Early life influences on cardio-metabolic disease risk in aboriginal populations – what is the evidence?

A systematic review of longitudinal and case-control studies

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Key Messages:

1) We systematically reviewed the evidence for the developmental origins of cardio-metabolic diseases among aboriginal populations in Australia, New Zealand, Canada and the United States.

2) Low birth weight was associated with increased blood pressure among aboriginal adults but not aboriginal children. Further studies are required to substantiate the observed evidence for the association between exposure to diabetes in utero and high blood pressure.

3) Low birth weight and high birth weight were associated with impaired kidney function among aboriginal adults. The association between high birth weight and impaired kidney function was explained by exposure to maternal diabetes during pregnancy.

4) Low birth weight and exposure to diabetes in utero were very strongly associated with metabolic abnormalities and type 2 diabetes among aboriginal children and adults.

5) There was insufficient evidence to show a strong relationship between birth weight or exposure to diabetes in utero with adiposity later in life.

Abstract

Background: We systematically reviewed the published evidence for the developmental origins of health and disease hypothesis among aboriginal populations from Australia, Canada, New Zealand and the United States.

Methods: Medline, EMBASE and the Informit Health databases were systematically searched (March 2012) using medical subject headings and keywords for studies that examined the effect of prenatal factors and birth outcomes on later life (≥ 3 years) cardio-metabolic diseases. Quality of studies was independently assessed by two reviewers using a risk of bias assessment tool; main findings from studies with a low to moderate risk of bias were summarised qualitatively.

Results: 844 studies were found; 50 were included in the review of which 41 had a low- moderate risk of bias. There was strong evidence for an association between birth weight and type 2 diabetes (6/7 studies), impaired kidney function (6/7 studies) and high blood pressure (5/6 studies) while there was limited evidence for an association with metabolic abnormalities (4/7 studies) and adiposity (4/7). Exposure to maternal diabetes was strongly associated with type 2 diabetes (9/10 studies) and metabolic abnormalities (5/7 studies) whereas the association with adiposity was low (3/9 studies); the limited number of studies, to date, also show a relationship with high blood pressure (2/2 studies).

Conclusions: This review highlights that interventions to reduce the burden of cardio-metabolic disease among aboriginal populations should focus on improving maternal health, particularly by reducing the prevalence of diabetes in pregnancy. Future research should also be directed towards potential protective actions, such as breastfeeding.

Keywords:

Aboriginal people, Indigenous people, Developmental origins of health and disease, Dohad, Fetal growth, Cardio-metabolic disease, Cardiovascular disease, Type 2 diabetes, Renal Disease

Introduction

The need for effective public health interventions to reduce the burden of chronic disease has never been greater. The global burden of non-communicable diseases such as cardiovascular disease, type 2 diabetes, kidney disease and related conditions such as obesity and the metabolic syndrome is increasing rapidly, with predictions that they may cause over three-quarters of all deaths by 2030.[1] Aboriginal populations in high-income countries are disproportionately affected by the chronic disease burden compared to their non-aboriginal counterparts.[2-4] Although, interventions targeting known proximal risk factors later in life among adults, such as high body mass (overweight and obesity), hypertension, poor diet (e.g. with high sugar, salt and saturated fats), sedentary lifestyle and tobacco smoking, have had some success in addressing the disease burden, public health strategies in both aboriginal and non-aboriginal groups must give greater consideration to the early origins of cardio-metabolic risk factors as potential intervention targets in order to effect change earlier in the life-course.[5]

The *Developmental origins of health and disease* (DOHAD) hypothesis, initially proposed by David Barker, is the term given to the fields of research encompassing the influence of early life exposures on later health.[6-8] DOHAD research now includes both environmental influences before birth that disrupt development (such as teratogens) and those that cause more subtle changes in structure or function to enable the offspring to adapt to the predicted needs for postnatal life (a concept known as *developmental plasticity*).[9] Developmental plasticity in response to environmental cues happening at critical time windows may produce irreversible changes in structure or function of organs and organ systems. It is suggested that the effects of such adaptations both influence and interact with choices and conditions throughout life to affect susceptibility to chronic disease.[9, 10] Adding further to the complexity in this field is emerging evidence that detrimental early life exposures may have consequences across generations.[11] Experimental evidence from animal studies suggests that certain exposures can influence the birth

weight of at least three subsequent generations even when the adverse conditions are removed. The DOHAD pathways across generations may have particular relevance for colonised aboriginal populations such as those in Australia, Canada, New Zealand and the United states, who have undergone relatively rapid nutritional and cultural transition and social trauma over recent centuries. In these aboriginal populations, where high rates of sub-optimal birth outcomes co-exist with high prevalence of chronic disease,[12] the DOHAD paradigm appears to have immediate relevance. However, the published evidence for this hypothesis in these populations has never been systematically reviewed. It is important to identify the exposures that have been studied; the findings of these studies and the gaps in the evidence examining *in utero* exposures and chronic diseases in order to best progress in this area of research.

The aim of this paper is to assess the published evidence for the developmental antecedents of disease risk among aboriginal populations across the lifespan by systematically reviewing studies examining the influence of prenatal exposures and birth outcomes on the risk of later life cardio-metabolic conditions (defined as metabolic abnormalities, adiposity, type 2 diabetes, impaired kidney function and/or kidney disease and cardiovascular disease in aboriginal populations. It is to be noted that the term aboriginal will be used to refer to all indigenous populations in the United States, Canada, Australia and New Zealand and includes Aboriginal and Torres Strait Islander people of Australia.

The specific question this review aims to answer is: what is the published evidence for the developmental origins of cardio-metabolic disease in aboriginal populations in Australia, Canada, New Zealand and the United States? The aims of this systematic review were to:

1) describe the main characteristics and study findings;

2) assess study quality by using a risk of bias assessment tool;

3) summarise the evidence arising from studies with a low to moderate risk of bias;

4) outline gaps in the evidence and the implications for future health policy and research.

Methods

Search Strategy

A systematic search was undertaken in Medline (1950 – March 8 2012), EMBASE (1949 –March 8 2012) and the Informit Health databases (1977- March 8 2012) to identify studies addressing the question of interest. The search strategy used a combination of MeSH (medical subject headings), subject headings and keywords to identify publications that addressed three search concepts: 1) cardio-metabolic conditions 2) aboriginal populations of Australia, Canada, New Zealand, and the United States 3) the prenatal and birth period. Appendix 1 shows the full search strategy used for MEDLINE which was adapted for specific MeSH terms for EMBASE and the Informit Health Database. We also hand searched reference lists of relevant reviews and included studies to locate other potentially relevant studies.

Selection criteria

Published original quantitative studies were included if they fulfilled the following selection criteria:

1) The study included: only aboriginal participants, a separate analysis of aboriginal participants, or predominantly aboriginal participants (>50% of total participants) from Australia, Canada, New Zealand, or the United States.

2) The study used a longitudinal (prospective or retrospective) or case-control design that reported both outcomes and exposures during the prenatal period or at birth AND disease markers/conditions/mortality relating to the risk of chronic cardio-metabolic conditions for the same individuals at a later time point in childhood (≥ 3 years), adolescence, middle or older age.

We chose to include studies with a minimum of three years follow-up in order to include a broad range of evidence across the life course. Further consideration was given to the duration of follow-up when weighing the contribution of the study to the body of evidence supporting or refuting the importance of early life health outcomes for the burden of disease in these aboriginal populations; the studies with shorter follow-up periods may not have detected an effect with a long latent period.

Publications that investigated the effect of a genetic polymorphism on disease risk, that were not original quantitative research (reviews, commentaries, and letters) were excluded. If non-English language publications were found, where possible the manuscripts were translated into English language.

Titles and abstracts were reviewed using the inclusion and exclusion criteria to determine potentially relevant citations. The full-text of potentially relevant publications and of any publications that were unclear from the title and abstracts were then reviewed in detail using the criteria. A second reviewer (LG) independently reviewed 20% of the citations (n=170) at each stage of the selection.

Data extraction

1. Characteristics of included studies:

Summary data for included studies was extracted into a standardised tool (using a Microsoft Excel © spreadsheet) by two reviewers (BM & SE) and was checked by other reviewers (CC & LG). Data extracted included first author, year of publication, country, aboriginal population, sample size, age at outcome, birth years, prenatal/birth measures studied, outcomes examined and the main findings with effect sizes (if reported).

2. Risk of bias assessment

A modified version of the risk of bias assessment tool designed by Shah *et al* [13] was used to assess the risk of bias in the longitudinal and case-control studies presented in the current review (Appendix 2). Risk of bias in the studies was assessed by two independent reviewers (BM, CC) with any disagreements discussed and consensus reached. A third reviewer (SE) was consulted where necessary to reach consensus. The risk of bias assessment tool assesses bias relating to selection, exposure and outcome measures, confounding, analysis and attrition (for prospective studies only).

Modification to the tool included changing the lowest risk of bias category from "none" to "very low," as it was felt that no studies would be completely without risk of bias. Exposure and outcome assessment criteria were also modified accordingly for the purposes of this review. Findings from the literature were used to devise the risk of bias scale relating to birth weight data sources. Birth weight obtained from medical records is considered the optimal source with the lowest risk of bias, birth certificates have an intermediate risk of bias and maternal recall is considered to have the highest risk of bias. Validation studies of birth certificate data from the United States demonstrate relatively high agreement in regards to the classification of birth weight into standard categories when compared to medical records, with agreement around 80-90%,[5, 12, 14] but few have compared individual values. Maternal recall of birth weight several years after birth has been shown to be a biased measure when used to recall individual birth weights in circumstances where birth weight is being used as an independent variable rather than obtaining a population mean value as an outcome. Mothers tended to overestimate the weights of infants born with birth weights in the lower end of the distribution and underestimate the weight of infants with high birth weights. Therefore in the exposure-disease analyses relevant to this review the bias would act to reduce the association between birth weight and the disease risk outcome measures.[2, 3]

The modified risk of bias assessment tool developed for this review (Appendix 2) also takes into account whether the studies account for gestational age in their use of birth weight as a measure

of fetal growth. Studies that had accounted for gestational age used birth weight corrected for gestational age to group the infant into one of the following categories: appropriate-for-gestational age (AGA), small- for-gestational age (SGA) or large-for-gestational age (LGA). Also, studies that restricted their analyses to births at a narrow gestational age range (such as only including term births) were classified as accounting for gestational age. This is important, since without knowledge of gestational age, it is not possible to tell if the lower weight in infants born with low birth weight is due to prematurity or due to intrauterine growth restriction;[4] as such, the pathological pathways are likely to be different, as are the health consequences.

3. Qualitative data analysis

Studies with a very low, low or moderate risk of bias were further examined and the main findings were summarized in a number of tables according to the outcome measures (metabolic abnormalities, adiposity, type 2 diabetes, kidney disease and cardiovascular disease). The population group, age groups, and the main findings with effect sizes were qualitatively described. Studies with multiple outcome measures were summarized in multiple tables. Publications arising from the same study population are grouped together in the tables such that findings from all studies related to the study population could be assessed together.

It was decided ‘a priori’ that a quantitative meta-analysis would not be undertaken since the main aim of the review was to describe the evidence for the DOHAD relationship rather than synthesizing outcome data from studies. Furthermore, due to the expected heterogeneity of the studies and the number of exposure and outcome measures assessed, a meta-analysis would not be informative.

Results

Of the 844 citations identified by the systematic search, 50 publications from Australia, Canada, New Zealand and the United States met the inclusion criteria. Figure 1 illustrates the review process of identified citations and summarises the main reasons for exclusion. There was a very high level of agreement regarding inclusion and exclusion between the two independent reviewers in the 20% of citations that were co-reviewed (Kappa 0.915). The three discrepancies were easily clarified with further consideration of the full text of publications.

1. Characteristics of included studies (Appendix 3)

The main characteristics of included studies are reported in Appendix 3. The majority of publications (n=43, 86%) were published after 1995, following the prominence of the DOHAD hypothesis in the research field. Studies were conducted in all four countries, with the largest number of publications reporting studies in aboriginal populations from the United States (n=29; 58%), followed by Australia (n=14; 28%), Canada (n=5; 10%) and New Zealand (n=2; 4%). However, it is worth noting that the majority of publications from the United States (n=26/29, 89%) report findings from a single research study among the Pima Indian population.

The included publications were predominantly retrospective cohort designs (n=39/50, 78%), whereby the disease risk outcomes were measured at the designated age, or cross-sectional time point across a range of specified ages, and the exposure information was sourced from medical records, study records from the ongoing collection in a larger research program, or by maternal recall. The main prospective cohort was the Australian Aboriginal and Torres Strait Islander Birth cohort, established in 1987-1990 which included all births of Aboriginal infants at the Royal Darwin Hospital (Northern Territory, Australia). Four publications from that birth cohort are included in this review; thus far, the children have been followed up for between 9 and 18 years of age. Four publications reported age- and sex- matched case-control studies; three publications utilised

registry data to identify cases in the Saskatchewan region of Canada,[15-17] and one was a clinic-based study in Manitoba, Canada.[18]

The range of early life exposures examined in the included publications was found to be limited. The four main exposures were: 1) birth weight (72%), 2) *in utero* exposure to diabetes or maternal hyperglycaemia (predominantly studies from the longitudinal research program in Pima Indian populations) (40%), 3) *in utero* exposure to maternal tobacco smoke (6%) and 4) breast feeding (8%). Prospective studies were limited to measuring disease markers in childhood, while certain retrospective and case-control studies provided information on a broader range of ages. Based on the primary and secondary outcomes of the studies, twelve studies examined metabolic abnormalities (24%), sixteen studies investigated measures of adiposity (38%), seventeen studies examined the risk of diabetes later in life (34%), thirteen studies examined kidney disease (26%), and finally twelve studies investigated cardiovascular disease outcomes (24%). There were three studies that examined the whole spectrum of cardio-metabolic diseases.[19-21]

2. Risk of bias assessment (Appendix 3)

Appendix 3 shows the risk of bias assessment for all included studies. There were no studies that were appraised as having a very low risk of bias. Of the fifty studies, thirty-six (72%) were assessed as having a low risk of bias, five (10%) were assessed as having a moderate risk of bias and nine studies (18%) had a high risk of bias. The reason for the high risk of bias in most of the studies was the use of recall as the measure of birth weight, or the use of recall of *in utero* exposures greater than 5 years after the pregnancy. With the exception of one study,[22] all studies used outcome measures of disease risk that had a very low or low risk of bias, typically direct measurement by the researchers or use of medical records. Sample size was a concern in a number of studies where the DOHAD relationship was examined as a secondary analysis,[23-25] and a moderate risk of bias resulted from the level of attrition in some prospective cohorts.[23-25]

3. Evidence arising from studies (Tables 1-5)

Metabolic abnormalities (Table 1)

Birth weight (7 Studies)[19-21, 26-29] Four of the seven studies showed no relationship between birth size and measures of metabolic abnormalities (glucose, insulin or c-peptide);[20, 21, 27, 28] three of those studies were in children (<18 years).[20, 21, 27] One study from Australia showed that low birth weight adults have higher fasting insulin levels but no difference in fasting glucose levels compared to normal birth weight adults.[19] Two studies (both from the Pima Indian population) showed that low birth weight was associated with higher glucose and insulin concentration compared to those born with normal birth weight among children and adults (10-29 years).[26, 29] Age and sex adjusted fasting glucose levels were significantly higher and insulin action and insulin secretory response was significantly lower in the low birth weight group compared to the normal birth weight group.[29] In the other study, there was a U-shaped relationship with birth weight and 2 h glucose concentration and there was an inverse association between birth weight and insulin concentration (independent of current body size, age and sex).[26]

Diabetes in utero (7 studies)[30-36] All seven studies were undertaken in the Pima Indian population in the United States and the range of exposures investigated included early onset of diabetes among mothers (before 35 years of age), diabetes during pregnancy, glucose-intolerance during pregnancy and maternal glucose levels during pregnancy. Two studies showed no association between exposure to diabetes in utero and any measure of metabolic abnormality among children.[30, 31] Among offspring of diabetic mothers, one study showed higher 2-h glucose levels and higher fasting insulin levels compared to offspring of non-diabetic mothers (mothers that did not develop diabetes);[32] whereas another study showed no differences in glucose concentration but lower mean plasma insulin concentration (after 15 minutes) in response to a standard meal challenge among offspring who were exposed to diabetes in utero compared to those who weren't exposed to diabetes in utero but whose mothers developed diabetes after

pregnancy.[36] Similarly, in another study, although there was no difference in fasting or 2 h glucose levels, insulin secretion rates were lower among adult offspring of mothers who developed diabetes before the age of 35 compared to offspring of mothers who did not develop diabetes until 49 years of age.[34] Acute insulin secretory response was also lower among offspring whose mothers had diabetes during pregnancy compared to mothers who developed diabetes after pregnancy.[34] Two studies measured maternal glucose levels during pregnancy and reported significant associations with glucose concentrations in the offspring (children and adults).[33, 35]

Adiposity (Table 2)

Birth weight (7 studies)[19, 27, 29, 37-40] Among the seven sudies that examined birth weight, four studies showed higher BMI among offspring with higher birth weight[19, 27, 38, 39] and three studies showed no association between birth weight and adiposity.[29, 37, 40] There was only one study that examined adipocyte size among adults and found no association with birth weight.[29]

Mescalero Apache Indian children from the United States born with high birth weight (>4000 g), were approximately 4 times more likely to develop obesity by 5 years of age compared to those born with low or normal birth weight; this finding was independent of maternal diabetes and maternal obesity.[38] In another study among children (<18 years) in New Zealand, there was a positive association between birth weight and current BMI.[27] Among Australian Aboriginal children from the Aboriginal birth cohort in Darwin, growth restricted (birth weight <10th percentile for gestational age) young adults had lower BMI and percentage fat compared to non-growth restricted young adults.[39] Similarly, among Australian Aboriginal people from a remote Northern coastal island, average BMI was lower among low birth weight adults compared to adults born normal birth weight.[19]

In two studies among the Pima Indian people[29, 40] and one study among the Native American people,[37] birth weight did not influence BMI or body fat composition in 25 year old adults. In one

study, birth weight did not correlate with fat mass among offspring of non-diabetic pregnancies.[40] In the other study, there was no difference in BMI, percent body fat, fat mass or fat free mass between those born with low birth weight compared to those born with normal birth weight.[29]

Diabetes in utero (9 studies)[30, 31, 34, 36, 41-45] Eight out of nine studies were undertaken among the Pima Indian population in the United States. Five studies showed no differences in BMI, percent body fat or adipocyte size among offspring of diabetic pregnancies compared to offspring of non-diabetic pregnancies;[30, 31, 34, 36, 44] all of these studies except one[34] were undertaken among children. No differences were observed among offspring of parents who had early-onset diabetes (before 35 years of age) compared to parents who developed diabetes later in life.[34]

Three studies showed that offspring exposed to diabetes in utero have higher body weight, higher BMI and/or percent body fat in adults and children.[41-43] Furthermore, sixty-four percent of Canadian First Nation children and adolescents (offspring of women with early onset type 2 diabetes) were obese.[45] However, this study did not include a group of offspring who were not exposed to maternal diabetes, hence; whether the prevalence was higher compared to a control group could not be truly assessed.

Maternal obesity (1 study)[38] One study found that among children, the offspring of obese mothers were almost five times more likely to be obese compared to offspring of non-obese mothers.[38]

Maternal smoking (2 studies)[37, 46] Two studies have examined the effect of maternal smoking on obesity later in life, both studies were among American Indian people.[37, 46] Three year old children had a 2 times higher odds of being overweight (BMI≥85th percentile) if mothers smoked during the initial prenatal visit.[37] By adulthood, however, another study showed that offspring of mothers who smoked during pregnancy were no more likely to be obese compared to offspring of non-smoking mothers.[46]

Breastfeeding (1 study) [37] The one study that examined the effect of breastfeeding on later life obesity showed no significant association between ever being breastfed and BMI.[37]

Type 2 diabetes / Impaired glucose tolerance (Table 3)

Birth weight (7 studies)[19, 26, 35, 47-50] Six studies showed an association between birth weight and type 2 diabetes and/or impaired glucose tolerance. Among the Pima Indian population, there was a U-shaped association between birth weight and prevalence of diabetes;[26, 51] however the higher risk of diabetes among high birth weight offspring was explained by exposure to maternal diabetes during pregnancy.[51] Two other studies among Canadian aboriginal people also showed an association between high birth weight and higher prevalence of diabetes (exposure to maternal diabetes was not examined in these studies).[47, 48] Furthermore, two studies have shown a higher risk of diabetes during pregnancy and gestational diabetes among women born with low birth weight[35, 50] For example, among Native American adult women, women born with a birth weight <2000 grams had a 3-fold higher risk of developing gestational diabetes compared to women born with a birth weight of 3000-3999 grams.[50] However, a single study from Australia showed that prevalence of diabetes was not different among adults born low birth weight compared to adults born normal birth weight.[19]

Diabetes in utero (10 studies) [28, 33, 35, 41, 42, 45, 52-55] Nine out of the ten studies were conducted among the Pima Indian population and all studies show a strong association between exposure to maternal diabetes and higher prevalence of diabetes in offspring, both during childhood and adulthood[28, 33, 35, 41, 42, 52-55] and abnormal glucose tolerance.[54, 55] For example, in a large study, offspring of mothers with type 2 diabetes during pregnancy had a 7 to 20 fold higher incidence of type 2 diabetes at all ages from 5-30 years of age compared to offspring of non-diabetic mothers.[42] Even among offspring of glucose tolerant mothers, a 1 standard deviation increase in maternal glucose levels increased the risk of diabetes in the offspring by 60%.[33] One study conducted among a cohort of First Nation Canadian children and adolescents born to women with type 2

diabetes before the age of 18 showed that 25% of the offspring had type 2 diabetes.[45] However, this study did not include a group of offspring who were not exposed to maternal diabetes, hence; whether the prevalence was higher compared to a control group could not be truly assessed.

Breastfeeding (1 study) [35] One study showed that breast feeding may reduce the risk of diabetes among offspring; offspring of non-diabetic mothers were 44% less likely to develop diabetes if they were breastfed for at least 2 months compared to those who were bottle fed.[35]

Kidney disease: kidney volume, kidney function and end stage kidney disease (Table 4)

Birth weight (7 studies)[17, 19, 21, 56-59] Six of seven studies examined showed an association between birth weight and markers of impaired kidney function or kidney disease. The children from the Aboriginal Birth Cohort did not show an association between birth weight and kidney volume or between birth weight and albumin/creatinine ratio.[21] However, in two studies from an Australian Aboriginal community in a remote Northern coastal island, kidney volume was positively associated with birth weight among children.[58, 59] For example, Spencer *et al* 2001[59] reported that children born with low birth weight (<2.5 kg) had reduced kidney volumes compared to children with birth weight greater than 3.3 kg. However, among children from the same Aboriginal community in Australia there was no association between birth weight and kidney function after adjusting for age and sex.[60] Nevertheless, among adults in the same study, low birth weight increased the risk of albuminuria.[19, 60] In support of this finding, among Pima Indian adults there was a U-shaped association between birth weight and impaired renal function (both low and high birth weight was associated with elevated urinary albumin excretion);[57] however, after maternal diabetes in pregnancy was controlled for, subjects with high birth weight were no longer more likely to have elevated urinary albumin excretion. Furthermore, among Canadian Saskatchewan people, high birth weight was associated with diabetic end stage kidney disease in females.[17]

Diabetes in utero (2 studies)[57, 61] Two studies among adults in the Pima Indian population have shown that exposure to diabetes in utero leads to elevated urinary albumin excretion.[57, 61] In one study, the odds of elevated urinary albumin excretion was approximately 4 times higher among offspring exposed to diabetes in utero.[61] In the other study, subjects who were exposed to diabetes during pregnancy were 6 times (95% CI 1.8-22.3) more likely to have elevated urinary albumin excretion.[57]

Cardiovascular risk factors and mortality (Table 5)

Birth weight (6 studies)[19, 20, 27, 62-64] Five of the six studies showed associations between birth weight and risk factors for cardiovascular disease;[19, 20, 62-64] three studies were conducted among adults and two were in children. Among adults from Northern Australia there was an inverse association between birth weight and blood pressure.[64] However, in the same population, although one study reported that low birth weight adults had a lower systolic blood pressure compared to normal birth weight adults,[19] in another study birth weight lower than the median for the population was associated with a four-fold higher risk of death from cardiovascular and renal causes compared to those born with birth weight above the median for the population.[63] In a birth cohort of Australian Aboriginal and Torres Strait Islander children from Darwin and surrounding areas (Aboriginal birth cohort), an inverse relationship was found between birth weight and systolic blood pressure at 11 years of age with and without adjustment for current weight.[20] However, in another sample of Australian Aboriginal and Torres Strait Islander children with high rates of underweight and little postnatal catch-up growth, there was no evidence of an inverse association between birth weight and blood pressure;[64] a single study among Maori children showed similar results.[27] There appears to be no association between birth weight and lipid levels among adults and children.[19, 20, 27] except for one study that showed a positive association between lipoprotein (a) levels and birth weight among girls.[62]

Diabetes in utero (2 studies)[31, 32] Exposure to maternal diabetes during pregnancy was associated with higher diastolic and systolic blood pressure and lower levels of high density lipoprotein in two studies of children from the Pima Indian population group in the United States.[31, 32]

Maternal smoking (1 study)[62] Only one study to date has examined the effect of maternal smoking on cardiovascular outcomes; in that study, there was no association between maternal smoking during pregnancy and levels of lipoprotein (a) among Australian Aboriginal children.[62]

Discussion

To our knowledge, this is the first systematic review to examine the evidence for the DOHAD hypothesis for cardio-metabolic diseases among the aboriginal populations of Australia, Canada, New Zealand and the United States. In support of the DOHAD hypothesis, there was substantial evidence showing a relationship between birth weight and type 2 diabetes, cardiovascular disease and impaired kidney function among aboriginal children and adults. Furthermore, there was a great deal of evidence to show that exposure to diabetes in utero was strongly associated with type 2 diabetes and metabolic abnormalities among aboriginal children and adults, particularly among the Pima Indian population. Although a small number of studies have been undertaken so far, exposure to maternal diabetes during pregnancy also increased the risk of impaired kidney function and cardiovascular disease; however further studies are required for definitive conclusions. We did not find strong support for the fetal origins of adiposity, although high birth weight was found to be associated with obesity in children and adults.

There has been a significant increase in the number of research studies that have explored the DOHAD pathway since the publication of David Barker's original studies that linked low birth weight to later risk of cardiovascular disease. Indeed, eighty percent of the publications identified in this review have been published since 1995. Overall, our findings demonstrate that the most common exposures investigated were birth weight and exposure to maternal diabetes *in utero*. The most common later life cardio-metabolic disease investigated was type 2 diabetes, followed by kidney disease and cardiovascular disease (incorporating high blood pressure). It is important to note that 46% (23/50) of all studies have resulted from a research program in the United States among the Pima Indian people examining the influence of diabetes in pregnancy on the risk of diabetes and associated metabolic abnormalities among offspring.

Low birth weight is a significant risk factor for high blood pressure, impaired kidney function and type 2 diabetes

From the studies included in this review, there was considerable support to show that low birth weight is an important risk factor for cardiovascular disease among aboriginal populations (five out of six studies showed a positive association). Although effects were not apparent in childhood or early adolescence,[27, 64] by adulthood there was an inverse relationship between birth weight and blood pressure in age and sex adjusted models. These findings are in accordance with previous studies among non-aboriginal population groups.[65] Furthermore, kidney volume was reduced among aboriginal children born with low birth weight;[58] accordingly, there was also evidence of impaired kidney function (elevated urinary albumin excretion)[19, 56] and more than 3 times higher odds of low birth weight among Canadian Saskatchewan people with end stage renal disease.[17] Among Australian Aboriginal adults, risk of death from cardiovascular and renal causes combined was significantly higher among those with a birth weight less than the group median compared to those with a birth weight higher than the group median.[63] Taken together, these findings suggest that low birth weight among aboriginal people is a manifestation of poor growth utero leading to adverse renal development. As proposed by Brenner and colleagues,[66] the reported increased blood pressure and impaired kidney function in adulthood may be due to the reduced nephron endowment at birth. No study to date has made a direct correlation between low birth weight, small kidney size and reduced nephron number among aboriginal people, however, an Australian study[67] demonstrated an association between nephron number and adult height (as a proxy for birth weight), however, this study was not included in the final analyses of the current review due to the high risk of bias (exact birth weights were not reported).

The risk of diabetes, impaired glucose tolerance and metabolic abnormalities was highest among those born with a low and high birth weight compared to those born with normal birth weight. Inverse associations between birth weight and risk of type 2 diabetes have previously been reported in a systematic review of studies among mostly non-Aboriginal people.[68] There was only one study (from the Australian Aboriginal birth cohort) that did not show an increased risk of type

2 diabetes or impaired kidney function among children born low birth weight.[21] This finding may be due to the younger age group of the study population (mean age 11.4 years) and/or the lack of postnatal catch-up growth among this cohort; the growth restricted offspring in this cohort remained smaller postnatally compared to the non-growth restricted group. In the current review the relationship between high birth weight and diabetes could be explained by exposure to maternal diabetes in utero. It is important to note that the majority of studies examining diabetes risk were conducted among the Pima Indian population in the United States, a community that is known to have a very high prevalence of type 2 diabetes from childhood. Importantly, two studies showed that women born low birth weight were more likely to develop gestational diabetes compared to women born with normal birth weight.[35, 50] Therefore, it can be speculated that low birth weight may perpetuate the cycle of adverse fetal growth leading to diabetes in pregnancy which then leads to increased risk of type 2 diabetes and diabetes in pregnancy in subsequent generations.

Exposure to maternal diabetes is a risk factor for metabolic abnormalities, type 2 diabetes, impaired kidney function and cardiovascular disease among offspring

From the studies reviewed, the relationship between high birth weight and impaired kidney function and type 2 diabetes could mostly be explained by exposure to diabetes in utero. Furthermore, there was substantial evidence to show the relationship between exposure to maternal diabetes and increased prevalence of type 2 diabetes in offspring during childhood and adulthood (all studies showed this association). However, the majority of the evidence arose from studies among the Pima Indian population and the findings have been reviewed previously;[69, 70] future studies among other indigenous populations are also required. There was one study among the First Nation people of Canada which showed that the prevalence of type 2 diabetes was highest ever reported among a cohort of offspring born to women with type 2 diabetes before 18 years of age.[45] This is a particularly important area for future interventions and future research

since reducing the rates of diabetes during pregnancy could potentially prevent the occurrence of type 2 diabetes and kidney disease in future generations of aboriginal people. Although, further studies are required to investigate the relationship between exposure to maternal diabetes and cardiovascular disease, the limited number of studies to date shows that exposure to maternal diabetes does increase the risk of high blood pressure in children and adolescents.[31, 32]

Later life adiposity does not appear to be influenced by prenatal or early life exposures

There was insufficient evidence to support the notion that prenatal and/or early life exposures increase the risk of obesity in later life (nine out of sixteen studies showed no association). Among the studies that did show a positive association, one study showed increased risk of obesity among children born with high birth weight and another study showed a positive association between birth weight and BMI.[27, 38] Two Australian studies from our review demonstrated lower BMI and percentage fat among Aboriginal adults born low birth weight.[19, 39] In support of this finding, previous systematic reviews of studies of non-aboriginal people have shown that only high birth weight was associated with obesity among adults whereas low birth weight does not increase the risk of obesity.[71, 72] The relationship between high birth weight and later life obesity is most likely related to exposure to diabetes in utero and maternal pre-pregnancy BMI. Indeed, in our review, three out of eight studies (all from the Pima Indian population) showed an association between exposure to diabetes during pregnancy and later life obesity among both children and adults.[41-43] A study from the Native American population also showed that maternal obesity was related to offspring obesity (independent of high birth weight).[38] A study among the Canadian First Nation population showed that prevalence of obesity was high (64%) among a cohort of offspring (≤19 years of age) born to mothers who developed diabetes before 18 years of age, however, as the study did not compare against an unexposed control group, whether the risk was substantially higher could not be assessed.[45] Interestingly, almost all of the studies that have examined obesity have been undertaken among children and young adults. Therefore, further studies are warranted

in this area, particularly studies among adults and in population groups other than the Pima Indian people. In future studies, it is also important to account for maternal pre-pregnancy BMI.

Implications for policy, practice and future research

The findings of the current review have highlighted the importance of increasing focus on the early origins of chronic disease among aboriginal populations in both health policy and research. Public health policy should be aimed at breaking the inter-generational cycle by being more focussed on improving maternal health during pregnancy. Pregnancy is often referred to as a "window of opportunity" for public health interventions as pregnant women have frequent scheduled contacts with health-care providers, and pregnant women are often highly motivated to adapt their behaviour to improve the health of their infant.[73, 74] Moreover, any effective interventions could potentially impact positively on the health of the entire family. Reducing the rates of gestational diabetes and diabetes in pregnancy among aboriginal mothers should be prioritised. In the current review, the range of maternal factors examined was found to be limited to diabetes during pregnancy. There were only two studies that examined maternal smoking during pregnancy and a single study that examined maternal obesity. Further studies that examine maternal stress, substance abuse (including tobacco, alcohol and other drugs), infections, pre-existing medical conditions, or complications of pregnancy other than diabetes are of utmost importance.

It is important to highlight protective mechanisms that may prevent disease occurrence among individuals at high risk. The only prospective longitudinal study included in the current review was the Aboriginal Birth Cohort. These Aboriginal children are now 18 years of age and appear to show very little risk factors for cardio-metabolic diseases; as these growth restricted offspring have remained smaller compared to the non-growth restricted group, the lack of substantial catch-up growth may be a protective against the development of chronic disease later in life. Future studies once these offspring reach adulthood will provide more substantial evidence. There was also some evidence that breastfeeding may reduce the diabetes risk among offspring, however, further high

quality studies are required to make definitive conclusions since three studies found in the current systematic review that examined breastfeeding were assessed as having a high risk of bias. Nevertheless, programs aimed at increasing the rates of breastfeeding among aboriginal populations may be highly beneficial.

Importantly, the findings from the current review have highlighted the need for high quality research studies using total population data. The majority of the published studies used a retrospective study design; although it is appropriate (given the long time periods between the exposure and outcome) it is associated with a number of limitations and biases. Therefore, future research in this area should be conducted using total population-based record linkage which has a low risk of bias and a number of exposures can be explored. Among the studies evaluated as having a high risk of bias, the main source of bias arose from the use of recall in assessing birth weight or other exposures; therefore in order to avoid such bias in future studies, it is important to examine validated and reliable sources of data on birth weight, birth characteristics and maternal exposures. One obvious source is routinely collected maternal and neonatal medical records. This would allow one to obtain accurate information on birth weight, gestational age and maternal medical conditions and relate that information to chronic disease occurrence during the offspring's lifetime and potentially in future generations. Another important consideration is selection bias which is particularly important in retrospective longitudinal studies. In the current review, assessing selection bias was difficult due to the fact that information on deaths and migrations was not adequately reported in all studies.

Strengths and Weaknesses

To date, there have been no published systematic reviews examining the DOHAD hypothesis among aboriginal populations around the world, with the exception of the Pima Indian people. The major strength of the current systematic review is the use of broad search terms in the search strategy to maximise sensitivity of the search and the inclusion of aboriginal populations from

Australia, Canada, New Zealand and the United States. Our strict selection criteria ensured that only longitudinal and case control studies that had sufficient follow-up periods were included, such that long-term outcomes could be adequately examined. . We have restricted our review to a discussion of cardio-metabolic conditions among aboriginal people, which we believe requires urgent attention. We decided 'a priori' that a meta-analysis would not be undertaken since the primary objective of the review was to describe the evidence for the DOHAD hypothesis rather than synthesizing outcome data from the studies. Also, given the broad range of exposures and outcomes examined in the studies and the heterogenous nature of the studies, results of a meta-analysis may not have been particularly informative. It is also important to acknowledge the possibility of publication bias since only published research papers were included in the current review.

Conclusions

The key findings in the 50 studies reviewed highlight the important influence of early fetal exposures on the risk of type 2 diabetes, impaired kidney function and cardiovascular disease. Health policy and preventive health care programmes for aboriginal people in Australia, Canada, New Zealand and the United States need to include an expanded focus that optimises the health of aboriginal women of child bearing age and provides access to high quality pregnancy and early childhood health care. Further studies are required that examine the influence of a broader range of pregnancy exposures and the intergenerational impacts of fetal growth on the risk of chronic preventable diseases in aboriginal populations.

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Conflict of Interest:

The authors have no conflict of interest to declare.

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Figure 1: Flow diagram of the review of citations identified by the search

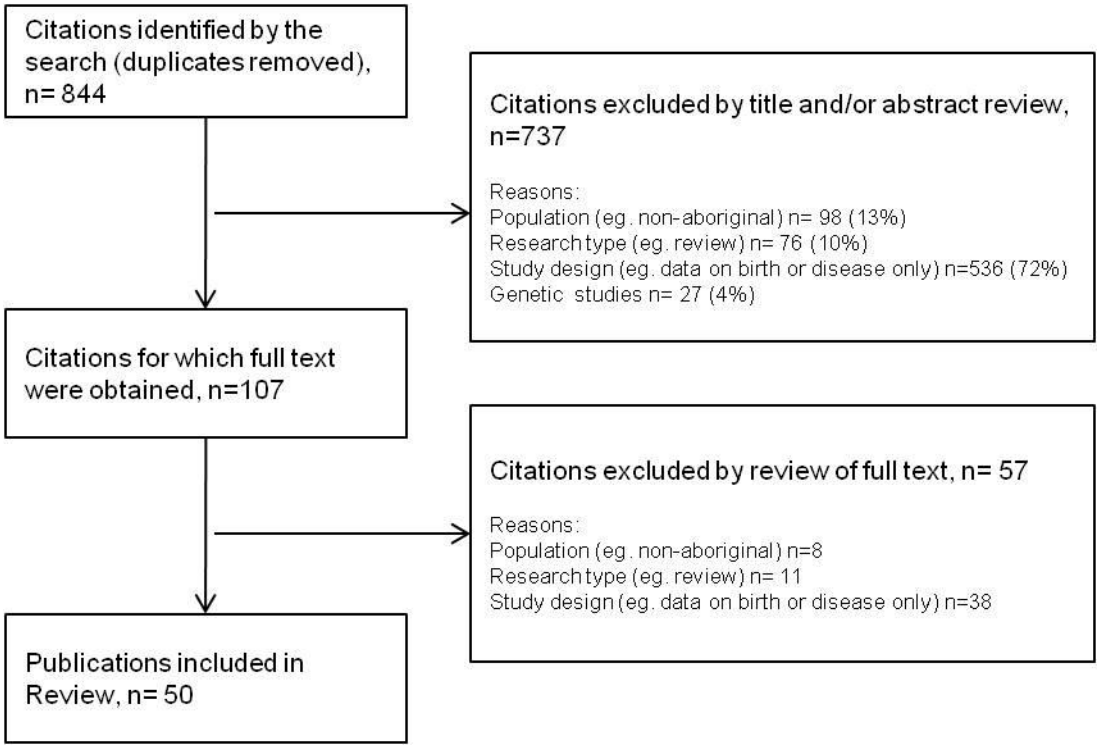

Table 1. Summary of main findings of studies (very low, low or moderate risk of bias) with metabolic abnormalities as outcome measures

Study Population	Author/Year	Age (mean and/or range)	Outcome measures			Main Findings/Exposures
			Glucose	Insulin	C-peptide	
Australia: Aboriginal birth cohort	Sayers 2004[21]	8-14 yrs	□	□	-	Among children, after adjusting for child size, there was no relationship between any measure of **birth size** and fasting glucose or insulin concentration.
	Sayers 2009[20]	(11.4 yrs) 8.9-14 yrs	□	□	-	Among children, after adjusting for child size, there was no relationship between any measure of **birth size** and fasting glucose or insulin concentration.
Australia: Aboriginal community in a remote Northern coastal island	Hoy 1999[19]	20 - 38 yrs	□	□	-	**Low birth weight** adults had higher fasting insulin levels compared to normal birth weight adults (9.4 mU/l vs 7.3 mU/l, p=0.02). There was no association between **low birth weight** and fasting glucose levels (4.7 vs 4.8 mmol/l, p=0.5).
New Zealand: Multi-ethnic including Maori	Daly 2005[27]	14-18 yrs	□	-	-	There was no association between **birth weight** and fasting glucose concentration (r= -0.01, p=0.83).
USA: Pima Indian	Stefan 2004[29]	25 yrs	□	□	-	Among adults born **low birth weight**, fasting glucose was significantly higher compared to adults born normal birth weight (5.0 v 4.8 mmol/L, p=0.04). Insulin action and insulin secretory response was also significantly lower (p=0.05 and 0.02, respectively).
	Dabelea 1999[26]	5-29 yrs	□	□	-	There was a U-shaped relationship between **birth weight** and 2 h glucose concentration (p<0.01). There was a negative relationship between birth weight and insulin concentration; those in the lowest birth weight group had the highest insulin concentration.
	Lindsay 2000a[28]	19.5 ± 9.2 yrs	□	-	-	There were no significant differences among **birth weight quintile groups** and mean 2-h glucose concentration (Analysis of variance: F=0.53, p=0.71).
	Charles 1994[32]	6-17 yrs	□	□	-	**Offspring of diabetic mothers** had higher 2-h glucose levels (5.58 vs 5.33 mM, p=0.004) and higher fasting insulin levels (107 vs 124, p=0.004).

	Abbot 1986[30]	9.1-9.8 yrs	□	□	□	Among children, offspring of **glucose-intolerant pregnancies** showed no differences in fasting glucose, insulin or c-peptide levels compared to the offspring of glucose-tolerant pregnancies.
	Gautier 2001[34]	29 yrs	□	□	□	Among adults, offspring of **diabetic pregnancies** showed no differences in fasting and 2-h glucose and insulin levels compared to non-diabetic pregnancies. In individuals whose mothers developed diabetes before 35 years of age, average insulin secretion rates were lower compared to those whose parents remained non diabetic to at least 49 years of age (369 vs 571 pmol/min, p=0.007). Among individuals with diabetic mothers during pregnancy, acute insulin secretory response was lower compared to mothers who developed diabetes after pregnancy (740 vs 1255, P<0.02).
	Bunt 2005[31]	7-11 yrs	□	□	-	Among children, **offspring of diabetic pregnancies**, there were no differences in glucose levels (87±6 vs 83±4 mg/dl, p=0.11) or insulin levels (38.6±11.4 vs 31.3±11.7 uU/ml, p=0.24) compared to offspring of prediabetic mothers.
	Salbe 2007[36]	9 yrs	□	□	-	Among children, **offspring of diabetic mothers** had lower mean plasma insulin concentration (p=0.01) after 15 min in the standard mixed meal challenge compared to offspring of prediabetic mothers; there were no differences in plasma glucose levels.
	Pettitt 1998[35]	5 - 34 yrs	□	-	-	Among children and adults, **maternal glucose during pregnancy** was significantly associated with glucose concentration in each age group (5-9 yrs: P<0.003, 10-14 and 15-19 yrs: P<0.001).
	Franks 2006[33]	0-39 yrs	□			Among children and adults, third trimester **maternal glucose levels were** not associated with fasting or 2-h glucose levels in children aged 5-9 or 15-19, but associations were observed in 10-14 year old offspring (β=0.08 SD/SD maternal glucose, p=0.028) and 20-24 year old offspring (β=0.15 SD/SD maternal glucose, p=0.03).

*All effect sizes reported are adjusted for age and sex and other confounders

Table 2. Summary of main findings of studies (very low, low or moderate risk of bias) with measures of adiposity as outcome measures

Study Population	Author/Year	Age (mean and/or range)	Outcomes		Main Findings/Exposures
			BMI/Body fat	Adipocyte size	
Australia : Aboriginal birth cohort	Sayers 2011[39]	18.3 yrs		-	Among adults who were **growth restricted**, mean BMI and percentage fat were significantly lower compared to non-growth restricted adults (BMI: 19.63 vs 22.02, p=0.0006; Percentage fat: 17.43% vs 21.60%, p=0.0043).
Australia: Aboriginal community in a remote Northern coastal island	Hoy 1999[19]	20 - 38 yrs		-	Among adults who were **low birth weight**, BMI was lower compared to adults born normal birth weight (21.7 vs 23.3 kg/m^2).
USA: Mescalero Apache	Gallaher 1991[38]	1-5 yrs		-	Children born with **high birth weight (>4000 g)** had a higher odds of obesity (OR 4.4, 95% CI 1.3-15.4). Children born to **obese mothers** were also more likely to be obese (OR 4.8, 95% CI 1.8-12.8).
New Zealand: Multi-ethnic including Maori	Daly 2005[27]	14-18 yrs			**Birth weight** was positively associated with current BMI (r=0.11, p=0.0047).
USA: Pima Indian	Stefan 2004[29]	25 yrs			Among adults, those born **low birth weight** compared to those born normal birth weight, there were no differences in BMI (34 vs 33 kg/m^2, p=0.68), percent body fat (32 vs 31%, p=0.86), fat mass (31 vs 30 kg, p=0.71), fat-free mass (62 vs 63 kg, p=0.45). Birth weight was not associated with average adipocyte cell size (adjusting for age, sex, percent body fat).
	Weyer 2000[40]	25.3yrs (18-49)		-	Among offspring of non-diabetic pregnancies, **birth weight** was positively correlated with adult height (r=0.20, p<0.001) and fat-free mass (r=0.21, p<0.001) but not with fat mass (r=0.01).
	Abbot 1986[30]	9.1-9.8 yrs			Among children of **glucose-intolerant pregnancies** compared to children of glucose-tolerant pregnancies, percentage body fat was not different (22% vs 24%). The groups also did not differ in abdominal (0.6 vs 0.62) or gluteal (0.69 vs 0.68) adipocyte size. The correlation between fasting insulin and abdominal adipocyte size was stronger in the **glucose intolerant pregnancy** group (r=0.91, p<0.0001).
	Gautier 2001[34]	29 yrs		-	Among offspring of **diabetic pregnancies** compared to offspring of non-diabetic pregnancies, percentage body fat was not different (34% vs 33%, p=0.8). Percentage body fat was also not different among offspring of parents with early onset diabetes (<35 years) compared to parents who developed diabetes after 49 years of age (31% vs 34%, p=0.5).

	Bunt 2005[31]	7-11 yrs	□	-	Among **offspring of diabetic pregnancies** there were no differences in percentage body fat (44.5±9.8 vs 38.5±10.0%, p=0.27) or levels of triglycerides (10 vs 89, p=0.32).
	Salbe 2007[36]	9 yrs	□	-	Among **offspring of diabetic mothers** compared to offspring of non-diabetic mothers there were no differences in height, weight, BMI z-score, or percent body fat.
	Dabelea 2000[41]	13 yrs	□	-	In offspring of **diabetic pregnancies,** mean BMI was 2.6 kg/m^2 higher (95% CI 0.9-4.3, p=0.003 compared to offspring of non-diabetic pregnancies. **Paternal diabetes** did not increase mean BMI among offspring (mean difference=0.4 kg/m^2 (95% CI 0.9-1.7, p=0.5).
	Lindsay 2000b[42]	5 - 30 yrs	□	-	**Maternal diabetes** was a significant predictor of BMI in offspring up to 19 yrs of age. BMI among offspring of diabetic pregnancies remained significantly higher at all age groups less than 20 yrs (p<0.05) compared to offspring of non-diabetic and pre-diabetic mothers.
	Pettitt 1983[43]	5 - 19 yrs	□	-	58% of offspring of **diabetic mothers** weighed 140 percent or more of their desirable weight, as compared with 17% of the offspring of non-diabetic mothers and 25% of those of pre-diabetics (p<0.001). Mean percentage of desirable weight in 15-19 year old offspring of diabetic mothers was 145% compared to 117% among offspring of non-diabetic mothers.
	Salbe 1998[44]	5 yrs	□	-	Among offspring of women with **diabetes during pregnancy** compared to offspring of women without diabetes during pregnancy, no differences were found in percent body fat (31±8 vs 33±8%), total energy expenditure (TEE) (6508 ± 1109 vs 6175 ± 942 kJ/d), resting metabolic rate (RMR) (4674 ± 786 vs 4483 ± 603kJ/d) or physical activity level (TEE/RMR) (1.40 ± 0.12 vs 1.38 ± 0.12).
<u>Canada:</u> Manitoba First Nations	Mendelson 2011[45]	2-19 yrs	□	-	Among offspring of **mothers with onset of type 2 diabetes before age 18,** 64% (23/36) were obese.
<u>USA:</u> Native American	Adams 2005[37]	3 yrs	□	-	Offspring of **mothers who smoked at the initial prenatal visit** were more likely to have a BMI≥85th percentile (OR 2.16 95% CI 1.05-4.47, p=0.04). The children of **smoking mothers** had a greater increase in weight for length z-scores between birth and 3 year of age (p<0.05). **Birth weight** (OR 1.82, 95% CI 0.09-3.71, p=0.10) and **ever being breastfed** (OR 0.53, 95% CI 0.26-1.06, p=0.07) were not significantly associated with BMI.
	Sharma 2008[46]	25 yrs	□	-	**Maternal smoking status** (before and during pregnancy) was not associated with childhood obesity (OR 0.96, 95% CI 0.67-1.36).

*All effect sizes reported are adjusted for age and sex and other confounders; **BMI**=body mass index

Table 3. Summary of main findings of studies (very low, low or moderate risk of bias) with type 2 diabetes and/or impaired glucose tolerance as the main outcome measure

Study Population	Author/Year	Age (mean and/or range)	Diabetes	Impaired glucose tolerance*	Main Findings
Australia: Aboriginal community in a remote Northern coastal island	Hoy 1999[19]	20 - 38 yrs	□	-	Among adults, the proportion of **low birth weight** people with diabetes was not different to the proportion of normal birth weight people with diabetes (4.2% vs 8.3%, p=0.32)
USA: Native American	Williams 1999[50]	Maternal age (<19->35)	□	-	Women with a **birth weight** < 2000 grams had a 3.1-fold higher risk (relative risk) (95% CI 1.2-8.2) of developing gestational diabetes compared to women with a birth weight 3000-3999grams.
Canada: Registered Indian (RI)	Dyck 2001[48]	31.8 (10.5-44.9 yrs)	□	-	There was a significant association between **high birth weight (>4000 g)** and diabetes for RI people (OR 1.63, 95% CI 1.20-2.24).
Canada: First Nation (FN) / Other Saskatchewan people (OSK)	Dyck 2010[47]	10-44 yrs	□	-	A 1kg increase **in birth weight** elevated diabetes risk among FN people (OR 1.23, 95% CI 1.01-1.5) and OSK people (OR 1.16, 95% CI 0.98-1.38) offspring. For every 1 year increase in **maternal age**, increased the odds of diabetes among male (OR 1.04 , 95% CI 1.01-1.06) and female (OR 1.08, 95% CI 1.06-1.10) offspring.
USA: Pima Indian	McCance 1994[51]	20-39 yrs	□	□	After adjusting for **maternal diabetes during pregnancy** adults born **low birth weight** (<2500g) had a 3.81 higher odds of diabetes (95% CI 1.7-8.52) compared to those born with higher birth weights. The association between diabetes and **high birth weight** (>4500g) was no longer significant (OR 1.8, 95% CI 0.63-5.10,p=0.269) .
	Dabelea 1999[26]	5-29 yrs	□	-	Among children and adults, **birth weight** showed a U-shaped relationship with diabetes prevalence (p<0.0001)
	Pettitt 1998[35]	5 - 34 yrs	□	-	Offspring of women with **diabetes during pregnancy** had a higher prevalence of diabetes regardless of whether they were breastfed or not (11.9% vs 43.6% among offspring who were not breastfed and 6.9% vs 30.1% among offspring who were breastfed). Among offspring of non-diabetic pregnancies who were **breastfed for at least 2 months**, the odds of diabetes was lower (OR 0.56, 95%CI 0.41-0.76) compared to those not breastfed; this finding did not reach significance in offspring of diabetic pregnancies. Women born **low birth weight** <2.5kg had the highest rate of diabetes during pregnancy (25%).
	Pettitt 1988[54]	10-24 yrs	□	□	Offspring exposed to non-insulin dependent **diabetes mellitus during pregnancy** had a higher prevalence of diabetes (45%), compared to the offspring of pre-diabetic women (8.6%) and non-diabetic women (1.4%). Prevalence of diabetes was higher at each age group (P<0.05 at 10-14 yr and P<0.001 at 15-19 and 20-14 yr) in offspring of diabetic women compared to non-diabetic

					women. Offspring exposed to non-insulin dependent diabetes mellitus during pregnancy also had a higher prevalence of impaired glucose tolerance (effect size not shown)
	Pettitt 1991[55]	5-24 yrs	□	□	A 1mm **higher maternal glucose level in pregnancy** was associated with abnormal glucose tolerance (OR 1.24, 95% CI 1.04-1.47) and diabetes (OR 1.62, 95% CI 1.20-2.18) in the offspring. Offspring of previously diabetic women were more likely to have abnormal glucose tolerance (OR 5.69, 95% CI 3.08-10.5) and diabetes (OR 12.17, 95% CI 4.81-30.77) compared to offspring of previously nondiabetic women.
	Dabelea 1998[52]	5-19 yrs	□	-	Among children and adults, **exposure to diabetes in utero** was the main contributing factor to the increasing prevalence of diabetes (OR 10.41, 95% CI 4.31-25.12, p<0.0001).
	Dabelea 2000[41]	22 - 24 yrs	□	-	Siblings born after the **mother developed diabetes** had a higher risk of developing diabetes before the age of 25 than siblings born before the diagnosis of diabetes (odds ratio 3.7, 95% CI 1.3-11.3, p=0.02).
	Lindsay 2000a[28]	19.5 ± 9.2 yrs	□	-	**Maternal diabetes** was a significant predictor of offspring diabetes in each tertile of birth weight category, effects increased with increasing birth weight (lowest tertile: 0.72, p<0.02; middle tertile: 1.1, p<0.003; highest tertile: 1.4, p<0.001).
	Lindsay 2000b[42]	5 - 30 yrs	□	-	Offspring of **diabetic mothers** (ODM) had an increased incidence of type 2 diabetes at all ages from childhood compared to offspring of pre-diabetic mothers (OPDM) (3 to 5 fold) and offspring of non-diabetic mothers (ONDM) (7 to 20 fold). Adjusted Incidence (per/1000) at 10-14 years: ODM=22.4 vs ONDM=1.0, 15-19 years: ODM=35.4 vs ONDM 4.6 and 20-30 years: ODM=32.7 vs ONDM=15.5.
	Franks 2006[33]	0-40 yrs	□	-	An increase in **maternal glucose levels** of 1 SD increased the risk of diabetes (HR 1.6, 95% CI 1.3-2.0, p<0.0001) in offspring; effects persisted even among offspring of glucose tolerant mothers (HR 1.3, 95% CI 1.04-1.71, p=0.026).
	Franks 2007[53]	5-19 yrs	□	-	**Parental diabetes before age 30** increased risk of diabetes in offspring compared to offspring of non-diabetic parents (HRR 3.6, 95% CI 2.2-6.0). **Intrauterine exposure to diabetes** increased the risk of diabetes in offspring (HRR 5.9, 95% CI 3.3-10.4). Parental diabetes or intrauterine exposure to diabetes did not modify the relationship between the markers of metabolic syndrome and risk of diabetes.
Canada: Manitoba First Nations	Mendelson 2011[45]	2-19 yrs	□	-	7/28 (25%) offspring (aged 2-19) of **mothers with onset of type 2 diabetes before age 18** have diabetes, including 6/14 (43%) aged 10-19 years.

All effect sizes reported are adjusted for age and sex and other confounders

*Defined as a 2-h postload plasma glucose concentration of ≥7.8 mM and <11.1 mM

Table 4. Summary of main findings of studies (low or moderate risk of bias) markers of kidney disease and end-stage-kidney disease as outcome measures

Study Population	Author year	Age at outcome (mean and/or range)	Outcomes assessed				**Exposure/**Main findings
			Kidney Volume	Albumin/Creatinine ratio (ACR)	Urinary Albumin Excretion (UAE)	ESKD / Death	
<u>Australia:</u> Aboriginal community in a remote Northern coastal island	Hoy 1998[56]	5-17 & 18+ yrs	-	□	-	-	Among children, **birth weight**,(per kilogram reduction) was inversely correlated with ACR but was not significant in adjusted models (OR 1.7, 95% CI 0.95-2.9). Among adults, **birth weight** (per kilogram reduction) was inversely correlated with ACR in adjusted models (OR for overt albuminuria versus lower ACR = 3.0, 95% CI 1.2-7.2).
	Hoy 1999[19]	20 - 38 yrs	-	□	□	-	Among adults, **birth weight** was inversely correlated with ACR. The odds ratio for overt aluminuria in low birth weight persons was 2.82 (95% CI 1.26-6.31). For every 100 g reduction in birth weight, there was a 6.3% (95% CI 2.2-10.0%) increase in g mean ACR and a higher odds of overt albuminuria (OR 1.11, 95% CI 1.02-1.21).
	Spencer 2001[59]	5 - 19 yrs	□	-	-	-	Among children, **low birth weight** (<2.5 kg) was associated with smaller kidney volume compared to those born with birth weight >3.3kg (221 ± 34 ml vs 253 ± 45 ml, p=0.02). In linear regression models for every 1kg increase in birth weight there is a 15ml increase in kidney volume (p=0.02).
	Singh 2004[58]	4.4 - 72.1 yrs	□	-	-	-	**Birth weight** was positively associated with kidney volume (the lowest birth weights were associated with the lowest quartile of kidney volumes).
<u>Australia:</u> Aboriginal birth cohort	Sayers 2004[21]	(11.4 yrs) 8.9-14 yrs	□	□	-	-	There was no association between **birth weight** and kidney volume (p=0.37) or between birth weight and albumin/creatinine ratio (p=0.37).
<u>Canada:</u> Saskatchewan Registered Indian (SKRI) and other Saskatchewan people (OSkP)	Dyck 2003[17]	not shown	-	-	-	□	There were increased rates of **low birth weight** among cases with ESRD compared to controls without ESRD among OSkP females (OR 3.66, 95% CI 1.05-12.73). Higher rates of **high birth weight** rates occurred in SKRI cases compared to controls and 3/5 female SKRI diabetic ESRD cases were high birth weight compared to 1/14 controls (p<0.05).
<u>USA:</u> Pima Indian	Nelson 1998a[57]	34 ± 8 (20-61 yrs)	-		□	-	**Birth weight** had a U-shaped association with the prevalence of elevated UAE (p=0.04). Adults born **low birth weight** had a 2.3 times higher odds (95% CI 0.72-7.2) and adults born **high birth weight** had 3.2 times higher odds (95% CI 0.75-13.4) of elevated UAE compared to normal birth weight adults. The higher odds of elevated UAE among high birth weight subjects (≥4500g) were explained by **maternal diabetes during pregnancy.** Adults exposed to **maternal diabetes during pregnancy** had higher odds of elevated UAE (OR 6.3, 95% CI 1.8-22.3).

	Nelson 1998b[61]	12 -77 yrs	-	-	□	-	**Offspring of diabetic mothers** had an increased odds of elevated urinary albumin excretion compared with offspring of prediabetic mothers (OR 3.8, 95% CI 1.7-8.4).

All effect sizes reported are adjusted for age and sex and other confounder

Table 5. Summary of main findings of studies (very low, low or moderate risk of bias) with cardiovascular disease and mortality as outcome measures

Study Population	Author year	Age at outcome (mean and/or range)	Outcomes assessed			**Exposure/**Main findings
			Blood pressure	**Lipids**	**Mortality**	
New Zealand: Multi-ethnic including Maori	Daly 2005[27]	14-18 yrs	□	□	-	There were no associations between **birth weight** and blood pressure or lipid levels.
Australia: Aboriginal community in a remote Northern coastal island	Singh 2003[64]	13.3 yrs and 28.3 yrs	□	-	-	Among children, **birth weight** was not correlated with blood pressure (effect size not stated). Among adults, **birth weight** was inversely correlated with blood pressure (a 1kg increase in birth weight was associated with a 2.9mmHg decrease in systolic blood pressure (95% CI 0.3-5.5 mmHg).
	Hoy 2010[63]	0 – 37 yrs	-	-	□	**Birth weight** (less than the group median relative to birth weight higher than the group median) was correlated with all cause deaths at every age, deaths associated with gastrointestinal causes/diarrhoea in children (HR 5.23) and with deaths due to cardiovascular and/or renal causes in adults (HR 4.09)
	Hoy 1999[19]	20 - 38 yrs	□	□	-	Among adults born **low birth weight** (<2.5 kg), systolic blood pressure was significantly lower compared to normal birth weight (≥2.5 kg) adults (115 vs 119 mmHg, p=0.02). There was no differences in diastolic blood pressure (71 vs 72, p=0.5). Among low birth weight adults, serum cholesterol levels were lower (4.3 vs 4.5 mmol/l, p=0.053) and there were no differences in serum triglycerids (1.7 vs 1.9 mmol/l, p=0.44).
Australia : Aboriginal birth cohort	Sayers 2009[20]	(11.4 yrs) 8.9-14 yrs	□	□	-	Among children, **birth weight** had a negative relationship with systolic blood pressure (regression coefficient= -0.02, p=0.02) and no association with lipid levels.
	Cunningham 2011[62]	11.4 yrs	-	□	-	**Among children, birth weight** was positively related to lipoprotein (Lp)(a) concentrations in girls (P=0.05). **Maternal smoking** during pregnancy was not related to Lp(a) levels (55.5% vs 60.9% in boys with low versus high Lp(a) and 54.1% vs 49% in low versus high Lp(a) in girls).
USA: Pima Indian	Charles 1994[32]	6-17 yrs	□	-	-	Among children with a diabetic mother, children exposed to **diabetes during pregnancy** had a significantly higher diastolic blood pressure (63.6 mmHg vs 59.2 mmHg, p=0.04) but not systolic blood pressure (108.0 mmHg vs 106.0 mmHg, p=0.43) compared to mothers who developed diabetes after pregnancy.
	Bunt 2005[31]	7-11 yrs	□	□	-	**Offspring of diabetic pregnancies** had significantly higher systolic blood pressure (118±13 vs 107±10 mmHg, p=0.02) and lower concentrations of high-density lipoprotein (41±9 vs 48±6 mg/dl, p=0.03) compared to offspring of prediabetic mothers.

*All effect sizes reported are adjusted for age and sex and other confounders

Appendix 1 Medline Search Strategy

1. exp Cardiovascular Diseases/
2. exp glucose metabolism disorders/
3. exp lipid metabolism disorders/
4. metabolic syndrome x/
5. exp Kidney Diseases/
6. exp malnutrition/
7. exp overnutrition/
8. (Cardiovascular disease* or Heart disease* or hyperten* or blood pressure*).mp.
9. (Diabet* or hyperglyc?mi* or glucose intoleran* or hyperinsulin* or insulin insen* or insulin resistan* or non?insulin?dependent* or pre?diabet*).mp.
10. (Dyslipid?mi* or hyper?lipid* or hyper?cholest*).mp.
11. Metabolic syndrom*.mp.
12. (kidney disease* or renal disease* or nephron number* or glomerular number*).mp.
13. (Mal?nutrition* or (nutrition* adj defici*) or (vitamin* adj defici*) or undernutrition* or under?weight*).mp.
14. (Obes* or over?weight*).mp.
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. exp american native continental ancestry group/
17. exp oceanic ancestry group/
18. Indigen*.mp.
19. Aborigin*.mp.
20. Torres Strait*.mp.
21. (First adj nations).mp.
22. (native adj american*).mp.
23. (Alaska* adj native*).mp.
24. American Indian*.mp.
25. Maori*.mp.
26. Eskimo*.mp.
27. inuit*.mp.
28. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. 15 and 28
30. (Pregnan* or birth* or pre?natal or post?natal or gestation* or intra?uterine or fetal* or fetus* or foetal* or foetus* or in?utero or offspring or maternal or paternal or parental).mp.
31. 29 and 30
32. limit 31 to animals
33. limit 32 to (animals and humans)
34. 32 not 33
35. 31 not 34
36. limit 35 to ("review articles" and (editorial or letter or "review"))
37. 35 not 36

Appendix 2: Risk of Bias Assessment Criteria (modified from Shah et al[13])

BIAS	VERY LOW	LOW	MODERATE	HIGH
Selection	• Consecutive unselected population • Sample selected from general population rather than a select group • Rationale for case control selection explained • Follow-up or assessment time explained	• Sample selected from large population; selection criteria not definedA select group of population (eg based on residence)	• Sample selection ambiguous; sample may be representative • Eligibility criteria not explained • Rationale for case and control subjects not explained • Follow-up or assessment time not explained	• Sample selection ambiguous; sample likely not representative • A very select population was studied, which made it difficult to generalize findings
Exposure assessment (eg in-utero exposures)	• Direct questioning (interview) or completion of survey by mother at the time of exposure or close to the time of exposure • Direct measurement of exposure (laboratory)	• Assessment of exposure from global dataset • Recall of exposure <1 year after birth • Indirect assessment (postal survey, mailed questionnaire)	• Recall 1-5 years after birth • Extrapolating data from population exposure sample (with some assumptions) and not direct assessment at any time	• Recall >5 years after birth • Indirect method of assessment (obtaining data from others and not from mother or father)
Birth weight/Fetal growth assessment	• Direct measurement or medical records for birth weight and gestational age (growth measure accounts for gestational age)	• Direct measurement or medical records for birth weight (gestational age not taken into account) • Birth certificate or registry used to obtain birth weight and gestational age information (growth measure accounts for gestational age)	• Birth certificate or registry used to obtain birth weight (gestational age not taken into account) • Maternal recall of birth weight and gestational age (growth measure accounts for gestational age)	• Maternal recall of birth weight (gestational age not taken into account)
Outcome assessment (disease or disease risk biomarker)	• Direct measurement or medical records	• Registry or total population hospital records database	• Parental-report or self-report of offspring	
Confounding factor	• Controlled for common confounders	• Only certain confounders adjusted	• Not controlled for confounders	
Analytical	• Analyses appropriate for the type of sample • (Analytical method accounted for sampling strategy in cross-sectional study) • Sample size calculation performed and adequate sample studied	• Analyses not accounting for common statistical adjustment (eg multiple) analyses when appropriate • Sample size calculation not performed; all eligible patients studied or results were statistically significant • Sample size calculated; reasons for not meeting sample size given	• Sample size estimation unclear, or only subsample of eligible patients was studied	• Analyses inappropriate for the type of sample/study
Attrition	• 0-10% attrition and reasons for loss to follow-up data explained • All subjects from initiation of the study to the final outcome assessment were accounted for	• 0-10% attrition and reasons for loss of follow-up data not explained • 11-20% attrition; reasons for loss of follow-up data explained	• 11-20% attrition; reasons for loss of follow-up data not explained • >20% attrition; reasons for loss of follow-up explained • All subjects from initiation of study to final outcome assessment not accounted for	• >20% attrition; reasons for loss of follow-up data not explained

Appendix 3: Characteristics of included studies and risk of bias assessment

First author & year	Country of Study	Study Design	Exposures	Outcomes	Sample size	Risk of Bias Assessment
Abbott 1986[30]	USA	Retrospective cohort	Diabetes in utero	Adiposity; metabolic abnormalities	26	LOW
Adams 2005[37]	USA	Retrospective cohort	Maternal smoking; breastfeeding; BW	Adiposity	252	LOW
Bunt 2005[31]	USA	Retrospective cohort	BW	Cardiovascular; Adiposity; Metabolic abnormalities	41	LOW
Charles 1994[32]	USA	Retrospective cohort	BW	Cardiovascular; Metabolic Abnormalities	1698	LOW
Cunningham 2011[62]	Australia	Prospective cohort	BW	Cardiovascular	570	MODERATE risk of attrition bias: >10% and reason for loss to follow-up not explained
Dabelea 1998[52]	USA	Retrospective cohort	BW, Diabetes in utero	Diabetes	2992	LOW
Dabelea 1999[26]	USA	Retrospective cohort	BW	Metabolic abnormalities	3061	LOW
Dabelea 2000[41]	USA	Retrospective cohort	Diabetes in utero	Diabetes, Adiposity	58-183 siblings	LOW
Daly 2005[27]	New Zealand	Retrospective cohort	BW	Cardiovascular; Adiposity; Metabolic abnormalities	548	MODERATE risk of analytical bias: no adjustment made for clustering
Dyck 2001[48]	Canada	Case Control	BW	Diabetes	1728	LOW
Dyck 2003[17]	Canada	Case Control	BW	Kidney disease	162	LOW
Dyck 2010[47]	Canada	Case Control	BW	Diabetes	1728	LOW

Franks 2006[33]	USA	Retrospective cohort	maternal glycaemia in pregnancy	Diabetes	1436	LOW
Franks 2007[53]	USA	Retrospective cohort	Diabetes in utero	Diabetes	1604	LOW
Gallaher 1991[38]	USA	Retrospective cohort	BW	Adiposity	261	LOW
Galloway 2010[75]	Canada	Retrospective cohort	BW, Breast feeding	Adiposity	388	HIGH risk of bias in exposure assessment: birthweight/fetal growth assessment: obtained through maternal recall and no adjustment for gestational age
Gautier 2001[34]	USA	Retrospective cohort	Diabetes in utero	Metabolic abnormalities	104	LOW
Haysom 2009a[25]	Australia	Retrospective cohort	BW	Cardiovascular; Kidney disease	1248	HIGH risk of bias in exposure assessment: Birthweight was obtained through maternal recall and only a small portion of the Aboriginal sample with follow up had birth weight data available
Haysom 2009b[23]	Australia	Retrospective cohort	BW	Cardiovascular; Kidney disease	773	HIGH risk of bias in exposure assessment: Birthweight was obtained through maternal recall and only a small portion of the Aboriginal sample with follow up had birth weight data available
Haysom 2009c[24]	Australia	Retrospective cohort	BW	Cardiovascular; Kidney disease	807	HIGH risk of bias in exposure assessment: Birthweight was obtained through maternal recall and only a small portion of the Aboriginal sample with follow up had birth weight data available
Hoy 1998[56]	Australia	Retrospective cohort	BW	Kidney disease	618	LOW
Hoy 1999[19]	Australia	Retrospective cohort	BW	Kidney disease; Cardiovascular; Metabolic abnormalities; Diabetes	317	LOW
Hoy 2006[67]	Australia	Cross-sectional	Adult height/body surface area (proxy for BW)	Kidney size (Glomerular number and size)	19	HIGH risk of bias in exposure (birth weight/fetal growth) assessment and outcome assessment (adult height used as a proxy for birth weight)
Hoy 2010[63]	Australia	Retrospective cohort	BW	Mortality	995	LOW

Lindsay 2000a[28]	USA	Retrospective cohort	BW, parental diabetes	Diabetes	1608	LOW
Lindsay 2000b[42]	USA	Retrospective cohort	Diabetes in utero	Diabetes, Adiposity	4557	LOW
McCance 1994[51]	USA	Retrospective cohort	BW, Diabetes in utero	Diabetes	1179	LOW
Mendelson 2011[45]	Canada	Retrospective cohort	Diabetes in utero	Adiposity	76	LOW
Nelson 1998a[57]	USA	Retrospective cohort	BW, diabetes in utero	Kidney disease	308	LOW
Nelson 1998b[61]	USA	Retrospective cohort	Diabetes in utero	Kidney disease	503	LOW
Pettitt 1983[43]	USA	Prospective cohort	Diabetes in utero, BW	Adiposity	1326	LOW
Pettitt 1988[54]	USA	Retrospective cohort	Diabetes in utero	Diabetes; Impaired glucose tolerance	1064	LOW
Pettitt 1991[55]	USA	Retrospective cohort	Diabetes in utero	Diabetes; Metabolic abnormalities	552	LOW
Pettitt 1997[76]	USA	Retrospective cohort	Breast feeding	Diabetes	933	HIGH risk of bias in exposure assessment: self reported exposure data through maternal interview
Pettitt 1998[35]	USA	Retrospective cohort	BW; diabetes in utero; breast feeding	Diabetes; Gestational diabetes	241 - 700	LOW
Salbe 1998[44]	USA	Retrospective cohort	BW; Diabetes in utero	Adiposity	88	LOW
Salbe 2002[77]	USA	Retrospective cohort	BW	Adiposity	138	HIGH risk of bias in exposure assessment (birthweight/fetal growth): Birth weight obtained from medical records or from parent recall and gestational age not taken into account
Salbe 2007[36]	USA	Retrospective cohort	Diabetes in utero	Metabolic abnormalities	41	LOW
Sayers 2004[21]	Australia	Prospective cohort	BW	Cardiovascular; Adiposity; Metabolic	279	LOW

				abnormalities; Kidney disease		
Sayers 2009[20]	Australia	Prospective cohort	BW	Cardiovascular; Adiposity; Metabolic abnormalities; Kidney disease	571	LOW
Sayers 2011[39]	Australia	Prospective cohort	BW	Adiposity	469	LOW
Sharma 2008[46]	USA	Retrospective cohort	Maternal smoking	Adiposity	2228	MODERATE risk of bias in exposure assessment (birthweight/fetal growth); birth registry data used and maternal recall of gestational age
Simmons 1995[78]	New Zealand	Cross-sectional	Diabetes in utero	Diabetes	744	HIGH risk of bias in exposure assessment; self reported exposure and outcome data
Singh 2003[64]	Australia	Retrospective cohort	BW	Cardiovascular; Adiposity	767	LOW
Singh 2004[58]	Australia	Retrospective cohort	BW	Kidney disease; Cardiovascular	672	MODERATE selection bias and exposure (birth weight /fetal growth assessment); source of birth weight unclear and gestational age not taken into account
Spencer 2001[59]	Australia	Retrospective cohort	BW	Kidney disease	174	LOW
Stefan 2004[29]	USA	Retrospective cohort	BW	Metabolic abnormalities; Adiposity	230	LOW
Weyer 2000[40]	USA	Retrospective cohort	BW	Adiposity	272	LOW
Williams 1999[50]	USA	Retrospective cohort	BW	Diabetes (Gestational)	7456	MODERATE risk of bias inexposure assessment (birthweigh/fetal growth) ; birth registry data used not adjusted for gestational age
Young 2002[79]	USA	Case Control	BW; Diabetes in utero; Breastfeeding; maternal diet; smoking; alcohol;	Diabetes	138	HIGH risk of bias in exposure and outcome assessment; self reported exposure and outcome data

BW = birth weight

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