

**The Relationship between Maternal  
Nutrition, Obesity or Diabetes in Pregnancy  
and Offspring Kidney Structure and Function  
in an Indigenous Australian Population**

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**A thesis submitted in fulfilment of the requirements for the**

**degree of Doctor of Philosophy (Human Physiology)**

**University of Newcastle, New South Wales, Australia**

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## Glossary of common abbreviations

Abbreviation	Full form of abbreviation
AGHE	Australian Guide to Health Eating
NRVs	Australian Nutrient Reference Values
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
BMI	Body Mass Index
GROW	Gestation Related-Optimal Weight
DOHaD	Developmental Origins of Health and Disease
NCDs	Non-communicable diseases
CVD	Cardiovascular disease
CKD	Chronic kidney disease
GFR	Glomerular filtration rate
ESRD	End-stage renal disease
NHMRC	National Health and Medical Research Council
EAR	Estimated average requirement
RDI	Recommended dietary intake
AI	Adequate intake
IOM	Institute of Medicine
GDM	Gestational diabetes mellitus
GWG	Gestational weight gain
LGA	Large-for-gestational-age
DM	Diabetes mellitus
LBW	Low birth weight
AGA	Appropriate-for-gestational-age
SGA	Small-for-gestational-age
IUGR	Intrauterine growth restriction
UAE	Urinary albumin excretion
HPA	Hypothalamic-pituitary-adrenal
HFD	High-fat diet
STZ	Streptozotocin
RAAS	Renin angiotensin-aldosterone system
RAS	Renin-angiotensin system
NATSISS	National Aboriginal and Torres Strait Islander Social Survey
ABS	Australian Bureau of Statistics
COAG	Council of Australian Governments
NATSINPAS	National Aboriginal and Torres Strait Islander Nutrition and Physical Activity Survey
AES	Australian Eating Survey
ARFS	Australian Recommended Food Score
FFQ	Food Frequency Questionnaire

ADA	American Dietetic Association
SYRCLE	Systematic Review Centre for Laboratory Animal Experimentation
BIA	Bioelectrical Impedance Analysis
NR	Nutrient Restriction



## **Author note**

The studies outlined in this thesis were set in Tamworth, Walgett and Newcastle, in the state of New South Wales (NSW), Australia. I would like to acknowledge the traditional custodians of these lands; the Gomeroi people of Tamworth, the Kamilaroi people of Walgett, and the Awabakal and Worimi people of Newcastle. I would like to pay my respects to Elders both past and present and children of the present and future, and extend this respect to Indigenous readers of this manuscript.

Throughout this document, the terms Indigenous and Aboriginal are both used. Indigenous Australians refer to both Aboriginal and Torres Strait Islander peoples, and the term Indigenous is used in this document to refer to Indigenous people throughout Australia, or Indigenous people internationally. In NSW, where the research described in this thesis takes place, the traditional custodians of the land self-identify as Aboriginal, rather than Indigenous. However, for publications in international journals, the term Indigenous has been used.

## Abstract

According to the Barker theory and Developmental Origins of Health and Disease (DOHaD) hypothesis, an impaired intrauterine environment, caused by exposure to maternal insults such as poor nutrition, severe stress or illness, can exert permanent effects on the developing fetus and increase the risk of offspring developing adult-onset diseases. These include: cardiovascular disease (CVD), hypertension, obesity, type 2 diabetes and metabolic syndrome, as well as chronic kidney disease (CKD). In animal models, maternal insults such as protein restriction or diabetes during pregnancy result in altered development of the fetal kidney and impaired renal function in later life.

The age-adjusted incidence of end stage kidney disease for Indigenous Australians is 6.8 times the rate for non-Indigenous Australians, with rates highest in remote and very remote areas of Australia. This huge disparity may originate through exposure to various maternal insults *in utero*. Therefore, the overall aim of my thesis was to address the evidence gap in research investigating the relationship between maternal nutrition, obesity and diabetes during pregnancy and offspring kidney structure and function in an Australian Indigenous population and to identify pathways to improve health outcomes for Indigenous communities. Most of my thesis utilised data from the *Gomeri gaaynggal* programme, which is a prospective longitudinal cohort of Indigenous Australian mothers and their children residing in a rural region of New South Wales, followed from pregnancy through the postnatal period until the children reach 10 years of age.

A cross-sectional study assessed nutrient sufficiency and diet quality in pregnant women from the *Gomeri gaaynggal* cohort (n = 58). Maternal dietary intake during pregnancy was assessed using the Australian Eating Survey Food Frequency Questionnaire (AES FFQ), which was self-administered in the third trimester. Diet quality was determined using the Australian Recommended Food Score (ARFS). None of the women met all Australian Guide to Health Eating (AGHE) daily food group serving recommendations and only one person consumed the optimal level of specific nutrients (folate, iron, calcium, zinc and fibre) important in pregnancy. The data indicated that the diets of these Indigenous pregnant women were inadequate.

A systematic review of the literature was used to identify and evaluate current research in humans that had examined the relationship between maternal nutrition, obesity and/or diabetes during pregnancy and offspring kidney structure and function. This review identified ten studies investigating the influence of maternal nutrition during pregnancy on offspring kidney outcomes and nine studies investigating the influence of maternal obesity and/or diabetes during pregnancy on offspring kidney outcomes. This area of research is relatively new and an emerging one given the majority of studies included were published since the year 2010. Studies were of low to moderate methodological quality. The results of the review aimed to highlight the research gap and provide direction for future longitudinal prospective studies, especially in Indigenous populations where the risk of renal disease is greater.

Animal research is valuable in the understanding of DOHaD. Systematic reviews of animal research are rare but crucial to improve translation of animal data to clinical practice. My systematic review of animal studies investigating the influence of maternal global nutrient restriction during pregnancy on offspring kidney structure and function is novel. 28 studies met the inclusion criteria: 16 studies were on rats, nine on sheep, two on baboons, and one on goats. The available evidence from these studies suggested that exposure to maternal global nutrient restriction during pregnancy had detrimental effects on offspring kidney structure and function. This systematic review highlighted the need for improvement of the internal validity of animal studies. Recommendations put forward included randomisation of animal into experimental groups and blinding of handler and outcome measure. Suggestions for future research, such as methods to appropriately determine nephron number were also detailed in the chapter.

A prospective longitudinal study examined the influence of maternal adiposity and birth outcomes on childhood obesity in an Indigenous Australian population participating in the *Gomeri gaaynggal* study (n=227). Findings suggested that being born preterm, large for gestational age or exposed to an obesogenic intrauterine environment and higher maternal non-fasting plasma glucose concentrations were associated with increased obesity risk in early childhood. Another study examined the influence of maternal adiposity during pregnancy on fetal kidney structure in late gestation (>28 weeks) and kidney function in

infants, <2.5 years of age, in an Indigenous Australian population. Our findings suggested that Indigenous babies born to obese mothers were likely experiencing glomerular hyperfiltration *in utero* possibly because nephron number was reduced relative to body weight, which may predispose them to increased risk of CKD in later life. No effect on renal function was observed in infants, however, long-term follow-up was needed to determine any impact to renal function in later life. These studies provided first evidence of such associations in Aboriginal and Torres Strait Islander Australians.

This thesis identified that, in humans, deficiencies in maternal folate, vitamin A, and total energy during pregnancy were associated with detrimental impacts on kidney structure and function, measured by kidney volume, proteinuria, estimated glomerular filtration rate (eGFR) and mean creatinine clearance in the offspring. Intrauterine exposure to maternal obesity and/or diabetes also adversely impacted renal programming in human offspring, with an increased risk of kidney disease in adulthood. In animals, exposure to maternal global nutrient restriction during pregnancy had detrimental effects on offspring kidney structure and function, such as lower kidney weight, lower nephron endowment, larger glomerular size and lower GFR. Furthermore, this thesis highlighted key areas for improving the dietary intake of Indigenous Australian women during pregnancy. To our knowledge, this thesis provided the first evidence that exposure to maternal obesity during pregnancy increased kidney disease and obesity risk in the offspring in an Indigenous Australian population. There are gaps in the current literature investigating the influence of maternal nutrition, obesity and diabetes during pregnancy on offspring kidney development and function in humans as well as in animals. Directions for future practice and research were discussed in the relevant chapters. This thesis provided evidence in the field of developmental programming of kidney disease in the Indigenous Australian population and will inform the development of government public health policies. In doing so, not only will the burden of kidney disease be reduced, the health, cultural and material wealth of Indigenous Australians will potentially improve. This is a long-term investment by the researchers in collaboration with the wider Indigenous community and with community consultation with the Elders.