[32] Therefore, the underestimation of CAKUT from exclusion of termination of pregnancies could be nondifferential between the diabetic and nondiabetic groups.

A further concern is that results may be explained by other, unmeasured, variables (i.e., confounders including BMI, maternal age, or intake of folic acid). However, sensitivity analyses that attempted to investigate the role of confounding did not identify evidence that these variables would reduce the strength of associations seen in this study.

This study has implications for maternal care during pregnancy. A meta-analysis suggests that preconception care is an effective intervention in reducing congenital malformations.[56] In Sweden, a prospective nationwide study concluded that poor metabolic control in early pregnancy contributes to an increased risk of fetal abnormalities.[57] Fetal kidney development begins in the first trimester, with an exponential increase in nephrons occurring between 18 and 32 weeks of gestation.[58] Any policy that improves glycemic control during this period may potentially reduce genitourinary abnormalities.[4] Pre-gestational diabetes can remain undiagnosed, and screening among at-risk women early in pregnancy provides an opportunity to diagnose and improve glycemic condition in utero during development, leading to improved outcomes.

In summary, this review raises the question of whether maternal diabetes is a contributing factor for incidence of CAKUT in both developed and developing settings. If this association is confirmed, there is a potential to improve kidney health by improving maternal health and by preventing and diagnosing diabetes in a timely manner in women of childbearing age.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1A. Quality assessment: rationale. This table explains the conditions that helped classify articles as having high/low risk of bias and confounding.

Table S1B. Case-control studies: quality assessment. This table provides a detailed qualitative assessment of all studies included in the review. All studies were assessed to have high/low risk or uncertain risk of bias based on the definitions set in Table S1A.

Table S1C. Cohort studies: quality assessment. This table provides a detailed qualitative assessment of all cohort studies included in the review. All studies were assessed to have high/low risk or uncertain risk of bias based on the definitions set in Table S1A.

Table S2A. In-depth analysis of confounding of all studies included in meta-analysis. This table captures an in-depth assessment of confounding factors that were adjusted and not adjusted for all identified studies. The table ranks studies as having residual cofounding and minimal confounding only. Articles ranked as having minimal were combined in sensitivity analysis that restricted meta-analysis only to those studies that adjusted for confounding.

Table S2B. Assessment of Crude and reported OR used for meta-analysis. This table describes if odds ratio or RRs for studies were reported in the publication or manually calculated for this systematic review. For those studies that reported both crude and adjusted OR, this table provides a side by side comparison of the difference in crude and adjusted OR.

Figure S1. (A) Funnel plot of studies considered for meta-analysis (RR of congenital genitourinary abnormalities with all maternal diabetes): 14 studies that compare genitourinary abnormalities in mothers with any diabetes types and controls with no diabetes are plotted in the funnel graph. The spread of studies here indicates minimal publication bias. (B) Funnel plot of studies considered for meta-analysis (RR of congenital genitourinary abnormalities with pre-existing diabetes): 18 studies that compare genitourinary abnormalities in mothers with pre-gestational diabetes and controls with no diabetes are plotted in the funnel graph. The spread of studies here indicates some publication bias. (C) Funnel plot of studies considered for meta-analysis (RR of congenital genitourinary abnormalities with gestational diabetes): 14 studies that compare genitourinary abnormalities in mothers with gestational diabetes and controls with no diabetes are plotted in the funnel graph. The spread of studies here indicates minimal publication bias.

Figure S2. (A) Forest plot of RR of congenital genitourinary abnormalities with combined diabetes types (after adjusting for confounding). Four studies comparing congenital genitourinary abnormalities in any diabetes type with control, nondiabetic women, and adjusted for

potential confounding variables, are summarized. The summary measure of association is RR, 1.56 (1.26–1.94). (B) Forest plot of RR of congenital genitourinary abnormalities with pre-existing diabetes (after adjusting for confounding). Eight studies comparing congenital genitourinary abnormalities in pre-existing diabetic women with control, nondiabetic women, and adjusted for potential confounding variables, are summarized above. The summary measure of association is RR, 2.10 (1.75–2.52). (C) Forest plot of RR of congenital genitourinary abnormalities with gestational diabetes (after adjusting for confounding). Seven studies comparing congenital genitourinary abnormalities in gestational diabetic women with control, nondiabetic women, and adjusted for potential confounding variables, are summarized above. The summary measure of association is RR, 1.42 (1.22–1.54).

Figure S3. (A) Meta-analysis of studies that adjusted for BMI as confounding factor with PGDM as exposure (*hypospadias as genitourinary abnormality; **bilateral agenesis and/or hypoplasia as urogenital abnormality). Two studies were combined in this summary and the summary measure of association is RR, 2.71 (0.77–9.59). (B) Meta-analysis of studies that adjusted for BMI as confounding factor with GDM as exposure (*hypospadias as genitourinary abnormality; **bilateral agenesis and/or hypoplasia as urogenital abnormality). Two studies were combined in this summary and summary measure of association is RR, 1.50 (1.16–1.93).

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