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The relationship between maternal obesity and diabetes during pregnancy on offspring kidney structure and function in humans: a systematic review

Y. Q. Lee[1,2], C. E. Collins[3,4], A. Gordon[5], K. M. Rae[2,6,7,8] and K. G. Pringle[1,2,6]

[1]School of Biomedical Sciences and Pharmacy, Faculty of Health and Medicine, University of Newcastle, Newcastle, NSW, Australia, [2]Priority Research Centre for Reproductive Sciences, University of Newcastle, Newcastle, NSW, Australia, [3]School of Health Sciences, Faculty of Health and Medicine, University of Newcastle, Newcastle, NSW, Australia, [4]Priority Research Centre in Physical Activity and Nutrition, University of Newcastle, Newcastle, NSW, Australia, [5]Charles Perkins Centre, University of Sydney, Sydney, NSW, Australia, [6]Gomeroi gaaynggal Centre, Faculty of Health and Medicine, University of Newcastle, Tamworth, NSW, Australia, [7]Department of Rural Health, School of Medicine and Public Health, Faculty of Health and Medicine, University of Newcastle, Tamworth, NSW, Australia and [8]Priority Research Centre for Generational Health and Ageing, University of Newcastle, Newcastle, NSW, Australia

Review

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Address for correspondence:
Dr. K. G. Pringle, Hunter Medical Research Institute, Lot 1 Kookaburra Circuit, New Lambton Heights, NSW 2305, Australia.
E-mail: kirsty.pringle@newcastle.edu.au

Abstract

Evidence from animal models indicates that exposure to an obesogenic or hyperglycemic intrauterine environment adversely impacts offspring kidney development and renal function. However, evidence from human studies has not been evaluated systematically. Therefore, the aim of this systematic review was to synthesize current research in humans that has examined the relationship between gestational obesity and/or diabetes and offspring kidney structure and function. Systematic electronic database searches were conducted of five relevant databases (CINAHL, Cochrane, EMBASE, MEDLINE and Scopus). Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines were followed, and articles screened by two independent reviewers generated nine eligible papers for inclusion. Six studies were assessed as being of 'neutral' quality, two of 'negative' and one 'positive' quality. Observational studies suggest that offspring exposed to a hyperglycemic intrauterine environment are more likely to display markers of renal dysfunction and are at higher risk of end-stage renal disease. There was limited and inconsistent evidence for a link between exposure to an obesogenic intrauterine environment and offspring renal outcomes. Offspring renal outcome measures across studies were diverse, with a large variation in offspring age at follow-up, limiting comparability across studies. The collective current body of evidence suggests that intrauterine exposure to maternal obesity and/or diabetes adversely impacts renal programming in offspring, with an increased risk of kidney disease in adulthood. Further high-quality, longitudinal, prospective cohort studies that measure indicators of offspring renal development and function, including fetal kidney volume and albuminuria, at standardized follow-up time points, are warranted.

Introduction

The Developmental Origins of Health and Disease (DOHaD) hypothesis, proposed by David Barker in 1989, postulated that chronic non-communicable diseases (NCDs) could be driven by environmental insults occurring during intrauterine development.[1] Epidemiological evidence suggests that maternal insults during critical windows of fetal development could induce compensatory fetal responses that permanently alter offspring phenotype at birth.[2,3] This theoretically impacts on offspring risk for various health conditions, including hypertension, obesity, type 2 diabetes, cardiovascular disease (CVD) and later chronic kidney disease (CKD).[4]

Globally, CKD has been recognized as a major NCD.[5] A substantial body of evidence indicates that proteinuria, hypertension and CKD in adulthood have childhood antecedents, beginning as early as *in utero* and prenatally.[6] Nephrogenesis in humans begins at 9 weeks gestation and is completed by approximately 36 weeks gestation, after which time, no further mature nephrons are formed.[7,8] Therefore, an adverse intrauterine environment at the beginning of life impacts on nephrogenesis, predisposing an individual to an increased risk of subsequent hypertension and renal disease.[9–11] The remaining glomeruli have to maintain normal fluid and electrolyte balance, leading to glomerular hyperfiltration.[9] Over time,

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glomerular hypertrophy occurs, followed by maladaptive modifications and eventually leading to glomerulosclerosis.[9] These adaptations increase the risk of subsequent development of hypertension, impaired kidney function and end-stage renal disease (ESRD) in adulthood, a process termed the 'Brenner hypothesis.'[9] This emphasizes the importance of the intrauterine environment for supporting optimal kidney development and function.[12]

The association between an intrauterine environment characterized by hyperglycemia and later renal disease has been investigated extensively in animal models,[13–15] where maternal hyperglycemia is associated with reduced nephron number, raised blood pressure, microalbuminuria and diminished glomerular filtration rate (GFR) in offspring. Tran *et al.* reported that neonatal offspring (sex not specified) of pregnant mice with severe diabetes (blood glucose concentration ~30 mM) have an increased risk of congenital malformations and impaired nephrogenesis, leading to smaller kidneys with reduced nephron endowment.[13] Similarly, Chen *et al.* reported that neonatal offspring (both male and female) of diabetic female mice had on average 40% fewer nephrons, compared with offspring of non-diabetic mice.[15] These offspring developed hypertension and impaired glucose tolerance and showed signs of renal dysfunction (i.e., microalbuminuria) in adulthood.[15] This indicates that exposure to intrauterine hyperglycemia is associated with impaired renal function.

Maternal overweight/obesity is an additional risk factor for developing gestational diabetes mellitus (GDM). Although the majority of studies examining fetal programming of renal disease in adulthood focus on fetal undernutrition, it is apparent that maternal obesity during pregnancy also poses a significant risk to offspring health and wellbeing. Researchers have attempted to model the effects of maternal human obesity in pregnant rats, mostly by feeding a high-fat, high-fructose, typical 'Western' diet.[16,17] Numerous animal studies have demonstrated that maternal overnutrition, which leads to maternal obesity, alters nephrogenesis, and increases markers of fibrosis and glomerulosclerosis in offspring kidneys.[18–21] Male Sprague-Dawley rat offspring exposed to a high-fat maternal diet *in utero* demonstrated increased inflammation, oxidative stress and fibrosis in their kidneys at 9 weeks of age. These are likely to accelerate the development of CKD later in life.[21] These results from animal studies provide some support for the hypothesis that in humans, maternal obesity has a detrimental impact on later renal health in offspring.

While there is convincing evidence from animal studies of a link between maternal obesity and/or diabetes during pregnancy and offspring kidney structure and function, limited studies have been conducted in humans. To our knowledge, a systematic review of human studies has not yet been conducted. Given the considerable evidence that the origins of many chronic diseases can be traced back to *in utero* conditions, this is an extremely important issue.[22,23] Understanding the relationship between maternal obesity and/or diabetes during pregnancy with offspring kidney structure and function in humans could therefore inform the development of future interventions aimed at improving maternal health and optimizing infant renal health.

Therefore, the objective of this systematic review was to synthesize the best available evidence on the relationship between maternal obesity and/or diabetes in humans during pregnancy and offspring kidney structure and function. This review considered two main questions:

1. What is known about the relationship between maternal obesity and/or diabetes in humans during pregnancy and offspring kidney structure and function?
2. What are the research gaps related to this area?

Methods

The systematic review protocol was registered on the Prospero database (CRD42016047758),[24] and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.[25]

Study Identification

Literature ever published in English up to November 2017 from five relevant databases (CINAHL, Cochrane, EMBASE, MEDLINE and Scopus) were identified in a search using keywords and index terms. The search terms were divided into three groups: (1) Pregnancy/ or pregnan*.mp., Maternal, Mother*, Prenatal.mp.; (2) nutrition.mp., dietary habits.mp. or Food Habits/, food intake.mp. or Eating/, diet.mp. or Diet/, dietary supplements.mp. or Dietary Supplements/, undernutrition.mp. or Malnutrition/, overnutrition.mp. or Overnutrition/ or Nutritional Physiological Phenomena/, diabetes.mp. or Diabetes, Gestational/, Hyperglycemia, Obesity/ or obesity.mp., Weight Gain.mp. or Weight Gain/, Overweight and (3) kidney.mp. or Kidney/, nephron.mp. or Nephrons/, renal.mp. The Boolean phrase AND was used between groups and OR within groups. The results of this systematic review search were separated into two distinct papers for publication due to the number of studies identified in the search. The nutrition aspect of the maternal intrauterine environment and its association with offspring kidney outcomes has been published elsewhere.[26] Therefore, the current systematic review focuses on studies investigating the association between maternal obesity and/or diabetes during pregnancy and offspring kidney structure and function in humans.

Inclusion Criteria

Types of Participants

This current review only considered human studies and all participants had to be pregnant (at any stage of gestation) at the time of the study.

Types of Studies

The study types included were experimental studies, including pre–post, pseudo-randomized controlled trials and randomized controlled trials. Observational studies, including cross-sectional studies, case–control studies and prospective and retrospective cohort studies were also considered.

Types of Exposures/Interventions

The type of exposure considered for this current review was maternal obesity and/or diabetes during pregnancy.

Types of Outcome Measures

Studies were considered for inclusion if they measured offspring kidney function and/or structure as a primary or secondary outcome. Kidney structure outcome measures in offspring were: kidney volume, kidney size, kidney mass, kidney structure, glomerular size and nephron endowment. Outcomes related to

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kidney function in offspring included: proteinuria, urinary albumin/creatinine, microalbuminuria, albuminuria, glomerular filtration rate, urinary protein/creatinine, urinary nephrin/creatinine and urinary sodium/potassium.

Study Selection

All studies identified were retrieved and exported to the reference management system EndNote (version X8; Thomson Reuters, New York, NY, USA). The first phase of study identification included an assessment of study inclusion based on screening of the title, abstract and description/MESH headings. Full texts were retrieved and those papers meeting all inclusion criteria were included in the final review and underwent critical appraisal of study quality and data extraction. All stages were conducted by two independent reviewers with conflicts resolved by a third reviewer who made the final decision.

Study Quality

All included studies were assessed for methodological quality using the American Dietetic Association (ADA) Quality Criteria Checklist,[27] which consisted of 10 criteria to assess strength of the research design, relevance and validity. The items assessed included: the method of sample selection, methods of controlling for confounding factors, reliability of outcome measures and statistical analysis. Using this checklist, two independent reviewers rated the overall quality of the studies as positive, neutral or negative. A third reviewer was consulted to resolve differences. No studies were excluded based on quality ratings. To address publication bias, a comprehensive search of the literature was conducted in five major databases. Effort was also taken to retrieve 'difficult to find studies' such as utilizing the intra-university library network to request the papers from other universities and printed copies of old papers that are not available online. A meta-analysis was not possible due to the heterogeneity in measures of kidney outcome and function.

Data Extraction and Synthesis

Data extraction was conducted by one reviewer and cross-checked by a second independent reviewer for accuracy and consistency. Participant information, study design and intervention characteristics as well as data related to review outcomes were extracted. A meta-analysis of data was not expected to be possible due to the anticipated heterogeneity in maternal exposures during pregnancy and measures of kidney outcome and function. Therefore, the effect of maternal obesity and/or diabetes during pregnancy on offspring kidney structure and function was described in a narrative synthesis. A structured summary, direction of effect, the strength of the evidence for the effect and whether this was consistent across studies were highlighted in the data synthesis.

Results

Study Selection

Figure 1 illustrates the flow of studies from the initial search to inclusion in the review. The initial database search identified 9501 articles after removal of duplicates, with 8962 records excluded following title and abstract review for eligibility. Despite online inter-library searches, full texts were unavailable for 205 records. Of the 334 full-text articles retrieved, 278 articles were animal studies, with 56 articles on humans. After screening the human studies based on inclusion criteria, 37 were excluded. The primary reasons for exclusion of full-text papers were outcomes not related to offspring kidney structure or function ($n = 28$) and exposure/intervention not related to maternal nutrition or obesity or diabetes during pregnancy ($n = 8$). Of the remaining 19 articles, nine articles focused on maternal obesity or diabetes during pregnancy and offspring kidney outcomes and were included in this current paper.

Study Characteristics

Included studies ($n = 9$) were published between 1994 and 2014 and were conducted in 12 countries including the United States of America,[28–30] Netherlands,[31,32] Canada,[33] France,[34] Italy[35] and Brazil.[36] The most common measures of kidney structure were kidney volume and length, while kidney function measures were albuminuria, albumin/creatinine and GFR. Two studies evaluated the relative risk of developing renal disease in later life.[29,30] All of the studies included approximately equal number of male and female offspring. Four studies did not specify the exact numbers for each sex.[29,31,35,36] There was a wide range in the age of offspring at the time of assessment, from late gestation to approximately 40 years of age.

All of the included studies were observational study designs (Table 1). Seven observational studies evaluated the relationship between maternal hyperglycemia during pregnancy and offspring kidney structure and function, of which, one was a cross-sectional study,[31] four were prospective cohort studies[29,33,35,36] and two were retrospective cohort studies.[28,34] One prospective cohort study evaluated the relationship between maternal obesity and offspring kidney structure and function[32] and another retrospective cohort study evaluated the relationship between both maternal hyperglycemia and obesity during pregnancy and offspring kidney structure and function.[30] Factors that prevented meta-analysis from being performed included the heterogeneity of outcome measures for kidney structure and function and the large variation in the age at follow-up of offspring.

Risk of Bias of Included Studies

Only one study[32] was classified as of high methodological quality, with inclusion/exclusion criteria and demographics of subjects clearly described. In this study,[32] important confounding factors were accounted for by appropriate adjustments in the statistical analyses. Six (66.7%) studies[28,30,33–36] were rated as of neutral quality, as it was unclear whether data collectors were blinded to study outcomes and risk factor assessments. It was also unclear whether important confounders were accounted for in statistical analyses. Two (22.2%) studies[29,31] were rated as of negative quality, as the criteria for study subject selection bias and generalizability were not met. Confounding factors were not clearly identified or taken into account in the statistical analyses, lack of participant and data collector blinding to study outcomes, and limitations were not clearly identified and discussed (Table 2).

Relationship Between Maternal Obesity and/or Diabetes During Pregnancy and Offspring Kidney Structure or Function

Nine observational studies investigated the effect of maternal diabetes or obesity during pregnancy on offspring kidney structure and function.[28–36] Neves *et al.* found that maternal hyperglycemia *in utero* was associated with a higher fetal kidney volume, measured between 22–38 weeks of gestation.[36] The median fetal kidney volume in pregnancies affected by hyperglycemia was significantly

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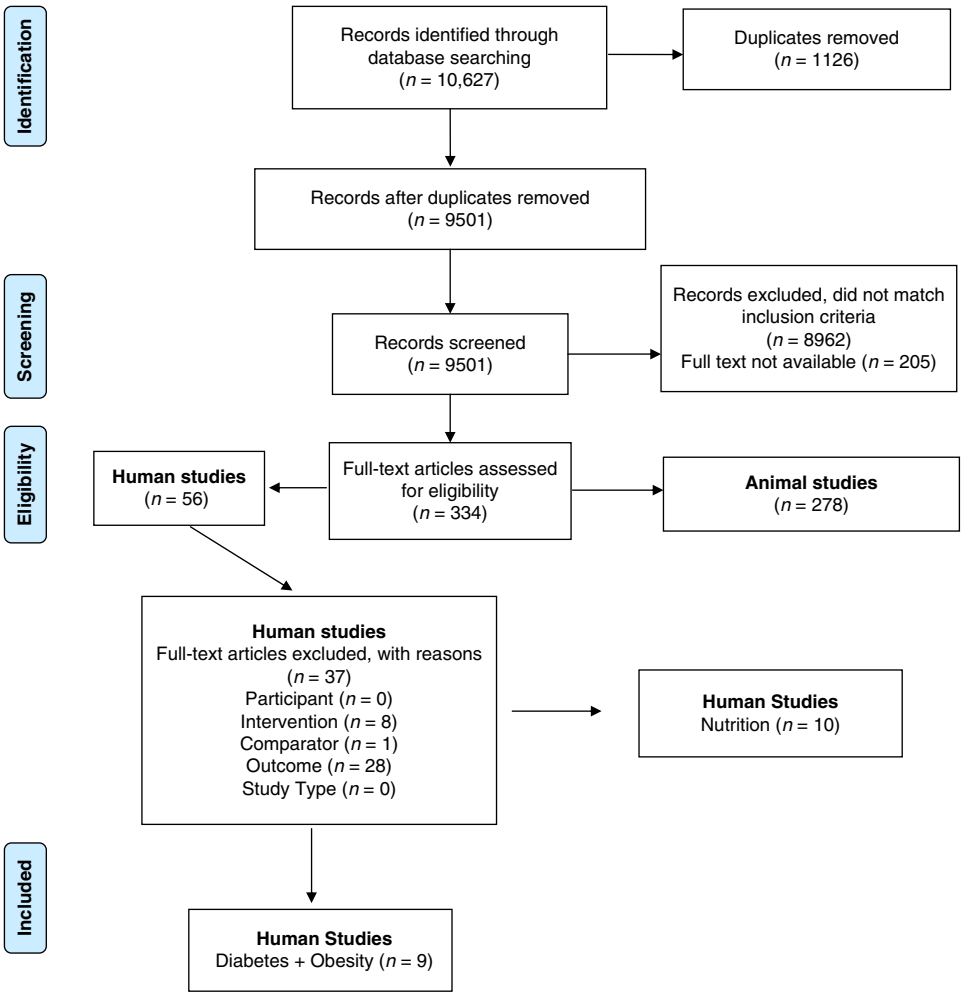

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram of the study selection process.

greater than the 75th percentile kidney volume in normoglycemic pregnancies.[36] In a large population-based prospective cohort study of 1215 women from the Netherlands, Verburg *et al.* examined the association between maternal characteristics with fetal kidney volume in late pregnancy (30.4 weeks gestation).[32] Maternal pre-pregnancy height and weight were positively associated with fetal kidney size; however, maternal obesity (measured using pre-pregnancy Body Mass Index) and diabetes during pregnancy (pre-existing type 1 or type 2 or pregnancy-induced diabetes) was not associated with fetal kidney size. A cross-sectional study (20 infants in each group) by Bos *et al.* found that the kidney size of infants born to mothers with tightly controlled insulin-dependent diabetes was not different from the kidney size of healthy control infants in the first week of life.[31] Only kidney size was assessed in this study and kidney function was not assessed (Table 3).

Dyck *et al.* measured albumin/creatinine in infants of mothers with diabetes (InfDM + : type 1 or type 2 or GDM) and infants of mothers without diabetes (InfDM −) and found that InfDM + had significantly lower albumin/creatinine than InfDM − at one day of age after other variables were adjusted for ($P = 0.05$). However at 9 months, there was no significant difference between groups.[33] Mean urinary albumin and urinary creatinine were also significantly higher in InfDM − neonates than in InfDM + neonates at one day of age.[33] Cappuccini *et al.* found that children (measured at 3 years of age) exposed to maternal hyperglycemia *in utero* throughout pregnancy had significantly lower mean kidney cortex volume and higher microalbuminuria levels compared with controls.[35]

Results from Abi Khalil *et al.*, who compared adult offspring without diabetes (mean age 24–25 years) of mothers with type 1 diabetes during pregnancy to a control group of adult offspring of fathers with type 1 diabetes, found reduced renal function in the former group, as measured by GFR, mean arterial pressure, renal plasma flow and renal vascular resistance, which was thought to be a consequence of a reduction in glomerular number, leading to hyperfiltration.[34]

Two epidemiological studies focused on the Gila River Pima Indian population with type 2 diabetes (offspring aged 12–77 years old).[28,29] Nelson *et al.* found that offspring with type 2 diabetes who were exposed to diabetes *in utero* (mother had pre-existing diabetes at the time of pregnancy or developed it during pregnancy) had a higher risk of developing albuminuria in adulthood, a key marker of renal disease.[28] Elevated urinary albumin excretion (UAE) was found in 58% of offspring (mean age 24 ± 9 years old) born to mothers with diabetes during pregnancy, 43% of offspring (mean age 38 ± 10 years old) from mothers who developed diabetes after pregnancy and 40% of offspring (mean age 44 ± 15 years old) from mothers without diabetes.[28] The odds of elevated UAE were almost four times higher among offspring exposed to diabetes *in utero*.[28] In the

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Table 1. Description of observational studies: diabetes and/or obesity

References	Setting	Aims, design	Inclusion/exclusion criteria	Study population	Offspring age at follow-up (years), sex
Late gestation					
Neves *et al.* 2013[36]	Prenatal outpatient in Rio de Janeiro state, South Eastern Brazil	Aim: To measure fetal renal volume in normoglycemic and hyperglycemic pregnancies Design: Prospective	Inclusion: Only singleton pregnant women Exclusion: 1. Women reporting alcohol abuse, hypertension, smoking, and systemic infections, collagenosis, or heart disease 2. Cases of fetal renal anomalies as evidenced by abnormal fetal kidney measurements	339 normoglycemic 92 hyperglycemic	22–38 weeks of gestation Numbers for each sex not specified
Verburg *et al.* 2007[32]	Generation R study: population-based prospective cohort study from fetal life onward in Rotterdam, The Netherlands	Aim: To examine whether maternal characteristics, fetal growth, fetal blood flow redistribution or inadequate placental perfusion in different periods of fetal life affect fetal kidney volume Design: Prospective	Exclusion: Twin pregnancies and pregnancies leading to perinatal death	1215 women	Median gestational age (95% range): 30.4 (28.4–32.6) Male (51%)
Infant/toddler					
Bos *et al.* 1994[31]	Department of Pediatrics, University Hospital Groningen, The Netherlands	Aim: To determine the relationship between kidney size and control of diabetes in infants of insulin-dependent diabetic (IDM) mothers Design: Cross-sectional	Inclusion: 1. IDM mothers and their infants 2. Healthy newborn infants from non-diabetic mothers were birth weight-matched controls	Infants of IDM mothers ($n = 20$) Healthy newborn controls ($n = 20$)	First week of life Numbers for each sex not specified
Dyck *et al.* 2011[33]	Royal University Hospital in Saskatoon, Canada	Aim: To establish the levels and distribution of urinary albumin:creatinine ratios (ACRs) in infants of diabetic mothers (InfDM+) and infants of non-diabetic mothers (InfDM-) Design: Prospective	Inclusion: Mothers with type 1, type 2 or gestational diabetes during pregnancy	Maternal/infant pairs whose mother had diabetes in pregnancy ($n = 65$): GDM ($n = 48$) Type 2 diabetes ($n = 13$) Type 1 diabetes ($n = 4$) Non-diabetic maternal/infant pairs ($n = 59$)	Mean: 1 day old, 9 months Male (Diabetic: 58.5%; Non-diabetic: 62.7%)
Cappuccini *et al.* 2013[35]	Santa Maria della Misericordia Hospital, University Hospital of Perugia, Perugia, Italy	Aim: To determine if maternal diabetes effects renal cortical volume in the offspring, and whether this effects albumin excretion in children of diabetic mothers compared with children of non-diabetic controls, evaluated at 3 years of age Design: Prospective	Inclusion: Born at term after an uncomplicated pregnancy	42 children born of mothers with diabetes mellitus (type 1, type 2 or gestational diabetes) 21 controls born of non-diabetic mothers	36–39 months old Numbers for each sex not specified
Adult					
Abi Khalil *et al.* 2010[34]	Hospital Saint-Louis, Hospital Bichat–Claude Bernard, Hotel-Dieu, Centre Hospitalier Universitaire in Poitiers, and Centre	Aim: To study kidney function in subjects who had been exposed to hyperglycemia during fetal development Design: Retrospective	Case subjects: Offspring of type 1 diabetic mothers Control subjects: Offspring of type 1 diabetic fathers Inclusion: Non-pregnant offspring whose mothers had type 1 diabetes at least 2 years before conception Participants were eligible if their spouses had neither type 1 nor type 2 diabetes at the time of the study	Cases: 19 Controls: 18	Case: 24 (18–41) Male (26%) Control: 25 (18–37) Male (50%)

Table 1. (*Continued*)

References	Setting	Aims, design	Inclusion/exclusion criteria	Study population	Offspring age at follow-up (years), sex
	Hospitalier Sud Francilien in Corbeil Essonne, France		Offspring were men or women age 18 years or older with no diabetes		
Pavkov *et al.* 2010[29]	Gila River Pima Indian Community of Arizona, USA	Aim: To examine the effect of intrauterine diabetes exposure on incidence of diabetic ESRD in Pima Indians with type 2 diabetes Design: Prospective	Inclusion: Diabetic subjects aged 5–45 years who attended research examinations and resided in the community	Exposed: 102 Unexposed: 1748	Median: Baseline: Exposed 17.5 Unexposed 34.2 ($P < 0.0001$) Follow-up: Exposed 26.7 Unexposed 45.0 ($P < 0.0001$) Median follow-up: 7.1 years (IQR: 3.2–12.5) Numbers for each sex not specified
Nelson *et al.* 1998[28]	Gila River Pima Indian Community of Arizona, United States of America	Aim: To examine the relationship between diabetes exposure in utero and renal disease in Pima Indians with type 2 diabetes Design: Retrospective	Inclusion: All offspring and their parents were at least half Pima or Tohono O'odham by heritage. Non-diabetic: Offspring of non-diabetic women who had normal glucose tolerance at the time of pregnancy (no previous 2 h post load plasma glucose concentration ⩾ 140 mg/dl), had a documented normal OGTT ⩾ 4 weeks after delivery, and did not subsequently develop diabetes. Pre-diabetic: Offspring of women who had normal glucose tolerance at the time of pregnancy and ⩾ 4 weeks after delivery, but who subsequently developed diabetes. Diabetic: Offspring of mothers who already had diabetes at the time of pregnancy or developed it during pregnancy. Exclusion: 1. Those whose non-diabetic mother was followed for <5 years after the index pregnancy 2. Those whose mother had a history of impaired glucose tolerance 3. Those whose mother's onset of diabetes could not be dated relative to the index pregnancy	207 offspring of non-diabetic women 246 offspring of pre-diabetic women 50 offspring of diabetic women	Mean ± SD: Non-diabetic 44 ± 15 Male (44%) Pre-diabetic 38 ± 10 Male (36%) Diabetic 24 ± 9 Male (34%)
Hsu *et al.* 2014[30]	Washington (WA) state birth records between 1987 and 2008	Aim: To evaluate the effects of abnormal birth weight, maternal pre-gestational diabetes mellitus, gestational diabetes and maternal overweight/obesity on childhood CKD Design: Retrospective		Cases: 1994 patients with childhood CKD Controls: 20,032	< 21 years Cases: Male (64.7%) Controls: Male (51.4%)

GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; IQR, interquartile range; ESRD, end-stage renal disease; IDM, insulin-dependent diabetic; InfDM+, infants of diabetic mothers; InfDM−, infants of non-diabetic mothers; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; CKD, chronic kidney disease

Table 2. Results of study quality based on the American Dietetic Association quality criteria[a]

Author	Quality Rating[b]	Relevance Q1	Relevance Q2	Relevance Q3	Relevance Q4	Validity Q1	Validity Q2	Validity Q3	Validity Q4	Validity Q5	Validity Q6	Validity Q7	Validity Q8	Validity Q9	Validity Q10
Neves *et al.* 2013[36]	Ø	NA	Yes	Yes	NA	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	No	No
Verburg *et al.* 2007[32]	+	NA	Yes	Yes	NA	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes
Bos *et al.* 1994[31]	–	NA	Yes	Yes	NA	Yes	Unclear	No	No	Unclear	No	Yes	Yes	No	Unclear
Dyck *et al.* 2011[33]	Ø	NA	Yes	Yes	NA	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes
Cappuccini *et al.* 2013[35]	Ø	NA	Yes	Yes	NA	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Abi Khalil *et al.* 2010[34]	Ø	NA	Yes	Yes	NA	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	No	Yes
Pavkov *et al.* 2010[29]	-	NA	Yes	Yes	NA	Yes	No	No	No	Unclear	Unclear	Yes	Yes	No	Yes
Nelson *et al.* 1998[28]	Ø	NA	Yes	Yes	NA	Yes	Yes	Unclear	No	Unclear	Yes	Yes	Yes	Yes	Yes
Hsu *et al.* 2014[30]	Ø	NA	Yes	Yes	NA	Yes	Unclear	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes

NA: not applicable

[a]American Dietetic Association quality criteria: Relevance questions: (1) Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies). (2) Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about? (3) Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice? (4) Is the intervention or procedure feasible? (NA for some epidemiological studies); Validity questions: (1) Was the research question clearly stated? (2) Was the selection of study subjects/patients free from bias? (3) Were study groups comparable? (4) Was method of handling withdrawals described? (5) Was blinding used to prevent introduction of bias? (6) Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described? (7) Were outcomes clearly defined and the measurements valid and reliable? (8) Was the statistical analysis appropriate for the study design and type of outcome indicators? (9) Are conclusions supported by results with biases and limitations taken into consideration? (10) Is bias due to study's funding or sponsorship unlikely?

[b]Studies were rated as 'positive' if they were assessed as a 'Yes' to all of the four 'essential' criteria, as follows: (1) Was selection of study subjects free from bias?; (2) Were study groups comparable?; (3) Were interventions and any comparisons described in detail?; (4) Were outcomes clearly defined and the measurements valid and reliable?; and, at least one additional 'yes' from the other six criteria. If six or more of the criteria were assessed as a 'No', the study was rated 'negative'. Studies were rated 'neutral' if the majority of the 10 criteria were met, but one of the 'essential' criteria were not met.

Table 3. Results of observational studies: diabetes and/or obesity

	Offspring kidney-related outcome reported			
	Measures	Significance of results	Results	Conclusion, limitations and recommendations
Late gestation				
Neves *et al.* 2013[36]	Fetal kidney volume (mm^3)	Median fetal kidney volume in hyperglycemic pregnancies was significantly larger than the 75th percentile kidney volume in normoglycemic pregnancies during nearly the entire follow-up period, even though normal glycemic mean values were achieved in 80% of the cases	–	Conclusion Maternal hyperglycemia is associated with fetal kidney volume growth modification, hyperglycemia *in utero* increases fetal kidney volume
Verburg *et al.* 2007[32]	Combined fetal kidney volume (cm^3)	Positively associated with maternal pre-pregnancy weight ($P < 0.05$)	Difference in total kidney volume (cm^3) (95% CI): 0.03 (0.01, 0.05)	Strength: The largest population-based cohort in which kidney size in late pregnancy was studied Conclusion: Maternal weight and height were positively associated with kidney volume Recommendation: Further research to disentangle the causal mechanisms underlying the demonstrated associations is needed
		Positively associated with maternal pre-pregnancy height ($P < 0.01$)	Difference in total kidney volume (cm^3) (95% CI): 0.07 (0.02, 0.11)	
		Not associated with pre-existing or pregnancy induced diabetes	Difference in total kidney volume (cm^3) (95% CI): −0.60 (−3.49, 2.30)	
Infant/toddler				
Bos *et al.* 1994[31]	Kidney length (cm) Mean ± SD	No significant difference between groups ($P < 0.10$)	Left kidney IDM: 4.2 ± 0.5 Controls: 4.3 ± 0.6 Right kidney IDM: 4.0 ± 0.4 Controls: 4.2 ± 0.5	Conclusion: Kidney size of infants of tightly controlled insulin-dependent diabetic mothers was not different from kidney size of healthy control infants
	Kidney length to body length ratio (KB ratio) (mm/cm) Mean ± SD	No significant difference between groups ($P < 0.10$)	Left KB-ratio IDM: 0.85 ± 0.10 Controls: 0.85 ± 0.10 Right KB-ratio IDM: 0.81 ± 0.08 Controls: 0.83 ± 0.09	
Dyck *et al.* 2011[33]	Median ACRs (mg/mmol; range)	1-day-old: Significantly lower in InfDM+ than InfDM− ($P = 0.05$) 9 months: No significant difference between InfDM+ and InfDM− ($P = 0.489$)	1-day-old: InfDM+: 6.0 (0.3, 82.7) InfDM−: 11.5 (0.2, 72.2)	Limitation: 1. Opportunistic sampling, which was more likely to include maternal/infant pairs with problems requiring longer hospital stays 2. Relatively small number of subjects from whom a urine sample could be collected at 5–19 months

			9 months: InfDM+: 1.9 (0.9, 44.8) InfDM−: 2.5 (0.9, 10.4)	Strength: The number of subjects recruited, the detailed maternal/infant data collected Conclusion: 1. InfDM+ had significantly lower ACRs than InfDM− at 1-day-old 3. The diagnostic value of ACR for identifying underlying renal disease in children under 6 months may be limited. Recommendation: 1. Future study using older offspring of diabetic and non-diabetic mothers 2. Larger studies required
Cappuccini *et al.* 2013[35]	Renal cortex volume mean of both kidneys (ml)	Significantly lower in children of diabetic mothers compared with controls – birth weight was comparable between groups No gender-related difference in renal cortical volume ($P < 0.001$)	Median (range) OD: 15.8 (6.2–24.1) Control: 17.9 (15.6–21.6)	Limitation: Small sample size Conclusion: Maternal diabetes may have adverse effects on the kidney in the offspring
	Microalbuminuria (mg/dl)	Higher levels in children of diabetic mothers ($P < 0.001$)	Median (range) OD: 0.385 (0.200–2.800) Control: 0.200 (0.200–0.300)	
Adult				
Abi Khalil *et al.* 2010[34]	Kidney volume (ml) Mean ± SD	No significant difference between groups Right: $P = 0.65$ Left: $P = 0.71$	Right kidney Case: 157 ± 35.5 Control: 165 ± 42.2 Left kidney Case: 155.9 ± 34 Control: 151.1 ± 18.6	Conclusion: Fetal exposure to maternal type 1 diabetes was associated with a reduced renal function in offspring of humans at adult age
	After amino acid infusion: Urinary sodium (mmol/24 h) Mean ± SD	No significant difference between groups ($P = 0.84$)	Case: 136 ± 78 Control: 131 ± 66	
	After amino acid infusion: Urinary potassium (mmol/24 h) Mean ± SD	No significant difference between groups ($P = 0.59$)	Case: 82 ± 58 Control: 72 ± 54	
	After amino acid infusion: Urinary albumin (mg/24 h) Median (range)	No significant difference between groups ($P = 0.11$)	Case: 9 (5–14) Control: 5 (4–8)	
	After amino acid infusion: Systolic/diastolic blood pressures (mmHg) Mean ± SD	No significant difference between groups Systolic: $P = 0.085$ Diastolic: $P = 0.36$	Systolic Case: 118 ± 6 Control: 114 ± 7 Diastolic Case: 72 ± 7 Control: 70 ± 8	
	After amino acid infusion: GFR (ml/min)	Baseline GFR did not differ between groups. There was a smaller increased in GFR in response to amino acids in cases compared with controls Case: $P = 0.019$ Control: $P = 0.002$	Case: 102 ± 14 to 111 ± 17 (8 ± 13%) Control: 108 ± 17 to 128 ± 23 (19 ± 7%)	

Table 3. (*Continued*)

	Offspring kidney-related outcome reported			
	Measures	Significance of results	Results	Conclusion, limitations and recommendations
	After amino acid infusion: Effective renal plasma flow (ml/min)	Smaller increase in response to amino acids in cases compared with controls Case: $P = 0.016$ Control: $P = 0.002$	Case: 509 ± 58 to 536 ± 114 (5 ± 9%) Control: 536 ± 114 to 620 ± 140 (16 ± 11%)	
	After amino acid infusion: Relationship between changes in GFR and birth weight	Highly significant in cases ($r = 0.61$, $P = 0.006$), but not in controls ($r = -0.08$, $P = 0.78$)	–	
Pavkov *et al.* 2010[29]	Cumulative incidence of ESRD by age 45	Higher in participants with IDE than in those without ($P = 0.001$) Age- and sex-adjusted incidence in those with IDE was 4.12 times that of the unexposed After adjusting for age at diabetes onset, incidence of ESRD was similar between those with IDE and unexposed	IDE: 19.3% Without IDE: 5.1% 4.12 (95% CI 1.54–11.02) 1.38 (95% CI 0.45–4.24)	Strength: First study to link IDE to an earlier onset of ESRD Conclusion: Exposure to IDE was associated with a four-fold increase in the incidence of ESRD in young adults with type 2 diabetes when adjusted for age and sex. This effect was explained largely by their earlier age at onset of diabetes. Recommendation: Implementation of appropriate behavior interventions to prevent or delay diabetes in women of child-bearing age may be an effective long-term strategy to reduce the increasing incidence of diabetic ESRD in young adults
Nelson *et al.* 1998[28]	Prevalence of elevated UAE	3.8 times higher in offspring of diabetic mothers than that of offspring of pre-diabetic mothers who later developed diabetes ($P = 0.001$) Maternal diabetes was strongly associated with prevalence of elevated UAE, adjusting for age, sex, duration of diabetes, HbA1c, mean arterial pressure in the offspring	Diabetic OR: 3.8 (95% CI 1.7–8.4)	Limitations: 1. The effect of maternal diabetes during pregnancy on the prevalence of renal disease in diabetic offspring could have been under or overestimated if postnatal survival or study participation among offspring differed according to maternal diabetes status. 2. Cross-sectional measures of time-dependent variables such as blood pressure, and level of glycemia, may be unreliable proxies for relevant past exposures. Conclusion: 1. Exposure to a diabetic intrauterine environment is a strong risk factor for renal disease in diabetic Pima Indians. 2. The risk of elevated UAE was nearly four times higher in offspring of diabetic mothers compared with offspring of non-diabetic or pre-diabetic mothers
Hsu *et al.* 2014[30]	Childhood CKD	More likely in children born to mothers with pre-GDM More likely in children born to mothers with GDM More likely in children born to overweight/obese mothers (BMI ⩾ 25)	Adjusted OR (95% CI) 1.12 (0.4–2.84) Adjusted OR (95% CI) 1.54 (1.13–2.09) Adjusted OR (95% CI) 1.25 (1.08–1.44)	Limitations: 1. Missing maternal BMI data in 44.4% of cases and 47.7% of controls 2. The use of self-reported data for maternal weight to calculate pre-pregnancy BMI when it was not available 3. Variation in classification for CKD between physicians Conclusion: Children with CKD were highly likely to have an abnormal prenatal history, including low birth weight, maternal overweight/obesity and maternal pre-gestational diabetes mellitus, diabetes and GDM Recommendation: Future studies should determine if modification of these factors could decrease the risk of childhood CKD

UAE, urinary albumin excretion; IDE, intrauterine diabetes exposure; IDM, insulin-dependent diabetic; ACRs, albumin:creatinine ratios; EPH syndrome: increase in blood pressure, proteinuria, edema; DM, diabetes mellitus; GDM, gestational diabetes mellitus; InfDM+, infants of diabetic mothers; InfDM−, infants of non-diabetic mothers; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; CKD, chronic kidney disease; BMI, body mass index; HPW, healthy pregnant women; SBP, systolic blood pressure; DBP, diastolic blood pressure; GFR, glomerular filtration rate; ESRD, end-stage renal disease; CI, confidence interval; OD, overall diabetes.

same population (Gila River Pima Indian population with type 2 diabetes), Pavkov *et al.* found that intrauterine diabetes exposure was associated with a four-fold increase in the incidence of ESRD in young adults (median age 26.7 years old).[29]

One large population-based, case–control study of 1994 patients with childhood CKD (<21 years of age at diagnosis) and 20,032 controls found that maternal pre-gestational diabetes mellitus (PDM), GDM, overweight and obesity were associated with significantly increased risk of CKD in offspring at <21 years of age (19, 54, 24 and 26% increased risk, respectively, compared with the controls).[30]

Discussion

In the past decade, fetal exposure to maternal obesity and/or diabetes has been identified as a risk factor for the development of NCDs in offspring once they reach adulthood.[37] CKD is a major global health issue due to its high prevalence and associated risk for CVD and premature mortality.[38,39] The Global Burden of Disease Study 2013 ranked CKD as the 19th highest condition attributed to years of life lost.[40] In addition, there was a 134.6% increase in deaths from 1990 directly caused by CKD.[40] Minority and Indigenous groups in many developed and developing countries, including Indigenous Australians, Maori, Pacific, and Torres Strait Islanders in New Zealand and First Nation Canadians are at an increased risk of developing CKD and disease progression.[41] To our knowledge, this is the first review to systematically examine the evidence for the effects of maternal obesity and/or diabetes during pregnancy on offspring kidney structure and function in humans. All of the studies included both male and female offspring, therefore limiting the sex bias evident in numerous animal studies.[42] There was a wide range in the age of offspring at the time of assessment, from late gestation to approximately 40 years of age. No age restriction was set in order to provide a comprehensive summary of evidence examining the relationship between maternal diabetes and/or obesity and offspring kidney structure and function throughout the whole lifespan. The heterogeneity of this age range meant that combining the results of separate studies in a meta-analysis was not possible.

Although the influence of maternal obesity or diabetes during pregnancy on fetal renal development has been clearly demonstrated in numerous experimental studies in large (e.g., sheep and pig) and small (e.g., mouse, rat and guinea pig) animal models,[11] human data on fetal programming of renal structure and function by maternal obesity or diabetes are lacking, with only nine human studies to date identified in this review. The limited evidence base related to these maternal risk factors for offspring CKD is a major knowledge gap.

Maternal Diabetes and Offspring Kidney Structure or Function

The prevalence of GDM and pre-existing diabetes (type 1 or type 2 diabetes) among young women of reproductive age is increasing, particularly in developing countries and is largely driven by obesity.[43–45] Pregnancies complicated by diabetes (type 1, type 2 or GDM) are associated with an increased risk of adverse outcomes, including congenital malformations, macrosomia, birth trauma and maternal preeclampsia.[45] Maternal diabetes is a risk factor for large-for-gestational-age (LGA) birthweight[46] and findings from population-based studies indicate a U-shaped relationship between birthweight and risk of CKD or ESRD.[47,48]

In rat models, exposure to hyperglycemia *in utero* impairs nephrogenesis, leading to reduced nephron numbers[49] and alterations in insulin-like growth factor (IGF) and IGF receptor expression in fetal kidneys.[50] Maternal hyperglycemia strongly affects the developing metanephros, leading to increased apoptosis in tubules and podocytes, thus increasing the risk of renal agenesis and dysgenesis.[13] Five studies found that exposure to a hyperglycemic intrauterine environment contributed to reduced renal function as measured by GFR, mean arterial pressure, renal plasma flow, renal vascular resistance and microalbuminuria and an increased risk of offspring CKD at ages ranging from 3 to 45 years.[28–30,34,35] Therefore, offspring exposed to hyperglycemia *in utero* could acquire a nephron deficit during nephrogenesis, which may influence the rate of progression of chronic renal disease[51] and hypertension in adulthood.[15,52] Additional longitudinal human cohort studies are warranted to further substantiate these findings.

Neves *et al.* reported that offspring exposed to hyperglycemia throughout pregnancy have significantly larger fetal kidney volumes, measured in the third trimester.[36] On the contrary, Verburg *et al.* found in a population-based cohort that maternal diabetes (pre-existing type 1 or type 2 or pregnancy-induced diabetes) did not influence fetal kidney volume in late pregnancy.[32] Cappuccini *et al.* found that there were lower mean renal cortex volumes and higher levels of microalbuminuria in 3-year-old children of diabetic mothers.[35] Human maternal diabetes is normally associated with LGA as a result of organomegaly and increased fat deposition in the fetus.[53] One possible explanation is that maternal hyperglycemia leads to fetal hyperinsulinemia. As insulin is a regulator of cell growth,[54] it provides a stimulating environment for fetal organomegaly. Kidney volume can be used as a surrogate clinical indicator of nephron number, where lower volumes possibly represent kidneys with reduced nephron numbers.[55,56] Furthermore, an inverse relationship between renal size and the incidence of hypertension[57–59] or renal function has been reported[60–62] in adulthood. Increase in kidney size due to overgrowth of the proximal tubule and glomerular hypertrophy can also be seen in adults with diabetes as a result of renal hyperfiltration.[63–66] To the best of our knowledge, these are the only three studies to date that have assessed fetal kidney or kidney cortex volume in late pregnancy or in early childhood in offspring exposed to maternal hyperglycemia, thus further investigation to elucidate these relationships is warranted.

Maternal Obesity and Offspring Kidney Structure or Function

In the United States and United Kingdom, there are an increasing number of women of childbearing age being classified as being overweight or obese.[67] This is a major concern as over-nutrition and obesity during pregnancy are associated with worse fetal health outcomes and an increased risk of morbidity and mortality from chronic diseases, such as heart disease, stroke and hypertension.[68–71] From this review, only two studies investigated the relationship between maternal obesity during pregnancy and offspring renal health.[30,32] Exposure to an obesogenic intrauterine environment increased the risk of childhood CKD in these offspring.[30] Maternal pre-pregnancy weight was positively associated with fetal kidney volume in late pregnancy, however, maternal obesity (measured using pre-pregnancy body mass index) was not associated with fetal kidney volume. Much of our understanding

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of the effect the maternal obesity has on offspring kidney outcomes has come from animal models.[72,73] A study in rats demonstrated that offspring of obese mothers (fed a maternal diet high in fat and fructose) had glomerulosclerosis and reduced kidney function (increased urine albumin excretion).[73] Maternal obesity can therefore have deleterious programming effects on the fetal kidney, however, there are limited studies and evidence assessing this in humans. In particular, there is a gap in research and knowledge pertaining to nephron development in infants born to mothers with obesity, which urgently warrants further investigation.

Strengths and Limitations

Strengths of this systematic review include: (1) a comprehensive search strategy across five databases with no date or age restrictions, (2) detailed data extraction allowing comparison between studies, (3) assessment of methodological quality in line with the PRISMA statement and (4) development of and adherence to an evidence-based protocol registered with PROSPERO. However, the current review also has limitations that need to be acknowledged. One limitation is the failure to include studies published in languages other than English, and articles that were not published at the time of review article search. An additional limitation is the large amount of heterogeneity between studies, particularly with regard to offspring age at follow-up, outcome measures of kidney function and the variability of cohorts studied. The majority of studies were rated as being of neutral or negative quality, thus the results should be interpreted with caution.

Implication for Practice

Women should be screened early to identify GDM and be treated appropriately relative to diagnosis. This will not only improve maternal health outcomes but might also improve long-term kidney health outcomes in offspring. From the current review, it was found that exposure to maternal hyperglycemia and/or obesity could potentially affect kidney growth, kidney function in terms of GFR and microalbuminuria, and increase the risk of CKD. This indicates the importance of developing clinical strategies and public health policies for screening and managing women with diabetes during pregnancy, especially in low-income and developing countries, and in populations where the burden of maternal diabetes is higher. Maternal overweight/obesity is an additional risk factor for developing diabetes. Therefore, ensuring an adequate maternal diet before and during pregnancy by eating a varied, balanced diet as well as maintaining a healthy bodyweight and/or appropriate gestational weight gain are vital steps in preventing GDM.

Implications for Research

Overall, the number of human studies investigating the DOHaD hypothesis from a kidney health perspective is relatively small, despite increasing interest in this area of research. By gaining more insight into the various adverse intrauterine environments under which kidney disease may develop and the pathophysiological mechanisms involved, we may be able to identify and develop new treatment/intervention strategies to alleviate the progression to chronic renal disease. There are a number of key issues that should be addressed in future research investigating the relationship between maternal diabetes or obesity and offspring kidney structure and function. These are:

1. High-quality longitudinal studies with longer follow-ups beyond childhood;
2. There is a need for consistent measurements of common indicators of renal development and function in the offspring, such as fetal kidney volume, GFR and albuminuria, and at similar offspring follow-up time points to facilitate meta-analysis of results across studies.

Conclusion

This systematic review critically evaluated the current evidence examining the association between maternal obesity and/or diabetes during pregnancy and offspring kidney structure and function in humans. The included studies were primarily observational (cohort studies), providing a low level of evidence to which causality cannot be applied. Across the limited studies to date, the measurement of offspring kidney outcomes was diverse. There was also a lack of consistency in the follow-up time-points at which offspring kidney structure and/or function were assessed, thus limiting comparability between studies. However, if studies are considered collectively, the evidence suggests a detrimental renal programming effect on offspring renal function due to exposure to maternal diabetes and/or obesity during pregnancy, reinforcing the concept of fetal programming of adult disease, which is consistent with the results from animal studies.[49] Further comprehensive longitudinal studies that assess common offspring kidney outcome measures are required to evaluate the relationship between hyperglycemia and/or maternal obesity during pregnancy, with renal programming in the offspring.

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Conflicts of Interest. None.

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