

**Pre-pregnancy predictors of pregnancy events and birth
outcomes in a cohort of Aboriginal and Torres Strait Islander
women in North Queensland, Australia**

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**A thesis submitted in accordance with the
requirements for admission to the degree of
Doctor of Philosophy**

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November 2012

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List of papers included as part of this thesis

1. Campbell S, Lynch J, Esterman A, McDermott R. Pre-pregnancy predictors linked to miscarriage among Aboriginal and Torres Strait Islander women in North Queensland. *Aust NZ J Public Health*. 2011; 35:343-351.
2. Campbell S, Lynch J, Esterman A, McDermott R. Pre-pregnancy predictors of diabetes in pregnancy among Aboriginal and Torres Strait Islander women in North Queensland, Australia. *Matern Child Health J*. 2012; 16:1284-92. DOI 10.1007/s10995-011-0889-3 Published online: 30 September 2011.
3. Campbell S, Lynch J, Esterman A, McDermott R. Pre-pregnancy predictors of hypertension in pregnancy among Aboriginal and Torres Strait Islander women in North Queensland, Australia.
4. Campbell S, Lynch J, Esterman A, McDermott R. Pre-pregnancy predictors of infant birth outcomes among Aboriginal and Torres Strait Islander women in North Queensland, Australia: Could increasing birthweights be misleading? *Aust NZ J Public Health*. (submitted, under review).

List of appendices

Appendix A: Ethics Approvals

Appendix B: Permissions to reprint published papers

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Abbreviations

AGA	appropriate-for-gestational-age
BMI	body mass index
CARDIA	Coronary Artery Risk Development in Young Adults study
CI	confidence interval
FAS	fetal alcohol syndrome
GCT	glucose challenge test
GDM	gestational diabetes mellitus
GLM	generalised linear model
GWG	gestational weight gain
HBW	high birth weight
HDLC	high density lipoprotein cholesterol
HDP	hypertensive disorder of pregnancy
HR	hazard ratio
HUNT 2	Norwegian Nord-Trøndelag study
ICD	International Classification of Disease
IOM	Institute of Medicine
IUGR	intrauterine growth restriction
LDLC	low density lipoprotein cholesterol
LGA	large-for-gestational-age
NHMRC	National Health and Medical Research Council (of Australia)
NTD	neural tube defect
OGTT	oral glucose tolerance test
OR	odds ratio
PCR	polymerase chain reaction
US(A)	United States (of America)
RR	relative risk
SD	standard deviation
SGA	small-for-gestational-age

WHO	World Health Organisation
WPHC	Well Person's Health Check

Abstract

Introduction: Healthy mothers tend to have healthy babies. Australian Indigenous women have birth outcomes that are significantly worse than those of other Australian women, across every major indicator of infant health. Challenges faced by many Indigenous women in maintaining good health throughout childbearing age include managing low family incomes, food insecurity and housing problems.

Methods: Data for this thesis are drawn from the north Queensland 1998-2000 Well Person's Health Check (WPHC) survey that included Indigenous women of childbearing age. Pregnancy and birth outcomes were ascertained using data linkage to hospital records. Four analyses examine associations between maternal pre-pregnancy health status and adverse events during subsequent pregnancies, and birth outcomes.

Main outcome measures: The thesis examines associations between maternal pre-pregnancy health status and the risk of becoming pregnant, the risk of miscarriage, diabetes in pregnancy, hypertensive disorders of pregnancy, and infant birthweight.

Results: Women who became pregnant were younger, more likely to report smoking (PR 1.38; 95% CI; 1.13-1.69) and have low serum folate (PR 1.33; 95% CI; 1.10-1.60) than women who did not. Miscarriage risk increased with age and was more prevalent among women who reported risky drinking (PR 2.24; 95% CI; 1.11-4.52) or who had elevated gamma-glutamyl transferase (PR 2.31; 95% CI 1.30-4.10). Chlamydia or gonorrhoea before pregnancy was associated with risk of miscarriage and co-infection increased magnitude of the risk (PR 4.57; 95% CI; 2.21-9.46).

A strong predictor for diabetes during pregnancy was suboptimal glucose control before conception. Metabolic syndrome predicted over a three-fold increase in risk among non-diabetic women (PR 3.50; 95% CI; 1.54-8.00). Each 1-cm increase in waist circumference increased risk by 4% (PR 1.04; 1.01-1.06) and each 1-mmHg increase in blood pressure (systolic and diastolic) increased risk by 3% (PR 1.03; 95% CI; 1.01-1.05 and 1.03; 1.00-1.07 respectively).

Pre-pregnancy adiposity and increasing blood pressure were predictors of a pregnancy affected by a hypertensive disorder. Each 1 cm increase in waist circumference increased

risk by 4% (PR 1.04; 95% CI; 1.02-1.06) and each 1 unit increase in BMI increased risk by 9% (PR 1.09; 95% CI 1.04-1.14). Each 1mmHg increase in systolic blood pressure increased risk by 6% and each 1 mmHg increase in diastolic blood pressure showed a 7% increased risk (PR 1.06; 95% CI; 1.03-1.09 and 1.07; 1.03-1.11 respectively). Cumulative incidence of the metabolic syndrome increased risk three-fold (PR 3.5; 95% CI; 1.50-8.17).

Infants with intrauterine growth restriction (IUGR) had smaller mothers. Each 1cm increase in waist circumference reduced risk by 5% (PR 0.95; 95% CI 0.91-0.99) and each 1 unit increase in BMI showed a 15% reduction (PR 0.85; 95% CI; 0.77-0.94). All mothers of IUGR infants smoked. Pre-term babies with normal birthweight despite their prematurity had larger mothers more likely to have elevated pre-pregnancy blood pressure. They were more likely to have features of the metabolic syndrome prior to pregnancy (PR 4.44; 95% CI; 1.30-15.13) and more likely to have diabetes (PR 7.81; 95% CI 2.45-24.95) or hypertension during pregnancy (PR 6.51 95% CI 6.51; 2.02-21.03).

Conclusions: Poor nutrition, tobacco smoking, obesity and other features of the metabolic syndrome and low levels of physical activity are highly prevalent among this group of women. Good pre-pregnancy health to improve the intra-uterine environment is important given our improved understanding of how ‘foetal programming’ predicts the immediate and long-term health of the next generation.

Declaration

I declare that this thesis presents work carried out by myself and does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; to the best of my knowledge it does not contain any materials previously published or written by another person except where due reference is made in the text; and all substantive contributions by others to the work presented, including jointly authored publications, is clearly acknowledged.

A handwritten signature in blue ink, appearing to read 'A. H. Campbell', is written over a light blue rectangular background.

21 November 2012

Acknowledgements

First and foremost I would like to acknowledge the traditional owners, ancestors and community members of each part of country involved in this research. Many thanks to every member of the Aboriginal and Torres Strait Islander communities who put their hand up and I hope this work contributes to improving the health of mothers and babies.

Next, I would like to thank my principal supervisor Professor Robyn McDermott for this comprehensive education. Some of the things I learned as an MAE graduate when I first worked with Robyn in North Queensland communities in 2003-2007, were that public health research is exciting, complex and rarely goes according to plan when you are out in the field collecting data. Those important lessons were followed by three years on campus at the University of South Australia City East, which was a golden opportunity to learn how to interpret data from some of the best. Addressing the challenges of learning about the language and theory of research and the application of statistical software packages has been a pleasure, with the guidance of such skillful educators. Professor Adrian Esterman has patiently provided ongoing advice about all things statistical at short notice and sometimes from other parts of the world. I have been very fortunate to have Professor John Lynch in my supervision team and couldn't have wished for a more interesting or enlightening teacher. Professor Leonie Segal and Professor Kerin O'Dea have also made enormous contributions to my education, possibly without even being aware of it. I would also like to thank the National Heart Foundation and the National Health and Medical Research Council for funding this research.

I would like to thank some special colleagues and friends who have shared this PhD journey with me. Ms Karla Canuto, Ms Odette Gibson, Ms Yvette Roe and Ms Terry Jones have been a constant source of everything good in the world. Dr Dr (that is not a typo) Katina D'Onise has been a mentor without comparison. Many thanks to the best friends anyone could have: Noomataora and Mim. You have been a wonderful back-up supervision team. To my excellent brother, all of his children, his children's significant others and each of their children – I can't wait to come to your houses for extended stays now I don't have a thesis to write.

Dedicated to Mum and Dad. (RIP Dad 10.07.1936-23.05.2010)

Thesis overview

This thesis is submitted as a Thesis Containing Published Research in accordance with University of South Australia Academic Regulations for Higher Degrees Research Clause 16.1.1.b. The contribution of each author to the publications is provided in Statement of Authorship declarations at Appendix C.

The introduction provides a contextual description of the health status of Aboriginal and Torres Strait Islander women of childbearing age who live in rural and remote communities in north Queensland. A description of the development of pre-pregnancy health promotion in the United States, and Australian health promotion programmes targeted for women of childbearing age follows.

The body of the thesis is presented in two sections. In Section 1: a literature review (Chapter 2) focused on existing national and international studies on the risk for adverse pregnancy outcomes according to maternal pre-pregnancy characteristics. The section includes the methodology and a summary of the findings of the literature search.

Section 2 includes four prospective cohort studies designed to assess pre-pregnancy status of a cohort of Aboriginal and Torres Strait Islander women and associations with events during future pregnancies and birth outcomes. The section provides an overview of the study methods (Chapter 3), and the research questions and study participants associated with the four studies (Chapter 4). Chapter 5 describes the four studies, including two published articles, one draft manuscript and one submitted manuscript. The included papers evaluate how pre-pregnancy health factors contribute to the experience of pregnancy and short-term outcomes for the offspring in this high risk population.

Chapter 6 brings together the two sections and discusses the results of the four studies in the context of the literature review. This chapter also includes the strengths and limitations of this thesis and concludes by suggesting directions for future research.

1. Introduction

This thesis aims first to review national and international evidence on pre-pregnancy risk factors for adverse pregnancy events and birth outcomes. The second aim is to provide evidence on potentially modifiable pre-pregnancy risk factors affecting a cohort of Aboriginal and Torres Strait Islander women from communities in north Queensland.

Healthy mothers tend to have healthy babies. It is widely recognised that one of the best protections against poor pregnancy outcomes is to have women commence pregnancy in good health. In rural and remote communities of north Queensland Australia, Aboriginal and Torres Strait Islander women of childbearing age have a high prevalence and incidence of central obesity and diabetes, poor nutrition and high rates of alcohol use and tobacco smoking.¹ The impact of this poor maternal health on the intra-uterine environment resonates in disparities in birth outcomes that are significantly worse among Aboriginal and Torres Strait Islander women across every major indicator of infant health.² The challenges faced by women in maintaining good health prior to and between pregnancies needs to be contextualised within a framework of socio-economic and environmental circumstances characterised by high levels of poverty, unemployment, food insecurity, and significant housing problems.

Residential overcrowding and sub-standard housing are common in rural and remote north Queensland. The percentage of households defined as overcrowded is more than four times higher among Indigenous residents of the region (33.4%) compared with non-Indigenous residents (6.9%). Two thirds of the Indigenous population (66.7%) are reported as having no income or an income less than \$400 per week compared with 48% of the non-Indigenous population.³ Issues of food security related to cost, quality and availability are exacerbated by long distances and seasonal variations which make many communities inaccessible by road for many months each year (usually November to April). The cost of a basket of basic healthy foods in Queensland is significantly higher in remote and very remote communities (20% and 31% higher, respectively) which are home to predominately Aboriginal and Torres Strait Islander populations.⁴ In addition, the Indigenous population of the north Queensland region is diverse, mobile and spread across a large geographical area.

Torres Strait Islander Australians are ethnically, culturally and historically distinct from Aboriginal Australians.⁵ Their traditional lands are the islands and waters of the Torres

Strait between the northern most tip of Queensland and Papua New Guinea. The national population of Torres Strait Islander people is approximately 30,000 and around 25% reside in the Torres Strait. Health service delivery is via 15 primary health centres on outer islands and 5 centres situated on the mainland in the Northern Peninsula Area. Thursday Island is the administrative centre for the region and its hospital provides inpatient care, visiting specialist services, allied health and ancillary services (e.g. pathology). Obstetric services at the hospital include care during labour and childbirth. The distance from Thursday Island to the main referral hospital in Cairns is 890 kilometres.

Figure 1.1 Health Service District boundaries in north Queensland. The districts relevant to this thesis include the Torres Strait and Northern Peninsula Area, Cape York and Mount Isa.



Queensland's Cape York communities are predominately home to Aboriginal Australians and the region covers over 137,000 square kilometres of mainland north Queensland. The population of Cape York totals approximately 18,000 people dispersed across a network of small communities and towns. Apunipima Cape York Health Service Council is the lead agency representing the health needs of the Indigenous people of Cape York.⁶ There are 11 primary health centres. Hospitals situated at Weipa and Cooktown do not routinely provide obstetric services for women during labour and childbirth and most women re-locate to Cairns to deliver their babies. Women who live in remote areas of the Mount Isa Health Service District communities in north western Queensland usually relocate to Mount Isa for birth. Despite geographical and demographic differences between the three districts, their Indigenous populations face similar levels of disadvantage.

Health promotion targeted for women of child-bearing age is potentially broad and recommendations arising from the United States address many aspects of pre-pregnancy health. In Australia, health promotion campaigns have been relatively narrow in scope; however, they have the potential to address important risk factors among pre-pregnant women including tobacco smoking, alcohol use and folic acid supplementation for the prevention of neural tube defects.

1.1 Pre-pregnancy health promotion: its beginnings

Reference to the importance of optimising the mother's pre-pregnancy health, to in turn optimise her chances of having a healthy pregnancy and baby can be found in documents from the early 19th century. In 1825, Dewees, an American university Professor of Midwifery stated that "...the physical treatment of children should begin as far as may be practicable, with the earliest formation of the embryo; it will therefore, necessarily involve the conduct of the mother, even before her marriage, as well as during her pregnancy".⁷ A program of pre-pregnancy health care was first described in the British Medical Journal in 1980 by Chamberlain⁸, however, it was limited in scope to women with poor obstetric histories. Also in 1980 it was revealed that the United States (US) had slipped from 10th in 1960 to 19th in infant death rate ranking among developed countries.⁹ It was recognised that the incidences of congenital malformations and low birthweight had remained steady for decades.¹⁰

For most American women, efforts to reduce infant mortality and morbidity at this time remained focused on improving the content and use of antenatal care to anticipate and manage risks during pregnancy.⁹ A movement which became known as ‘preconceptional health promotion’ gained momentum over the 1980s premised on the argument that ‘prenatal’ care starts too late to impact on many adverse reproductive outcomes.¹⁰ Maternity care strategies were re-thought and by the 1990s, as a measure to restart improvements to birth outcomes, healthcare leaders in the US advised that pre-pregnancy care should be made available to all prospective parents.¹¹ A major distinction between antenatal care and the proposed pre-pregnancy care was a shift in the focus from anticipation and management during pregnancy into a paradigm of prevention and health promotion prior to pregnancy.

In 1995, the American College of Obstetrics and Gynecology recommended opportunistic emphasis on maternal pre-pregnancy health at all routine visits by any woman who may at some time become pregnant.¹² This was re-iterated in 2002 in the American national "Guidelines for Perinatal Care" which recommended that "all health encounters during a woman's reproductive years...should include counselling on appropriate medical care and behaviour to optimize pregnancy outcomes".¹³ The non-profit sector also became engaged in the preconceptional health promotion movement. In 2002, the influential March of Dimes organisation recommended that "care providers...take advantage of every health encounter to provide preconception care and risk reduction before and between conceptions – the time when care really can make a difference".¹⁴ The potential importance of pre-pregnancy health and health care was enthusiastically recognised and supported across nursing and medical disciplines in the US.⁹

In 2008, a series of papers published in the *American Journal of Obstetrics and Gynecology* presented current evidence regarding the degree to which specific pre-pregnancy interventions can impact the effect of pre-pregnancy risk factors on birth outcomes. The series addressed immunisations,¹⁵ infectious diseases,¹⁶ chronic medical conditions,¹⁷ psychiatric conditions,¹⁸ alcohol, tobacco and illicit drug exposures,¹⁹ genetics and genomics,²⁰ nutrition and dietary supplements,²¹ care of psychosocial stressors,²² the use of medications and supplements by women of reproductive age,²³ reproductive history,²⁴ care for special populations including women with disabilities or cancer, and immigrant and refugee women,²⁵ and pre-pregnancy care for men.²⁶ Despite this comprehensive collection of work, it has been suggested that without significant

changes to the American health care system, the benefits of pre-pregnancy care will remain an unrealised opportunity.²⁷

1.2 Health promotion for women of childbearing age in Australia

The recommendations in the US for pre-pregnancy care described above were very wide in scope covering a diverse range of topics from immunisations to nutrition. In Australia over the last three decades, there have been three main areas of health promotion targeted for women of child-bearing age. There has been specific health promotion campaigns aimed at folic acid supplementation for the prevention of neural tube defects (NTDs) and broader programs targeting alcohol use and tobacco smoking have been implemented.

1.2.1 Folic acid supplementation for the prevention of neural tube defects

In response to the convincing body of evidence of the 1980s demonstrating the benefits of periconceptual folic acid supplementation in reducing risk of neural tube defects (NTDs), some Australian states started from 1992 to recommend that women of reproductive age take 0.5 mg of folic acid in tablet form daily. Voluntary folate fortification of specified foods was recommended by a National Health and Medical Research Committee (NHMRC) Expert Panel in 1995.²⁸ From 1996 increasing numbers of breakfast cereals, fruit juices and milk were fortified with the vitamin. A Cochrane systematic review involving over 6,000 women published in 2001 confirmed the irrefutable benefit of folate supplementation prior to and in the early gestational period for prevention of NTDs²⁹ and in September 2009, mandatory fortification of wheat flour was introduced nationally to provide additional protection.³⁰ A continued downward trend in the overall prevalence of all NTDs has been observed with an average annual decline of 0.22 NTDs per 10,000 births between 1998 and 2008 (14 and 11.8 per 10,000 respectively).³¹ The impact of the 2009 mandatory fortification of food has not been assessed.

1.2.2 Alcohol use

Alcohol is widely used and generally accepted as part of Australia's society and culture. The NHMRC released new Australian guidelines³² aimed at reducing health risks from drinking alcohol in 2009 (updated from 2001³³). For the first time it was recommended that "for women who are pregnant or planning pregnancy, not drinking is the safest option". This guideline was not based on scientific evidence, rather on limitations in available evidence which made it impossible to set 'safe' drinking levels. However, it was conceded

that low-level drinking in pregnancy (one or two standard drinks per week) was unlikely to put the foetus at risk. Currently it is believed the Australian prevalence of Fetal Alcohol Syndrome (FAS) is under-ascertained³⁴ however, a Western Australian study found that the condition was rare among non-Aboriginal children over the period 1987-1997 (0.02 per 1,000).³⁵

1.2.3 Tobacco smoking

Australia is considered a world leader in tobacco control.³⁶ A successful collaborative national tobacco control campaign was implemented in Australia from 1996, and though the interventions weren't aimed at improving pre-pregnancy health, they did aim to engage adults of childbearing age (18-40 years). The proportion of adult regular smokers has fallen from 35% in the 1980s to the current prevalence of 18% and it is predicted that by 2020, rates will have decreased further to 14%.³⁷ Among pregnant women attending their first clinic visit in 1987, 34% were identified as smokers.³⁸ Research has found that in 2005 about 17% of Australian women reported smoking during pregnancy.³⁹

1.3 Limited impact of the health promotion for Indigenous Australians

Australian health promotion campaigns with potential to impact on three modifiable pre-pregnancy risk factors for serious adverse birth outcomes (folate deficiency, alcohol use and tobacco smoking) have so far not demonstrated a significant impact on Aboriginal and Torres Strait Islander communities according to state and national data. It is suggested that one of the reasons for the disappointing outcomes from conventional approaches to health promotion in Australian Indigenous communities, relates to the focus of many campaigns on individual risk factors.⁴⁰ An alternative approach, that focuses on family and community may be more effective because social, political and cultural contexts of health can be taken into account.

1.3.1 Neural tube defects

In Western Australia, the falling prevalence of NTDs among non-Indigenous infants has resulted in an increased disparity compared with Indigenous infants.⁴¹ Prior to the promotion of folic acid and voluntary folate fortification of food (1980-1992) the prevalence of NTDs was 42% higher among Indigenous infants (PR 1.42; 95% CI 1.04-1.94). In the period following the campaigns (1996-2000), the prevalence in Indigenous infants was almost twice that of non-Indigenous infants (PR 1.98; 95% CI 1.25-3.15) even

though there had been no change in Indigenous rates of NTDs over the two study periods (25.5 and 25.6 per 10,000 births respectively). The study highlighted circumstances where health promotion that was successful in reducing the risk of NTDs overall, failed to be effective for Indigenous infants. Future surveillance may show a more equitable effect of national strategies to reduce NTDs due to the as yet unmeasured impact of the 2009 introduction of mandatory fortification of wheat flour.

1.3.2 Foetal alcohol syndrome

FAS was reported over a 100 times more frequently among Aboriginal children (2.76 per 1,000) compared with non-Indigenous children (0.02 per 1,000) in the Western Australian Birth Defects registry between 1980-1997.³⁵ In a prospective national surveillance study between 2001 and 2004, 92 cases were reported by paediatricians to the Australian Paediatric Surveillance Unit and a disproportionate 65% of the children were Indigenous.⁴² The 2009 NHMRC recommendation for abstinence from alcohol for women before and during pregnancy seems unrealistic for many Australian women, given a continued high rate of unplanned pregnancy. To achieve pre-pregnancy and pregnancy alcohol abstinence among women who habitually use alcohol at hazardous levels seems even less likely. Pre-pregnancy interventions (including preventing unplanned pregnancies) could potentially prevent harm to foetuses of women who drink alcohol at both safe and harmful levels.

1.3.3 Tobacco smoking

National statistics show that the smoking rate among Aboriginal and Torres Strait Islander men is 51% and 47% among women. Overall there has been a decline in rates from 53% in 2002 to 50% in 2008.⁴³ Among the Indigenous women who had a baby during 2009, 47% self-reported smoking during pregnancy.² Awareness among women that smoking during pregnancy is discouraged is high, however, knowledge about specific reasons for not smoking is not.^{44,45} Australia's tobacco control campaigns have been very successful in reducing smoking at a population level, but they provide another example of health promotion activities that have failed to benefit Indigenous children. Many Aboriginal and Torres Strait Islander people who smoke have not yet been exposed to years of the interplay of tobacco control interventions that have influenced the smoking behavior of other Australians.

1.4 Current disparities associated with birth outcomes among Indigenous Australians

Australia's national perinatal surveillance data are aggregated by the Australian Institute of Health and Welfare annually and published in the Australia's Mothers and Babies series of reports. In 2009,² 11,284 Australian births (3.8%) were identified as being to Aboriginal and Torres Strait Islander women. The Indigenous status of fathers is not recorded. The women started childbearing earlier (19.6% of the Indigenous births were to teenage mothers compared with 3.4% of non-Indigenous births) and they had larger families (27.2% of Indigenous mothers had given birth three or more times compared with 9.8%). The pre-term birth rate was higher (13.4% versus 8.0%), the fetal death rate was higher (12.9 versus 7.5 per 1,000), the neonatal death rate was higher (6.8 versus 2.8 per 1,000) and the post neonatal death rate was higher (3.5 versus 1.3 per 1000 neonatal survivors). The average birthweight of Indigenous babies in 2009 was 3,183 grams (199 grams lighter than other babies) and 12% weighed <2,500 grams (low birthweight) compared with 6.2% of non-Indigenous babies.

1.5 A place for pre-pregnancy health promotion in addition to antenatal care for Indigenous Australians

Development of new national evidence-based Antenatal Care Guidelines is currently underway in a collaboration of state and territory governments and the NHMRC.⁴⁶ However, the potential for successful interventions to improve many reproductive outcomes in the antenatal period is limited. By the time a pregnant woman attends her first antenatal appointment, even if the visit occurs in the first trimester, most of the fetal organs are formed⁴⁷ and opportunities to prevent birth defects are missed (e.g. immunisation against rubella) or less effective (e.g. folic acid supplementation). If a woman presents for care later in her pregnancy, opportunities to effectively manage antenatal complications such as detection and control of maternal diabetes or hypertension and sexually transmitted infections also decline.⁴⁸

Of the 250,000 women who give birth in Australia each year, almost all receive some antenatal care.⁴⁹ For many Indigenous women however, initiation of the care can be late in pregnancy^{50,51} or the care may be sporadic,⁵² decreasing the scope for potential benefits. In north Queensland, a ten year review of birth records (1901-2001) has demonstrated that those who did not access antenatal care at all were more likely to be Indigenous women

(OR 7.17; 95% CI 5.31-9.68), women of low maternal age (25 years or less) (OR 1.78; 95% CI 1.37-2.32) and women who reported using tobacco (2.03; 95% CI 1.56-2.65) and alcohol (OR 1.70; 95% CI 1.28-2.24).⁵³ In addition, the review found that women who did not access antenatal care were more likely to have a birth complicated by early pre-term delivery (OR 6.96; 95% CI 4.96-9.75) or post-partum haemorrhage (OR 1.81; 95% CI 1.15-2.85). The infants were more likely to have birthweights < 2500 grams (OR 4.47; 95% CI 3.35-5.98), low Apgar scores (OR 4.96; 95% CI 3.06-8.05), and to die in the perinatal period (OR 6.30; 95% CI 3.72-10.96). These outcomes are observed despite the fact that mothers in north Queensland have good access to high quality medical care around the time of birth.⁵⁴

Failure to observe a reduction in the comparatively higher prevalence of teenage pregnancies, preterm birth, low birth weight and perinatal mortality among Australian Indigenous women and babies,² combined with the frequency with which women fail to initiate timely routine antenatal care, suggests that the *availability* of antenatal care alone is insufficient to address maternal and infant morbidity and mortality among women and their babies.

1.6 Summary

Australia is one of the richest countries in the world and has one of the lowest perinatal mortality rates.⁵⁵ Antenatal, intrapartum and postnatal specialist health services are of high quality and provide care that results in the best possible and usually satisfactory outcomes of pregnancy for most women. A major obstetric and perinatal problem in Australia is the comparative poor health of Aboriginal and Torres Strait Islander mothers and their babies.

The model of primary health care offered in rural and remote north Queensland provides opportunities for pre-pregnancy and between pregnancy health promotion and interventions that are often missed by clinicians and health promotion programs. The missed opportunities for pre-pregnancy health care may be important for all women and they may be particularly important for women who are late in attendance or do not attend antenatal care. An example of a model for successful health promotion in Indigenous communities highlights crucial principles that include a focus on community strengths (rather than deficits) and community control and participation in planning and decision making from the outset.⁴⁰

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2. Literature Review

The effect of maternal pre-pregnancy health status on adverse pregnancy events and birth outcomes.

Abstract

Aim: The aim of this literature review is to assess and quantify the risk for selected adverse pregnancy events and birth outcomes according to maternal pre-pregnancy characteristics.

Methods: The design is a general literature review of national and international studies published over the last 20 years. Four electronic databases (Amed, Embase, Ovid Medline and Ovid Nursing Database) were searched for epidemiological studies that examined pre-pregnancy health (title search, 1991-2011). Eighty-seven studies are included in the final review.

Results: Maternal adiposity is by far the most commonly studied pre-pregnancy exposure. Overall, pre-pregnancy body mass outside normal BMI categories seems detrimental to maternal health and birth outcomes.

- Elevated maternal pre-pregnancy adiposity is associated with a higher risk of hypertensive and glucose disorders of pregnancy
- Women with lean pre-pregnancy body mass are at higher risk of spontaneous preterm birth. Obesity may increase the risk of medically induced preterm birth
- Women who were overweight or obese prior to pregnancy had a higher risk of caesarean section delivery
- Elevated pre-pregnancy BMI seems to increase the risk of perinatal mortality, particularly among nulliparous women. Overweight and obesity increased risk of having an infant with a cardiac and perhaps neural tube defect, however, women in these BMI categories had lower risk for having an infant with gastroschisis
- Low maternal pre-pregnancy BMI is associated with smaller offspring. High maternal BMI is associated with larger offspring
- Overweight and obesity may play a role in failure to establish effective breastfeeding
- Abnormal pre-pregnancy cardio-metabolic profile increases the risk of gestational diabetes, preeclampsia, and perhaps preterm birth
- Physical activity prior to pregnancy is probably effective in improving glucose tolerance however, it was not associated with risk of GDM. Strenuous pre-pregnancy

physical activity may reduce the risk of preeclampsia. Alcohol use prior to pregnancy increased the risk of unintended pregnancy and was a predictor of alcohol use during pregnancy. Smoking around the time of conception had an additive effect on increasing the risk of having a small-for-gestational age baby given other risk factors for the outcome

Conclusion: The body of literature on the effect of maternal pre-pregnancy health on subsequent pregnancies and birth outcomes is growing. A considerable number of biologically plausible hypotheses regarding causal relationships have been generated. The strength of associations and the consistency of results from diverse study settings add validity to many findings.

2.1 Introduction

There has been increasing recognition in recent years that achieving a healthy pregnancy outcome is strongly influenced by a woman's health status and her lifestyle behaviours prior to pregnancy. This is reflected in the growing body of epidemiological literature aimed at assessing and quantifying the risk for adverse antenatal events and birth outcomes according to maternal pre-pregnancy characteristics. In the United States during the 1980's, pre-pregnancy health promotion started to gain momentum in response to the realisation that the incidence of the leading causes of infant mortality and morbidity (congenital malformations and low birthweight) had remained constant for about 80 years.¹ Over the past 2 decades, a substantial body of international epidemiological research on relationships between pre-pregnancy risk factors and subsequent maternal and infant health outcomes has been developed.

The structure of this chapter follows a format that includes a methods description followed by results organised according to exposures and outcomes that are summarised in tables and described in text. The final section includes a discussion of the common characteristics, strengths and weaknesses inherent in epidemiological studies on pre-pregnancy health. The chapter provides a broad summary of national and international studies addressing potentially modifiable maternal pre-pregnancy characteristics and their impact on the course of pregnancy and infant birth outcomes.

2.2 Methods

The initial literature searches for this review were conducted in 2008. They have been periodically updated and the last update was undertaken in January 2012.

Data collection and organisation of study exposures and outcomes was undertaken in two stages. During the first stage, described in more detail below, the medical literature was searched broadly with the aim of capturing a collection of existing studies to address the question, "*What is the effect of maternal pre-pregnancy health status on the course of pregnancy and birth outcomes?*" In the second stage, after tabulating the relevant studies, three categories were developed based on maternal pre-pregnancy exposures: 1. maternal pre-pregnancy adiposity, 2. pre-pregnancy cardio-metabolic risk factors, and 3. pre-pregnancy lifestyle risk factors. This categorisation was undertaken to facilitate a baseline understanding of causal associations in the literature. However, it is recognised that with regard to causal pathways, there is likely to be significant overlap and intersection between

the three categories. For example, pre-pregnancy lifestyle risk factors (low levels of physical activity or poor nutrition) may contribute to maternal adiposity, which in turn is known to be associated with cardio-metabolic risk factors.

2.2.1 Data Sources

The published medical literature from 1991 to 2011 was searched, including Allied and Contemporary Medicine, Embase and Medline via the Ovid SP platform, and the Ovid Nursing Database. Only English language articles were included in the search. The databases were searched using key words in the manuscript titles including “pre-pregnancy”, “prepregnancy”, “pre-conception”, “preconception”, “pre-gravid” or “pregravid”. This was augmented with a further manual title search of the reference lists of each of the included articles.

2.2.2 Study Eligibility

Eligible studies were limited to original research on humans. They included a measured maternal pre-pregnancy exposure (e.g. body mass index) and a defined primary outcome measure that occurred over the course of subsequent pregnancies (e.g. diagnosis of gestational diabetes) or around the time of birth (e.g. infant birthweight). The exposures of particular interest were those potentially amenable to intervention. The primary outcome measures of interest were those that are known to potentially have an adverse impact on maternal and fetal health during the pregnancy, or on the pregnancy outcome. Studies that examined models of pre-pregnancy health care or pre-pregnancy health promotion were not included in the review.

2.2.3 Study Selection

After removal of duplicates, the initial literature search produced 914 results and the titles were reviewed for inclusion eligibility. If the title did not provide sufficient information to determine if the study met criteria, the electronic abstract was reviewed. Over 100 articles remained after this procedure.

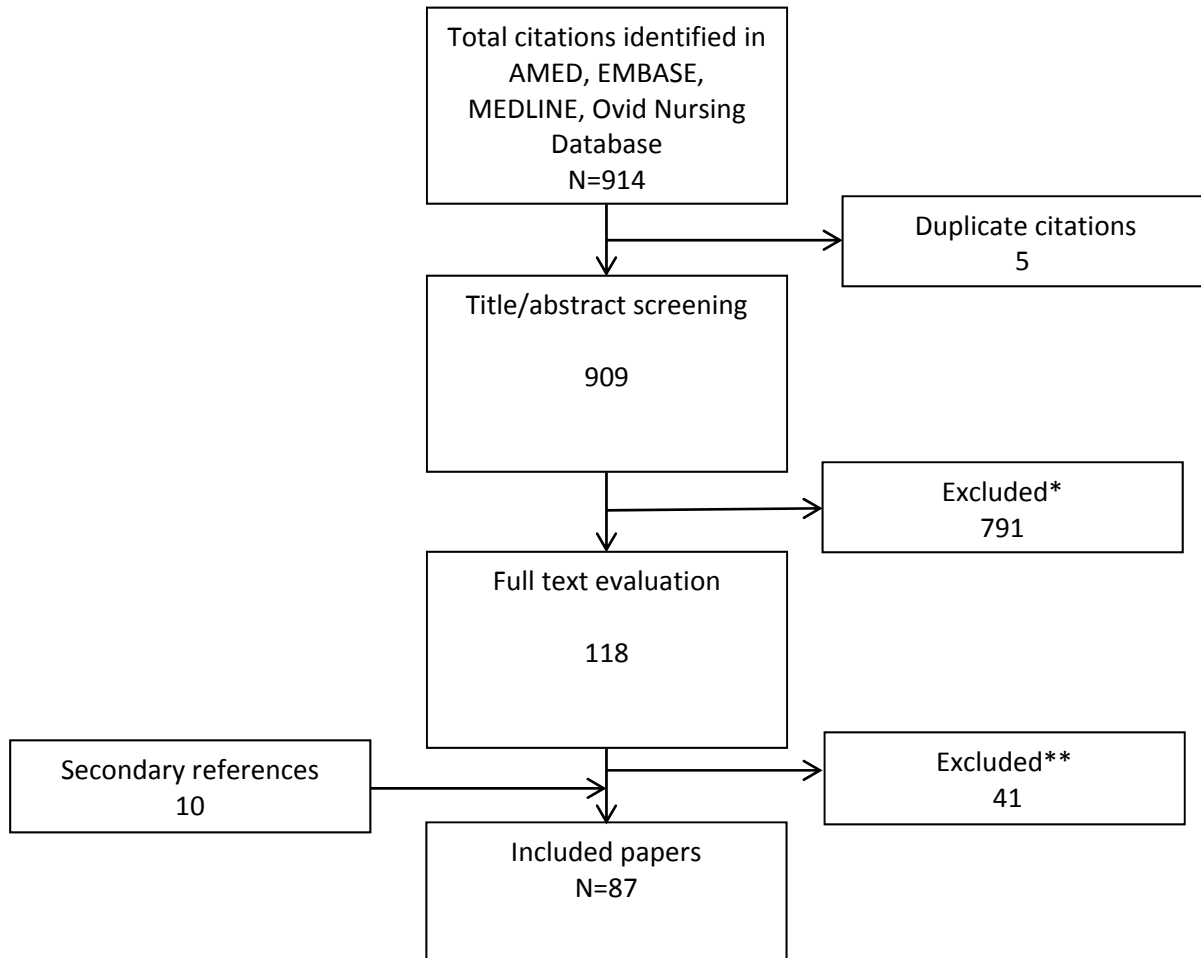
The abstract and/or text of these articles was read to determine final inclusion. Citations included in the reference list of articles reporting eligible studies were manually reviewed to identify additional eligible studies that may have missed the electronic search. Review articles were deemed ineligible, and this was always evident from the abstract, however, citations included in these works were also searched manually.

2.2.4 Data Extraction

Abstracted data from the full text of eligible studies was according to a pre-determined abstraction template. Data included information regarding the year of publication, study design and year/s of data collection, study setting, population and sample size, primary exposures and outcome measures, and reported statistics and adjustment variables. In studies where there was more than one exposure or outcome variable, the results in this review report on what were determined as the primary exposure or outcome variables. The abstracted data were summarised in tables with adjustment variables footnoted.

2.3 Results

Figure 2.1 Flow diagram of the process of identifying and including references for the literature review

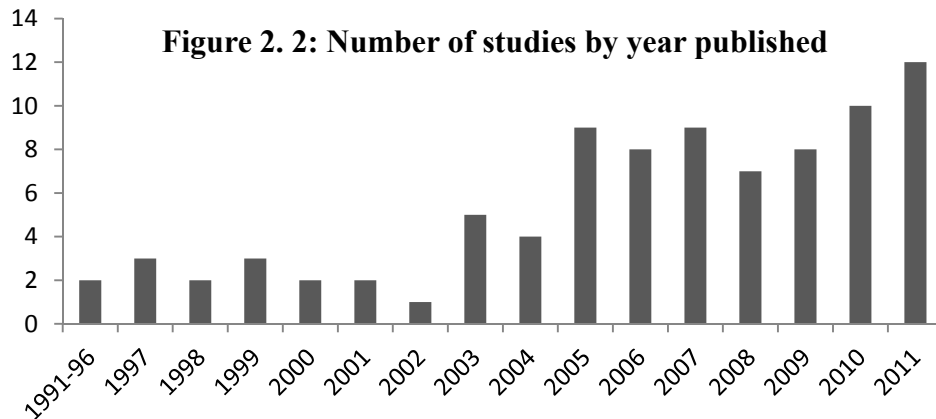


* papers describing pre-pregnancy health promotion or models of care, animal studies, review papers, conference abstracts, language other than English, ineligible study exposures and/or outcomes

** ineligible study exposures (e.g. pre-pregnancy pertussis booster) and/or outcomes (e.g. breast cancer in adult offspring)

Recent expansion of research

Between 1991 and 2011, the number of published studies on relationships between maternal pre-pregnancy health status and subsequent maternal and infant health has steadily increased. The graph below depicts the 87 studies included in this review, by year of publication.



Primary exposure and outcome measures

The results of this review are organised into categories of maternal pre-pregnancy characteristics (study exposures). In the first category, 71 studies have **maternal pre-pregnancy adiposity** as the primary exposure under investigation. The studies were then further classified according to associations with the following primary outcomes measures:

- Table 2.1: diabetes mellitus and/or hypertensive disorders of pregnancy (17 studies)
- Table 2.2: preterm birth (17 studies)
- Table 2.3: progress of labour and/or method of birth (11 studies)
- Table 2.4: perinatal mortality/congenital malformations (12 studies)
- Table 2.5: infant birthweight (10 studies)
- Table 2.6: breastfeeding (4 studies)

In the second category, **maternal pre-pregnancy cardio-metabolic risk factors** are the exposures of interest. Seven studies presented in Table 2.7 have examined associations between pre-pregnancy blood lipids, glucose and blood pressure and pregnancy events and outcomes.

In the final category, there are 9 studies presented in Table 2.8 that have examined relationships between **maternal pre-pregnancy lifestyle risk factors** (e.g. physical activity, alcohol use and smoking) and subsequent pregnancy events and outcomes.

Primary exposure and outcome definitions

Definitions of primary pre-pregnancy study exposures and subsequent pregnancy and birth outcomes are provided in the following section that describes the included studies, and in the tables. Definitions for similar exposures and outcomes vary slightly, because they are reported according to those provided by the authors in each study. However, maternal body mass index (BMI) requires further explanation. As a study exposure it is interesting because it is relied on so often, and because definitions of its categories are so variable. Most studies used three to four categories of BMI, defined according to World Health Organisation (WHO) categories. Therefore generally, maternal underweight was defined as $\text{BMI} < 18.5 \text{ kg/m}^2$, normal weight as $\text{BMI} 18.5 - 24.9 \text{ kg/m}^2$, overweight as $\text{BMI} 25-29.9 \text{ kg/m}^2$, obesity as $\text{BMI} 30+ \text{ kg/m}^2$ and less frequently studies included a fourth category, morbid obesity defined as $\text{BMI} > 34.9 \text{ kg/m}^2$. Examples of alternative categories have normal weight classified as $\text{BMI} 19.8-26 \text{ kg/m}^2$, overweight as $\text{BMI} 26.1-29.0 \text{ kg/m}^2$ and obese as $\text{BMI} > 29.0 \text{ kg/m}^2$ and very obese as $\text{BMI} \geq 35 \text{ kg/m}^2$. Many other BMI ranges and point estimates are used in the following studies to assess relationships between maternal adiposity and pregnancy and birth outcomes.

2.3.1 Maternal pre-pregnancy adiposity

2.3.1.1 Maternal pre-pregnancy adiposity and diabetes mellitus and/or hypertensive disorders in pregnancy

Thirteen cohort studies summarised in Table 2.1 provide a total sample size of 711,584 women to investigate associations between maternal pre-pregnancy adiposity and diabetes mellitus and/or hypertensive disorders during pregnancy. More than two thirds of the women (486,491) were participants in research that took place in the United States (US). One American study recruited self-identified Latina women only (n=1,043) and another compares data on 19,135 white women with data on 19,053 black women. The remaining studies provide information about women in Canada (3 studies N=55,843; including 1 study on 603 First Nations women), Australia (n=2,827), Japan (n=633), Israel (n=13,722) and Sweden (n=151,025). Seven of these cohort studies drew their samples from clinic or hospital-based settings and the remainder have population-based samples. Four studies with case-control designs are included, two arising from the US, one from Poland and the other from Thailand.

Three studies (2 cohort studies and 1 nested case-control design) undertaken by Bodnar et al²⁻⁴ in the US focus on the occurrence of preeclampsia, defined as gestational hypertension (new onset of hypertension with systolic blood pressure persistently ≥ 140 mm Hg and/or diastolic blood pressure persistently ≥ 90 mm Hg occurring after 20 weeks gestation) combined with proteinuria, which both subside to the normal state during the post-partum period. Their consistent results show that women with overweight and obese pre-pregnancy BMI are at higher risk for preeclampsia compared with women in the normal weight range. One study² demonstrated an additional protective effect of lean maternal body size (BMI =17 kg/m² and BMI =19 kg/m²) when compared with women who have a BMI =21 kg/m² (OR 0.43; 95% CI; 0.25-0.76 and 0.66; 0.50-0.87 respectively). However, it is well-documented that underweight women are at higher risk for preterm birth (Table 2.2) potentially resulting in less time during a pregnancy to develop preeclampsia.

In Bodnar's study comparing black and white women using data collected between 1958 and 1964, the effect of pre-pregnancy overweight and obesity showed similar associations with preeclampsia among both racial groups.³ In their analysis, BMI was specified as a series of spline terms and odds ratios could be calculated for any BMI value. Compared to white women with a BMI=20 kg/m², white women with BMIs=25 and 30 kg/m² were at

higher risk for preeclampsia (OR 1.7; 95% CI; 1.1-2.5 and 3.4; 2.1-5.6 respectively). Using the same referent group, black women with BMIs ≥ 25 and 30 kg/m^2 had higher risks of similar magnitude (OR 2.1; 1.4-3.2 and 3.2; 2.1-5.0 respectively).

In a nested-case control study, Bodnar et al⁴ showed the total effect of BMI on preeclampsia risk was such that a 4 unit increase in BMI increased risk by 70% (OR 1.7; 95% CI; 1.3-2.3). This effect was mediated by inflammation (C-reactive protein) and raised triglycerides (OR 1.4; 95% CI; 1.0-1.9). These findings indicated that nearly one third of the total effect of BMI on preeclampsia risk was mediated through inflammation and triglyceride levels suggesting an active role for visceral fat accumulation.

Samuels-Kalow et al⁵ analysed a subset of population-based data on 13,722 consecutive Jewish births that occurred in Israel over two years in the 1970's to examine the relationship between pre-pregnancy BMI and hypertensive disorders of pregnancy (HDP - defined as preeclampsia or gestational hypertension). Compared with normal weight women (BMI 18.5-24.9 kg/m^2) women who were overweight or obese prior to pregnancy were at much higher risk of developing HDP (OR; 2.82; 95% CI: 2.40-3.31 and 5.51; 4.15-7.31 respectively). Long term follow-up of the mothers using data linkage to national registries assessed the impact of HDP on maternal mortality. Survival analysis was used to examine the risk of death after HDP for women in each BMI category. Among women of all pre-pregnancy BMI categories who survived at least 15 years, there was a significant increase in mortality for women who had HDP compared to those who did not (HR; 1.94; 95% CI; 1.42-2.67). The study demonstrated the importance of pre-pregnancy BMI in attenuating the association between HDP and death. HDP was not associated with increased mortality among women who were underweight or normal weight before their pregnancy (HR 1.31; 95% CI; 0.18-9.76 and 1.26; 0.74-2.14 respectively). However, women who were overweight had almost two-fold increased risk of death (HR 1.86; 95% CI 1.07-3.20) and among obese women the risk was greater (HR; 2.90; 95% CI; 1.28-6.58).

Fortner et al⁶ in a hospital-based sample of self-identified Latina women living in the US, found women with pre-pregnancy obesity had more than double the risk for gestational hypertension and preeclampsia, compared to women in the normal weight range (OR 2.5; 95% CI; 1.3-4.8 and 2.7; 1.2-5.8 respectively). In addition, they found that excessive gestational weight gain (GWG) increased the risk of both conditions (OR 2.9; 95% CI; 1.1-

7.2 and 4.2; 1.2-14.5 respectively). Using guidelines developed in the US and published by the Institute of Medicine (IOM),⁷ GWG was classified as “inadequate, adequate or excessive”. These guidelines recommend a weight gain of 12.5 to 18 kg for women with a pre-pregnancy BMI of $< 19.8 \text{ kg/m}^2$; 11.5-16 kg for women with a pre-pregnancy BMI of $19.8\text{-}26.0 \text{ kg/m}^2$; and 7 to 11.5 kg for women with a pre-pregnancy BMI > 26 to 29 kg/m^2 . An adequate pregnancy weight gain recommended for obese women (BMI $> 29.0 \text{ kg/m}^2$) is a minimum of 6.8 kg, but an upper limit is not suggested in the guidelines for this group.

A study of 603 First Nations women (Cree women living in 9 remote or rural communities in northern Quebec) also aimed to determine the effect of pre-pregnancy weight and GWG on pregnancy outcomes including preeclampsia and gestational diabetes mellitus.⁸ The first and final maternal weight during pregnancy extracted from medical records was used to assess pre-pregnancy weight and GWG. At the beginning of pregnancy 23.1% of the women had normal weight (BMI $18.5\text{-}24.9 \text{ kg/m}^2$), 27.9% were overweight (BMI $25\text{-}29.9 \text{ kg/m}^2$) and 49.1% were obese (BMI $\geq 30 \text{ kg/m}^2$). Nearly one-half of the women gained excessive weight during pregnancy according to the IOM guidelines. Compared to normal weight women, obese women had higher unadjusted odds of developing gestational hypertension, preeclampsia and GDM (OR's 4.25 95% CI; 2.80-5.70; 3.45; 2.21-4.69; and 8.32; 6.20-10.44 respectively). Obese women with excessive weight gain had a higher prevalence of preeclampsia (14.9%) than obese women with low (3.7%) or acceptable (6.3%) weight gain. However, GDM was found to be more prevalent among obese women with low GWG. This modified relationship may be related to circumstances where obese women with the lowest GWGs, had the highest body weights at the beginning of pregnancy.

Six other studies include the outcome of preeclampsia among a combination of outcome measures, most commonly, gestational diabetes mellitus (GDM defined as new onset diabetes during pregnancy), gestational hypertension (new onset hypertension during pregnancy) and preeclampsia. Overall, when compared with normal weight women, women who were overweight prior to pregnancy were at higher risk for each condition.⁹⁻¹⁴ Among a Canadian hospital-based sample ($n=18,643$)⁹ there were significant increases in risk among overweight, obese and morbidly obese women compared with normal weight women for GDM (ORs 1.89, 3.22 and 4.71 respectively), gestational hypertension (ORs 2.28, 4.65 and 6.26 respectively) and preeclampsia (ORs 1.56, 2.01 and 2.77 respectively). In a smaller hospital-based study in Perth, Australia ($n=2,827$),¹⁰ compared with normal

weight women, obese women had much higher odds of GDM (OR 6.5; 95% CI; 3.32-12.74), gestational hypertension (OR 7.93; 95% CI; 4.74-13.27) and preeclampsia (OR 3.74; 95% CI; 1.95-7.17). In a large population-based, ethnically diverse sample from New York City (n =213,208)¹³ risk was assessed based on maternal pre-pregnancy weight measured in kg. Compared with women who weighed 45-67 kg, the women in the heaviest group (> 136kg) had the highest ORs for GDM (5.2; 95% CI; 3.8-7.2) and preeclampsia (5.0; 95% CI: 3.5-7.1). Black women were disproportionately represented in the heaviest groups and made up 63.9% of women weighing over 136 kg.

Among 633 Japanese women¹² compared with those who had normal pre-pregnancy weight (BMI 18.5-25 kg/m²), women with a BMI > 25 kg/m² had much higher odds of developing gestational diabetes (OR 7.9; 95% CI; 2.09-30.18) and/or preeclampsia (8.13; 3.78-17.49). The study categorised BMI according to WHO guidelines based on data from Western countries which may have introduced bias. A WHO expert group has proposed that the range of normal BMI for Asian populations should be narrowed to 18.5-23 kg/m² (in preference to 18.5-25 kg/m²).¹⁵ A case-control study of Thai women adopted the ranges recommended for Asian women and found no increased risk for GDM or preeclampsia among obese women (BMI ≥ 27.5 kg/m²; n =120) compared to women with normal pre-pregnancy weight (BMI 18.5-23 kg/m²; n =120) (GDM; OR 0.9; 95% CI; 0.6-1.4, and preeclampsia; 0.7; 0.2-3.3).¹¹ They did find the risk of gestational hypertension was significantly higher among obese Thai women (OR 12; 95% CI 1.6-90.8). The study excluded women with potentially confounding risk factors such as previous GDM, preeclampsia and a family history of diabetes, however, it was limited by a small sample size which meant some outcome variables had cells of < 5.

Villamor et al¹⁴ studied the effect of inter-pregnancy weight change on the risk of GDM, gestational hypertension and preeclampsia in second pregnancies among a population-based cohort of Swedish women (n =151,025). Compared with women who experienced minimal weight change since their index pregnancy (-1.0 and 0.9 BMI units), women who gained 3 or more BMI units were at higher risk for each condition in their subsequent pregnancy (GDM; OR 2.09; 95% CI; 1.68-2.61, gestational hypertension; OR 1.76; 1.39-2.23 and preeclampsia; 1.78; 1.52-2.08). The effect of adult weight change (in the period from age 18 years of age up to 3 months prior to an index pregnancy) on preeclampsia was studied by Frederick et al¹⁶ in a prospective cohort study of 1,644 women in the US. Relative to women with stable weight, women who gained 5-9.9 kg as adults prior to their

pregnancy had an increased risk for preeclampsia (RR 2.6; 95% CI; 1.0-6.7) and women who gained more than 10 kg had a five-fold greater risk (RR 5.1; 95% CI; 2.2-12.2). The number of episodes in which women intentionally lost and unintentionally gained at least 6.8 kg (weight cycling) during the time period was not associated with increased risk (RR 1.1; 95% CI; 0.6-1.8).

Hedderson et al¹⁷ used a case-control design to evaluate the effect of rate of weight change during the 5 years before pregnancy and the risk of GDM among Californian women (GDM cases n =251; healthy controls n =204). Compared with women who had stable weight prior to pregnancy, women who gained weight at the rate of 1.1 to 2.2 kg/year had an increased risk of GDM (OR 1.63; 95% CI: 0.95-2.81) and women who gained weight at the rate of 2.3 to 10 kg/year were at higher risk (OR 2.61; 1.50-4.57). Whiteman et al¹⁸ retrospectively studied the effect of inter-pregnancy weight change on GDM among 232,272 women in the US. Across all BMI categories, mothers with significant weight gain (moving from a lower to higher BMI category) had increased risk. The greatest risk for GDM was among women who moved from normal to obese pre-pregnancy weight (OR 3.21; 95% CI; 2.76-3.73). Mothers with stable BMI's and those who moved to a lower category had reduced risk (for example: remained underweight OR 0.42; 95% CI; 0.19-0.92, obese to normal (0.21; 0.09-0.50) and overweight to normal (0.46; 0.32-0.67).

In a case-control study of 1,121 Polish women with GDM (cases) and 1,011 healthy controls Ogonowski et al¹⁹ found, excepting underweight women, there were significant relationships between all pre-pregnancy weight ranges (including normal weight women) compared with women who had a pre-pregnancy BMI of 18.5-20.9 kg/m² (BMI 21-22.9 kg/m²: OR 1.21; 95% CI; 1.01-1.48; BMI 30-34.9 kg/m²: 3.51; 2.21-5.39 and BMI > 35 kg/m²: 9.01; 3.47-23.3).

At a population level, Davenport et al²⁰ reasonably hypothesised that rises in GDM reported in Canada, the US and Australia would be associated with increases in the prevalence of pre-pregnancy BMI. However, in their study undertaken in London, Canada (n =36,597), no such association was evident. The population incidence of GDM rose from 2.9% to 4.2% (p =0.002) in the study period from 2000 to 2009. However, the prevalence of pre-pregnancy overweight and obesity did not significantly change and were, respectively, 22.1% and 14.4% in 2000, and 22.2% and 16.0% in 2009 (p =0.79 for overweight and p =0.43 for obesity). While there was a positive association between higher

pre-pregnancy BMI and risk of developing a glucose disorder in pregnancy, the temporal increase in GDM over a ten year period was not explained by BMI or excessive pregnancy weight gain suggesting that there are other important variables affecting the prevalence of glucose disorders in pregnancy at the population level. However, this was an ecological study, where individual records were not examined to enable comparisons between exposed and unexposed groups. It is therefore not possible to know whether pregnancies affected by GDM were more likely to be exposed to pre-pregnancy overweight or obesity.

Summary

With the exception of the small case-control study of Thai women, the evidence for associations between elevated maternal pre-pregnancy adiposity and hypertensive and glucose disorders of pregnancy seems clear. Importantly, there is also consistent evidence that maintaining a stable weight or reducing overweight or obesity before pregnancy and during inter-pregnancy intervals is effective in reducing risk of adverse events during subsequent pregnancies.

Table 2.1 Maternal pre-pregnancy adiposity and diabetes during pregnancy and/or hypertensive disorders of pregnancy

Author, Year, and Study Design and Study Year	Sample Size, and Setting	Main pre-pregnancy and pregnancy exposures	Main outcome variables or case definition	Main study findings	Reported Statistics
Abenhaim et al ⁹ (2007); retrospective hospital-based cohort study (1987-1997)	Data on 18,643 Canadian deliveries at a tertiary teaching hospital recorded in an obstetric database. BMI was available for the selected women	Pre-pregnancy BMI calculated either from maternal <i>self-report</i> on admission to the delivery room or from review of office records	GDM Preeclampsia Gestational hypertension defined as any hypertension in pregnancy without pre-existing hypertension	Compared to women with normal BMIs, overweight, obese and morbidly obese women had an increased risk of GDM Preeclampsia Gestational hypertension	OR ¹ 1.89 (95 % CI; 1.63-2.19), (3.22; 2.68-3.87) and (4.71; 2.89-7.67) respectively (2.28; 1.88-2.77), (4.65; 3.71-5.83) and (6.26; 3.48-11.26) respectively (1.56; 1.35-1.81), (2.01; 1.64-2.45) and (2.77; 1.60-4.78) respectively
Bodnar et al ³ (2007); retrospective hospital-based cohort study (1958-1964)	Data on 38,188 women in the Collaborative Perinatal Project (19,135 white and 19,053 black) who had singleton pregnancies and were receiving care at 12 US hospitals	Pre-pregnancy BMI calculated from <i>self-reported</i> information collected by in-person interview	Preeclampsia defined as gestational hypertension and proteinuria, with return to normal in the postpartum period. Gestational hypertension defined as 2 or more measurements of systolic BP $\leq$ 140 mmHg or diastolic BP $\leq$ 90 mmHg	Compared with white women with BMI of 20, white women with BMI of 25 or 30 were at higher risk for severe preeclampsia. Black women with BMIs of 25 or 30 were also at higher risk compared to white women with BMI of 20	OR ² 1.7 (95% CI; 1.1-2.5) and (3.4; 2.1-5.6) respectively (2.1; 1.4-3.2) and (3.2; 2.1-5.0) respectively
Bodnar et al ⁴ (2005); nested case-control study using data from a prospective cohort study (1997-2001)	55 preeclamptic women (cases) and 165 pregnant controls from the Pregnancy Exposures and Preeclampsia Prevention Study (PEPPS) conducted in Pennsylvania (US)	Pre-pregnancy BMI calculated from <i>self-reported</i> weight at first visit and measured height Inflammatory marker (C-reactive protein) and a marker of hyperlipidemia (triglycerides) measured $\leq$ 20 weeks gestation	Case definition: preeclampsia defined as gestational hypertension and proteinuria, with return to normal by 12 weeks postpartum.	The total effect of pre-pregnancy BMI on preeclampsia risk was mediated through inflammation and triglycerides Total effect of 4 and 8 unit increases in BMI Direct effect mediated by inflammation and triglycerides.	OR ³ 1.7 (95% CI; 1.3-2.3) and (2.9; 1.6-5.2) respectively (1.4; 1.0-1.9) and (2.0; 1.0-3.8) respectively
Bodnar et al ² (2005); hospital/clinic based prospective cohort study (1997-2001)	Data on 1,179 primiparous Pennsylvanian women in the PEPPS (study of the pathogenesis of preeclampsia) carrying singleton pregnancies (US)	Pre-pregnancy BMI calculated from <i>self-reported</i> weight at first visit and measured height	Preeclampsia defined as gestational hypertension and proteinuria, and return to normal by 12 weeks postpartum. Gestational hypertension defined as systolic BP persistently $\geq$ 140 mmHg and/ or diastolic BP persistently $\geq$ 90 mmHg after 20 weeks gestation	Overall incidence of preeclampsia was 4.9% Compared to women with BMI of 21, risk of preeclampsia doubled at BMI of 26 and nearly tripled at BMI of 30 Women with BMI of 17 and 19 had reduced risk compared with women with BMI of 21	OR ⁴ 2.1 (95% CI 1.4-3.4) (2.9; 1.6-5.3) respectively 0.43 (0.25-0.76) and (0.66; 0.50-0.87) respectively

¹ Adjusted for age, parity, smoking and diabetes

² Adjusted for maternal age, smoking status, marital status, socioeconomic status, parity, and maternal height

³ Adjusted for gestational age at blood sampling, marital status, C-reactive protein concentration, triglyceride concentration and pre-pregnancy multivitamin use

⁴ Adjusted for maternal race and smoking status in the year before the index pregnancy

Brennand et al ⁸ (2005); hospital-based retrospective cohort study (1994-2000)	Data on 603 First Nations women (Cree) were abstracted from medical records in Quebec, Canada	Pre-pregnancy BMI calculated from medical records when weight was assessed in early pregnancy. Method of measurement <i>not stated</i> GWG calculated from first and final pregnancy weight recorded in medical records	Gestational hypertension Preeclampsia GDM	Compared to normal weight women, obese women had higher unadjusted odds of developing gestational hypertension, preeclampsia and GDM Obese women with excessive weight gain had a higher prevalence of preeclampsia than obese women with low or acceptable weight gain However, GDM was found to be more prevalent among obese women with low GWG than obese women with acceptable or excessive weight gain	OR ⁵ 4.25 (95% CI: 2.80-5.70) (3.45; 2.21-4.69) and (8.32; 6.20-10.44) respectively 14.9%, 3.7% and 6.3% respectively 38.6%, 27.3% and 19.3% respectively
Davenport et al ²⁰ (2010); population-based retrospective cohort study using perinatal database (2000-2009)	Data on 36,597 women without type 1 diabetes, with singleton pregnancies who gave birth in Ontario, Canada	Pre-pregnancy BMI calculated from information taken from medical records and method of collection <i>not stated</i> GWG defined as excessive if pre-pregnancy weight to delivery weight was ≥ 20 kg	Change in prevalence of type 2 diabetes, GDM and impaired glucose tolerance (IGT) from diagnosis entered in database between 2000 and 2009	Pregnancies affected by type 2 diabetes increased significantly from 0.5% in 2000 to 0.9% in 2009 Prevalence of GDM increased from 2.9% to 4.2% Prevalence of IGT increased from 0.7% to 1.2% The prevalence of overweight and obesity did not significantly change over the time period, however, there was a positive association between BMI and glucose disorders	p =0.001 p =0.002 p =0.001 p ⁶ =0.79 for overweight and p =0.43 for obesity
Doherty et al ¹⁰ (2006); retrospective analysis of hospital-based data collected in a randomised controlled trial on the use of ultrasound imaging (1989-1991)	Data on 2,827 women with singleton pregnancies recruited in a Perth hospital setting in Australia . Data arose from baseline questionnaires administered at enrolment and medical records	Pre-pregnancy BMI method of data collection <i>not stated</i>	Included pre-existing maternal diabetes and/or development of GDM Chronic hypertension or onset of preeclampsia	Compared with normal weight women, obese women were more likely to develop: GDM Gestational hypertension Preeclampsia	OR ⁷ 6.5 (95% CI;3.32-12.74) (7.93; 4.74-13.27) and (3.74; 1.95-7.17) respectively
Fortner et al ⁶ (2009); hospital-based prospective cohort study (2000-2004)	1,043 self-identified Latina women who were recruited into the Latina GDM Mellitus Study at a single hospital in the US prior to 24 weeks gestation	Pre-pregnancy BMI calculated from <i>self-reported</i> weight at last menstrual period and height reported during first visit GWG calculated from last recorded weight prior to delivery less pre-pregnancy weight and classified as inadequate, adequate or excessive	Gestational hypertension defined as two blood pressure measurements $> 140/90$ mm Hg Preeclampsia defined as above with additional proteinuria	Obese women had a higher risk of a hypertensive disorder of pregnancy and preeclampsia, compared with women with normal pre-pregnancy BMI. Women with excessive GWG had higher risk of a hypertensive disorder of pregnancy and preeclampsia compared with women achieving weight gain guidelines	OR ⁸ 2.5 (95% CI; 1.3-4.8) and (2.7; 1.2-5.8) respectively (2.9; 1.1-7.2) and (4.2; 1.2-14.5) respectively

⁵ Unadjusted

⁶ Adjusted for maternal age, parity and pre-pregnancy BMI

⁷ Adjusted for maternal age and parity

⁸ Adjusted for parity and age

Frederick et al ¹⁶ (2006); clinic based prospective cohort study (1996-2002)	Data on 1,644 pregnant women drawn from the Omega study (which examines maternal dietary and other risk factors of preeclampsia and GDM) who were interviewed. Hospital labour and delivery records reviewed (US)	Pre-pregnancy BMI calculated from <i>self-report</i> of weight 3 months before index pregnancy and height at 18 years BMI at 18 years from <i>self-reported</i> information on height and weight. Weight cycling defined as the number of times women intentionally lost and unintentionally gained at least 6.8 kg (not related to pregnancy)	Preeclampsia defined as sustained blood pressure reading of $\geq$ 140/90 mm Hg (or a sustained increase of 15 mm Hg diastolic or 30 mm Hg systolic pressure above first trimester values, with proteinuria	Relative to women with stable weight, women who gained 5.0-9.9 kg had an increased risk of preeclampsia The risk for women who gained > 10 kg was higher Intentional weight cycling was not associated with increased risk of preeclampsia	RR ⁹ 2.6 (95% CI; 1.0-6.7) (5.1; 2.2-12.2) (1.1 ¹⁰ ; 0.6-1.8)
Hedderson et al ¹⁷ (2008); case-control study (1996-1998)	Cases and controls selected from a multiethnic cohort (N =14,235) who delivered a live birth. GDM cases (n =251) and controls (n =204) from participants in a northern Californian medical care program spanning 15 hospitals and 23 outpatient clinics (US)	To determine weight gain in the 5 years before pregnancy, body weights were assessed at 2 time points; baseline (the earliest measured non pregnant weight in the 5 years before the index pregnancy and pre-pregnancy weight which was <i>self-reported</i> on prenatal form for the index pregnancy	Case definition: A GDM case was defined as having 2 out of 4 abnormal plasma glucose values obtained during a 100-g glucose, 3h oral glucose tolerance test, according to the National Diabetes Data Group criteria	Compared with women with stable weight, women who gained weight at a rate of 1.1 to 2.2 kg/year had small increased risk of GDM Women who gained weight at a rate of 2.3 to 10.0 kg/yr were at higher risk	OR ¹¹ 1.63 (95% CI; 0.95-2.81) (2.61; 1.50-4.57)
Kongubol and Phupong ¹¹ (2011); case-control study for prospective evaluation (2009-2010)	240 women aged 20-34 years with no chronic medical conditions, no history of GDM, no family history of diabetes and no history of foetal macrosomia and no metabolic syndrome. Recruited in Bangkok, Thailand . Half of the women with normal BMI became controls (n =120) & women were with BMI $\geq$ 27.5 kg/m ² in the study group (n =120)	Pre-pregnancy BMI method of data collection <i>not stated</i>	Case definition: GDM diagnosed with two-step diagnostic procedures (50-g glucose challenge test at 24-28 weeks and 100-g glucose tolerance test as indicated) Preeclampsia defined as new onset hypertension (BP $\geq$ 140/90 mmHg after 20 weeks gestation) Gestational hypertension, as above with no proteinuria Foetal macrosomia defined as birthweight $\geq$ 4000g	Compared to normal weight women, obese women had no increased risk for: GDM Preeclampsia, or Foetal macrosomia Obese women were at greater risk for gestational hypertension	RR ¹² 0.9 (95% CI; 0.6-1.4) (0.7; 0.2-3.3) (1.4; 0.5-4.3) (12.0; 1.6-90.8)

⁹ Adjusted for maternal age, ethnicity/race, parity, educational attainment, and weight at age 18 years

¹⁰ Adjusted for maternal age, ethnicity/race, parity, BMI at age 18, and weight change since age 18 years

¹¹ Adjusted for age, race/ethnicity, baseline BMI and parity

¹² Unadjusted

Murakami et al ¹² (2005); hospital-based retrospective cohort study (2001)	Data on 633 women who delivered singleton babies (24-42 weeks gestation) in a large Japanese hospital in Sakarta with a larger proportion of high-risk mothers and children than surrounding hospitals	BMI calculated from <i>self-report</i> of pre-pregnancy weight during an interview at first outpatient visit. Height was measured at the same time.	GDM Preeclampsia Caesarean delivery Preterm delivery	Compared with women who had normal pre-pregnancy BMI, women with BMI ≥ 25 were at higher risk of GDM Preeclampsia Caesarean delivery Underweight and BMI ≥ 25 had greater odds (though not statistically significant) of preterm birth compared with normal weight women	OR ¹³ 7.94 (95%CI; 2.09-30.18) (8.13; 3.78-17.49) (2.42; 1.05-5.58) (1.55; 0.58-4.15) and (1.10; 0.33-3.65) respectively
Ogonowski et al ¹⁹ (2009); case control study for retrospective evaluation (2001-2005)	Data on 1,121 women with GDM (cases) referred to an outpatient clinic for diabetic pregnant women, and 1,011 healthy pregnant women (controls). All the women were Caucasian and had singleton pregnancies (Poland)	Pre-pregnancy BMI calculated from most recent <i>measured</i> weight before conception and height measured at first visit	Case definition: GDM diagnosed by two-step diagnostic procedure using a glucose challenge test and a 75-g oral glucose tolerance test	Excepting underweight, compared with BMI 18.5-20.9 kg/m ² significant relationships between all pre-pregnancy BMI ranges (including normal weight women) were associated with GDM. BMI was the strongest predictor for GDM treated with insulin. The percentage of women requiring insulin therapy significantly increased with an increase of BMI categories	Range: BMI 21-22.9 kg/m ² OR ¹⁴ 1.21 (95% CI; 1.01-1.48) to BMI 30.0-34.9 kg/m ² (3.51; 2.21-5.39) and BMI < 35 kg/m ² (9.01; 3.47-23.3) P =0.0055 for trend across the groups
Rosenberg et al ¹³ (2003); population-based cohort data from birth certificates (1998-1999)	213,208 women who delivered singleton babies, with New York City birth files that included information about pre-pregnancy weight (USA)	Pre-pregnancy BMI based on <i>self-reported</i> weight and height	GDM Preeclampsia Caesarean delivery	Compared with women who weighed 45-67 kg, women > 136 kg had higher risk for: GDM Preeclampsia Caesarean delivery	OR ¹⁵ 5.2 (95% CI; 3.8-7.2) (5.0; 3.5-7.1) (2.7; 2.2-3.4)
Samuels-Kalow et al ⁵ (2007); subset of a population-based cohort study (1975-1976)	Data on 13,722 Jewish women (consecutive births) in the Jerusalem Perinatal Study (Israel) Long-term follow-up conducted by data linkage with national registries	BMI calculated from pre-pregnancy weight and height <i>self-reported</i> at interview.	Hypertensive disorders of pregnancy (HDP) defined as gestational hypertension (systolic BP ≤ 140 mm Hg or diastolic BP ≤ 90 mmHg) or preeclampsia defined as gestational hypertension with proteinuria and oedema	Compared with normal weight women, overweight and obese women were at increased risk for HDP Compared with normal weight women there was a greater increase in risk of death after HDP among overweight and obese women	OR ¹⁶ 2.82 (95% CI; 2.40-3.31) and (5.51;4.15-7.31) respectively Normal weight - HR 1.26 (0.74-2.14), overweight (1.86; 1.07-3.20) and obese (2.90; 1.28-6.58) respectively

¹³ Adjusted for maternal age, parity, smoking, weight gain during pregnancy, gestational weeks

¹⁴ Adjusted for all GDM, GDM treated with diet and GDM treated with insulin

¹⁵ Adjusted for maternal age, race or ethnicity, marital status, education, parity, social risk, trimester prenatal care began and prenatal care payer

¹⁶ Adjusted for age

Villamor and Cnattingius ¹⁴ (2006); retrospective analysis of cohort data from national birth registry (1992-2001)	Data on the first two consecutive births of 151,025 women in the Swedish Birth Registry to examine associations between change in pre-pregnancy BMI and adverse outcomes in the second pregnancy	Inter-pregnancy BMI weight change was calculated as the difference between BMI at the first antenatal visit of the first and second pregnancies. Method of assessment of BMI <i>not stated</i>	GDM Gestational hypertension Preeclampsia Caesarean delivery	Compared with women with BMI change between -1.0 and 0.9 units, women who gained 3 or more units were at higher risk for: GDM Gestational hypertension Preeclampsia Caesarean delivery	OR ¹⁷ 2.09 (95% CI; 1.68-2.61) (1.76; 1.39-2.23) (1.78; 1.52-2.08) (1.32; 1.22-1.44)
Whiteman et al ¹⁸ (2011); retrospective analysis of population-based cohort data from maternally linked data files (1989-2005)	232,272 women with two consecutive live, singleton birth (20-44 weeks gestation) in the Missouri vital record system (US)	Pre-pregnancy BMI calculated from <i>self-reported</i> weight and measured height at first prenatal visit Inter-pregnancy weight change using categories from first and second pregnancy BMI groups e.g. obese-obese, obese-normal	Development of gestational or type 2 diabetes during the second pregnancy	Across all BMI categories, mother s with significant weight gain (moving from a lower to a higher category) had increased risk for development of diabetes Greatest increase in risk was among women who moved from normal to obese pre-pregnancy weight Mothers with stable BMI's and those who moved to a lower category had reduced risk (for example: underweight-underweight, obese-normal; overweight-normal	OR ¹⁸ 3.21 (95% CI; 2.76-3.73) (0.42; 0.19-0.92), (0.21; 0.09-0.50) and 0.46; 0.32-0.67) respectively

¹⁷ Adjusted for baseline BMI (at first pregnancy), height, inter-pregnancy interval, and maternal characteristics at second pregnancy, including age, country of origin, years of education, year of delivery, and smoking

¹⁸ Adjusted for maternal age, maternal race, education, marital status, smoking and drinking during pregnancy, prenatal care, inter-pregnancy interval and first pregnancy BMI

2.3.1.2 Maternal pre-pregnancy adiposity and preterm birth

Fifteen cohort studies were included in this review. They investigated associations between maternal pre-pregnancy adiposity and preterm birth, representing a combined sample of over one million women (N=1,485,508). Eleven of the studies were undertaken in the US (N=1,081,341), one of which included only African American women (n=59,000). Three of the American studies examined the effect of racial differences between black, white and Hispanic women. A Scottish study provided a sample of 187,290, a Swedish study had a sample of 167,750, a study of women in Argentina included 46,964 women, and an Iranian study had 2,163 participants. Seven of the 15 studies were clinic or hospital-based and the remaining eight studies used population-based samples. A further two studies with case-control designs are included; one arising from data in the US and the other in Canada.

All of the studies define the outcome measure of preterm birth as delivery of an infant prior to 37 completed weeks of gestation, however, many do not differentiate between preterm births that occur spontaneously and those that are due to medically indicated interventions. The differentiation is important because of the many factors that are taken into consideration in the clinical decision to end a viable pregnancy prior to term. Maternal obesity carries an increased risk of diabetes, hypertension and cardiovascular disease (Tables 2.1 and 2.7), each of which may increase the likelihood of medically induced preterm birth.

Cnattingius et al²¹ examined pregnancy outcomes among 167,750 Swedish women and compared with lean women, they reported a higher correlation between pre-pregnancy obesity and very preterm birth (< 32 weeks gestation) among nulliparous women (OR 1.6; 95% CI; 1.1-2.3). Preterm birth was classified as very preterm or moderately preterm (33-36 weeks) but the study did not differentiate between spontaneous and medically induced births. However, among early preterm births, except where a clinical decision is taken to end the pregnancy to preserve maternal life, it is unlikely that a large proportion of the births were induced prior to 32 weeks, given the probability of serious risk to the infant's health due to prematurity.

Other studies that have found an association between pre-pregnancy overweight or obesity and preterm birth show that these exposures increased the risk of *medically induced births only*, whereas increasing body mass index demonstrated an apparent protective influence

against spontaneous preterm birth. In Scotland ($n = 187,290$), Smith et al²² reported that compared with normal weight women, the risk of medically induced preterm delivery increased with increasing maternal pre-pregnancy BMI among nulliparous women (BMI 30-34.9 kg/m²: OR 1.52; 95% CI: 1.31-1.77, BMI ≥ 35 kg/m²: 2.13; 1.75-2.58) however, the risk of spontaneous preterm labour decreased (BMI 30-34.9 kg/m²: OR 0.85; 95% CI: 0.73-0.99, BMI ≥ 35 kg/m²: 0.81; 0.64-1.03). In the US, using population based data on 169,881 women, Johnson et al²³ reported that underweight and lean women (BMI < 19.8) had a significantly higher risk of preterm birth (OR 1.4; 95% CI: 1.3-1.5) and overweight and obese women had a decreased risk (OR; 0.9; 95% CI: 0.8-0.9 and 0.8: 0.8-0.9 respectively). While the results seemed to demonstrate that overweight and obesity were protective against preterm birth, the study included all preterm births and did not examine the effect of BMI categories on spontaneous and medically induced preterm births separately.

Among self-reported data on 59,000 black women in the United States²⁴ (recruited via a lifestyle magazine aimed at black women), again the risk of medically induced preterm birth increased with increasing pre-pregnancy waist circumference (WC), (compared with women who had a WC < 27 inches, women with a waist > 35 inches had almost a three-fold risk of medically induced preterm birth: OR 2.8; 95% CI: 1.68-4.77) while underweight black women were not at statistically significantly increased risk of spontaneous or medically induced preterm birth, though the results were borderline (OR 1.69; 95% CI 0.99-2.87 and 1.70; 0.90-3.21 respectively). A study of generally white, well-educated, affluent women in Washington State, Rudra et al²⁵ found that each 5 kg/m² increase in BMI was associated with a 71% increase in medically induced preterm birth. An attenuated association remained after adjustment for hypertension and diabetes before and/or during pregnancy (OR 1.40; 95% CI: 1.20-1.75).

Other studies in this review provide consistent evidence of associations between lean maternal pre-pregnancy status and an increased risk for preterm birth. Lean or underweight BMI is generally defined according to the WHO recommendation of < 18.5 kg/m², however, alternative definitions adopted in these studies include < 19.8 kg/m² and < 20 kg/m². In a hospital-based prospective cohort study, Hauger et al²⁶ found that the risk of preterm delivery decreased as maternal BMI increased among 46,964 women in Argentina, and the highest risk was among underweight (BMI < 18.5 kg/m²) women (OR 1.45; 95%

CI; 1.26-1.67). Haas et al²⁷ used a prospective cohort study design to demonstrate that compared with normal weight women, women who were underweight (BMI < 18.5 kg/m²) prior to pregnancy had more than double the risk of preterm delivery (OR; 2.30; 95% CI 0.96-5.53).

Salihu et al²⁸, using data on 437,403 singleton births from the Missouri vital data system, stratified lean women to mildly (BMI < 17-18.5 kg/m²), moderately (BMI 16-16.9 kg/m²) and severely underweight (BMI ≤ 15.9 kg/m²) categories and found that when compared to normal weight women, the risk of spontaneous preterm delivery increased in a dose response fashion (mildly underweight OR 1.33; 95% CI; 1.37-1.45, moderately underweight 1.49; 1.41-1.58 and severely underweight 1.60; 1.47-1.74). Severely underweight mothers (BMI ≤ 15.9 kg/m²) with very low (< 0.12 kg/week) and very high (> 0.79 kg/week) weight gain were at greatest risk for spontaneous preterm birth (OR 5.06; 95% CI; 2.61-9.81 and 5.50; 2.42-10.6 respectively). A similar finding was reported by Simhan et al²⁹, again in the US, who found that compared with women who had a pre-pregnancy BMI of 22 kg/m², BMIs of 14, 16, 18 and 20 kg/m² were inversely associated with higher risk (ORs: 2.8, 1.9, 1.4 and 1.2 respectively). Kosa et al³⁰ demonstrated that BMI categories may obscure the preterm delivery risk associated with low-normal BMI (e.g. 19kg/m²). Higher BMI up to 24kg/m² was increasingly protective against preterm delivery, beyond which higher BMI became detrimental.

Six of the studies considered the impact of GWG in addition to pre-pregnancy BMI on the risk of preterm birth. In 1990, the IOM made recommendations for appropriate weight gain during pregnancy according to maternal pre-pregnancy weight⁷. The guidelines are as follows: Underweight (BMI < 19.8 kg/m²): recommended pregnancy weight gain from 12.5-18 kg, Normal (BMI 19.8-29.9 kg/m²): 11.5-16 kg, Overweight (BMI 25-29.9 kg/m²): 7-11.5 kg, Obese (BMI ≥ 30 kg/m²): ≥ 6.8 kg. The IOM guidelines further recommend that black American women and adolescents should gain weight at the upper end of each range and that women of short stature (< 157 cm) should aim for the lower end.

Dietz et al³¹ examined routinely collected data on 113,019 women in the US and the strongest association for preterm birth was among women who were underweight prior to their pregnancy (BMI < 19.8 kg/m²) and had very low weight gain (< 0.12 kg/week) during their pregnancy (OR 9.8; 95% CI; 7.0-13.8). Similar findings were reported by Schieve et al³² in a smaller US study (n = 3,511) which found that low GWG (0.5 lb/week or 0.23

kg/week) increased risk for women across all BMI categories, but the association with the greatest magnitude was among underweight ($\text{BMI} < 19.8 \text{ kg/m}^2$) women (OR 6.7; 95% CI; 1.1-40.6). Maroosi et al³³ studied 2,163 Iranian women and compared with average weight women (not defined) who had average GWG (not defined), the risk of preterm delivery was increased among women with average BMI and low GWG ($< 0.16 \text{ kg/week}$) (OR 2.47; 95% CI; 0.98-6.28). They reported a non-significant increase in risk among women with low BMI (not defined) who had high GWG (not defined) (OR 2.03; 0.44-9.31 respectively). Schieve et al³⁴ analysed surveillance data on 266,172 women and found that risk for preterm birth increased with lower GWG among lean women ($< 25^{\text{th}}$ percentile; 0.26 kg/week) and higher GWG among obese women ($> 75^{\text{th}}$ percentile 0.46 kg/week). Compared to women with intermediate weight gain ($0.35 - < 0.46 \text{ kg/week}$), the highest risk for preterm birth was among underweight women ($\text{BMI} < 19.8 \text{ kg/m}^2$) who gained $< 0.10 \text{ kg/week}$ (risk difference +9.5%; 95% CI +6.5, +12.4). In a case-control study of Canadian women (cases=244 and controls=311) Kramer et al³⁵ found that short stature ($\leq 157.5 \text{ cm}$), low pre-pregnancy BMI ($< 19.8 \text{ kg/m}^2$) and low GWG ($< 0.27 \text{ kg/week}$) were associated with spontaneous preterm birth (OR 1.85; 95% CI; 1.25-2.74, 2.63; 1.09-2.44 and 1.74; 1.16-2.62 respectively).

Three of the US studies stratified their data to compare risk among white, black and Hispanic women. Using data on 12,459 women (white $n=4,898$, black $n=5,382$, Hispanic $n=2,179$), Hickey et al³⁶ found that low pre-pregnancy BMI ($< 16.5 \text{ kg/m}^2$) increased risk for pre-term birth among white and black (OR 3.6; 95% CI; 2.0-6.4 and 1.9; 0.9-4.0 respectively), but not Hispanic women and the authors concluded that Mexican immigrants may bring a cultural orientation towards protective lifestyle behaviours including less smoking and drinking and better diet. Simhan et al²⁹ on the other hand, found that underweight ($\text{BMI} < 18.5 \text{ kg/m}^2$) had a greater impact on preterm birth among black and Hispanic women but not among white women. They analysed their data on 13,917 women taking BMI as a continuous, rather than a categorical variable. In an analysis of 169,881 birth certificate records, Johnson et al²³ found overall that black and Hispanic women had a higher risk of preterm birth compared with white women when obesity, diabetes, hypertension, and prenatal care were controlled for (OR 2.5; 95% CI; 2.4-2.6 and 1.4; 1.2-1.5 respectively).

Summary

The evidence presented by most of the studies, and its consistency, suggests that pregnancies exposed to low pre-pregnancy BMI, particularly those with additional risk factors of low or high weight gain during the pregnancy and maternal ethnicity of a minority group, are at increased risk of spontaneous preterm birth. Obesity on the other hand, may increase the risk of medically induced preterm birth.

Table 2.2 Maternal pre-pregnancy adiposity and preterm birth

Author, Year Published, Study Design and Study Date	Sample Size, and Setting	Main pre-pregnancy and pregnancy exposures	Main outcome variable/s or case definition	Main study findings	Reported Statistics
Chen et al ³⁷ (2009); clinic-based retrospective cohort study (1959-1966)	Data on 1,892 women from the Collaborative Perinatal Project (CPP) which enrolled women at 15-18 weeks gestation in 12 US medical centres who had two consecutive singleton pregnancies (the first of which resulted in live birth)	Pre-pregnancy BMI calculated from <i>self-reported</i> height and weight obtained at first prenatal visit Weight change between pregnancies categorised as BMI decrease, stable BMI and BMI increase	Preterm birth defined as gestational age of < 37 completed weeks estimated from last menstrual period	BMI reduction between pregnancies was associated with a non-significant increased risk of preterm birth BMI increase had effects close to null Estimates associated with BMI reduction were higher in women whose index pregnancy ended preterm Estimates also higher in those with BMI < 25 kg/m ² at the index pregnancy	HR ¹⁹ 1.17 (95% CI; 0.90-1.53) (1.08; 0.83-1.41) (1.49; 0.90-2.44) (1.30; 0.98-1.71)
Cnattingius et al ²¹ (1998); population-based cohort study from birth register data (1992-1993)	Data on 167,750 singleton pregnancies recorded in the Swedish Medical Birth Register that had information on pre-pregnancy BMI	Pre-pregnancy BMI calculated from <i>self-reported</i> weight and height at the first antenatal visit	Very preterm birth ($\leq$ 32 weeks) Preterm birth (< 37 weeks completed gestation)	Among nulliparous women risk of very pre-term birth was higher among obese women, compared with lean women Whereas among parous mothers, obese women seemed to have lower risk compared with lean women	OR ²⁰ 1.6 (95% CI; 1.1-2.3) (0.8; 0.6-1.1)
Dietz et al ³¹ (2006); retrospective cohort study using routinely collected population based data system (1996-2001)	Data from Pregnancy Risk Monitoring System (PRAMS) on 113,019 women from 21 states in the US on maternal attitudes and experiences before, during and shortly after pregnancy from mailed questionnaires	Pre-pregnancy BMI calculated from <i>self-reported</i> height and weight Total GWG recorded on birth certificates	Very preterm birth (20-31 weeks); moderately preterm (32-36 weeks); and term birth (37-44 weeks) calculated from information on birth certificates and PRAMS data	There was an association between very low GWG and preterm birth, that varied by pre-pregnancy BMI The strongest association was among underweight women The weakest association was among very obese women.	OR ²¹ 9.8 (95% CI; 7.0-13.8) (2.3; 1.8-3.1)

¹⁹ Adjusted for centre, maternal age at pregnancy, race, maternal smoking during pregnancy, socio-economic index, marital status and inter-pregnancy interval

²⁰ Adjusted for maternal age, education, cigarette smoking, height and whether the mother was living with the father

²¹ Adjusted for maternal race-ethnicity, Medicaid recipient, parity, and marital status

Haas et al ²⁷ (2005); data from a clinic-based cohort of pregnant women (2001-2002)	Data from Project WISH (Women and Infants Starting Healthy) on 1,619 women from San Francisco Bay (US) area who delivered a singleton infant and completed 4 telephone surveys during pregnancy	Pre-pregnancy BMI calculated from <i>self-reported</i> height and weight	Preterm delivery (< 37 weeks completed gestation)	Compared with normal weight women, women who were underweight prior to pregnancy were at higher risk of preterm birth Women who reported poor physical function during the month before conception had a higher risk of preterm birth	OR ²² 2.30 (95% CI; 0.96-5.53) (1.97; 1.19-3.30)
Hauger et al ²⁶ (2008); hospital-based cohort study using prospectively recorded data (2003-2006)	46,964 women who delivered in 10 public hospitals in Argentina and who had a live birth of at least 22 weeks gestation and information on pre-pregnancy BMI	Pre-pregnancy BMI calculated from <i>self-reported</i> pre-pregnancy weight and height measured at 1 st prenatal visit.	Preterm birth defined as birth before 37 weeks gestational age (the interval between first day of LMP and infant birth date)	The risk of preterm delivery decreased with increasing BMI Highest risk for preterm birth was among underweight women.	OR ²³ 1.45 (95% CI; 1.26-1.67)
Hickey et al ³⁶ (1997); prospective clinic-based multicentre trial (1982-1986)	Data on a total of 12,459 women; 5,382 black, 4,898 white and 2,179 Hispanic women from primarily low-income populations who registered for prenatal care across 5 states in the US and delivered a live singleton infant at 20-42 weeks gestation	Pre-pregnancy BMI obtained from <i>self-reported</i> weight and measured height documented in medical records	Preterm birth defined as delivery < 37 weeks gestation (late preterm 33-36 weeks, early preterm 20-32 weeks) Categorised as due to: 1. spontaneous preterm labour without ruptured membranes, 2. spontaneous rupture of membranes followed by labour, and 3. medically indicated preterm birth	20.1% of black, 28.6% white and 11.7% Hispanic women were underweight Prevalence of preterm delivery was 8.1% in black, 7.3% in white and 4.8% in Hispanic women Low pregravid BMI was associated with increased risk of late pre-term delivery among black and white, but not Hispanic women Low pregravid BMI was associated with increased risk of spontaneous preterm labour among black and white (but not Hispanic women)	OR ²⁴ 1.9 (95% CI; 0.9-4.0) and (3.6; 2.0-6.4) respectively (2.6; 1.1-5.9) and (4.1;2.1-8.0) respectively
Johnson et al ²³ (2009); population-based sample of birth certificate records (1998-2000)	169, 881 records that contained maternal and neonatal anthropometrics of singleton births from the state of Missouri (US)	Pre-pregnancy BMI calculated from <i>self-reported</i> height and weight in birth records	Preterm delivery defined as birth < 37 weeks gestation	Overweight and obese women had decreased risk compared with BMI < 19.1 Black and Hispanic women had a higher risk of preterm birth compared with white women	OR ²⁵ 0.9 (95% CI; 0.8-0.9) and (0.8; 0.8-0.9) respectively OR ²⁶ 2.5 (95%CI;2.4-2.6) and (1.4; 1.2-1.5) respectively

²² Adjusted for age, country of birth, race/ethnicity, level of education, parity, site of care, body mass index, physical function prior to and during pregnancy, depressive symptoms prior to and during pregnancy, health conditions prior to and during pregnancy, level of exercise during the month prior to pregnancy, other pregnancy complications, use of illicit drugs during pregnancy and inadequate prenatal care

²³ Adjusted for age, parity, smoking, history of chronic hypertension, history of diabetes mellitus, previous caesarean delivery, number of prenatal visits, gestational diabetes and preeclampsia

²⁴ Adjusted for maternal age, education, smoking, previous spontaneous pre-term delivery, parity, last birth within 1 year and height

²⁵ Unadjusted

²⁶ Adjusted for obesity, diabetes, hypertension and prenatal care

Kosa et al ³⁰ (2011); participants from a nested, population-based case-control study (2002-2003)	354 preterm cases and 710 term normal birthweight controls in the Juggling Work and Life During Pregnancy designed to examine maternity leave, stress and pregnancy outcomes from employed participants in a prenatal screening program in California (US) who undertook a telephone interview	Method of collection of components of pre-pregnancy BMI <i>not stated</i>	Case definition: pre-term delivery (delivery < 37 weeks gestation). Gestation estimated from information in medical records	Preterm delivery was significantly associated with pre-pregnancy underweight category BMI categories obscured the preterm delivery risk associated with low-normal (19 kg/m ²), overweight and obese BMI Higher BMI up to 24kg/m ² was increasingly protective of preterm delivery, beyond which higher BMI became detrimental	OR ²⁷ 2.11 (95% CI; 1.03-4.32) For women with BMI ≤ 24 kg/m ² , each unit increase in BMI reduced odds of preterm birth (0.81; 0.73-0.91) Women with BMI > 24 kg/m ² the odds of preterm birth increased with increasing BMI relative to BMI of 24 kg/m ² (BMI 29 kg/m ² : 1.07; 1.02-1.13) (BMI 34 kg/m ² : 2.01; 1.20-3.39)
Kramer et al ³⁵ (1995); case-control study (1990-1992)	555 women recruited and interviewed face to face in Montreal, Canada . 244 cases of idiopathic preterm delivery and 311 controls matched by race and smoking history	Pre-pregnancy BMI calculated from <i>self-reported</i> height and weight during interviews	Case definition: spontaneous onset of labour before 37 completed weeks	Short stature, low pre-pregnancy BMI, and low rate of GWG were associated with idiopathic preterm birth	OR ²⁸ 1.85 (95% CI; 1.25-2.74), (1.63; 1.09-2.44) and (1.74; 1.16-2.62) respectively
Marsoosi et al ³³ (2004); retrospective cohort study (2001-2003)	Data on 2,163 women receiving care in University Hospital clinics in Tehran, Iran	Method of collection of components of pre-pregnancy BMI and GWG <i>not stated</i> Low GWG defined as 0.16 kg/week	Pre-term delivery defined as birth before 37 weeks of completed gestation	Pregnancy weight gain was inversely related to pre-pregnancy BMI Compared with women who had average pre-pregnancy BMI and average GWG, the risk of preterm delivery was increased among two groups: average BMI with low GWG and low BMI with high GWG	Weight gain (kg/week) Mean ± S.D. Low BMI: 0.38 ± 0.15 Average BMI: 0.36 ± 0.16 High BMI: 0.32 ± 0.16 OR ²⁹ 2.47 (0.98-6.28) and (2.03; 0.44-9.31)
Rudra et al ²⁵ (2008); prospective analysis on data from a clinic-based cohort study (1996-2005)	2,468 participants attended prenatal care clinics in Washington state (US) in a study primarily designed to examine risk factors for preeclampsia and took part in a structured interview	Pre-pregnancy BMI calculated from <i>self-reported</i> height and weight recalled to 3 months before pregnancy GWG in early pregnancy calculated from measured weight at 18-22 weeks, less pre-pregnancy weight	Spontaneous preterm delivery (delivery before 37 gestational weeks gestation) after spontaneous labour Indicated preterm delivery (from medical intervention)	Each 5 kg/m ² BMI increase was associated with indicated preterm delivery (independently of hypertension or diabetes) High early weight gain increases indicated preterm delivery risk among women with normal BMI, but not among overweight/obese women	OR ³⁰ 1.40 (95% CI; 1.12-1.75) (1.22 ³¹ ; 1.02-1.45) and (1.02; 0.87-1.20) respectively

²⁷ Adjusted for race, birth month, parity, marital status, nightly sleep hours and weight gain during pregnancy

²⁸ Unadjusted. Adjustment for parity, marital status, language, age and maternal education did not substantially alter point estimates

²⁹ Adjusted for age, education and parity

³⁰ Adjusted for maternal age, race/ethnicity, parity, history of chronic hypertension, pregnancy-induced hypertension or preeclampsia, and history of pre-pregnancy or gestational diabetes mellitus

³¹ Adjusted for above (at footnote 30) and pre-pregnancy BMI

Salihi et al ²⁸ (2009); retrospective population-based cohort study of maternally linked data files (1989-1997)	437,403 singleton live births recorded in the Missouri vital data system linked with birth certificate data (US)	Pre-pregnancy BMI calculated from <i>self-reported</i> weight at first prenatal visit and measured height used to define low and normal pre-pregnancy weight groups Weekly GWG defined as total gain divided by gestational age in weeks	Spontaneous preterm delivery (< 37 weeks gestation) Very preterm birth (< 33 weeks gestation)	Compared with normal weight women, mildly, moderately and severely underweight mothers were more likely to experience a preterm delivery For each BMI category, risk for spontaneous preterm birth increased among women with low GWG (< 0.12kg per week) Severely thin mothers with very low and very high weight gain were at greatest risk for spontaneous preterm birth	OR ³² 1.33 95% CI; 1.37-1.45), (1.49; 1.41-1.58) and (1.60; 1.47-1.74) respectively (5.06; 2.61-9.81) and (5.05; 2.42-10.6) respectively
Schieve et al ³² (2000); retrospective population-based cohort study (1988)	Data on 3,511 mother-infant pairs of singleton live births in the National Maternal and Infant Health Survey arising from 35-page questionnaires mailed in 48 states in the US	Pre-pregnancy BMI calculated from <i>self-reported</i> height and weight Rate of pregnancy weight gain derived from regression models using pre-pregnancy weight, gestational age and data from 14 to 28 weeks gestation	Delivery before 37 weeks of completed gestation	Compared with average weight women with average pregnancy weight gain women with low pregnancy weight gain were at increased risk and magnitude of risk which varied according to pre-pregnancy BMI: Low gain among underweight Low gain among average weight Low gain among overweight	OR ³³ 6.7 (95%CI 1.1-40.6) (3.6; 1.6-8.0) (1.6; 0.7-3.5)
Schieve et al ³⁴ (1999); retrospective population-based cohort study (1990-1993)	Data on 266,172 women who delivered a live born, singleton infant and participated in federally funded prenatal public health programs. Data recorded in the state-based Pregnancy Nutrition Surveillance System (PNSS) in the US	Pre-pregnancy BMI calculated from <i>self-reported</i> weight and measured height Pregnancy weight gain self-reported at postpartum visit	Preterm and very preterm delivery defined as < 37 and < 32 weeks completed gestation	Lower and higher pregnancy weight gains increased risk compared to intermediate weight gain. Compared with women gaining 0.35-< 0.46 kg/week, risk of preterm birth for women gaining < 0.10kg/week was greater for underweight women compared with average weight, overweight and obese women	RR ³⁴ +9.5% (+6.5, +12.4), (+6.7% ; +5.6, +7.9), (+3.5 %; +2.0 , +4.9) and (+0.4% ; -0.4,+1.2) respectively
Simhan et al ²⁹ (2006); retrospective clinic-based cohort study (1984-1989)	13,917 women from antepartum clinics in 7 centres in the US enrolled in the Vaginal Infections and Prematurity Study (VIPS) between 23 and 26 weeks gestation. Standard questionnaire and genital specimens.	Pre-pregnancy BMI based on <i>self-reported</i> weight and measured height	Spontaneous delivery occurring after preterm labour with intact membranes, or preterm pre-labour rupture of foetal membranes	Compared to women with BMI of 22, BMI of 14 almost tripled risk for preterm birth, and BMI of 16 nearly doubled risk Compared with BMI of 22, BMI's of 18 and 20 were associated with 40% and 20% increased risk Underweight had a greater impact on preterm birth among Blacks and Hispanics than among Whites	OR ³⁵ 2.8 (95%CI; 1.8-4.5) and (1.9; 1.5-2.6) respectively. (1.4;1.2-1.7) and (1.2; 1.1-1.2) respectively

³² Adjusted for maternal age, parity, race, smoking, education, marital status, adequacy of prenatal care, weight gain during pregnancy, gender of the infant and year of birth

³³ Adjusted for maternal age, parity, race-ethnicity, marital status, education, and prenatal smoking status

³⁴ Unadjusted. Results from multivariable models were not substantially different from unadjusted or stratified results.

³⁵ Adjusted for age, ethnicity, parity, smoking, height, education and marital status

Smith et al ²² (2006); retrospective population-based cohort study, using data linkage (1991-2001)	Data on 187,290 Scottish women who had a singleton live birth between 22 and 43 weeks gestation, from a registry with demographics and outcomes from maternity hospital and data linkage with a national register of perinatal deaths	Maternal BMI calculated from height and weight recorded in registers. Method of assessment <i>not stated</i> Demographics obtained from registry data	Preterm delivery defined as birth at < 37 weeks gestation. Elective delivery defined as a birth in which the woman did not experience spontaneous labour	Among nulliparous women, compared with normal weight women the risk of elective preterm delivery increased with increasing BMI, whereas risk of spontaneous preterm labour decreased Obesity and elective preterm delivery were only weakly associated among multiparous women	Elective preterm birth: (BMI 30-34.9 kg/m ² : OR ³⁶ 1.52 95% CI: 1.31-1.77, BMI ≥ 35 kg/m ² : 2.13; 1.75-2.58) Spontaneous preterm birth: (BMI 30-34.9 kg/m ² : 0.85; 0.73-0.99, BMI ≥ 35 kg/m ² : 0.81; 0.64-1.03).
Wise et al ²⁴ (2010); population-based prospective cohort study of women who subscribed to a women's lifestyle magazine aimed at African American women (1995- 2003)	The Black Women's Health Study of 59 000 African-American women aged 21-69 at baseline. Mailed periodical questionnaires for data on demographic, lifestyle, reproductive, and medical history over an 8 year period (US)	BMI calculated from <i>self-reported</i> pre-pregnancy weight and height Self-reported data on singleton births, preterm birth Pre-pregnancy waist circumference self-reported	Preterm birth defined as birth occurring "3 or more weeks early"	Compared to normal weight women, underweight women were not at statistically increased risk of spontaneous or medically induced preterm birth (borderline result) Compared to WC < 27 inches, increasing WC was positively associated with medically indicated preterm birth	OR ³⁷ 1.69 (95% CI: 0.99-2.87) and (1.70; 0.90-3.21) respectively WC 27-28.9 inches (1.76; 1.03-2.99) WC > 35 inches (2.83; 1.68-4.77)

³⁶ Adjusted for age, deprivation category, smoking, marital status, numbers of previous spontaneous early pregnancy losses and therapeutic abortions

³⁷ Adjusted for age, questionnaire cycle, marital status, education, smoking, parity, participant born preterm and previous preterm birth

2.3.1.3 Maternal pre-pregnancy adiposity and progress of labour and/or method of birth

It is generally accepted that spontaneous vaginal birth without complication or intervention is the most desirable method of birth. However, the caesarean section rate in Australia has increased by 50% over the last decade and is currently the method of birth for over 30% of deliveries.³⁸ The Australian caesarean section rate is similar to that in the US and higher than other developed countries (New Zealand: 23.7%, United Kingdom: 26.3%, Canada: 26.3% and the Netherlands: 13.5%).³⁹ A decision to undergo or perform a caesarean section delivery can involve many factors from preservation of maternal or fetal life, to maternal preference or even risk of exposure to malpractice litigation among clinicians.⁴⁰

This section of the review focuses on associations between maternal pre-pregnancy adiposity, progress of labour and method of birth reported in a total of 11 cohort studies. Nine studies summarised in Table 2.3 have caesarean section as a primary outcome and provide a total sample size of over 180,000 women. Six of the studies were undertaken in the US (N =163,096), a French study provided a sample size of 16,952 women, an Australian study had a sample of 6,528 women and a study in Japan had 915 participants. A study on 4,258 women in Denmark also considers associations between pre-pregnancy adiposity and interventions during labour (e.g. augmentation with oxytocin and artificial rupture of membranes) and a study on 612 women in the US compared the progression and duration of labour among women of different BMI categories.

The clear evidence from these studies is that pre-pregnancy overweight and obesity is associated with a higher risk of caesarean section delivery compared with women in leaner BMI categories. Barau et al.⁴¹ studied 17,462 women on a French Island (La Reunion) situated in the Indian Ocean and found a significant linear association (χ^2 linear trend, $p < 0.001$) between pre-pregnancy BMI and the odds of having a caesarean section delivery. Taking underweight women (BMI 15-19.9 kg/m²) as the referent group, women in all other BMI categories (20-24.9, 25-29.9, 30-34.9, 35-39.9, 40-44.9 kg/m²) were at significantly higher risk (OR's: 1.42, 1.89, 2.31, 2.71, 3.6 respectively). Dempsey et al.⁴² in their study of 738 nulliparous US women also showed that lean women (BMI < 20 kg/m²) had the lowest risk for caesarean section compared with other BMI categories. They reported a joint additive association between BMI and short stature (height < 163 cm). When compared with tall, lean women (height > 163 cm, BMI < 25 kg/m²), short, overweight

women (height < 163 cm, BMI > 25 kg/m²) were nearly three times more likely to have a caesarean delivery (RR 2.79; 1.72-4.52). Chichara et al⁴³ also reported among 915 Japanese women, that being underweight prior to pregnancy (BMI < 18.5 kg/m²) demonstrated a protective effect against caesarean section compared with normal weight women (BMI 18.5-24.9 kg/m²) (OR 0.5; 95% CI; 0.2-1.1), while overweight women had nearly three times the risk (OR 2.7; 95% CI; 1.4-5.4). This study adopted BMI categories recommended for Western women.

In a population-based cohort study in the US (n = 113,789), Getahun et al⁴⁴ studied the effect of changes in BMI between women's first two successive pregnancies. Compared with women with normal BMI in their first two pregnancies, women who increased their BMI between pregnancies had increased risk of primary caesarean section in the secondary pregnancy. For example, increases in BMI from normal (BMI 18.5- 24.9 kg/m²) to obese (BMI > 30 kg/m²), or from lean body mass (BMI < 18.5 kg/m²) to normal, increased the risk two to three-fold (OR; 1.96; 95% CI; and 1.71-2.26 3.04; 1.78-5.21 respectively). However, women who lowered their BMI from obese to overweight (BMI 25-29.9 kg/m²), or from overweight to normal had similar risk as women who had normal BMI in both the primary and secondary pregnancies (OR 1.16; 95% CI; 1.00-1.34 and 1.16; 1.05-1.28 respectively). In Australia, Manum et al⁴⁵ found that while pre-pregnancy overweight and obesity increased risk of caesarean compared to normal weight women, excessive GWG (defined as > 11.5kg) increased risk for all women (OR 1.29; 95% CI; 1.09-1.54).

It has been proposed that one biological pathway through which obesity affects the process of labour is related to dystocia due to the presence of increased soft tissue within the maternal pelvis. Young and Woodmansee⁴⁶ found that among 3,375 middle-class women attending their private obstetric practice in the US, obese women (BMI > 30 kg/m²) were over six times more likely than lean women (BMI < 20mg/kg²) to have a caesarean section indicated by cephalo-pelvic disproportion and failure to progress (OR 6.5; 95% CI: 6.2-6.9). Lean women with excessive GWG (> 35 lbs or 15.9 kg), had almost a four-fold increased risk of caesarean section compared with lean women who gained < 30 lbs (13.6 kg) (OR 3.8; 95% CI; 3-4.6). Using a population-based sample of surveillance data in the US, Dietz et al⁴⁷ compared nulliparous women who had identified medical, labour or delivery complications with those who had no complications. Among women with any complication (diabetes, hypertension, fever, meconium liquor, premature rupture of

membranes, placental abruption, placenta praevia, seizures during labour, precipitous labour, malpresentation, cord prolapse, anaesthetic complication, fetal distress, dysfunctional labour, prolonged labour (>20 h) and cephalo-pelvic disproportion) the RR for caesarean was 1.1 (95% CI; 1.0-1.2) among overweight women (BMI 26.1-29 kg/m²), 1.3 (95% CI; 1.1-1.4) among obese women (BMI > 29-34.9 kg/m²), and 1.4 (95% CI 1.2-1.6) among very obese women (BMI ≥ 35 kg/m²) compared with normal weight women (BMI 19.8-26 kg/m²). Among women without any complications, the RR was 1.4 (95% CI; 2.3-4.8) among overweight women, 1.5 (95% CI; 1.0-1.8) among overweight women, 1.5 (95% CI: 1.1-2.1) among obese women, and 3.1 (95% CI; 2.3-4.8) among very obese women. Reasons for the much greater risk for caesarean delivery among very obese women independent of complications of pregnancy or labour are not known, however, the results suggest when other risk factors for caesarean section exist increasing pre-pregnancy BMI only contributes a slight additional risk compared to normal weight women. It was unfortunate that the study could not differentiate between the number of caesareans that occurred before and after the onset of labour.

Interestingly, in their hospital-based study at a single Danish institution of 4,258 women, Jensen et al⁴⁸ found that while overweight and obese body mass index (taking BMI 20-24.9 as the referent category) was related to more oxytocin infusion (χ^2 $p < 0.05$) and early artificial rupture of membranes (χ^2 $p < 0.05$), there was no significant increase in instrumental or caesarean delivery, given a normal pregnancy. However, the prevalence of caesarean section among overweight and obese women was higher (10% and 11% respectively) than the prevalence among lean and normal weight women (4% and 6% respectively). The overall rate of caesarean section delivery with uncomplicated pregnancies at this institution also seemed comparatively low (primiparae -15% and multiparae – 12%). The findings that obesity is only a minor risk factor during delivery, may be a reflection of alternative models of medical decision making and care at this hospital. In addition, a larger sample size may investigate more thoroughly the trend towards more caesarean sections in the overweight and obese groups shown by the study.

The increased use of oxytocin infusion and artificial rupture of membranes in the above study may indicate that maternal overweight and obesity is related to inertia in the first stage of labour. This may be due to larger a foetus and subsequent cephalo-pelvic disproportion needing more contractions and time to overcome the obstruction (without

increased use of operative delivery). Vahratian et al⁴⁹ in their study of a sub-sample of 612 nulliparous women who were recruited to a population-based cohort study in the US, found that the mean duration of labour (from 4 to 10 cm cervical dilation) was significantly longer for overweight and obese women, compared with normal weight women (mean duration of labour 7.5, 7.9 and 6.2 hours respectively $p < 0.01$). These two studies together may suggest that it is important to consider differences in labour progression by maternal pre-pregnancy BMI before performing additional interventions.

Summary

Women who were overweight or obese prior to pregnancy had a higher risk of caesarean section delivery compared with women in leaner categories. However, it was also demonstrated that women in higher BMI categories had longer labours that were more likely to be augmented (perhaps due to their larger infants), that did not necessarily result in caesarean section.

Table 2.3 Maternal pre-pregnancy adiposity and progress of labour and/or method of birth

Author, Year, and Study Design and Study Year	Sample Size, and Setting	Main pre-pregnancy and pregnancy exposures	Main outcome variable/s or case definition	Main study findings	Reported Statistics
Barau et al ⁴¹ (2006); hospital based prospective cohort study (2001-2005)	Data on 16,952 women who delivered at a single hospital in France who had single live infants after 21 weeks gestation	Pre-pregnancy BMI calculated from weight and height recorded by a physician. Method of assessment <i>not stated</i>	Caesarean delivery	The caesarean section risk was lowest in leaner women and increased linearly as BMI increased (underweight, normal, overweight, obese, severe obese and very severe obese)	Adjusted ³⁸ χ^2 , $p < 0.001$
Chihara et al ⁴³ (2011); retrospective analysis of survey data (1998-2000)	Data from the Human Milk Survey on 915 Japanese nulliparous women carrying singleton babies from one city were interviewed in the third trimester and one month after delivery. The women were aged in their twenties and thirties	Pre-pregnancy BMI calculated from height and weight <i>self-reported</i> in the third trimester	Caesarean delivery (self-reported by the mother one month after delivery)	Overweight women were more likely to have a caesarean delivery compared to normal weight women. Underweight women were half as likely to have a caesarean delivery compared to normal weight women	OR ³⁹ 2.7 (95% CI; 1.4-5.4) (0.5; 0.2-1.1)
Crane et al ⁵⁰ (1997); population-based perinatal database (1994-1995)	Data on 20,130 women in the Central New York Regional Perinatal Data System containing all births in the region (US)	Pre-pregnancy BMI calculated from <i>self-reported</i> height and weight	Caesarean delivery	Obese women with singleton pregnancies and no prior caesarean deliveries were more likely than normal weight women to undergo caesarean	OR 1.66 (95% CI; 1.46-1.83)
Dempsey et al ⁴² (2005); hospital-based prospective cohort study (1996-2000)	Data on 738 nulliparous women who initiated pre-natal care prior to 16 weeks gestation, drawn from the Washington based Omega Study (designed to examine maternal dietary risk factors of preeclampsia and GDM) (US). Women participated in a structured interview. Pregnancy outcome information from medical records	Pre-pregnancy BMI calculated from <i>self-reported</i> weight and height during interview	Caesarean delivery	Women who were overweight were more likely to deliver their infants by caesarean section compared with lean women Obese women experienced higher risk The joint association between BMI and short stature was additive. When compared with tall, lean women, short overweight women were nearly three times more likely to have a caesarean delivery	RR ⁴⁰ 2.09 (95% CI; 1.27-3.42) (3.05; 1.80-5.18) (2.79 ⁴¹ ; 1.72-4.52)

³⁸ Adjusted for gestational diabetes, term deliveries, very short maternal height, primiparity and maternal age ≥ 35 years

³⁹ Adjusted for maternal age, smoking status, pregnancy complications and infant birthweight

⁴⁰ Adjusted for height (< 1.55 metres: yes/no), race/ethnicity (Asian: yes/no), maternal age (≥ 35 : yes/no)

⁴¹ Further adjustment for diagnosis of preeclampsia (yes/no), and diagnosis of gestational diabetes (yes/no)

Dietz et al ⁴⁷ (2005); data from a population-based surveillance system (1998-2000)	Data on 24,423 nulliparous women with single, term infants in the Pregnancy Risk Assessment Monitoring System (PRAMS). Randomly selected women in 19 states completed mailed questionnaires on attitudes and experiences before, during and shortly after pregnancy (US)	Pre-pregnancy BMI calculated from <i>self-reported</i> height and weight	Caesarean delivery	Among women with any complication, risk for caesarean was increased among overweight, obese and very obese women compared to normal weight women Among women without complications risk for caesarean was increased among overweight, obese and very obese women compared to normal weight women	OR⁴² (1.1; 95% CI; 1.0-1.2), 1.3; 1.1-1.4) and (1.4; 1.2-1.6) respectively (1.4; 1.0-1.8), 1.5; 1.1-2.1) and (3.2; 2.3-4.8) respectively
Getahun et al ⁴⁴ (2007); retrospective cohort study on maternally linked birth and infant death surveillance datasets (1989-1997)	Data on 113,789 women in a cohort with first 2 successive pregnancies and pre-pregnancy BMI recorded in the Missouri vital record system (US)	Pre-pregnancy BMI calculated from <i>self-reported</i> height and weight	Primary caesarean section in the secondary pregnancy	The rate of primary caesarean section in the secondary pregnancy was 9.2% Increases in pre-pregnancy BMI between first 2 pregnancies from underweight or normal to obese is associated with increased risk of caesarean section Women who lowered their BMI from obese to overweight, or overweight to normal had similar risk as women who had normal BMI in both pregnancies	OR⁴³ 3.04 (95% CI; 1.78-5.21) and (1.96; 1.71-2.26) respectively (1.16; 1.00-1.34) and (1.16; 1.05-1.28)
Jensen et al ⁴⁸ (1999); hospital-based retrospective study (1993-1998)	Data on 4,258 women who delivered a single child after an optimal pregnancy drawn from the hospital database of a single institution (Denmark)	Pre-pregnancy BMI calculated from weight and height in the database Method of measurement <i>not stated</i>	Interventions during labour (e.g. oxytocins, amniotomy, vacuum extraction forceps, caesarean, episiotomy)	More obese women experienced labour augmentation with oxytocins or early amniotomy compared with lean women The prevalence of instrumental delivery was not increased Non-significant trend towards more caesarean sections among overweight and obese groups compared with lean and normal weight women	57% vs 39% (p < 0.01)⁴⁴ 10% and 11% vs 4% and 6% respectively
Mamun et al ⁴⁵ (2011); prospective population-based cohort study (1981-1983)	Data on 6,528 mothers and infants from the Mater-University Study of Pregnancy (MUSP) and its outcomes. Women received antenatal care at a single institution and were assessed prospectively via questionnaires (Australia)	Pre-pregnancy BMI calculated from <i>self-reported</i> weight and height recorded at baseline from maternal questionnaires GWG assessed as average weight gain per gestational week. Weight gain < 11.5 kg classified as excessive	Method of birth (categorised as normal, caesarean and others) Pregnancy complications (hypertensive disorder of pregnancy or GDM) Preterm birth defined as gestation 21 to 36 weeks	Women who were overweight or obese prior to pregnancy and those who gained excess weight were at greater risk for pregnancy complications and caesarean section (compared with women in normal weight range) Women who gained inadequate weight or were underweight before pregnancy were at greater risk of preterm birth and lower risk of pregnancy complications	OR⁴⁵ 1.40 (95% CI; 1.13-1.75, (2.10; 1.74-2.54) and (1.29; 1.09-1.54) respectively (2.27; 1.71-3.00) and (0.58; 0.44-0.77) respectively

⁴² Adjusted for pre-pregnancy BMI, age, race, height, weight gain during pregnancy, infant birthweight, gestational age

⁴³ Adjusted for maternal age, race, education, marital status, prenatal care, smoking and inter-pregnancy interval

⁴⁴ Unadjusted

Vahratian et al ⁵¹ (2005); population-based prospective cohort study (1995-2002)	Data on 641 nulliparous women who were recruited to the North Carolina Pregnancy, Infection, and Nutrition (PIN) Study during their second trimester and completed telephone interviews and self-administered questionnaires. Information on pregnancy complications and delivery abstracted from medical records (US)	Pre-pregnancy BMI based on <i>self-reported</i> information or <i>measured</i> at enrolment if pregnancy was < 16 weeks gestation GWG calculated as weight at last prenatal visit less weight at the first prenatal visit	Caesarean delivery	Compared with normal weight women, the risk for caesarean was higher among overweight and obese women	RR ⁴⁶ 1.2 (95% CI; 0.8-1.8) and (1.5; 1.05-2.0) respectively
Vahratian et al ⁴⁹ (2004); population-based prospective cohort study(1995-2002)	Data on 612 nulliparous women who were recruited to the PIN Study during their second trimester and completed telephone interviews and self-administered questionnaires. Information on pregnancy complications and delivery abstracted from medical records (US)	Pre-pregnancy BMI based on <i>self-reported</i> information or <i>measured</i> at enrolment if pregnancy was < 16 weeks gestation GWG calculated as weight at last prenatal visit less weight at the first prenatal visit	Labour progression based on median duration of labour by each centimetre of cervical dilation	Median duration of labour from 4 to 10 cm was significantly longer for overweight and obese women, compared with normal-weight women	Mean duration of labour ⁴⁷ 7.5, 7.9 and 6.2 hours respectively (p < 0.01)
Young and Woodmansee ⁴⁶ (2002); clinic-based retrospective cohort study (1993-2001)	Data on 3,375 primiparous women who attended a private obstetric practice (US)	Pre-pregnancy BMI calculated from <i>self-reported</i> weight or <i>measured</i> weight before 20weeks gestation and <i>self-reported</i> height	Caesarean section	Compared with women with BMI < 20 kg/m ² , primiparous woman with BMI > 30 kg/m ² were at much greater risk of caesarean delivery	OR ⁴⁸ 5.8 (95% CI; 5.4-6.2)

⁴⁵ Adjusted for maternal age

⁴⁶ Adjusted for maternal height, education, weight gain during pregnancy, and labour induction

⁴⁷ Adjusted for maternal height, labour induction, membrane rupture, oxytocin use, epidural analgesia, net maternal weight gain and fetal size

⁴⁸ Unadjusted

2.3.1.4 Maternal pre-pregnancy adiposity and perinatal mortality/congenital malformations

During the second half of the 20th century, overall perinatal mortality in Western countries improved steadily with a decrease of 65-80% (using European, US, and Canadian hospital-based data) largely due to advances in medical management of serious problems of early life.⁵² One of the prominent remaining causes accounting for nearly 30% of current fetal and neonatal deaths is congenital malformations. This section reviews 12 studies that have investigated associations between maternal pre-pregnancy adiposity and serious or catastrophic pregnancy outcomes related to congenital malformations and perinatal mortality. Eight of the studies summarised in Table 2.4 examine relationships between pre-pregnancy BMI and selected congenital malformations (cardiac defects, neural tube defects and gastroschisis) and all but one have used case-control designs which are particularly appropriate for study of rare outcomes.⁵³ Six of the studies arise from data in the US (five case-control studies, one of which also includes Canadian data, and one prospective cohort study). Another two case-control studies describe women and occurrence of congenital malformations among their offspring in China and Australia. Four large cohort studies (3 population-based samples in the US, Sweden and Denmark and a hospital-based sample also in Denmark) focus on perinatal mortality as the primary outcome measure.

Maternal pre-pregnancy adiposity and perinatal mortality

The WHO defines perinatal mortality as deaths (fetal deaths and neonatal deaths) of babies of at least 500 grams birthweight or a gestational age of at least 22 weeks if birthweight is unknown, that occur up to 28 completed days after birth.⁵⁴ The Australian Bureau of Statistics recommends a slightly broader definition and includes babies of at least 400 grams birthweight or a gestational age of at least 20 weeks gestation.⁵⁵ Fetal deaths or 'stillbirths' are frequently categorised as early (20-28 completed weeks gestation) or late (more than 28 completed weeks gestation). Neonatal mortality refers to death of a live-born baby within 28 days since birth and these deaths are further categorised as early (within the first 7 days) or late (8-28 days). Post neonatal mortality is a term used to describe neonatal death after 28 days and up to 1 year. Together, early, late and post neonatal mortality are referred to as infant mortality (Figure 2.2).

Figure 2.3 Australian perinatal and infant mortality definitions

Gestational age		Infant age		
20 weeks (or 400g)	> 28 weeks to birth	7 days	8-28 days	29 days - 1 year
Early foetal death	Late foetal death	Early neonatal mortality	Late neonatal mortality	Post neonatal mortality
Foetal death or 'stillbirth'		Neonatal mortality		
		Infant mortality		

Using population-based data from the Swedish birth register ($n = 167,750$), Cnattingius et al²¹ studied associations between maternal pre-pregnancy BMI and the frequency of late fetal death (at least 28 weeks completed gestation) and early neonatal death (in the 7 days since birth). Among nulliparous women, when compared with lean women ($BMI < 20 \text{ kg/m}^2$), women with normal pre-pregnancy weight ($BMI 20-24.9 \text{ kg/m}^2$), overweight women ($BMI 25-29.9 \text{ kg/m}^2$) and obese women ($BMI > 30 \text{ kg/m}^2$) had higher odds ratios for late fetal death (OR 2.2; 95% CI; 1.2-4.1, 3.2; 1.6-6.2 and 4.3; 2.0-9.3 respectively). Among parous women, only obese mothers had a significantly increased risk (OR 2.0; 95% CI; 1.2-3.3). With regard to early neonatal death, the risk among nulliparous women followed a similar, though non-significant trend. Compared with lean women, odds ratios increased with increasing BMI categories (normal weight; OR 1.9; 95% CI; 0.9-3.8, overweight; 1.8; 0.8-4.0 and obese; 2.5; 0.9-6.4). There was no association found between pre-pregnancy BMI and early neonatal death among parous women.

Kristensen et al⁵⁶ studied associations between maternal pre-pregnancy BMI and late fetal death or neonatal death (in the 28 days since birth) among 24,505 Danish women in a hospital-based cohort study. Compared with women of normal pre-pregnancy weight ($BMI 18.5-24.9 \text{ kg/m}^2$), maternal obesity ($BMI > 30 \text{ kg/m}^2$) more than doubled the risk of both outcomes (late fetal death; OR 2.8; 95% CI; 1.5-5.3, neonatal death; 2.6; 1.2-5.8). However, there was no significant decrease or increase in risk among underweight or overweight mothers. The Danish study did not stratify women according to parity, which was important in the above study (nulliparous versus parous), though the statistical models included adjustment for this variable.

Nohr et al⁵⁷ also examined data on Danish women. In this study they were recruited to a national birth cohort from 1998-2001 (n = 54, 505) to examine the association between high pre-pregnancy BMI and late fetal death. In addition they were interested in the outcome of 'spontaneous abortion' which was defined as pregnancy loss prior to 28 weeks gestation. Compared with women of normal weight (BMI 18.5-24.9 kg/m²), pre-pregnancy obesity (BMI $\geq$ 30 kg/m²) was associated with an increasing excess risk of fetal death independent of GWG, particularly as gestation advanced. Expressed as hazard ratios, the risks for obese women were as follows: Spontaneous abortion: Fetal death before gestational week 14: HR 0.8; 95% CI; 0.5-1.4, Weeks 14-19: 1.6; 1.0-2.5, Weeks 20-27: 1.9; 1.1-3.3. Late fetal death: Weeks 28-36: 2.1; 1.0-4.4, Weeks 37-39: 3.5; 1.9-6.4, and 40+ Weeks: 4.6; 1.6-13.4. The study found that overweight women (BMI 25-29.9) had an increased risk for late fetal death only ($\geq$ 28 weeks gestation), but to a lesser degree than obese women and particularly after 40 weeks gestation (40+ Weeks: HR 2.9; 95% CI 1.1-7.7).

Belogolovkin et al⁵⁸ analysed data on 1,063,888 live singleton births in the US (20 to 44 weeks gestation) to examine the prevalence of small for gestational age (SGA; defined as $<$ 10th percentile of birthweight for gestational age according to national data), large for gestational age (LGA; defined as $\geq$ 90th percentile) and adequate for gestational age (AGA; normal birthweight) born to mothers who were underweight prior to pregnancy. The primary study outcome was neonatal death (death in the 28 days since birth) and the aim was to determine if SGA programming in utero was an adaptive mechanism that improved infant survival. Their results showed that compared to normal weight mothers, those who were underweight (BMI $<$ 18.5 kg/m²) were more likely to have an SGA infant. The rate of SGA increased according to the severity of pre-pregnancy underweight ($p < 0.01$) which was further classified as mild thinness (BMI 17-18.5 kg/m²), moderate thinness (BMI 16-16.9 kg/m²) and severe thinness (BMI $\leq$ 15.9 kg/m²). AGA and LGA infants of underweight mothers, when compared to those programmed by normal weight mothers had a higher risk of neonatal mortality (OR 1.22; 95% CI; 1.12-1.33 and 1.84; 1.24-2.72 respectively). SGA infants of underweight mothers seemed more resilient and had a decreased risk of death when compared to SGA infants of normal weight mothers (OR 0.85; 95% CI; 0.75-0.96). The results suggest that underweight mothers are more successful at programming SGA fetuses than the other phenotypes.

Maternal pre-pregnancy adiposity and congenital malformations

Congenital malformations are a leading cause of morbidity, mortality and health service expenditure for which pre-pregnancy diabetes mellitus is a recognised risk factor.⁶¹ Other conditions that are associated with poor glycemic control, such as pre-pregnancy overweight and obesity must also therefore also be considered as potential risk factors for congenital malformations. Given the increased prevalence of overweight and obesity and a corresponding increase in disorders of glucose metabolism among women of childbearing age, it is important to clarify the association between maternal pre-pregnancy adiposity and congenital malformations in offspring. This section describes eight studies that have explored this possible causal pathway.

Using data from a 1984-87 prospective cohort study of 22,951 women in the US, Moore et al⁵⁹ evaluated the effects of maternal pre-pregnancy obesity and diabetes mellitus (type 1, type 2 or gestational diabetes) on the risk of major non-chromosomal malformations. A major defect was defined as “those that resulted in death, disability, or substantial social stigma and those that required follow-up medical or surgical intervention”. They calculated prevalence ratios for major malformations associated with obesity and diabetes, both separately and among women with both exposures. Overall, the prevalence of any major defect was similar in three BMI categories (BMI < 25, 25-< 28, and ≥ 28 kg/m²) (PR’s 1.37, 1.10, and 1.47 respectively). Women who had pre-existing diabetes had a higher prevalence of infants with major malformations than both women without diabetes and women who developed gestational diabetes (5.88%, 1.34% and 1.38% respectively). In the absence of diabetes, compared with women with pre-pregnancy BMI < 28 kg/m² (normal and overweight categories were collapsed because there was no increased risk among women in the 25-< 28 BMI category for any abnormality), obese women had no overall higher risk for having an infant with a major abnormality (PR 0.95; 95% CI; 0.62-1.5), however, there was a higher frequency of certain types of craniofacial and musculo-skeletal defects. Women with pre-existing diabetes or gestational diabetes who were not obese also had no overall excess risk (PR 0.98; 95% CI; 1.2-7.6). Women with pre-existing or gestational diabetes who were obese had three-fold greater risk of an infant with an abnormality than non-obese, non-diabetic women (PR 3.1; 95% CI 1.2-7.6). The results suggest a complex relationship between diabetes and obesity as they act together in the pathogenesis of congenital malformations.

Cardiac defects are among the most frequent major congenital malformations and are estimated to affect at least 1 in 150 newborn infants.⁶⁰ Three case-control studies in Table 2.4 examine relationships between maternal pre-pregnancy BMI and infant cardiac defects.⁶⁰⁻⁶² Two of the studies are on data from the US and the other from Australia. In Australia, Oddy et al⁶² reviewed a range of congenital malformations and identified cases with cardiac defects from the population-based Western Australian Birth Defects Registry that includes live births, stillbirths and terminations of pregnancy (cases: n=111). The control group (n=418) was randomly selected from the statutory Midwives' Notification System of all births in Western Australia. They found that compared with normal weight women (BMI 20-24.9 kg/m²), infants of obese women (BMI > 30 kg/m²) had an approximate 30% increased risk of being born with a heart defect, however, the estimate was not statistically significant (OR 1.34; 95% CI; 0.63-2.84). Among the 111 cases, 38 infants had conotruncal heart defects (malformations of the outflow tract of the heart) and compared with normal weight women, the odds of obese women having a baby with this cardiac abnormality was 2.59 with borderline statistical significance (95% CI; 0.94-7.11). In a much larger study, Gilboa et al⁶¹ (cases =6440, controls =5673) found more statistically conclusive results. Compared with women in the normal BMI category before pregnancy (BMI 18.5- 24.9 kg/m²), overweight, obese and severely obese women (BMI > 35 kg/m²) had elevated risk of having a baby with a congenital heart defect (OR 1.16; 95% CI; 1.05-1.29; 1.15; 1.00-1.32; 1.31; 1.11-1.56 respectively). Taking conotruncal defects as a separate phenotype, compared with normal weight women, severely obese women had 36% greater risk of having an infant with this particular category of heart defect (OR 1.36; 95% CI 1.01-1.83).

Watkins et al⁶⁰ compared 851 US women who gave birth to a live born or stillborn infant that had a major cardiac defect, with 2,767 randomly selected women who had an infant with no defect. Importantly, diabetic mothers were excluded. Compared with women with average pre-pregnancy BMI (19.9-22.7 kg/m²), they found that underweight women (BMI < 16.5 kg/m²) had a decreased risk of having an affected infant (OR 0.64; 95% CI; 0.43-0.97). Among overweight or obese women (BMI > 26 kg/m²) they found a non-significant 36% increased risk (OR 1.36; 95% CI; 0.95-1.93). Further, they found that use of periconceptional multivitamins was associated with the outcome in some BMI categories. Taking average weight women who did not take vitamins as the referent group, there was reduced risk among average weight and underweight women who did use periconceptional

vitamins (with identical OR's and CI's; 0.61; 0.36-0.99), but not among women with a pre-pregnancy BMI > 26 (OR 1.69; 95% CI; 0.69-3.84). Though the study was quite large, the sample size nevertheless limited the ability to evaluate subgroups of cardiac defects and associations with BMI and multivitamin use.

A meta-analysis of published evidence up until 2007 included 4 cohort and 8 case-control studies (all but two conducted in the US) on the relationship between maternal obesity and the risk of neural tube defects. Based on their meta-analysis, Rasmussen et al⁶³ reported the unadjusted odds ratios for a pregnancy affected by neural tube defect (NTD) as 1.22 (95% CI; 0.99-1.49), 1.70 (1.34-2.15) and 3.11 (1.75-5.46) among overweight, obese and severely obese women respectively, compared with normal weight women. In the Western Australian study mentioned above, Oddy et al⁶² found the following non-significant estimates. Compared with normal weight women the odds of NTD were 0.60 (95% CI; 0.17-2.12) among underweight women and 0.65 (0.21-2.01) and 2.09 (0.64-6.84) among overweight and obese women respectively. A study of 511 NTD cases and 687 controls in China found no significantly increased risk of NTDs for obese women (OR; 0.65; 95% CI; 0.29-1.49) though they reported a decreased risk among underweight women (OR 0.40; 95% CI; 0.26-0.62) compared with normal weight women. BMI categories were classified according to WHO recommendations for Western women. Nutritional factors, particularly folate, have been implicated in the development of NTDs. It is possible that overweight and obese women in the Chinese population had a more nutrient rich diet around conception compared to Western women. Among Western women, compared with those who were underweight, perhaps overweight women were more likely to restrict their calorie (and nutrient) intake in the periconceptual period in an effort to lose weight.

Three studies with case-control designs investigated associations between pre-pregnancy BMI and the risk of having an infant with gastroschisis (a severe birth defect of the abdominal wall which enables the intestines and sometimes the stomach to protrude). Seiga-Riz et al⁶⁴ examined the joint effects of maternal pre-pregnancy BMI and age on the risk of infants having the condition among 464 cases compared with 4,842 controls. The data showed that women who are younger and who have a lower BMI have the highest risk. For example, a young woman (15 years) with a BMI 17 kg/m² had 7 times the risk of a woman aged 24 with a BMI of 23 kg/m² (OR 7.0; 95% CI; 4.2-11.5). Among 104 cases of gastroschisis compared with 220 healthy controls in California, US, Lam et al⁶⁵ also

found that underweight women (BMI < 18.1 kg/m²) had a higher risk compared with normal weight women (BMI 18.1-28.3 kg/m²) (OR 3.2; 95% CI; 1.4-7.3). Overweight women (BMI > 28.3 kg/m²) had a much lower risk (OR 0.2; 95% CI; 0.05-0.9). Using US data from the National Birth Defects Prevention Study, Waller et al⁶⁶ found that mothers of infants with gastroschisis (n =400) were significantly less likely to be obese than mothers of controls (n =3,904). Maternal overweight (BMI ≥ 25 kg/m²) was associated with decreased risk (OR 0.69; 95% CI; 0.50-0.92) and obesity (BMI ≥ 30 kg/m²) was associated with a strong decreased risk of an infant with gastroschisis (OR 0.19; 95% CI; 0.10-0.34) compared with normal weight women (BMI 18.5-24.9 kg/m²). The OR for underweight women (BMI < 18.5 kg/m²) compared to normal weight women was 0.85 (95% CI; 0.58-1.23).

Summary

The risk of perinatal mortality (late fetal death or early neonatal death) seemed to increase as pre-pregnancy BMI increased, particularly among nulliparous women. Overweight and obese women had an increased risk of having an infant with a cardiac and perhaps neural tube defect, however, they had lower risk for having an infant with gastroschisis. The risk of gastroschisis seemed to increase as maternal pre-pregnancy BMI decreased.

Table 2.4 Maternal pre-pregnancy adiposity and perinatal mortality/congenital malformations

Author, Year, and Study Design and Study Year	Sample Size, and Setting	Main pre-pregnancy and pregnancy exposures	Main outcome variable/s or case definition	Main study findings	Reported Statistics
Belogolovkin et al ⁴⁸ (2009); population-based cohort study (1978-1997)	1,063,888 live singleton births (20-44 weeks) in the Missouri vital record system (USA) linked to maternal data	Pre-pregnancy BMI calculated from <i>self-reported</i> weight and height at the first prenatal visit	Small for gestational age (SGA) defined as 10 th percentile of birthweight for gestational age Large for gestational age (LGA) defined as $\geq 90^{\text{th}}$ percentile Adequate for gestational age (AGA) defined as normal birthweight Neonatal death defined as death of an infant in the first 28 days since birth	Women with pre-pregnancy underweight were less likely to have infants with AGA and LGA phenotypes There was an increasing trend in programming SGA infants with declining maternal BMI status AGA and LGA infants of underweight gravidas had elevated risk of neonatal mortality compared to those programmed by normal weight mother. SGA neonates of underweight mothers had reduced risk of neonatal mortality compared to those of normal weight mothers	p = < 0.01 p = < 0.01 OR ⁴⁹ 1.22 (95% CI; 1.12-1.33) and (1.84; 1.24-2.72) respectively (0.85; 0.75-0.96)
Cnattingius et al ²¹ (1998); population-based prospective cohort study from birth register data (1992-1993)	Data on 167,750 singleton pregnancies recorded in the Swedish Medical Birth Register that had information on pre-pregnancy BMI	Pre-pregnancy BMI calculated from <i>self-reported</i> weight and height at the first antenatal visit	Late foetal death (after 28 weeks gestation)	Among nulliparous women, risk for late foetal death increased among normal weight, overweight and obese women, compared with lean women Among parous women, only obese women had increased risk	OR ⁵⁰ 2.2 (95% CI; 1.2-4.1), (3.2; 1.6-6.2) and (4.3;2.0-9.3) respectively (2.0; 1.2-3.3)

⁴⁹ Adjusted for maternal age, parity, race, smoking, education, marital status, adequacy of prenatal care, weight gain during pregnancy, gender of the infant and year of birth

⁵⁰ Adjusted for maternal age, education, cigarette smoking, height and whether the mother was living with the father

Gilboa et al ⁶¹ (2010); case-control study (1997-2004)	6,440 cases and 5,673 live born control infants enrolled in the National Birth Defects Prevention Study which spans 10 birth defects surveillance systems throughout the US. Mothers participated in telephone interviews 6 weeks to 2 years after birth	Pre-pregnancy BMI calculated from <i>self-reported</i> weight and height (reported up to 2 years after birth)	Case definition: Congenital heart defect (CHD) medically confirmed	Compared with normal weight women, overweight, moderately obese and severely obese women had increased risk of having an infant with a CHD	OR ⁵¹ 1.16 (95% CI 1.05-1.29), (1.15; 1.00-1.32) and (1.31; 1.11-1.56) respectively
Kristensen et al ⁵⁶ (2005); hospital-based cohort study (1989-1996)	24,505 women with singleton pregnancies at a single institution in Denmark completed questionnaires at 12-16 weeks gestation	Pre-pregnancy BMI calculated from <i>self-reported</i> weight and height on questionnaire	Stillbirth defined as delivery of a dead foetus after 28 weeks completed gestation and neonatal death as death of a live born child on days 1-28 following delivery	There were 112 stillbirths and 75 neonatal deaths among the cohort Maternal obesity was associated with a more than doubled risk of stillbirth and neonatal death compared with women of normal weight. No increased risk was found among underweight and overweight women	OR ⁵² 2.8 (95% CI; 1.5-5.3) and (2.6; 1.2-5.8)
Lam et al ⁶⁵ (1999); case-control study (1988-1990)	Data from the California Birth Defects Monitoring Program (CBDMP) identified 104 cases with gastroschisis, which were matched with 220 healthy controls. Mothers were interviewed within 3 to 6 months of delivery	Pre-pregnancy BMI calculated from <i>self-reported</i> weight and height	Case definition: gastroschisis confirmed by a clinical geneticist	There was a higher risk of gastroschisis for underweight mothers and a lower risk for overweight mothers compared with normal weight mothers For every unit increase in BMI, the risk for gastroschisis decreased by 11%	OR ⁵³ 3.20 (95% CI; 1.38-7.42) and (0.19; 0.04-0.83) respectively
Li et al ⁶⁷ (2010); case-control study (2003-2007)	Data on 511 cases with neural tube defect and 687 controls born to after 20 weeks gestation to women in four rural counties in China . Participants interviewed in the first week after delivery	Pre-pregnancy BMI calculated from <i>self-reported</i> weight and height after delivery	Case definition: neural tube defect (NTD)	There was no increased risk of NTDs for obese women or for underweight women compared to normal weight women There was a significantly reduced risk of NTDs and anencephaly for overweight women compared to normal weight women	OR ⁵⁴ 0.65 (95% CI; 0.29-2.49) and (1.00; 0.62-1.62) respectively (0.56; 0.41-0.76) and (0.40; 0.26-0.62) respectively

⁵¹ Adjusted for maternal age, race-ethnicity, education, hypertension, parity, smoking in the month prior to conception or the first month of pregnancy and periconceptual folic acid use

⁵² Unadjusted. Adjustment for maternal age, height, parity, smoking, years of schooling, working status, alcohol and caffeine intake, cohabitation with partner and gender of the child did not substantially alter the results

⁵³ Adjusted for mother's age and ethnicity

⁵⁴ Adjusted for maternal age at pregnancy, education, occupation, parity, history of pregnancy affected by birth defects and use of folic acid supplements

Moore et al ⁵⁹ (2000) prospective study of early pregnancy exposure and outcomes (1984-1987)	Data 22,951 women from over 100 obstetric practices who underwent amniocentesis or alpha- fetoprotein screening who had complete data on height and pre- pregnancy weight and pregnancy outcome. Telephone interviews between 15-20 weeks gestation and mailed questionnaires to delivering physician (US)	Pre-pregnancy BMI calculated from <i>self- reported</i> weight and height during telephone interview Self-reported diabetes history	Major nonchromosomal malformation reported by delivering physician	In the absence of diabetes, obese women had no higher overall risk of an offspring with a major defect Women with pre-existing or GDM who were not obese also had no excess risk Pregnancies of women who were obese and diabetic were more likely to have affected offspring than non-obese, non- diabetic women	PR ⁵⁵ 0.95 (95% CI; 0.62-1.5) (0.98; 0.43-2.2) (3.1; 1.2-7.6)
Nohr et al ⁵⁷ (2005); population- based cohort study (1998- 2001)	54,505 women in the Danish National Birth Cohort who participated in a telephone interview at approximately 16 weeks gestation. There were 679 foetal deaths	Pre-pregnancy BMI calculated from <i>self- reported</i> weight and height during telephone interview	Foetal death defined as either spontaneous abortion (< 28 weeks gestation) or stillbirth (28+ weeks gestation).	Pre-pregnancy obesity was associated with an increasing excess risk of foetal death with advancing gestation	HRs and 95% CIs ⁵⁶ : Before week 14: (0.8; 0.5-1.4), weeks 14-19: (1.6; 1.0-2.5), weeks 20-27: (1.9; 1.1-3.3) weeks 28-36: (2.1; 1.0- 4.4), weeks 37-39 (3.5; 1.9-6.4), and weeks 40+: (4.6; 1.6-13.4) (2.9; 1.1-7.7)
Oddy et al ⁶² (2009) population- based case- control study. (1997-2000)	296 cases identified from Western Australian Birth Defects Registry. Control group of 418 randomly selected live births from Midwives' Notification System of all births. Mailed questionnaires and telephone follow-up of non-responders	BMI calculated from <i>self-report</i> of pre- pregnancy weight and height	Case definition: heart defects conotruncal defects neural tube defects urinary tract defects orofacial clefts limb reduction defects	Compared with normal weight women, those who had pre- pregnancy obesity were at higher non-significant risks of: heart defects conotruncal defects neural tube defects urinary tract defects orofacial clefts limb reduction defects	OR ⁵⁷ 1.34 (95% CI; 0.63, 2.85) (2.59; 0.94-7.11) (2.09; 0.64-6.84) (1.41; 0.85-2.34) (1.97; 0.73-5.32) (2.70; 0.65-11.28)

⁵⁵ Adjusted for age, education, first-trimester cigarette and alcohol use, and supplemental folate and retinol per day (weeks 3-8)

⁵⁶ Adjusted for age, height, parity, socio-occupational status, physical exercise, smoking, and alcohol and coffee consumption

⁵⁷ Adjusted for marital status, maternal age, maternal education and periconceptual folic acid supplementation

Siega-Riz et al ⁶⁴ (2003) data from a case-control study (1997-2003)	Data from the National Birth Defect Prevention Study (NBDPS), a multi-state case-control study of over 30 birth defects. The study included 464 case infants and 4,841 healthy controls. Maternal interviews were conducted by telephone between 6 weeks and 24 months after birth. Cases identified using ICD codes. (US)	Pre-pregnancy BMI calculated from <i>self-reported</i> weight and height during postpartum telephone interview Self-reported maternal age	Case definition: gastroschisis	A bivariate spline showed that decreasing maternal BMI and age were significantly associated with gastroschisis Younger women with lower BMI are at greatest risk; For example, compared with a woman aged 24 years with a BMI of 23, a woman aged 15 years with a BMI of 17 was at higher risk	p =0.0001 ⁵⁸ OR 7.0 (95% CI; 4.2-11.5)
Waller et al ⁶⁶ (2007) multi-site case-control study (1997-2002)	Infants in the NBDPS. Birth defects for this study were selected only if more than 150 cases existed and maternal telephone interviews had been completed (US)	Pre-pregnancy BMI calculated from <i>self-reported</i> height and weight	Case definition: 16 structural birth defects identified according to ICD codes	Mothers of offspring with spina bifida, heart defects, anorectal atresia, hypospadias, limb reduction defects, diaphragmatic hernia, and omphalocele were more likely to be obese than mothers of controls Compared with normal weight women, obese women had a decreased risk for an infant with gastroschisis	OR's ⁵⁹ ranging from 1.33-2.10 (0.19; 0.10-3.4)
Watkins and Botto ⁶⁰ (2001); data from a birth defects case-control study (1968-1980)	Data from the Atlanta Birth Defects Case-Control Study (ABDCCS) of infants born with birth defects (851 cases) and without birth defects (2,767 controls). Cases ascertained from registry data. Exposure assessment was obtained via telephone interviews with mothers (US)	Pre-pregnancy BMI calculated from <i>self-report</i> of weight gain during pregnancy subtracted from reported weight just before delivery	Case definition: Infants with cardiac defect according to ICD codes	Compared with average weight women, underweight women were less likely to have a child with a major heart defect Overweight or obese women were at higher risk than average weight women Compared with average weight women who did not take periconceptual vitamins, average weight women who did had lower risk Periconceptual vitamins did not lower risk among overweight or obese women	OR ⁶⁰ 0.64 (95% CI; 0.43-0.97) (1.36; 0.95-1.93) (0.61; 0.36-0.99) (1.69; 0.69-3.84)

⁵⁸ Adjusted for study centre, maternal race/ethnicity, education, household income, smoking, alcohol use, vitamin use, vasoconstrictor medication use and gestational diabetes

⁵⁹ Adjusted for maternal age, ethnicity, education, parity, smoking in the month prior to conception and supplemental folic acid intake in the month prior to conception

⁶⁰ Adjusted for race, birth period, age, education, alcohol use, smoking, chronic illness, and vitamin use

2.3.1.5 Maternal pre-pregnancy adiposity and infant birthweight

Over the past three decades, epidemiological and other research has improved our understanding of the importance of infant birthweight for predicting at a population level, the immediate and long term health of the next generation. Birthweight is a powerful predictor of an individual infant's survival, and generally the risk of mortality increases as birthweight decreases.⁶⁸ At a population level, groups that have lower mean birthweight (e.g. mothers who smoke or with lower socioeconomic status) usually have a higher infant mortality.^{68,69} Low birthweight (defined as < 2500 g) has also been associated with asthma and neurologic and developmental deficits in childhood,⁶⁹ as well as increased risk of central obesity,⁷⁰ cardiovascular disease, diabetes, renal disease and some cancers in adulthood.⁷¹ High birthweight increases the risk of caesarean section delivery, shoulder dystocia, perinatal morbidity and the risk of early obesity.⁷² A large number of epidemiological studies have shown a clear relationship between birthweight and BMI attained in later life.⁷⁰ Birthweight is a useful epidemiological tool because it is routinely measured, easily and inexpensively recorded and often historically available.

Ten studies summarised in Table 2.5 examine associations between maternal pre-pregnant BMI and adverse outcomes related to infant anthropometry. Low birthweight infants are usually categorised as growth restricted (intrauterine growth restriction - IUGR) or small-for-gestational-age (SGA). IUGR describes a pattern of restricted intrauterine growth that deviates from normal expectations, whereas SGA is a category based on birthweight < 10th percentile for weight of all foetuses of a particular gestational age. Overall, the studies consistently showed associations between low maternal pre-pregnancy BMI and smaller offspring, and high maternal BMI and larger offspring. The importance of GWG in mediating the associations is demonstrated in a number of the studies. Although data in any particular study may be limited by a lack of information on potentially confounding risk factors (e.g. socioeconomic factors, smoking and alcohol use, nutrition or physical activity), the associations seem similar and robust across diverse study populations. The studies included in this review examine data from the US, Iran, Korea, Denmark, Norway, Japan, China and Italy.

Fredericks et al⁷² evaluated the relationship among pre-pregnancy BMI, GWG, and infant birthweight in a prospective study of a cohort of 2,670 women with singleton pregnancies recruited in the US from 1996 to 2004. Compared with women who had a pre-pregnancy

BMI 19.8-20.6 kg/m², lean women (BMI < 19.8 kg/m²) had a 51% higher risk of delivering a LBW (< 2,500 grams) infant (RR 1.51; 95% CI; 1.02-2.25) and obese women (BMI > 29 kg/m²) had a 65% higher risk of delivering a macrosomic infant (≥ 4,000 grams). Institute of Medicine guidelines⁷ were adopted to further evaluate the risk of LBW and macrosomic infants according to GWG.

Compared with women who had GWG within the IOM recommended guidelines,^{*} women who gained weight below the guidelines had a 51% decreased risk of delivering a macrosomic infant (RR 0.49; 95% CI; 0.31-0.78). Women who gained above the guidelines had a 76% increased risk (RR 1.76; 95% CI: 1.40-2.22) compared with women who gained below the guidelines. Compared to women with normal weight, lean women whose GWG was below median (< 15.9 kg) had nearly a three-fold risk of delivering a LBW infant (RR 2.97; 95% CI; 1.63-5.43). The results demonstrate the importance of balancing pre-pregnancy weight and GWG to decrease the risk of LBW and macrosomia among lean and obese women, respectively.

Yekta et al⁷³ reported similar findings among 270 women in Iran. GWG was categorised as normal (within the IOM guidelines) or abnormal (below or above the guidelines). Pre-pregnancy BMI < 19 kg/m² and abnormal GWG were both associated with LBW offspring. In Korea, among 3,554 singleton pregnancies, overweight women had higher risk for macrosomia (unadjusted OR 2.7; 95% CI; 1.3-5.5). Women of normal weight prior to pregnancy, who also had low GWG, had a higher unadjusted risk for SGA (OR 2.8; 95% CI; 1.8-4.4). In Iran, Sekhavat et al⁷⁴ evaluated excessive GWG among non-diabetic women with normal pre-pregnancy weight (BMI 19.8-26 kg/m²). The odds of having a macrosomic baby (≥ 4000 grams) were elevated among women who gained above the IOM recommendations (> 16 kg) despite their normal range pre-pregnancy BMI (OR 3.3; 95% CI; 2.2-5.1).

Zhou and Olsen⁷⁵ reported on a follow-up study of 7,122 non-diabetic pregnant women and their term newborns (37-42 weeks gestation) in Denmark. The objective was to study the association between GWG and infant birthweight considering maternal pre-pregnancy BMI. They found that birthweight increased with increasing GWG with regression coefficients that were lower at higher pre-pregnancy BMIs. The linear regression

^{*}Underweight (BMI <19.8 kg/m²): recommended pregnancy weight gain from 12.5 – 18 kg; Normal (BMI 19.8 – 29.9 kg/m²): 11.5 – 16 kg; Overweight (BMI 25 - 29.9 kg/m²): 7 – 11 kg; Obese (BMI ≥ 30 kg/m²): ≥ 6.8 kg (with no upper limit recommended for this group)

coefficient went from 31.0g (birthweight gain)/kg GWG (95% CI; 26.9-35.1) for women with a BMI < 19.8 kg/m² down to 18.2 g/kg (95% CI; 12.6-23.8) for women in the highest BMI category (> 26 kg/m²). The proportion of LBW was greatest among women with low pre-pregnancy BMI and low GWG. There was a similar association for intrauterine growth restriction (IUGR: defined as newborns with a birthweight < 3000 grams in spite of a placenta weight higher than 491 grams: > 66th percentile), however, there was a marked lower risk for IUGR among women who had more than 16 kg GWG irrespective of pre-pregnancy BMI. The proportion of babies with high birthweight (macrosomia: > 4,500 grams) increased by GWG as well as by pre-pregnancy BMI. Compared to women with BMI < 19.8 kg/m² who had a GWG < 11 kg, women with BMI > 26 kg/m² who gained more than 16 kg had more than forty-five times the risk of having a macrosomic baby (OR 45.6; 95% CI 6.0-349).

Nohr et al⁷⁶ also studied Danish women to explore separate and joint associations between pre-pregnancy BMI and GWG, on pregnancy outcomes. The population-based sample included 60,892 women who had term pregnancies. High maternal pre-pregnancy BMI and greater GWG decreased the risk of IUGR and increased the risk of large-for-gestational-age infants (LGA: defined as having a standardised birthweight > 90th percentile based on fetal weight derived from a Scandinavian population). They reported that overall, low GWG was advantageous; however, it increased the risk of having a small baby, especially among women who were underweight prior to pregnancy.

In their study of 43,705 pregnant Norwegian women and their singleton term offspring, Fleten et al⁷⁷ estimated associations between maternal pre-pregnancy BMI and infant birthweight, and the indirect association between maternal BMI and birthweight explained by exercise during pregnancy. In two questionnaires (one self-administered at 17 weeks gestation and the second at 30 weeks) women answered questions about how often they engaged in physical activity before 17 weeks and between 17 and 30 weeks gestation of their pregnancy. Exercise was defined as the sum of frequencies per month of all activities reported. The crude association between exercise during pregnancy and birthweight was a 3.9 gram decrease in birthweight per unit increase in exercise per month. For example, infants of women who exercised 20 times per month weighed approximately 78 grams less than infants of women who were inactive. The direct association between pre-pregnancy BMI and birthweight was 20.3 g (95% CI: 19.2-21.4 grams; $p < 0.001$) increase in

birthweight for each one-unit increase in BMI. The association between BMI and birthweight explained by exercise during pregnancy was 1.5% of the total association, suggesting that exercise during pregnancy has only a minor impact on birthweight.

Three studies focused on associations between low maternal pre-pregnancy weight and infant birthweight. Watanabe et al⁷⁸ analysed data on Japanese women with BMI < 25 kg/m² for risk factors for small for gestational age infants (SGA: defined < 10th percentile of birthweight adjusted for parity, infant sex and gestational age according to growth curves among Japanese infants). Lean maternal pre-pregnancy weight was associated with increased risk of having an SGA infant. Compared with women who had a BMI 21-< 25 kg/m², women who had a BMI < 18.5 had a 60% increased risk and women with BMI between 18.5 and 21 kg/m² had a 40% increased risk (OR 1.6; 95% CI: 1.3-2.2 and 1.4; 1.2-1.7 respectively). They found that women with < 9 kg weight gain during pregnancy were nearly twice as likely to have an SGA infant compared with women who gained 9-12 kg. In addition, they showed that maternal smoking of over 10 cigarettes a day, more than doubled the risk of a SGA infant (OR 2.5; 95% CI: 1.8-3.5). In a case-control study in Italy (n = 555 women who delivered SGA infants) Ricci et al⁷⁹ also showed that underweight women and women with low GWG were at greater risk of delivering an SGA infant (OR 1.9; 95% CI: 1.6-2.4 and 1.4; 95% CI: 1.1-1.9). However, gaining more pregnancy weight than recommended in the IOM guidelines was not significantly protective against the outcome (OR 0.7; 95% CI: 0.5-1.0).

Ronnenberg et al⁸⁰ aimed to determine how the risk of adverse birth outcomes (assessed by infant birthweight) is influenced by the extent to which women are underweight prior to pregnancy. A cohort of 575 Chinese women was studied prospectively. They were married, nulliparous, non-smokers aged 20-34 years. They were enrolled before pregnancy when the women's height and weight was *measured* in light clothing to the nearest 0.1 cm and 0.1 kg. Normal pre-pregnancy weight range was defined as BMI 19.8-< 26 kg/m² and the lean category was dichotomised to severely underweight (BMI ≤ 18.5 kg/m²) and moderately underweight (BMI > 18.5-19.8 kg/m²). Compared with normal weight women, being severely underweight was associated with a mean birthweight reduction of 219 grams (SEM; ± 40) and an 80% increase in risk of IUGR (defined as < 85% of birthweight ratio: actual birthweight/mean birthweight of infants of the same gestational age in the cohort) (OR 1.8; 95% CI 1.0-3.3; p = 0.05). Being in the moderately underweight category

prior to pregnancy did not significantly increase risk of the outcomes. They found that measures of birthweight, length and head circumference increased with increasing pre-pregnancy BMI up to 22-23 kg/m², beyond which (within the normal BMI category) there was a plateau in intrauterine infant growth. This study provides further evidence that maternal BMI prior to conception and weight gain during pregnancy are important factors in programming infant weight at birth. This is the only prospective study in this review with pre-pregnancy BMI as the primary exposure that objectively measured height and weight prior to pregnancy.

Summary

Women with low maternal pre-pregnancy BMI tend to have smaller infants and high maternal BMI results in heavier offspring. Importantly, the relationship between pre-pregnancy BMI and infant birthweight is mediated by the amount of weight gain that occurs during the pregnancy.

Table 2.5 Maternal pre-pregnancy adiposity and infant birthweight

Author, Year, and Study Design and Study Year	Sample Size, and Setting	Main pre-pregnancy and pregnancy exposures	Main outcome variable/s or case definition	Main study findings	Reported Statistics
Fleten et al ⁷⁷ (2011); prospective population-based nationwide cohort study (1999-2006)	Data on 43,705 pregnancies from 2 questionnaires administered among women in the Norwegian Mother and Child Cohort Study at around 17 and 30 weeks gestation	Pre-pregnancy BMI calculated from <i>self-reported</i> weight and height Exercise during pregnancy defined as the sum of frequencies per month of all physical activities reported around weeks 17 and 30	Infant birthweight measured in grams as registered in the Medical Birth Registry of Norway	The direct association between exercise around week 30 and birthweight was a 2.9 gram decrease in birthweight per unit increase in exercise (episodes per month) The direct association between BMI and birthweight was a 20.3 gram increase in birthweight for a one-unit increase in BMI, and the indirect association explained by exercise was only 0.3 gram decrease in birthweight	-2.94 g ⁶² (95% CI; -3.58 to -2.30g) (+20.3 g ⁶³ ; 19.2-21.4 g)
Frederick et al ⁷² (2008); prospective cohort study (1996-2004)	Data on 2,670 women who delivered a singleton infant, collected as part of the Omega study of risk factors for preeclampsia and GDM among pregnant women attending prenatal clinics in Tacoma, US . Face to face interviews after 20 weeks gestation	Pre-pregnancy BMI calculated from <i>self-reported</i> weight and height at interview (recalled to 3 months before pregnancy) GWG calculated as difference between last recorded maternal weight before delivery and weight 3 months before conception	Infant birthweight categorised as low birthweight (LBW) < 2500g, normal birthweight 2500-3999g and macrosomia ≥ 4000	Pre-pregnancy BMI was independently and positively associated with infant birthweight GWG was positively associated with infant birthweight. Less than median gestation weight gain was associated with twice the risk of LBW Risk of macrosomia increased with increasing pre-pregnancy BMI and GWG	Estimated regression coefficient β 44.67 (p =0.001) (β =19.5, p < 0.001) RR ⁶⁴ 2.04 (95% CI; 1.34-3.11) (p for linear trend < 0.001)

⁶² Adjusted for exercise during the other period (17 weeks), maternal age, parity, cohabitant status, education, smoking during pregnancy, and exercise during the three months before pregnancy

⁶³ Adjusted for maternal height, age, parity, smoking, cohabitant status, education, exercise during the 3 months before pregnancy

⁶⁴ Adjusted for maternal age, race/ethnicity, parity, education, marital status, smoking status, preterm birth, infant gender, gestational diabetes, and preeclampsia

Nohr et al ⁷⁶ (2008); data linkage of birth cohort and hospital registers (1996-2002)	60,892 pregnancies that resulted in live born, full-term singletons (≥ 37 weeks) among 57,700 women in the Danish National Birth Cohort (DNBC). Data collected during 2 telephone interviews around 16 and 30 weeks of gestation and postnatal interviews at 6 and 18 months	BMI calculated from <i>self-reported</i> weight and height during telephone interview GWG self-reported in telephone interview 6 months after birth	Small-for-gestational age SGA <10 th percentile Large for gestational age LGA > 90 th percentile	High and very high GWG combined with high maternal BMI decreased the risk of growth restriction and increased risk of LGA and low Apgar score Low GWG increased risk for having a small baby, particularly for underweight women	OR ⁶⁵ 0.5 (95% CI; 0.5-0.5), (2.6; 2.4-2.8) and (1.3; 1.0-1.6) respectively (1.9; 1.7-2.1)
Park et al ⁸¹ (2010); hospital-based retrospective cohort study (2005-2007)	2,311 women who delivered a live singleton infant between 28 and 42 weeks gestation at a single hospital in Seoul, Korea . Women were interviewed at first clinic visit	Pre-pregnancy BMI calculated from <i>self-reported</i> weight and measured height at first visit GWG calculated from weight just before delivery	Macrosomia, LGA, SGA, caesarean section	Overweight gravidas and women with excessive GWG had higher risk for macrosomia, LGA and caesarean section A higher risk for SGA found in underweight, normal weight and overweight gravidas and those with low GWG	OR ⁶⁶ 2.7 (95% CI; 1.3-5.5), (2.7 ⁶⁷ ; 1.4-5.2) and (1.6 ⁶⁸ ; 1.0-2.7) respectively (1.8 ⁶⁹ ; 0.7-4.4), (2.8 ;1.8-4.4) and (2.2; 0.9-5.5) respectively
Ricci et al ⁷⁹ (2010); case-control study (1989-1999)	555 cases of SGA among women recruited in two Italian clinics. 1,966 controls gave birth at term to healthy normal weight infants born at the same hospitals as cases.	Method of pre-pregnancy height and weight measurements <i>not stated</i> GWG calculated from weight just prior to delivery	SGA	Underweight women had elevated risk of delivering an SGA infant. Less than recommended GWG increased risk of SGA infant Excess GWG (above guidelines) was not protective against SGA	OR ⁷⁰ 1.9 (95% CI: 1.6-2.4) (1.4; 1.1-1.9) (0.7; 0.5-1.0)
Ronnenberg et al ⁸⁰ (2003) prospective population-based reproductive health study (study dates not stated)	575 nulliparous married women, aged 20-34 yrs, who were attempting to become pregnant and were employed as textile workers in Anqing, China . Participants were interviewed at enrolment	Maternal BMI calculated from <i>measured</i> height and weight prior to pregnancy	Infant birthweight (kg) Intrauterine growth restriction (IUGR) Infant head circumference	Compared with normal BMI, being severely underweight was associated with mean reductions in infant birthweight and an 80% increase in risk of IUGR Being severely underweight was associated with smaller infant head circumference	Mean reduction (± SEM): 219± 40g OR ⁷¹ 1.8 (95% CI; 1.0-3.3) Infants of severely underweight mothers had HC 0.83 cm less than that of infants whose mothers had a normal BMI (p < 0.0001)

⁶⁵ Adjusted for age, parity, height, smoking, alcohol consumption, social status, exercise, and gestational age

⁶⁶ Unadjusted

⁶⁷ Adjusted for BMI, smoking status, parity, education, husband's education and gestational age

⁶⁸ Unadjusted

⁶⁹ Unadjusted

⁷⁰ Adjusted for age, education, parity, alcohol consumption and smoking during the third trimester of pregnancy, gestational hypertension, history of SGA birth

Sekhavat et al ⁷⁴ (2011); hospital-based retrospective cohort study 2002-2004	940 births to Iranian mothers at a single hospital who were non-diabetic, had normal pre-pregnancy BMI and delivered at term (37-42 weeks gestation)	Normal pre-pregnancy BMI from medical records. Method of measurement <i>not stated</i>	Macrosomic infant	Compared with mothers with normal GWG, women with excessive GWG had elevated risk of having an infant with macrosomia	OR 3.3 ⁷² (95% CI; 2.2-5.1)
Watanabe et al ⁷⁸ (2010); hospital-based cross-sectional study (2003-2004)	Data on 3,604 women who gave birth to a single term infant (37-42 weeks) at 2 institutions in Tokyo, Japan . Women with complications (pregnancy hypertension, diabetes, renal disease excluded). Overweight women also excluded	Maternal pre-pregnancy BMI and GWG from <i>self-reported</i> information extracted from hospital records	SGA defined as infant birthweight < 10 th percentile	Women with <9 kg GWG were more likely to have an SGA infant compared with women who gained 9-12 kg. Maternal smoking > 10 cigarettes per day increased risk of SGA Women with BMI < 21.0 kg/m ² were associated with increased risk for SGA	OR ⁷³ 1.8 (95% CI; 1.6-2.2) (2.5; 1.8-3.5) (1.6; 1.3-2.2 for BMI < 18.5kg/m ² or 1.4; 1.2-1.7 for 18.5 ≤ BMI ≤ 21.0 kg/m ²)
Yekta et al ⁷³ (2006); prospective cross-sectional study (2002-2003)	Data on 270 women enrolled in public health care centres in an urban area were recruited in first 8 weeks of pregnancy. Women interviewed and weighed monthly during pregnancy (Iran)	Pre-pregnancy BMI calculated from height and weight <i>measured at 1st visit before 8 weeks gestation</i> GWG from measured weight during pregnancy	Infant LBW (< 2500g)	Compared with obese women, women with pre-pregnancy BMI < 19 kg/m ² were associated with birthweight LBW Abnormal GWG (low and high) was associated with LBW compared with women who had a normal weight gain	4% vs 12.7% (p < 0.05) OR ⁷⁴ 2.37 (95% CI; 1.7-3.2)

⁷¹ Adjusted for maternal age, height, education, work stress, maternal exposure to dust, noise, passive smoking and infant gender and gestational age

⁷² Unadjusted

⁷³ Adjusted for parity, sex and gestational age

⁷⁴ Adjusted for maternal age, parity and education

Zhou and Orlsen ⁷⁵ (1997); follow-up study of consecutively recruited participants (1984-1987)	7,122 non-diabetic women with singleton pregnancies who gave birth between 37 and 42 weeks gestation in two well defined geographical areas in Denmark . Self-administered questionnaire completed after 36 weeks gestation	Pre-pregnancy BMI calculated from <i>self-reported</i> information GWG calculated as difference between pre-pregnancy weight and weight measured at hospitalisation for confinement	Infant birthweight LBW defined as < 2500g High birthweight defined as > 4500g Placental weight measured shortly after delivery	Birth and placenta weight were associated with GWG but with lower regression coefficients at higher BMI Proportion of high birthweight newborns increased with increasing GWG, especially in women with pre-pregnancy BMI above 26	Study results ⁷⁵ represented in graphs
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⁷⁵ Adjusted for maternal age, parity and education

2.3.1.6 Maternal pre-pregnancy adiposity and breastfeeding

Human breast milk is widely recognised as the optimal infant food and there is a large body of evidence to show that breastfeeding provides value not only to mothers and their babies, but also to societies. Breastfed babies are less likely to suffer from a range of childhood illnesses and conditions (gastroenteritis, respiratory illness and otitis media) and may have better cognitive development.⁸² Long lasting benefits can extend to reducing risks of obesity and chronic disease in later life, in turn reducing the cost to society of providing health care across the lifespan.⁸³ Mothers who breastfeed recover from childbirth more quickly and may have decreased risk for developing some cancers (breast and ovarian).⁸² Four studies summarised in Table 2.6 examine associations between high pre-pregnant maternal BMI and aspects of breastfeeding.

Rasmussen et al⁸⁴ measured serum prolactin levels and progesterone concentrations during the first week post-partum among 40 breastfeeding mothers of whom 23 had normal pre-pregnancy BMI, with the remainder in overweight or obese categories. The study was ambitious due to the reasonably burdensome level of participation required at a particularly sensitive time for the women. Participants were asked for blood samples before and after breastfeeding on two occasions in the first week after birth (at 48 hours and 7 days post-partum). To measure infant milk intake, babies were weighed before and after feeding for two 24 h periods during the week. Consequently, the sample size was small and the research team was not able to collect all the data they would have liked (e.g. fasting blood samples would have provided optimal results). The study found that overweight/obesity, primiparity and infant birthweight were negatively associated with prolactin response to an episode of breastfeeding at 48 hours after birth. At day 7, only overweight/obesity remained as a significant negative predictor of prolactin response (after adjusting for time since delivery and duration of breastfeeding episode). Progesterone concentrations, assessed at the same time points did not differ between normal weight women and those in the higher BMI categories. The findings suggest a biological basis for early termination of breastfeeding among women who are overweight or obese prior to pregnancy. However, the study is significantly compromised by its sample size and restricted variable collection and as such, the results should be interpreted with caution, particularly with regard to generalisability.

Baker et al⁸⁵ studied 37,459 Danish women (drawn from the Danish National Birth Cohort) to determine whether increasing maternal pre-pregnancy weight was associated with early termination of breastfeeding in an environment, which they report as similar to other Scandinavian countries where there is considerable social support for breastfeeding and generous maternity leave. They found that the risk of early termination (within 7 days of birth) of any, or full breastfeeding increased in line with increasing pre-pregnancy BMI. Compared with normal weight women (BMI 18.5-24.9 kg/m²), underweight women (< 18.5 kg/m²) were less likely to terminate any breastfeeding early (OR 0.94 95% CI: 0.89-1.00). At the end of the first week after delivery 6% of women with BMI > 40 had ceased any breastfeeding compared to 1.2% of normal weight women. Overweight women (BMI 25-29.9 kg/m²) and obese women, especially women with a pre-pregnancy BMI > 40 kg/m² had significantly higher odds of stopping any breastfeeding within the first seven days (OR 1.24 95% CI: 1.18-1.31 and 1.39; 1.19-1.63 respectively). The associations were not modified according to weight gain during pregnancy.

Hilson et al⁸⁶ were interested in whether high pre-pregnancy BMI was associated with timing of the onset of lactogenesis among 151 white, rural women with an intention to breast feed who had care in a 10-county service area in the United States. The women were interviewed by telephone daily from day 1 post-partum until their milk had 'come in' which was the definition of onset of lactogenesis. Pre-pregnant BMI and primiparity were both associated with later onset of lactogenesis (≥ 72 hours). Women with later onset of lactogenesis had higher pre-pregnancy BMI values (28.3 ± 6.3 vs 25.4 ± 5.9 kg/m², $P < 0.05$) however, only primiparity remained significant when both variables were considered together. The results suggest that as well as first time mothers, women with higher pre-pregnancy BMI's may benefit from extra breastfeeding support to assist in the prevention of early termination of breastfeeding.

Leonard et al⁸⁷ investigated the practice of breast milk expression among women of different BMI categories in a study of 2,288 women in the US using mailed questionnaires. They found that overall; breast milk expression was associated with feeding infants breast milk for a longer duration. Their study also found that in the first 2 months after birth, compared with women who had normal pre-pregnancy BMI, obese women (BMI ≥ 30) were more likely to attempt breast milk expression ($p = 0.04$), however, they were also more likely to be unsuccessful (in response to a question about whether they had ever

obtained milk if they had ever tried to express) ($p=0.01$). There were however, no differences between BMI groups beyond 2 months postpartum, suggesting that once breastfeeding practices are established, BMI has a lesser impact. The study was not able to establish whether breast milk expression was beneficial for women in higher BMI categories, or if it was, at what stage postpartum this might be true.

Summary

The studies indicate that overweight and obesity may play a role (perhaps biological) in failure to establish effective breastfeeding. Adjustment for maternal socioeconomic variables (e.g. occupation, education, household income) was carried out in two of the studies^{85,88} however, this may not account for maternal attitudinal factors and strong social patterning associated with infant feeding practices.

Table 2.6 Maternal pre-pregnancy adiposity and breastfeeding

Author, Year, and Study Design and Study Year	Sample Size, and Setting	Main pre-pregnancy and pregnancy exposures	Main outcome variable/s or case definition	Main study findings	Reported Statistics
Baker et al ⁸⁵ (2007); population-based cohort study (1999-2002)	37,459 women from the Danish National Birth Cohort who had completed at least 3 telephone interviews, linked to registry data with information about pregnancy and birth complications and infant outcomes (Denmark)	Pre-pregnancy BMI calculated from <i>self-reported</i> weight and height during interview at 12 weeks gestation GWG self-reported from interview 6 months postpartum	Infant feeding variables collected during telephone interviews at 6 months postpartum	Compared with normal weight women, risk of early termination of breastfeeding increased progressively with increasing pre-pregnant BMI GWG did not add to or modify the association between pre-pregnant BMI and breastfeeding	OR ⁷⁶ 1.12 (95% CI; 1.09-1.16) for overweight women to (1.39; 1.19-1.63) for morbidly obese women (BMI ≥ 40 kg/m ²)
Hilson et al ⁸⁶ (2004); prospective pregnancy cohort (1998)	151 pregnant women with intention to breast feed, aged 19-45 years were identified from an obstetric database of all pregnant women in a 10 county area over a 4 month period (August to November). Oral questionnaires administered at enrolment and during telephone interviews on days 1-5 postpartum (US)	Pre-pregnancy BMI calculated from <i>self-reported</i> weight and height at interview on enrolment	Onset of lactogenesis considered timely if women reported their milk coming in < 72 hours postpartum. Late lactogenesis defined as ≥ 72 hours	Compared with women who had earlier onset of lactogenesis (< 72 hours), those with later onset had higher BMI Only primiparity remained significant when pre-pregnancy BMI and primiparity were considered simultaneously	Pre-pregnant BMI OR ⁷⁷ 1.1 (95% CI; 1.0-1.2) p < 0.8 Primiparity (4.2; 1.5-11.8) p =0.007
Leonard et al ⁸⁷ (2011); population-based cohort study (2005-2007)	2,288 women recruited in 7 th month of pregnancy completed mailed questionnaires until their infant was 1 year old as part of the Infant Feeding Practices Study II.(US)	Pre-pregnancy BMI from information <i>self-reported</i> in mailed questionnaires	Information related to breastfeeding practices including breast-milk production and expression	Before 2 months postpartum, compared with normal weight and overweight women, obese women were more likely to try milk expression They were less likely to succeed	85.2 %, 84.8% and 89.6% respectively (p ⁷⁸ =0.01) 96.6%, 97.6% and 93.9% (p ⁷⁹ =0.08)

⁷⁶ Adjusted for gestational weight gain, caesarean delivery, maternal age, smoking during lactation, parity, maternal occupation, spouse or partner present in early pregnancy, physical activity during late pregnancy and infant sex as appropriate.

⁷⁷ Variables that were significantly associated with onset of lactogenesis and/or obesity were added to the logistic regression model

⁷⁸ Adjusted for maternal age, education, postpartum work status, and parity; household income as a percentage of the Poverty Income Ratio and intended duration of breastfeeding

⁷⁹ Adjusted for maternal education, race, parity and breast pump problem or injury

Rasmussen and Kjolhede ⁸⁴ (2004); prospective cohort study of women enrolled over 24 month period (study years not stated)	40 women enrolled in the first week post-partum after being identified from a New York obstetric database. They were reviewed 48 and 78 hours after delivery and had blood samples drawn (US)	Pre-pregnancy BMI calculated from information abstracted from medical records. Method of measurement <i>not stated</i> GWG calculated from information in medical records	Serum prolactin and progesterone concentration	Women who were overweight or obese before conception had a lower prolactin response to suckling than normal weight women at 48 hours but not at day 7. Decreases in progesterone concentrations from 48 hours to 7 days postpartum did not differ between the pre-pregnancy BMI groups	-10.3 ng/mL $\pm$ 28.3 vs 26.0 $\pm$ 61.5 (p ⁸⁰ < 0.05)
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⁸⁰ Adjustment variables not specified

2.3.2 Maternal pre-pregnancy cardio-metabolic risk factors and pregnancy outcomes

Since Barker pioneered epidemiological research on the fetal and infant origins of disease,⁸⁹ our understanding of the concept of metabolic programming and the importance of the intrauterine environment as a predictor of immediate and long health has greatly improved.⁹⁰ This area of investigation seems increasingly important, in light of a world-wide rise in the incidence and prevalence of metabolic syndrome and type 2 diabetes, and their associations with cardiovascular disease, that is propelled by the growing prevalence of overweight and obesity.⁹¹ Co-morbidities associated with obesity and overweight (elevated blood pressure, dyslipidemia, insulin resistance and type 2 diabetes) are appearing more frequently in younger adults and at an alarming rate in children.⁹² Table 2.7 summaries 7 studies that examine maternal pre-pregnancy cardio-metabolic risk factors and associations with pregnancy events and birth outcomes.

Gunderson et al⁹³ examined pre-pregnancy cardio-metabolic risk factors and the risk of subsequent gestational diabetes mellitus (GDM). They selected data on 1,164 women selected from the Coronary Artery Risk Development in Young Adults (CARDIA study) which included participants from four states in the US. The participants were free of diabetes and delivered 1,809 live newborns over a 20 year period. The women provided fasting blood samples 5 times between 1985 and 2006. The repeated pre-pregnancy tests assessed triglycerides, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), total cholesterol, glucose, and insulin and the measures nearest and prior to each pregnancy were analysed. Blood pressure, and *measured* weight, height and waist circumference were recorded. Among the pregnancies, 1,655 were classified as non-GDM and the remainder (n =154) as GDM. The median time from pre-pregnancy assessments to conception was 31 months for non-GDM and 33.6 months for GDM pregnancies. The study found that impaired glucose (100-125 vs < 90 mg/dL), elevated insulin (>15-20 and > 20 vs < 10µU/mL), and low levels of HDL (< 40s vs > 50 mg/dL) were associated with GDM independently of pre-pregnancy BMI. The ORs for the associations were glucose; OR 4.74; 2.14-10.51; middle insulin levels: 2.19; 1.5-4.17; highest insulin levels: 2.36; 1.20-4.63 and low HDL: 3.07; 1.62-5.84. The presence of any cardio-metabolic risk factors (e.g. elevated diastolic or systolic blood pressure) among overweight women (BMI 25-29 kg/m²) was associated with a four-fold increased rate of GDM (26.7% for one or more risk factors versus 7.4% for women with none). Among

research on pre-pregnancy health, this study stands out for the fact that maternal anthropometric data were measured, not self-reported. The main outcome measure, whether or not a woman developed GDM, was however, self-reported.

A case-control study (GDM cases $n=199$ and controls $n=381$) conducted by Hedderson et al⁹⁴ in the San Francisco Bay area had somewhat similar findings. Health checks were performed on average 7 years before conception among cases and controls. Elevated pre-pregnancy serum glucose levels, elevated BMI ($\geq 25\text{kg/m}^2$) and elevated blood pressure were associated with increased risk for GDM in the subsequent pregnancy. The risk of GDM increased significantly with the number of cardio-metabolic risk factors. Compared with women with no pre-pregnancy risk factors, women who had 3 or 4 risk factors (overweight or obese BMI, hypertension, random glucose levels of 100-140 mg/dL and/or cholesterol levels ≥ 200 mg/dL) had over 3.6-fold increased risk (p trend < 0.001).

Catov et al⁹⁵ also used data from the CARDIA study to test their hypothesis that dyslipidemia would be associated with preterm birth. This time, data on a cohort of 1,010 women who did not report diabetes mellitus or hypertension at baseline were analysed. In the analysis, serum lipid concentrations were evaluated as quartiles. Analysis was conducted on data for women who were on average, 24 years of age and 6 years prior to the birth. A U-shaped relationship between pre-pregnancy cholesterol levels and the risk of preterm birth was found. Women with cholesterol concentrations in the lowest quartile (< 156 mg/dl) compared to the second quartile (156-171 mg/dl) had three time the risk of preterm birth prior to 34 weeks gestation (OR 3.04; 95% CI; 1.35-6.81), and nearly double the risk for birth between 34 and 37 weeks (OR 1.8; 95% CI 1.10-3.15). Cholesterol in the highest quartile increased risk of preterm birth at less than 34 weeks gestation among women with normotensive pregnancies (OR 3.80; 95% CI 1.07-7.57). There were no associations between triglycerides, LDLC, or HDLC and preterm birth. In this study the mothers again self-reported the main outcome variable; gestational age at birth from which preterm birth was calculated. The study was not designed to examine mechanisms by which maternal pre-pregnancy cardiovascular risk may be associated with preterm birth, which remain unknown.

In a study of similar size in Finland ($n=1142$ primiparous women), Harville et al⁹⁶ did not demonstrate a relationship between fasting pre-pregnancy cholesterol levels and preterm birth. This study used data from the Cardiovascular Risk in Young Finns Study (linked to

birth registry data). Children and adolescents (3-18 years) were recruited in 1980 and seven follow-up assessments took place up to 2007 and the mean time between this study visit and pregnancy was 7.4 years. Birth registry data provided information on 1,142 primiparous women. The risk for preterm birth associated with one standard deviation increase in total cholesterol was RR 1.10; 95% CI; 0.84-1.44. Higher pre-pregnancy triglyceride concentrations however, were associated with a higher risk of gestational diabetes (RR 1.68; 1.25-2.25) and preeclampsia (RR 1.70; 95% CI; 1.08-2.65).

Magnussen et al⁹⁷ examined associations between pre-pregnancy cardiovascular risk factors and preeclampsia in a subsequent pregnancy. They linked data on 3,494 women > 19 years of age who participated in a cross-sectional study of residents from one Norwegian county (HUNT-2 study), with birth registry data. They found a strong linear association between pre-pregnancy diastolic and systolic blood pressure and preeclampsia that included blood pressures within the normal range (< 120 mm Hg systolic and < 80 mm Hg diastolic). Women with pre-pregnancy diastolic blood pressure 68-71 mmHg had a four-fold increased risk for preeclampsia compared with women with diastolic blood pressure < 64 mm Hg (OR 4.3; 95% CI 1.9-9.9). Women with systolic blood pressure in the 117-121 mm Hg range also had four-fold higher risk than women with systolic blood pressure < 111 mm Hg (OR 4.3; 95% CI; 1.8-10.6). They also found positive associations between pre-pregnancy levels of cholesterol and triglycerides. Among 1,488 nulliparous women in the study, triglycerides ≥ 1.54 mmol/l compared to < 0.70 mmol/l doubled risk for preeclampsia (OR 2.3; 95% CI 1.0-4.9), as did cholesterol levels ≥ 5.6 mmol/l compared to < 4.1 mmol/l (OR 2.3; 95% CI 1.1-4.8).

Romundstad et al⁹⁸ also used HUNT-2 data on 3,461 women to examine associations between pre-pregnancy cardiovascular risk factors and infant birthweight. They found (using differences in z scores for birthweight) an inverse negative relationship between pre-pregnancy blood pressure levels and infant birthweight, and an inverse positive relationship between pre-pregnancy lipids and glucose and birthweight. Women with higher blood pressure had smaller babies and women with dyslipidemia and elevated glucose had larger babies. Total cholesterol, HDLC, triglycerides and glucose were measured in the non-fasting state, which may have attenuated the results.

In Canada, Ray et al⁹⁹ prospectively studied outcomes of singleton pregnancies among 196 women who had pre-pregnancy type 1 (n=146) or type 2 diabetes (n=50), and 428 women

who developed GDM. Compared with women with GDM, women with pre-pregnancy diabetes were at increased risk for caesarean section (OR 3.6; 95% CI; 2.3-5.6), shoulder dystocia or cephalo-pelvic disproportion (2.2; 1.3-3.6), gestational hypertension or preeclampsia (3.0; 1.7-5.4) and preterm birth (3.8; 2.5-5.9). The infants of women with pre-existing diabetes were more likely to be admitted to intensive care (4.0; 2.3-6.8) and be large-for-gestational-age (3.5; 2.2-5.9). The study had no control group, so there was no comparison with women who did not have diabetes and there was no assessment of glycaemic control before or during pregnancy. Nevertheless, the study demonstrates the importance of the mother's pre-pregnancy metabolic state and its impact on the intrauterine environment and birth outcomes.

Summary

The studies reviewed in this section show some inconsistencies in their results suggesting links between particular cardio-metabolic risk factors (lipids, blood pressure, glucose) and specific outcomes is likely complex and depends on which exposures and outcomes are being studied. However, certain aspects of abnormal cardio-metabolic profile prior to pregnancy, seems to increase the risk of gestational diabetes mellitus, preeclampsia, and perhaps preterm birth.

Table 2.7 Pre-pregnancy cardio-metabolic risk factors

Author, Year, and Study Design and Study Year	Sample Size, and Setting	Main pre-pregnancy and pregnancy exposures	Main outcome variable/s or case definition	Main study findings	Reported Statistics
Catov et al ⁹⁵ (2010); population-based multicentre prospective cohort study (1985-1986)	Data on 1,010 (49% black) enrolled in the Coronary Artery Risk Development in Young Adults Study (CARDIA) who had at least one singleton birth in a 20 year follow-up	Fasting total cholesterol, triglycerides, HDLC	Pre-term birth 34 - < 37 weeks and pre-term birth < 34 weeks gestation	There was a U-shaped relationship between pre-pregnancy cholesterol and preterm birth Women with cholesterol in the lowest quartile (< 156 mg/dl) compared with the second (156-171 mg/dl) had increased risk of pre-term birth at < 34 weeks and 34-37 weeks Pre-pregnancy cholesterol in the highest quartile (> 195 mg/dl) increased risk for preterm birth < 34 weeks among women with normotensive pregnancies	(OR ⁸¹ 3.04; 1.35-6.81) and (1.86; 1.10-3.15) respectively (3.80; 1.07-7.57)
Gunderson et al ⁹³ (2010); population-based multicentre retrospective cohort study (1985-1986)	Data on 1,164 women without diabetes (participants in the CARDIA study) who delivered 1,809 live births during 20 years	Fasting triglycerides, HDLC, LDLC, total cholesterol, glucose and insulin Pre-pregnancy BMI calculated from <i>measured</i> pre-pregnancy height and weight <i>up to 20 years ago</i>	GDM	Impaired fasting glucose, elevated fasting insulin and low HDLC before pregnancy were associated with GDM among women with no family history of diabetes	(OR ⁸² 4.74; 95% CI; 2.14-10.51; 2.36; 1.20-4.63) and (3.07; 1.62-5.84)
Harville et al ⁹⁶ (2011); population-based cohort data linked to birth registry data (1980-2007)	Data from 1,142 participants in the Cardiovascular Risk in Young Finns study who had a singleton registered first birth, who did not have type 1 diabetes or familial hypercholesterolemia.	Cholesterol, triglycerides, insulin and glucose. Sitting blood pressure	Overall hypertensive disorders of pregnancy Preeclampsia Gestational diabetes	Higher triglycerides were associated with preeclampsia and gestational diabetes	OR ⁸³ 1.70 (95% CI; 1.08-2.65) and (1.68; 1.25-2.25) respectively

⁸¹ Adjusted for race, age, parity, BMI, hypertension in pregnancy, physical activity and years from measurement to birth

⁸² Adjusted for race, family history of diabetes, parity at conception, number of births during the interval, time to the first conception, smoking, and age at preconception examination

⁸³ Adjusted for age, BMI, smoking and socioeconomic status

Hedderson et al ⁹⁴ (2011); case-control study (1984-1996)	GDM cases (n =199) and controls (n =381) were selected from a cohort of women who had a health check examination and a subsequent pregnancy	Serum glucose, total cholesterol levels and diastolic and systolic BP. Pre-hypertension/ hypertension was defined as systolic BP > 120 mm Hg and/ or diastolic > 80 mm Hg or use of antihypertensive treatment Mild hyperglycaemia was defined as serum glucose $\geq$ 100 mg/dL but $\leq$ 140 mg/dL	GDM	Pre-gravid mild hyperglycaemia and pre-hypertension/ hypertension levels were associated with higher risk for GDM The risk of GDM increased with the number of cardio-metabolic risk factors	(OR ⁸⁴ 4.8; 95% CI; 1.7-13.9) and 1.5; 1.0-2.3) respectively (p < 0.001)
Magnussen et al ⁹⁷ (2007); population-based cohort study (1995-1997)	Data on 3,494 women who gave birth after participating in a Norwegian health study	Non-fasting serum total cholesterol, HDLC, triglycerides and glucose BP measured in the sitting position	Preeclampsia	The odds of developing preeclampsia for women with baseline systolic BP > 130 mm Hg were seven fold higher than women with BP < 111 mm Hg Positive associations were found between pre-pregnancy serum levels of triglycerides, cholesterol, LDLC, non-HDLC and risk of preeclampsia. Associations between total cholesterol, LDL cholesterol and non-HDL cholesterol reached statistical significance.	OR ⁸⁵ 7.1 (95% CI; 2.2-23.5) OR 2.1 (95% CI 1.2-3.8), (2.4; 1.3-4.3) and (2.7; 1.5-5.0) respectively
Ray et al ⁹⁹ (2001); hospital-based prospective cohort study (1993-1998)	Data on 624 consecutive pregnancies affected by diabetes mellitus (DM) at one institution. 196 women with pre-gestational DM (146 women with type 1 and 50 women with type 2 DM) and 428 who developed GDM (Canada)	Pre-gestational diabetes or GDM Pre-pregnancy weight, height from antenatal records. Method of measurement <i>not stated</i>	All-cause caesarean section Shoulder dystocia Cephalopelvic disproportion Development of GDM or hypertension	Compared with women with GDM, women with pregestational diabetes were at increased risk for; caesarean section shoulder dystocia, or cephalopelvic disproportion gestational hypertension or toxemia Pre-pregnancy obesity independently associated with large for gestational age and preterm birth	OR ⁸⁶ 3.6 (95% CI; 2.3-5.6) (2.2;1.3-3.6) (3.0;1.7-5.4) 3.3 (1.0-10.6) and 5.1 (1.4-18.6) respectively
Romundstad et al ⁹⁸ (2007); population-based cohort data linked to birth registry data (1995-2005)	Data on 3,461 women who participated in a 1995-1997 (HUNT-2) study on Norwegian women who subsequently had a registered birth up to 2005	Non-fasting serum total cholesterol, HDL cholesterol, triglycerides and glucose Sitting BP	Infant birthweight	Pre-pregnancy BP was inversely associated with birthweight for gestational age. Women with relatively high BP tended to deliver smaller babies. Unfavourable levels of total cholesterol, HDLC, triglycerides and glucose were positively associated with birthweight. Women with unfavourable lipid levels tend to give birth to large babies	Adjusted ⁸⁷ results presented as differences in z score for birthweight and p values for trend

⁸⁴ Adjusted for race/ethnicity, body mass index, parity, family history of diabetes mellitus, alcohol use, smoking, and coffee intake

⁸⁵ Adjusted for maternal age at birth, duration between baseline study and index delivery, education, smoking, time since last meal, and receiving social security benefits

⁸⁶ Adjusted for diabetes class (gestational or pregestational), maternal age, parity pre-pregnancy BMI, net weight gain during pregnancy, history of chronic hypertension, history of preterm delivery before 34 weeks, history of neonatal death or stillbirth, history of prior caesarean section or uterine surgery, presence of placenta praevia. Fetal presentation was added to the analysis of caesarean delivery

⁸⁷ Adjusted for maternal smoking, height, parity, age, education, socioeconomic position, and duration between measurement date and offspring's birth. Additional adjustment for time since the last meal was performed in the analyses of lipids and glucose

2.3.3 Maternal pre-pregnancy lifestyle behaviours (smoking, alcohol use and physical activity) and pregnancy

Six studies summarised in Table 2.8 have examined associations between self-reported maternal pre-pregnancy physical activity levels and the progress of pregnancy. Baptiste-Roberts et al¹⁰⁰ prospectively analysed data on 152 pregnant women who were participants in the Parity, Inflammation and Diabetes study recruited at a medical centre in the US. They examined associations between self-reported pre-pregnancy physical activity and nutrition and test results from a non-fasting oral glucose challenge test (GCT) carried out between 26 and 28 weeks gestation. Leisure time physical activity was assessed using a pre-designed questionnaire (developed by Baecke et al¹⁰¹) commonly used in epidemiological studies. Activity level scores ranged from 1 (low) to 5 (high). In the analysis the scores were classified according to the median (2.75) and low leisure activity (< 2.75) was compared with high activity (≥ 2.75). Dietary intake was assessed at a baseline interview to identify high-fat or low fruit and vegetable intake. A positive GCT was defined as blood glucose measurement ≥ 140 mg/dL in response to a 50g glucose load, and negative as < 140 mg/dL. After adjusting for race, age, parity, GWG and pre-pregnancy BMI, they found that women with high leisure time activity scores (≥ 2.75) compared with women in the low activity category (< 2.75) were 68% less likely to have a positive GCT result (OR 0.31; 95% CI; 0.12-0.86), however, they found no associations between the nutritional measures and GCT.

A hospital-based cohort study of 851 Canadian women also showed a beneficial association between pre-pregnancy self-reported physical activity and glucose tolerance during the subsequent pregnancy. However, it was vigorous sports related activity that was important in this study, rather than leisure time activity measured by Baptiste-Roberts. Retnakaran et al¹⁰² also used the questionnaire developed by Baecke to assess total physical activity and its components (occupation-based activity, leisure time activity and vigorous activity related to sport). The study population was stratified by quartiles of pre-pregnancy physical activity score. Glucose tolerance during pregnancy was determined according serum glucose response to a GCT followed by a fasting 3-h 100g oral glucose tolerance test (OGTT). They found that while mean total physical activity was highest among women who had normal glucose tolerance according to GCT and OGTT, mean pre-pregnancy work activity and leisure time activity components did not differ according to glucose tolerance. They found that only vigorous activity related to sport was significantly

higher in women with normal glucose tolerance, compared to women with impaired or abnormal glucose tolerance. Vigorous activity was also an independent predictor of improved insulin sensitivity ($r=0.21$, $p < 0.0001$).

In an Australian study, van der Ploeg et al¹⁰³ aimed to examine associations between pre-pregnancy physical activity, sedentary behaviour and the development of GDM. They hypothesised that physical activity would have a role independent of pre-pregnancy overweight and obesity. They used data on 2,913 women from the Australian Longitudinal Study on Women's Health who self-reported physical activity and GDM. Physical activity was assessed with a 7-day recall questionnaire to measure frequency and duration of exercise of light, moderate or vigorous intensity. Compared with normal weight women (BMI 18.5-24.9 kg/m²), women who were overweight (BMI 25-30 kg/m²) or obese (BMI $\geq$ 30 kg/m²) had significantly higher risk for GDM (OR 1.92; 95% CI; 1.25-2.96 and 3.11; 1.92-5.03 respectively). They found no relationships between total physical activity or sedentary behaviour and GDM in the subsequent 3 years. An additional separate analysis of vigorous activity also showed no significant association with GDM, even where women reported > 90 min/week (OR 0.95; 95% CI; 0.62-1.46). It is possible that in the time frame between measuring physical activity and the development of GDM (up to 3 years later), women may have changed their behaviours in relation to physical activity and the study may have benefitted from more frequent measurement of the pre-pregnancy exposure.

Lof et al¹⁰⁴ examined the effects of maternal self-reported physical activity levels and pre-pregnancy BMI, on GWG in the second and third trimesters, and on infant birthweight. They studied 223 women recruited prior to 12 weeks gestation at a maternity unit in Sweden. Physical activity levels were scored as the ratio between total activity (defined as work and leisure time activity combined) and energy expended at rest (basal expenditure) and women were classified as having low (1.40-1.69), medium (1.70-1.99) or high (2.00-2.40) physical activity levels. GWG was calculated according to maternal weights measured during gestational weeks 12, 25 and 33. Infant birthweight was extracted from medical records. They found no differences in GWG in the second trimester between women with low, medium or high physical activity levels, However, women who reported high pre-pregnancy physical activity levels gained 0.10kg/week less during the third pregnancy trimester compared with women who reported medium ($p=0.04$) or low levels ($p=0.06$). They also reported a positive association between pre-pregnancy BMI and

GWG. An increase of 5 kg/m² in BMI was associated with a higher 0.05 kg weekly GWG ($p=0.03$). When considered with smoking, parity, education and age, pre-pregnancy physical activity levels and BMI accounted for only 4% of the variation in GWG during the second and third trimesters (adjusted $R^2=0.040$ and 0.042 respectively). Pre-pregnancy BMI was positively associated with infant birthweight, however, there was no association found between physical activity levels and birthweight.

Rudra et al¹⁰⁵ tested an hypothesis that women who are physically active before pregnancy have a decreased risk of preeclampsia. They used data from a 1998-2000 case-control study which recruited women in Washington State and included 244 preeclampsia cases and 470 normotensive controls. They found that participants whose self-perceived usual physical activity in the year prior to pregnancy was reported as very strenuous or involving maximal exertion were 78% less likely to have developed preeclampsia than women who reported negligible or minimal exertion (OR 0.22; 95% CI; 0.11-0.44) independent of pre-pregnancy adiposity. Tyldum et al¹⁰⁶ tested the same hypothesis. They used data on 3,656 women who were participants in the 1984-1986 Norwegian HUNT-1 population-based prospective health study, linked to birth registry data. The frequency, intensity and duration of physical activity were self-reported using a previously validated questionnaire. Only among women who reported physical activity of 120 min/week or more had a tendency for reduced risk of preeclampsia (OR 0.6; 95% CI; 0.3-1.2), otherwise women who were physically active prior to pregnancy were not at reduced risk. Overall, the participants in Rudra's study were more active than the women who took part in the Norwegian study. In the former, 20% reported no physical activity in the year before pregnancy, whereas in the latter 37% reported no or negligible activity. It is also possible, though not evident from the study report, that the participants in Rudra's study may have been younger than the mean age at pregnancy (31 years) of the women in the latter study.

Maternal pre-pregnancy alcohol consumption is the exposure of interest in two studies included in Table 2.8. Naimi et al¹⁰⁷ conducted a large case-control analysis of women who had a live birth following an unintended pregnancy, compared with women who had a birth following an intended pregnancy (cases $n=32,494$, controls $n=40,413$). Women who participated in the Pregnancy Risk Assessment Monitory System in 15 North American states from 1996-1999 provided survey information about pregnancy intention and pre-pregnancy alcohol consumption. Overall 14% of the sample reported binge drinking

(defined as the consumption of 5 or more alcoholic drinks on one occasion). Women with unintended pregnancies were more likely to report pre-pregnancy binge drinking (OR 1.43; 95% CI; 1.13-1.54) and the proportion of women with unintended pregnancies increased with the number of binge drinking episodes (χ^2 test for trend =494.3, $p < 0.001$). Forty percent of pregnancies were unintended among women who reported no pre-pregnancy binge drinking, compared with 60% of pregnancies among women who reported four or more occasions of binge drinking in the 3 months prior to conception (OR 2.3; 95% CI; 2.12-2.57). Women who reported pre-pregnancy binge drinking were also more likely to report smoking and exposure to violence before pregnancy, and to drink alcohol and smoke during pregnancy.

Zammit et al¹⁰⁸ reported that pre-pregnancy drinking quantity predicted intention to drink during pregnancy among Australian women who drank alcohol after confirmation of pregnancy. The Australian study included 248 pregnant women who completed questionnaires at 17-21 gestational weeks. Over half ($n=136$) the women were drinkers prior to and after pregnancy confirmation. Higher household income was associated with higher pre-pregnancy alcohol consumption, intention to drink during pregnancy and actual drinking in pregnancy.

Bakketeig et al¹⁰⁹ reported on tobacco smoking around the time of conception as a risk factor for small-for-gestational-age (SGA) birth among parous women in Scandinavia. Among 4,705 mothers, women who reported smoking and had no other risk factors for SGA (1. previous low birthweight (LBW) infant, 2. low pre-pregnancy weight < 50 kg, 3. a previous perinatal death, 4. presence of chronic renal disease, hypertension or heart disease) had nearly double the risk for SGA birth (RR 1.8; 95% CI; 1.5-2.2). Mothers who had a previous LBW infant also had more than double the risk of SGA (RR 2.4; 95% CI; 1.7-3.3), however, mothers with previous LBW who also smoked had over five and a half times the risk (RR 5.4; 95% CI 4.2-7.0). Risk for SGA doubled among women with low pre-pregnancy weight (RR 1.9; 95% CI; 1.2-3.0), while a combination of low weight and smoking increased the risk four-fold (RR 3.9; 95% CI 2.9-5.4). Women who had low pre-pregnancy weight, a previous LBW infant, who also smoked around the time of conception had nearly six times the risk of having a SGA infant compared to mothers with none of the risk factors (RR 5.7; 95% CI 3.3-9.8).

Summary

The studies reviewed in this section suggest that physical activity prior to pregnancy is probably effective in improving glucose tolerance during pregnancy, however, it was not associated with GDM. Strenuous pre-pregnancy physical activity may reduce the risk of preeclampsia. It is surprising to note that pre-pregnancy physical activity levels were not clearly shown to decrease BMI and in turn the risk of these outcomes. Self-report measures of physical activity have been shown to be both higher and lower than directly measured levels of physical activity which poses a problem among studies assessing its impact on health outcomes.¹¹⁰ Lifestyle behaviours, such as tobacco smoking and alcohol use before and during pregnancy remain as preventable factors associated with complications in pregnancy, low birthweight, preterm birth and serious long-term health consequences for women and their infants.^{71,111,112} The adverse effects of tobacco and alcohol use during pregnancy, combined with high prevalences of unintended pregnancy, suggest that effective intervention strategies in place prior to conception will potentially have the most benefit for optimal health across the lifespan.

Table 2.8 Pre-pregnancy lifestyle behaviours (smoking, alcohol use and physical activity)

Author, Year, and Study Design and Study Year	Sample Size, and Setting	Main pre-pregnancy and pregnancy exposures	Main outcome variable/s or case definition	Main study findings	Reported Statistics
Bakketeig et al ¹⁰⁹ (1993); prospective population-based cohort study (1986-1988)	Data on 5,722 women in Norway and Sweden were categorised to 3 groups. First, a random sample (10% n =561) was selected to serve as control group. A high risk group (n =1,384) had one or more risk criteria for SGA. The remaining 3,777 were low risk.	Maternal cigarette smoking around the time of conception	SGA infant	Mothers who smoked around conception and had no other risk factors had nearly double the risk for SGA infant Previous LBW and smoking increased risk of SGA almost five and a half times Low pre-pregnancy weight, previous LBW delivery and smoking had nearly six times the risk	RR ⁸⁸ 1.8 (95% CI; 1.5-2.2) (5.4; 4.2-7.0) (5.7; 3.3-9.8)
Baptiste-Roberts et al ¹⁰⁰ (2011); hospital-based prospective cohort study (2006-2008)	Subset of data on 152 pregnant women in the first trimester who were participants in the Parity, Inflammation and Diabetes (PID) study recruited in a medical centre in the US	Pre-pregnancy physical activity (self-reported in a questionnaire) Dietary intake before pregnancy assessed at interview	Positive non-fasting oral glucose challenge test (GCT)	Women who scored higher with regard to pre-pregnancy physical activity were 68% less likely to have a positive GCT There was no association between dietary intake and response to the GCT	(OR ⁸⁹ 0.32; 95% CI; 0.12-0.86)
Lof et al ¹⁰⁴ (2008); clinic-based prospective cohort study (2000-2003)	Data on 223 women who accessed antenatal care prior to 12 weeks gestation recruited at a single clinic in Sweden	Pre-pregnancy physical activity levels (self-reported in a questionnaire)	Infant birthweight	High pre-pregnancy BMI and low physical activity levels were associated with excessive GWG Physical activity levels were not associated with birthweight Considered with smoking, parity, education and age, pre-pregnancy physical activity level and BMI explained only 4% of the variation in GWG	In the 3 rd trimester, an increase of 5 kg/m ² in BMI was associated with a 0.05 kg/week higher GWG (p =0.03) (r =0.07; p =0.28) (adjusted ⁹⁰ R ² =0.040 and 0.042, respectively)

⁸⁸ Unadjusted

⁸⁹ Adjusted for race, age, parity, gestational weight gain, and pre-pregnancy body mass index

⁹⁰ Adjusted for smoking, parity, education and age

Naimi et al ¹⁰⁷ (2003); case-control study (1996-1999)	Data on women who experienced an unintended pregnancy (cases: n =32,494) and those who had an intended pregnancy (controls: n =40,413)	Alcohol consumption during the 3 months before pregnancy	Unintended pregnancy	After adjustment for confounders, preconception binge drinking was associated with unintended pregnancy for white women, but not black women. Pre-pregnancy smoking and physical abuse were also significant risk factors for unintended pregnancy among white women	OR ⁹¹ 1.63; 95% CI; 1.47-1.80) and (0.96; 0.77-1.20) respectively (1.46; 1.34-1.59) and (1.48; 1.25-1.75)
Retnakaran et al ¹⁰² (2009); hospital-based cohort study (year/s of data collection not stated)	851 Canadian women completed questionnaires that included questions about physical activity in the year before pregnancy, while they undertook an oral glucose tolerance test during pregnancy	Pre-pregnancy physical activity (self-reported in a questionnaire)	Glucose intolerance during pregnancy	Glucose tolerance improved with increases in pre-gravid physical activity Pre-gravid vigorous/sports activity was significantly higher in women with normal glucose challenge test compared to women with an abnormal glucose challenge test, gestational impaired glucose tolerance and gestational diabetes mellitus	p =0.0244 (p =0.0018), (p =0.0025), and (p =0.0044) respectively
Rudra et al ¹⁰⁵ (2005) case-control study (1998-2002)	Preeclampsia cases (n=244) and 470 normotensive controls in a study conducted in to health care institutions in Washington US	Frequency and self-perceived intensity of physical activity during the year before pregnancy.	Preeclampsia	Independent of pre-pregnancy adiposity, compared to women who reported negligible or minimal exertion prior to pregnancy, women who reported very strenuous to maximal exertion were 78% less likely to have developed preeclampsia	OR ⁹² 0.22 (95% CI; 0.11-0.44)
Tyldum et al ¹⁰⁶ (2010); prospective study based on data linkage between a population-based study and birth registry data (1984-1986)	3,656 women with singleton live births after participation in a Norwegian health study (the HUNT-1 study) and completed two questionnaires and a physical examination	Pre-pregnancy physical activity level self-reported in a questionnaire	Preeclampsia risk	There was no association between pre-pregnancy physical activity and preeclampsia. Only among women who reported a minimum of 120 minutes of physical activity a week was there a tendency for reduced risk	(OR ⁹³ 0.6; 95% CI; 0.3-1.2)
van der Ploeg et al ¹⁰³ (2011); population-based cohort study (2000-2003))	Data on women born between 1973 and 1978 recruited to the Australian Longitudinal Study on Women's Health (ALSWH)	Physical activity self-reported in a 7-day recall questionnaire Sedentary behaviour assessed as total sitting time during a week	GDM assessed through self-report	Physical activity and sedentary behaviour reported in 2000-2003 were not associated with the development of GDM in the subsequent 3 years. Women in the highest quartiles for total sitting time and total moderate and physical activity had no significant higher or lower risk for GDM	OR ⁹⁴ 1.26; 95% CI: 0.72-2.20 and (1.22; 0.70-2.11) respectively

⁹¹ Adjusted for age, education, marital status, parity, preconception health insurance, preconception Medicaid, birth control use at conception, preconception smoking, and preconception physical abuse

⁹² Adjusted for maternal age, race or ethnicity, parity, family history of chronic hypertension, smoking during pregnancy, fruit and vegetable consumption during pregnancy and pre-pregnancy BMI

⁹³ Adjusted for maternal age, parity, smoking and body mass index from participation in the health study to the index birth

⁹⁴ Adjusted for BMI, age, number of children, age at first birth, country of birth and education

Zammit et al ¹⁰⁸ (2008); cohort study (year/s of data collection not stated)	Data on a sub-sample 248 Australian women recruited via a range of sources (health clinics, exercise classes, multi-media) to a project exploring health and well- being during pregnancy	Pre-pregnancy alcohol consumption (self-reported in telephone interviews)	Alcohol use during pregnancy	Women who drank prior to and following pregnancy confirmation significantly decreased alcohol intake in the fortnight after pregnancy confirmation, compared to the fortnight before For women who drank after their pregnancy was confirmed, pre-pregnancy drinking quantity predicted intention to drink, which in turn predicted alcohol consumption in later pregnancy Women with higher family income were more likely to be drinkers, more likely to intend to and consume higher quantities	Mean 67 g alcohol consumption in fortnight prior to confirmation to Mean=18.g post confirmation (p< 0.0001)
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2.4 Summary

The studies included in this literature review have provided a basis from which to understand associations between maternal pre-pregnancy exposures and the course of pregnancy and birth outcomes. However, it should be recognised that there is likely to be significant overlap and intersection between various pre-pregnancy risk factors that may affect women of childbearing age at individual, community and population levels. Daily exposure to increasingly complex social, economic and environmental factors, is likely to create equally complex relationships between disease cause and risk factor effect that are characterised by non-linearity.¹¹³ Explanatory models that accurately describe causal pathways between pre-pregnancy exposures and pregnancy outcomes will no doubt be multifactorial and complex and evidence supporting them will come from many sources.¹¹⁴

2.4.1 Pre-pregnancy adiposity

Diabetes and/or hypertensive disorders of pregnancy

The evidence presented by the studies included in Table 2.1 suggest that elevated maternal pre-pregnancy adiposity is associated with higher risks of hypertensive and glucose disorders of pregnancy. Maintaining stable weight, or reducing overweight or obesity before pregnancy and during inter-pregnancy intervals, seems effective in reducing risk in subsequent pregnancies.

Preterm birth

In Table 2.2, the evidence presented by most of the studies, and its consistency, suggests that pregnancies exposed to low pre-pregnancy BMI, and particularly those with additional risk factors of low or high weight gain during the pregnancy, and maternal ethnicity of a minority group, are at increased risk of spontaneous preterm birth. Obesity may increase the risk of medically induced preterm birth.

Progress of labour and/or method of birth

In Table 2.3, women who were overweight or obese prior to pregnancy had a higher risk of caesarean section delivery compared with women in leaner categories. However, it was also demonstrated that women in higher BMI categories had longer labours that were more

likely to be augmented (perhaps due to their larger infants), that did not necessarily result in caesarean section.

Perinatal mortality/congenital malformations

The results of studies included in Table 2.4 are somewhat mixed. The risk of perinatal mortality (late fetal death or early neonatal death) seemed to increase as pre-pregnancy BMI increased, particularly among nulliparous women. Overweight and obese women had an increased risk of having an infant with a cardiac or neural tube defect, however, they had lower risk for having an infant with gastroschisis. Low pre-pregnancy BMI, especially among very young mothers seemed to increase the risk of gastroschisis.

Infant birthweight

Overall, the studies in Table 2.5 consistently showed associations between low maternal pre-pregnancy BMI and smaller offspring, and high maternal BMI and larger offspring. The importance of gestational weight gain in mediating the relationships is demonstrated in a number of the studies. Low and high weight gains during pregnancy seem to exacerbate the prevalence of abnormal birthweight categories, especially among women with low and high pre-pregnancy BMIs, respectively.

Breastfeeding

The studies in Table 2.6 indicate that overweight and obesity may play a role (perhaps biological) in failure to establish effective breastfeeding. Adjustment for maternal socioeconomic variables (e.g. occupation, education, household income) was carried out in three of the studies,^{85,88} however, this would not account for maternal attitudinal factors and strong social patterning associated with infant feeding practices.¹¹⁵

2.4.2 Cardio-metabolic risk factors

The studies in Table 2.7 show some inconsistencies in their results suggesting links between particular cardio-metabolic risk factors (lipids, blood pressure, glucose) and specific outcomes is likely complex, and depends on which exposures and outcomes are being studied. However, certain aspects of abnormal cardio-metabolic profile prior to pregnancy seem to increase the risk of gestational diabetes mellitus, preeclampsia, and perhaps preterm birth.

2.4.3 Life-style behaviours

The studies reviewed in this section (Table 2.8) suggest that physical activity prior to pregnancy is probably effective in improving glucose tolerance during pregnancy however, it was not associated with risk of GDM. Strenuous pre-pregnancy physical activity may reduce risk of preeclampsia. Alcohol use prior to pregnancy increased the risk of unintended pregnancy and was a predictor of alcohol use during pregnancy. Smoking around the time of conception had an additive effect on increasing the risk of having a small-for-gestational-age baby given other risk factors for the outcome.

2.5 Ethical and practical considerations of research on maternal pre-pregnancy health

To date, the study of maternal pre-pregnancy health status and associations with events in the course of pregnancy and birth outcomes has generated an extensive list of hypotheses about causal associations. Case-control designs are particularly useful for this purpose. For estimating causal effects of risk factors for most health outcomes, randomised experiments are generally considered the gold standard. However, such experiments are usually not feasible in the study of maternal pre-pregnancy health for reasons high costs (both money and time). Further, randomised experimental designs may be inadequate for exploring complex causal pathways associated with the multifactorial nature of obstetrical disease causality.

Ethical considerations are particularly important when studying pregnant women and their foetuses. Randomisation of women to a non-intervention group where it is hypothesised that the intervention may be beneficial is difficult to justify, particularly where a developing foetus may be compromised or saved. However, an example of a useful randomised controlled trial may be on interventions to normalise pre-pregnancy BMI among women *at risk* of pregnancy. Overall, information from observational studies is probably essential to the delivery of high quality evidence-based care by health service providers, but it is important that there is adequate and careful control of confounding.

Each of the studies included in this review has an observational design and most rely on data originally collected for another purpose. Many research questions are studied retrospectively using pre-existing data, often combined with linkage to data in one or more other registers or datasets. These studies on adult populations require no further

participation from the original cohort (where in one case consent was provided in childhood). In most of the studies, no further intervention apart from cleaning, coding, analysing and reporting of data takes place. Pre-existing data provide excellent opportunities for constructing cohorts efficiently and inexpensively. However, data collected for another purpose is frequently incomplete for testing a new hypothesis and it may be difficult to control for confounding variables.

Observational studies are generally regarded as low risk and make no attempt to alter the care that participants undergo. Due diligence regarding referral to appropriate services should however, be exercised when poor health of an individual is identified during a study according to an *a priori* study protocol. The observational methods adopted in the studies presented here are practical for studying the impact of maternal pre-pregnancy health status on subsequent events related to pregnancy and birth. For instance, investigators of these questions usually have no opportunity for predicting when pregnancy will occur. The feasibility of measuring timely pre-pregnancy exposures of interest and outcomes which occur during pregnancy or at birth is fraught with difficulty, though not impossible. For example, in a study on women of child-bearing age that took place in six villages surrounding Pune City in India (1994-1996),¹¹⁶ field workers visited married participants every month to record the date of their last menstrual period. Women who missed consecutive menstrual periods entered the study if pregnancy was confirmed. Pre-pregnancy anthropometric measurements were taken every 3 months and the last measurements made before pregnancy, were used as the pre-pregnancy anthropometry.¹¹⁷ (Publications from this particular study did not meet the inclusion criteria for this review). Because this careful approach to exposure assessment is rare, a limitation among the body of literature on pre-pregnancy health generally is the frequently extended length of time between assessment of exposures, and the outcome occurring (which in many instances is a number of years).

A strength of prospective observational studies for studying pre-pregnancy health is that potential causes of the outcome are measured prior to the occurrence of the outcome. Because prospective studies, by their sequential design can demonstrate that the cause preceded the outcome, the obfuscation around differentiation between cause and effect is decreased. However, extraneous unmeasured factors associated with the exposure and outcome under study are likely to exist. Mann¹¹⁸ provides a summary of factors to consider

when making a judgment with regard to whether a significant association between an exposure and an outcome indicates a causal link or merely an association. Factors to consider, that are demonstrated by some studies in this review includes a dose-response association between the exposure and outcome (e.g. increases or decreases in BMI that demonstrate increases or decreases in the outcome under study) and the biological plausibility of the finding (e.g. leaner mothers more likely to have smaller babies).

The strength of the association is important and Mann argues the greater the magnitude, the more likely it is to be causal. Additionally, if the same associations are observed in various study settings (as is the case with many of the studies included here), the more likely they are to be valid. However, there are well-defined examples where randomised controlled trials have failed to confirm even seemingly robust findings from observational studies¹¹⁹ George Davey Smith provides examples in a 2002 BMJ editorial.¹²⁰ Results from three randomised controlled trials have not confirmed the protective effect of hormone replacement therapy on coronary heart disease reported in a 1991 meta-analysis of observational epidemiological results (RR 0.50; 95% CI 0.43-0.56).¹²¹ The randomised controlled trials resulted in a pooled odds ratio of 1.1 (95% CI; 0.96-1.30). Similar earlier examples are related to dietary vitamins (β carotene and Vitamin E) and their role in the reduction of lung cancer and coronary heart disease respectively. The first observational study that found an association between vitamin β carotene and decreased risk of lung cancer was published in *Nature* in 1981¹²² and a review confirmed the finding in 1990.¹²³ Four years later however, as Davey Smith reports, a randomised controlled trial showed an 18% increase in lung cancer among those taking the vitamin. Randomised controlled trials on Vitamin E and coronary heart disease also failed to reach the same protective conclusions as observational studies on the subject.¹²⁰

2.5.1 Assessment of maternal pre-pregnancy adiposity and study outcomes by self-report

The majority of the studies on pre-pregnancy health had maternal adiposity as a primary exposure variable. Only three of the studies objectively measured height and weight before conception. In a prospective study of Chinese women where enrolment was prior to pregnancy, height and weight were measured by trained technicians with the participants dressed in light clothing.⁸⁰ An important limitation of the study was lack of data on maternal weight gain during pregnancy which could modify associations between pre-pregnancy BMI and birth outcomes. Gunderson et al⁹³ used a retrospective study design

and pre-pregnancy BMI was calculated from measured height and weight, however, the follow-up period in the study was 20 years and the mean interval between measurement of the exposure and the outcome was > 30 months. Ogonowski et al¹²⁴ also accessed pre-existing data that included the most recent measured weight prior to conception obtained from medical records to carry out a retrospective case control study.

Three studies that enrolled participants early in pregnancy used BMI calculated from height and weight measured up to 20 weeks gestation as a proxy for pre-pregnancy adiposity.^{46,49,73} Fourteen studies did not state the methods of measurement and the remaining studies have relied on self-reported measurements. In some studies, height was measured and pre-pregnancy weight was self-reported at enrolment during a first antenatal visit. In one study,⁶¹ participants were asked to recall their pre-pregnancy weight up to two years after the birth. It is not possible to ascertain the benefit of measured over self-reported maternal anthropometry here, primarily due to co-existing study limitations among the three studies that did use anthropometric data that were measured (extended period of time between measurement of exposure and outcome occurring, unmeasured variables and self-reported outcome variables).

Most researchers have listed self-reported height and weight measures among the limitations of their research. Studies that have assessed the validity of self-reported height and weight by comparison with measured height and weight demonstrate that both men and women tend to overestimate their height and underestimate their weight.^{125,126} A Scottish study found a tendency to underestimate both measures.¹²⁷ Other studies have reported that bias and unreliability in self-report increased in relation to the magnitude of underweight or overweight.^{128,129} Underweight adults were more likely to overestimate their weight and overweight adults were more likely to provide a self-reported underestimation. A study of validity of self-reported height and weight in the US among 381 women of reproductive age found that they overestimated height and underestimated weight to a degree that resulted in an average underestimation of BMI by 0.8 kg/m^2 .¹³⁰ Birth certificate data in Florida which is widely used in population-based maternal and infant health research in the US, was also found to overestimate underweight and underestimate obesity prevalence.¹³¹

While some studies suggested that direct measurement of height and weight should be performed wherever possible to avoid invalid findings,^{128,132} others concluded that self-

reported measures are valid for identifying relationships in epidemiological studies.^{127,130,131} However, a 2003 review¹³³ of published research that examined the accuracy of self-reported height and weight reported that of 26 studies on the accuracy of self-reported height (N =39,244 women), 21 studies found that women overestimated their height. Among 34 studies that reviewed the accuracy of self-reported weight (N =57,172 women), all reported that women underestimated weight. The mean variations between self-reported and measured height and weight values were small. However, as the reviewers pointed out, there were very large errors among a significant proportion of women which would lead to significant inaccuracies in the calculation of their body mass indices.

Self-report of anthropometric measurements has advantages of being economical, efficient and non-invasive. Self-report was often a necessity in study designs where participants were recruited at some time during the outcome pregnancy or beyond it, adding an additional element of possible recall bias to others problems associated with self-reported data.

In a number of the studies in this review, the participants were required to self-report the study outcome. The level of detail with which women can recall their experiences of pregnancy and birth may vary among participants, with women whose birth was more recent possibly having greater recall. However, pregnancy and birth is a special event in the lives of women and though there is debate around the level of validity of information provided retrospectively, maternal recall has been shown to be highly accurate despite the passage of time between the event in question and her responses.¹³⁴ Consistent and detailed recall of birth experiences has been documented over periods of time beyond twenty years.¹³⁵

2.6 Conclusion

The body of literature on the effect of maternal pre-pregnancy health status on subsequent pregnancies and birth outcomes is growing and it is characterised by the consistent use of observational epidemiological designs. A considerable number of biologically plausible hypotheses on causal relationships have been generated. The statistical strength of associations and the consistency of results from diverse study settings add validity to many findings. However, future randomised trials, for example of pre-pregnancy encouragement

2. Literature Review

to lose weight among obese women, versus standard care may confirm (or refute) hypotheses established by the studies in this review.

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3. Overview of study methods

This thesis describes a series of four prospective cohort studies, which examine modifiable pre-pregnancy risk factors and their effect on subsequent pregnancy events and birth outcomes. The studies utilised existing cross-sectional health survey data that included Aboriginal and Torres Strait Islander women of childbearing age who participated in the 1998-2000 north Queensland Well Person's Health Check (WPHC) survey. Pregnancy and birth outcomes were ascertained using data linkage to hospital records.

3.1 Ethics approvals

The studies were approved by the Cairns Base Hospital and the University of South Australia's Human Research Ethics committees with support from the peak health councils representing Indigenous people in the region: Apunipima and the Torres Strait Islands and Northern Peninsula Area Health Councils. Approval for access to perinatal data was provided by the Chief Executive Officer – Centre for Healthcare Improvement, under delegation by the Director-General, Queensland Health (Appendix A).

3.2 Data sources and study population

3.2.1 Well Person's Health Check

Between 1998 and 2000, all Indigenous residents aged 15 years and over, in 26 rural and remote Indigenous communities in north Queensland were invited to participate in the WPHC survey. A total of 2,862 Indigenous participants took part. Of that population, there were 1009 women of childbearing age. Six hundred and ten Aboriginal women, 320 Torres Strait Islander women and 79 women who identified as both Aboriginal and Torres Strait Islander, were aged between 15 and 44 years at the time of their health check. The women gave their consent to have their medical (including hospitalisation) records reviewed.

The program was implemented as a partnership between Queensland Health, Apunipima Cape York Health Council, and the Torres Strait and Northern Peninsula Area Health Council.

Methods for the WPHC are reported in detail in the manuscripts in Section 5. Briefly, the survey data included measured anthropometric variables, self-reported lifestyle data, blood pressure and biochemical measures. Table 3.1 below outlines the variables for the WPHC used in the studies and some detail of the data collection methods.

Table 3.1 Pre-pregnancy health status variables from the Well Person's Health Check

Variable	Data collection methods	
<i>Demography</i> Full name Date of birth Residential address Indigenous Australians	- Information provided by participants attending Well Person's Health Check - Aboriginal, Torres Strait Islander, Aboriginal and Torres Strait Islander	
<i>Anthropometry</i> Height Weight Waist circumference	- Fixed stadiometer - To nearest 0.1kg (digital electronic scales) after removing heavy clothing and footwear - Measured to nearest centimetre	
<i>Lifestyle measures</i> Physical activity Alcohol intake Nutrition Smoking status	- Self-report 7 day recall - Self-report 7 day recall - Self-report 24 hour recall - Self-report	- interviewer recorded the number of days with physical activity of moderate intensity for 30 minutes or more. - consumption translated into daily and weekly standard drink totals and women were categorised as non-drinkers, safe drinkers, or 'risky' drinkers (NHMRC guidelines). - number of serves of fruit and vegetables recorded. One serve defined as one piece of fruit, half a cup of vegetables, or one cup of salad. Picture of examples of serving sizes were used to aid data collection - current smokers were asked how many cigarettes they smoked daily. Non-smokers were asked if they had ever smoked and if so, when they had stopped.
Blood pressure	Three separate measurements over approximately 10 minutes using Dinamap 800 automated blood pressure monitor. Mean systolic and diastolic measurement calculated.	
<i>Venous blood collection</i> Total cholesterol HDL cholesterol Triglycerides Glucose Red cell folate Gamma-glutamyl transferase RPR for syphilis	- Fasting venous blood samples collected in 4ml ethylenediamine tetra-acetic acid vacuum tube and 8.5ml clotted vacuum tube. Clotted tubes were spun for 10 minutes in a portable centrifuge within one hour of collection. Glucose and blood lipids were measured using photometric enzyme endpoint assay with Cobas Integra 700/400 (Roche Diagnostic, USA). - Red cell folate was measured using the Bayer Advia Centaur automated immunoassay system (Bayer, Australia) by Queensland Health Pathology Service in Brisbane (Ref. range 295-1800 nmol/L) - Gamma-glutamyl transferase was measured with kinetic photometric procedure with Cobas Integra 800 (Roche Diagnostic, USA). - High titres were referred to specialised treatment services and appropriate treatment was confirmed.	
<i>Urine collection</i> Urinary albumin:creatinine ratio Chlamydia/gonorrhoea PCR	- Urine from first morning void or two hours since most recent void self-collected in 50ml containers and sample transferred to 10ml tube. - If protein was detected by dipstick urinalysis (Combur-test, Roche) or if the participant was obese or known to have diabetes or hypertension, albumin:creatinine ratio was measured by immunoassay in grams per mole. From May 1999, to the end of the project, the albumin: creatinine ratio was measured in all urine specimens. - Polymerase Chain Reactions were measured with Roche Amplicor <i>Chlamydia Trachomatis/Neisseria Gonorrhoea</i>, Branchburg NJ, USA	

3.2.2 Linkage of WPHC and hospitalisations data

To complete the requirements of a longitudinal aspect of the WPHC survey, data on individuals who participated were linked to Queensland hospitalisations data (using probabilistic methods based on name, date of birth and address). The purpose of the linkage was to assess the number of and reasons for hospital admissions among the health check participants subsequent to the WPHC and up to the study censor date in March 2008. The linkage meant that each WPHC participant could now be identified using a unique Queensland hospital Unit Registration number. From this point, the data were de-identified.

3.2.3 Hospitalisations related to childbearing among WPHC participants

An analysis of International Classification of Disease (ICD) 9 and ICD10 and corresponding Diagnosis Related Groups from hospitalisations data of WPHC participants identified women of childbearing age (15-44 yrs) within the cohort who had been hospitalised for a pregnancy related condition. The details of the relevant ICD9 and 10 codes are outlined in Table 3.2.

Table 3.2 ICD codes related to pregnancy, childbirth and the puerperium

ICD Version	ICD Code	Description
ICD -9 codes 630-676: Complications of pregnancy, childbirth, and the puerperium	630-633	Ectopic and molar pregnancy
	634-639	Other pregnancy with abortive outcome
	640-648	Complications mainly related to pregnancy
	650-659	Normal delivery, and other indications for care in pregnancy, labour and delivery
	660-669	Complications occurring mainly in the course of labour and delivery
	670-676	Complications of the puerperium
ICD-10 codes O00-O99: Pregnancy, childbirth and the puerperium	O00-O08	Pregnancy with abortive outcome
	O10-O16	Oedema, proteinuria and hypertensive disorders in pregnancy, childbirth and the puerperium
	O020-O29	Other maternal disorders predominantly related to pregnancy
	O030-O48	Maternal care related to the foetus and amniotic cavity and possible delivery problems
	O60-O75	Complications of labour and delivery
	O80-O84	Delivery
	O85-O92	Complications predominantly related to the puerperium
	O95-O99	Other obstetric conditions, not elsewhere classified

3.2.4 Linkage of WPHC data to Queensland perinatal data

Perinatal data is collected routinely in all Australian states and Territories. It is aggregated and reported at state and national levels. Perinatal data for women who took part in the WPHC who were subsequently hospitalised for a birth (birth of an infant of at least 20 weeks completed gestation or a birthweight > 400 g where gestation is unknown) were requested from Statistical Output, Health Statistics Centre, Queensland Health. Table 3.3 provides a summary of perinatal data variables provided. If a woman had more than one birth in the study period, only data for the birth nearest to her health check were requested.

Table 3.3 Variables of interest from the Queensland Perinatal Data Collection

Mother's details	- Name, DOB, address and Indigenous status - Admission date and place of delivery - Serology - Antenatal transfer?
Previous pregnancies	- Number and outcome of previous pregnancies - Method of delivery last birth - Number of previous caesareans
Present pregnancy	- Last menstrual period and expected date of confinement - Number of antenatal visits - Current medical conditions - Pregnancy complications - Smoking (incomplete) - Procedures and operations
Labour and delivery	- Onset of labour - Presentation of foetus - Method of delivery - Labour and delivery complications
Baby	- DOB - Birthweight, gestation, head circumference and length at birth - Born alive, stillborn - APGAR score at 1 and 5 minutes - Resuscitation
Postnatal details	- Neonatal morbidity and treatment - Congenital abnormality - Was baby admitted to intensive or special care nursery - Maternal complications of puerperium and discharge status and date - Infant discharge status and date

3.3 Exclusions

Women who were likely to have been pregnant at the time of their health check were excluded based on the date of their health check, the date of their subsequent delivery and the estimated gestation of the pregnancy at the time of birth.

4. The Studies

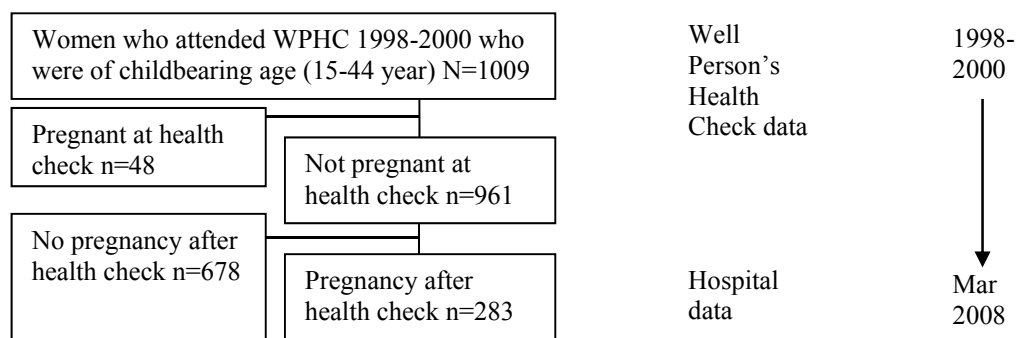
The section below presents the research questions and flow of participants for each analysis.

4.1 Study 1: Pre-pregnancy characteristics of women who did and did not become pregnant

Research question

What are the pre-pregnancy characteristics of women who experienced pregnancy in the 8-10 years subsequent to participation in the WPHC survey when they were aged 15-44 years?

Figure 4.1 Study flow chart: women who did and did not become pregnant

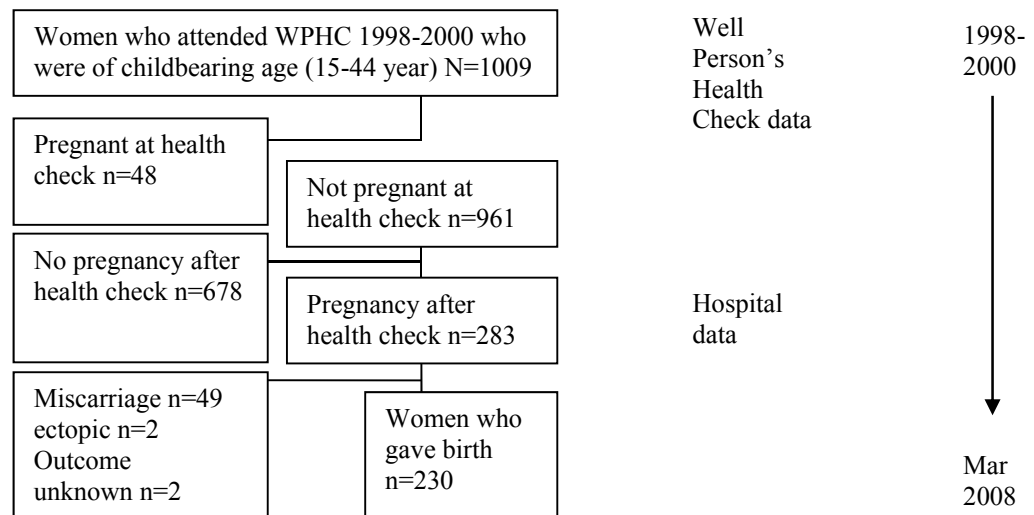


4.2 Study 2: Associations between pre-pregnancy health and miscarriage

Research question

Is maternal pre-pregnancy health status associated with miscarriage?

Figure 4.2 Study flow chart: women who miscarried



4.3 Study 3: Associations between pre-pregnancy health and events during pregnancy

Research questions

Is maternal pre-pregnancy health status associated with adverse events in the course of pregnancy?

Is maternal pre-pregnancy health status associated with:

- diabetes in pregnancy?
- hypertensive disorders in pregnancy?

Figure 4.3 Study flow chart: diabetes in pregnancy

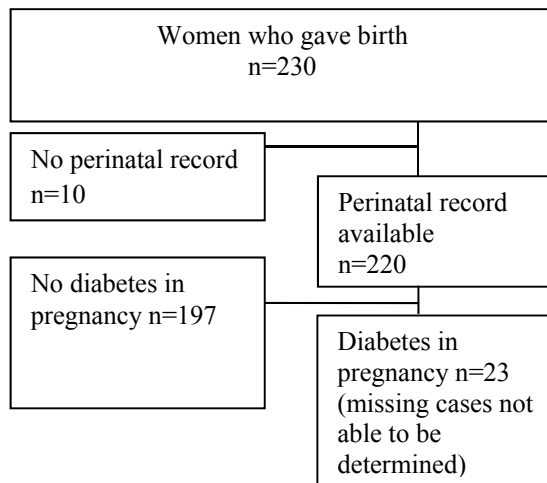
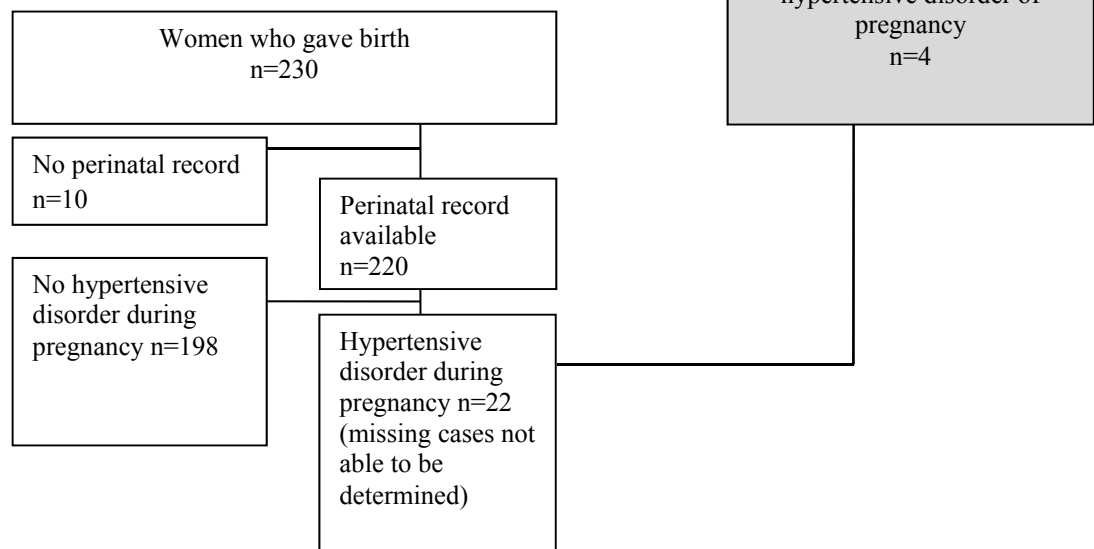


Figure 4.4 Study flow chart: hypertension in pregnancy



4.4 Study 4: Associations between pre-pregnancy health and infant birth outcomes

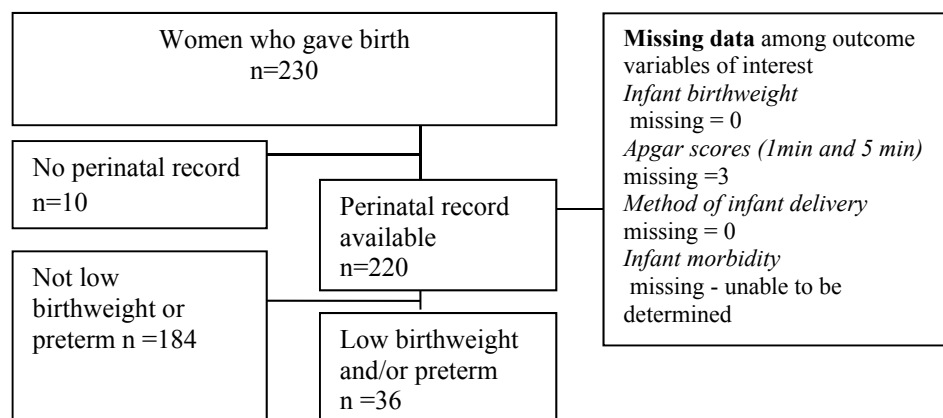
Research questions

Is maternal pre-pregnancy health associated with infant birth outcomes?

Is maternal pre-pregnancy health associated with:

- infant birthweight?
- infant Apgar scores?
- method of infant delivery?
- infant morbidity in the early postnatal period?

Figures 4.5 Study flow chart: infant birth outcomes



5. Presentation of the studies

This thesis includes a combination of two published papers, and two unpublished empirical manuscripts (one is under review at the time of submission). As such, the format brings unavoidable duplication that includes repeated descriptions of the study setting and study methods. With permission from the respective journals (Appendix B), the two published papers are presented as reproductions. Contributions of each author are provided in Statement of Authorship at Appendix C.

The papers and manuscripts are ordered so that they follow a logical pathway of events that may occur in pregnancy. The first paper describes the pre-pregnancy characteristics of women who became pregnant after the baseline health check compared with the women who did not become pregnant during the study follow-up period. Among the women who became pregnant, the paper then examines pre-pregnancy risk factors for miscarriage in the subsequent pregnancy. The second and third papers focus on adverse events in the course of pregnancy. Associations between maternal pre-pregnancy characteristics and subsequent diabetes in pregnancy and hypertensive disorders of pregnancy are presented in papers 2 and 3 respectively. Finally associations between maternal pre-pregnancy health status and birth outcomes according to infant anthropometry and events in the early postnatal period are examined (paper 4).

5.1 Paper # 1: Pre-pregnancy predictors linked to miscarriage among Aboriginal and Torres Strait Islander women in North Queensland, Australia

Pre-pregnancy predictors linked to miscarriage among Aboriginal and Torres Strait Islander women in North Queensland

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Australia has one of the lowest perinatal mortality rates in the developed world.¹ High-quality antenatal, intrapartum and postnatal specialist health services provide care that results in the best possible and usually satisfactory outcome of pregnancy for most women. The comparative poor health of Indigenous mothers and their babies, however, remains a major problem.²

Health during pregnancy depends largely on maternal health before pregnancy. In 2003, a World Health Organization (WHO) expert group developed a strategy to optimise fetal development and concluded that a mother's ability to meet the needs of a developing pregnancy is dependent on her physical and emotional health and her health behaviours both *before* and during pregnancy.³ This study describes pre-pregnancy health factors among a cohort of Indigenous women and their association with subsequent pregnancy and miscarriage.

Indigenous Australians of all age groups suffer a higher prevalence of a large number of health conditions ranging from acute injuries and infections to chronic diseases.

The impact of this generally poor health status on fertility, pregnancy complications and outcomes has not been well documented. The importance of determining the nature of pre-pregnancy factors, the extent of their influence on maternal and child health and the extent to which the factors are amenable to intervention, is increasingly important in the light of our better understanding of how the intra-uterine environment can affect the immediate and long-term health of the next generation.^{4,5} Recommendations and clinical guidelines for pre-pregnancy care to promote health and prevent disease in women of reproductive age have been developed in the United States⁶ but targeted pre-pregnancy initiatives have not been a priority in Australia, particularly in Indigenous communities.⁷

Antenatal care has the specific aim of improving the health of pregnant women and their babies and it is an expected and accepted part of pregnancy for most women.⁸ For many Indigenous women however, initiation of the care can be late in pregnancy⁹⁻¹¹ or the care may be sporadic. Some interventions are contra-indicated after conception (immunisation against

Abstract

Objective: Identify preventable pre-pregnancy risk factors that may affect the prevalence of miscarriage among a cohort of Australian Indigenous women.

Methods: Data from 1,009 Indigenous women of childbearing age who participated in a 1999-2000 health screening program in far-north Queensland were linked to Queensland hospitalisation data. Women who attended hospital after their health check (censor date: March 2008) for a pregnancy-related condition were identified. Characteristics associated with becoming pregnant and subsequent miscarriage were analysed using generalised linear models.

Results: After adjusting for age and ethnicity, women who became pregnant were more likely to be smokers and to have low red cell folate at baseline. The risk of miscarriage increased with age. Women who reported risky drinking or had elevated gamma-glutamyl transferase were also at higher risk. After further adjustment for risky drinking, the presence of chlamydia or gonorrhoea before pregnancy was associated with miscarriage. The presence of both infections at baseline compared with women who had no infection, again after further adjustment for risky drinking, was strongly associated with miscarriage; these women had more than a four-fold increase in risk (PR: 4.57 [2.21-9.46]). Elevated body mass index, high blood pressure and smoking were not statistically significantly associated with risk of miscarriage.

Conclusions and implications: A high prevalence of pre-pregnancy sexually transmitted infections and high rates of risky drinking are associated with miscarriage among young Indigenous women in rural and remote communities in north Queensland.

Key words: Indigenous, pre-pregnancy, miscarriage

Aust NZ J Public Health. 2011; 35:343-51
doi: 10.1111/j.1753-6405.2011.00729.x

Submitted: September 2010

Revision requested: January 2011

Accepted: March 2011

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rubella) or are less effective (folic acid supplementation) and need to be addressed pre-pregnancy.¹² Additionally, it is more difficult to provide optimal medical treatment for women with chronic conditions such as hypertension and diabetes during pregnancy.¹³ Considered together, these factors suggest that the *availability* of antenatal care alone is insufficient to address maternal and infant morbidity and mortality among Indigenous Australians.

Miscarriage is one of the most common complications of pregnancy and is associated with maternal psychological and physical risks. It is estimated that 10-15% of clinically confirmed pregnancies and up to 31% of all pregnancies result in the condition.^{14,15} In more than half the pregnancies that end in miscarriage, the presence of a genetic abnormality in the conceptus can be identified,¹⁶ however in a substantial proportion of cases the causes remain undetermined.

The aim of this study was to identify pre-pregnancy risk factors amenable to prevention or early intervention to improve pregnancy health among Indigenous mothers.

Methods and procedures

Participants

The Aboriginal and Torres Strait Islander women in this study were participants in the 1999-2000 Well Person's Health Check (WPHC) cross-sectional survey when they were aged between 15 and 44 years. Methods for the survey have been reported in detail elsewhere.¹⁷ Briefly, the WPHC was conducted in 26 rural and remote Indigenous communities in the Bowen, Cairns, Cape York, Torres Strait and Mount Isa Health Service Districts with support from peak Indigenous Health Councils. All Indigenous residents aged 13 years and older were invited to attend a health check through print media, local radio, word-of-mouth via the health service, community council and community groups. 2,862 Indigenous people aged 15 years and or more attended the WPHC, leading to an overall participation rate of 44.5%¹⁸ (according to local census data). Of these, 51.7% were female and 1,009 were women of childbearing age (15-44 years).

Ethics approval to examine the WPHC data and subsequent hospitalisations data relevant to the WPHC participants in the current study, was provided by the Cairns Base Hospital and University of South Australia's Human Research Ethics committees. The study is also supported by Apunipima and the Torres Strait Islands and Northern Peninsula Area Health Councils.

Baseline health check

At baseline participants were weighed to the nearest 0.1 kg after removing any heavy clothing and footwear using digital electronic scales (UC300; A.N.D., Tokyo, Japan) and height was measured to the nearest centimetre (Harpender anthropometer; Holtain Ltd, Crymych, UK). Body mass index (BMI) was calculated as weight (kg) divided by height squared (m²). Waist measurements were recorded to the nearest centimetre. Anthropometric cut-offs were set according to WHO criteria.¹⁹

Blood pressure was assessed after recording three separate

measurements over approximately 10 minutes while the participant remained seated, using a Dinamap 800 automated blood pressure monitor (Criticon; Tampa FL, US). The mean systolic and diastolic measurements were calculated from the three readings.

Participants were asked to recall the number of serves of fruit and vegetables eaten over the 24 hours before their health check interview. A seven-day recall method was used to assess the duration and intensity of physical activity during the week leading up to the health check, as well as the number of days a participant performed at least 20 minutes of moderate physical activity. If the participant undertook this minimum of 20 minutes exercise on at least five days in the week, they were categorised as having an adequate level of physical activity.

Smoking status was self-reported. Alcohol consumption was assessed using a seven-day recall method, with drinkers being asked to report the types and amounts of alcohol consumed. Participants were then categorised as being non-drinkers or safe or harmful ('risky') drinkers according to the NHMRC guidelines (National Health and Medical Research Council, 2001). Risky drinking for women was defined as more than two standard drinks per day or more than four on any single occasion. The physical activity, smoking and alcohol intake measures have been used in other studies (International Diabetes Institute) and the 24-hour recall dietary questionnaire and red cell folate (RCF) have been validated against other measures of micronutrient intake and the quality of the diet with respect to fruit and vegetables.^{20,21}

Early morning fasting venous blood samples were collected in ethylenediamine tetra-acetic acid vacuum tubes and clotted serum separator vacuum tubes. Blood products in the clotted tubes were separated using a portable centrifuge within one hour of collection. Biochemical measurements of the blood specimens included fasting glucose, triglycerides, total cholesterol, high density lipoprotein cholesterol (HDL), gamma-glutamyl transferase (GGT), RCF and rapid plasma reagin (RPR) for syphilis.

Blood glucose and blood lipids were measured using photometric enzyme endpoint assay with Cobas Integra 700/400 (Roche Diagnostic). GGT was measured by a kinetic photometric procedure with Cobas Integra 800 (Roche Diagnostic, USA). Elevated GGT was defined as GGT ≥ 50 U/L, and GGT < 50 U/L as normal according to criteria established by Queensland Health Pathology Service (www.health.qld.gov.au/qhcss/qhps/default.asp). RCF was measured using the Bayer Advia Centaur automated immunoassay system (Bayer, Australia) by Queensland Health Pathology Service in Brisbane. The reference range was 295-1800 nmol/L.

Urine specimens provided by participants in sterile 50 mL containers were from the first morning void or a sample at least two hours from the most recent void. Dipstick urinalysis (Combur-test, Roche) tested the samples for protein, pH, nitrites, leucocytes and blood. If protein was detected, or if the participant was known to have diabetes, hypertension or obesity (BMI > 30 kg/m²) albumin creatinine ratio (ACR) was measured by immunoassay in g/mol. Microalbuminuria was defined as ACR = 3.4-34 g/mol, and overt albuminuria as ACR > 34 g/mol.²² From May 1999 to the end of the project, ACR testing was performed on all urine specimens.

Polymerase Chain Reaction testing (Roche Amplicor CT/NG, Branchburg NJ) for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* was conducted on all urine specimens. Those with a detected sexually transmitted infection (STI) were recalled for treatment and referred to district sexual health services for contact tracing and follow-up testing.

Linkage of WPHC data and hospitalisations data

Unique WPHC identification numbers were linked to Queensland hospital Unit Registration numbers using probabilistic deterministic matching of name, date of birth and residential address. An analysis of International Classification of Disease (ICD) 9 and ICD 10 and corresponding Diagnostic Related Groups from the hospitalisations data for WPHC participants has identified those women of childbearing age (15-44 yrs) who were hospitalised for a pregnancy-related condition in the time from their health check to March 2008. Hospitalisation data identifies births of at least 20 weeks completed gestation (or of 400 g or more birthweight where gestation is not known)²³ and miscarriages (pregnancy loss occurring before 20 weeks' gestation or of a fetus less than 400 g weight if the gestation is unknown). None of the hospitals included in the study offered services for women seeking elective termination of pregnancy during the study period.

Forty-eight women who were pregnant at the time of their health check were excluded from analysis. Of the remaining 961, if a woman experienced more than one pregnancy, only the pregnancy and pregnancy outcome that occurred nearest their health check was included. Two hundred and eighty-three women had a pregnancy-related hospital admission in the subsequent 8-10 years after baseline and 49 of the admissions were due to miscarriage or for a post-miscarriage procedure. Two women whose pregnancy loss was due to ectopic pregnancy and two women whose pregnancy outcome is unknown were also excluded from analyses predicting miscarriage.

Statistical analysis

Log binomial generalised linear modelling (GLM) was used to calculate prevalence ratios and 95% confidence intervals for baseline characteristics associated with becoming pregnant, and with subsequent miscarriage. The model was adjusted for age and ethnicity. Associations between sexually transmitted bacterial infections and miscarriage were further adjusted for risky alcohol drinking. Poisson modelling was used where the log binomial model did not converge. The analysis was conducted using STATA 11 (STATAcorp, College Station, Texas, USA).

Results

Table 1 describes the pre-pregnancy characteristics of the 678 women who did not have a subsequent pregnancy-related hospital admission and those who did. The likelihood of pregnancy decreased with age. Women aged 25-34 years at the time of their health check were less likely to experience a subsequent pregnancy compared to younger women (PR 0.64 [95%CI 0.53-0.77]). Women aged 35 to 44 were much less likely to become pregnant (PR 0.10 [0.06-

0.17]). Adjustment for ethnicity and age greatly diminished many associations (waist circumference ≤ 90 cm, BMI 30+, elevated blood pressure, presence of gonorrhoea or chlamydia, elevated total cholesterol or triglycerides, fasting blood glucose > 5 , elevated GGT).

Of the cohort, only 14 women reported having the recommended two serves of fruit and five serves of vegetables in the 24 hours before their health check. Approximately 20% of the cohort had low serum RCF. It was this group of women that were more likely to become pregnant (PR 1.33 [1.10-1.60]) and pre-pregnancy low RCF was a factor among nearly 30% of pregnancies. Women who experienced a subsequent pregnancy were also more likely to report current smoking at their health check (PR 1.38 [1.13-1.69]).

Among the 283 women who did become pregnant, 49 (17.3%) were admitted to hospital for care due to miscarriage or for a post-miscarriage procedure. Table 2 shows that the risk of miscarriage increases with age and highlights an association between 'risky' alcohol intake and miscarriage. After adjusting for age and ethnicity, women who reported risky drinking at their pre-pregnancy health check, and those who had elevated levels of the liver enzyme GGT were more than twice as likely to have their subsequent pregnancy end in miscarriage compared to non-drinkers (PR 2.24 [1.11-4.52]; PR 2.31 [1.30-4.10], respectively). After further adjustment for risky drinking, the presence of chlamydia or gonorrhoea before pregnancy was associated with miscarriage (PR 2.24 [1.26-3.99]; PR 3.07 [1.80-5.24], respectively). The presence of both infections at baseline compared with women who had no infection, again after further adjustment for risky drinking, was strongly associated with miscarriage; these women had over a four-fold increase in risk (PR: 4.57 [2.21-9.46]). Elevated body mass index, high blood pressure and self-reported smoking were not statistically significantly associated with risk of miscarriage.

Discussion

This study demonstrates that women of child-bearing age living in rural and remote communities in north Queensland face numerous health challenges before their first pregnancy and during intervals between pregnancies. Women who experienced pregnancy after their health check were younger, more likely to be smokers and to report poor nutrition and have low RCF. Pregnancy loss due to miscarriage was more prevalent with increasing maternal age, risky drinking (and elevated GGT) and with diagnosis of prior STI.

Self-reported tobacco use in this study was high. Tobacco use during pregnancy has been associated with low birthweight, premature birth, placental abruption, and other adverse maternal and infant outcomes.²⁴ Serum folate levels in smoking pregnant women have been shown to be 33% lower than non-smokers in the first 10 weeks of pregnancy. By the end of pregnancy, continuous decreases led to a 60% difference in folate levels in smokers compared with non-smokers.²⁵ Though the mechanisms by which tobacco smoking produces adverse fetal effects are not known precisely, smoking does influence patterns of nutrition, and tobacco independently reduces the bio-availability of folate.²⁶

Table 1: Characteristics of women who became pregnant in the 8-10 years following their 1998-2000 health check and those that did not become pregnant (n=961).

Characteristic	No pregnancy subsequent to health check		Became pregnant subsequent to health check		PR (95% CI)	Adjusted for age and ethnicity PR (95% CI)
	n=678	%	n=283	%		
Indigenous group						
Aboriginal	426	72.4	162	27.6	1.00	
Torres Strait Islander	198	67.1	97	32.9	1.19 (0.97-1.47)	
Aboriginal and Torres Strait Islander	54	69.2	24	30.7	1.12 (0.78-1.60)	
Age						
15-24	162	50.6	158	49.4	1.00	
25-34	239	68.5	110	31.5	0.64 (0.53-0.77)	
35-44	277	94.9	15	5.1	0.10 (0.06-0.17)	
Height						
<157	149	75.6	48	24.4	1.00	
157-161	163	68.8	74	31.2	1.28 (0.94-1.75)	
>161-166	195	68.7	89	31.3	1.29 (0.95-1.73)	
>166	169	70.1	72	29.9	1.23 (0.89-1.68)	
Waist circumference						
<80cm	145	62	89	38	1.00	1.00
80-89cm	109	63	64	37	0.97 (0.75-1.25)	1.23 (0.99-1.54)
≥90cm	420	76.5	129	23.5	0.62 (0.49-0.77)	1.00 (0.80-1.26)
BMI category (kg/m ²)						
<18.5	68	67.3	33	32.7	0.87 (0.64-1.21)	1.00
18.5-25	170	62.7	101	37.3	1.00	1.00 (0.80-1.25)
25-30	161	69.7	70	30.3	0.81 (0.63-1.04)	0.85 (0.67-1.09)
30+	277	77.8	79	22.2	0.60 (0.46-0.76)	0.84 (0.62-1.13)
Alcohol intake						
Non-drinker	203	71	83	29	1.00	1.00
Alcohol drinker (safe)	174	68.5	80	31.5	1.09 (0.84-1.40)	0.97 (0.78-1.22)
Alcohol drinker (risky)	274	70.4	115	29.6	1.02 (0.80-1.29)	1.06 (0.86-1.31)
Smoker						
No	290	77.3	85	22.7	1.00	1.00
Yes	384	66.6	192	33.3	1.50 (1.20-1.86)	1.38 (1.13-1.69)
Fruit and vegetable intake						
<2 and 5 serves	668	70.5	279	29.5	1.00	1.00
≥2 and 5 serves	10	71.4	4	28.6	0.97 (0.42-2.23)	0.77 (0.37-1.62)
Enough physical activity						
No	525	69.2	234	30.8	1.00	1.00
Yes	153	75.7	49	24.3	0.79 (0.60-1.03)	0.80 (0.63-1.02)
Systolic blood pressure						
≤110	162	63.5	108	36.5	1.00	1.00
111-120	171	67.9	81	32.1	0.80 (0.64-1.01)	0.85 (0.69-1.05)
121-130	173	79.4	45	20.6	0.52 (0.38-0.70)	0.65 (0.49-0.87)
131-140	101	74.3	35	25.7	0.64 (0.47-0.89)	0.91 (0.67-1.24)
>140	68	84	13	16	0.40 (0.24-0.67)	0.85 (0.51-1.43)
Diastolic blood pressure						
≤60	189	60.2	125	39.8	1.00	1.00
61-70	229	70.3	97	29.7	0.75 (0.60-0.93)	0.97 (0.78-1.19)
71-80	165	79	44	21	0.53 (0.39-0.71)	0.88 (0.65-1.18)
81-90	62	84.9	11	15.1	0.38 (0.22-0.66)	0.82 (0.47-1.41)
>90	30	85.7	5	14.3	0.36 (0.16-0.82)	0.90 (0.41-2.01)

Table 1: Characteristics of women who became pregnant in the 8-10 years following their 1998-2000 health check and those that did not become pregnant (n=961) (continued).

Characteristic	No pregnancy subsequent to health check		Became pregnant subsequent to health check		PR (95% CI)	Adjusted for age and ethnicity PR (95% CI)
	n=678	%	n=283	%		
RPR for syphilis						
Non-reactive	513	69	231	31	1.00	1.00
Reactive	139	76.4	43	23.6	0.76 (0.57-1.01)	1.06 (0.83-1.37)
Chlamydia						
Not detected	591	72.1	229	27.9	1.00	1.00
Detected	69	59	48	41	1.47 (1.15-1.87)	0.99 (0.79-1.24)
Gonorrhoea						
Not detected	642	71.3	259	28.7	1.00	1.00
Detected	17	51.5	16	48.5	1.69 (1.17-2.43)	0.93 (0.66-1.32)
Chlamydia and gonorrhoea						
No infection	584	72.6	220	27.4	1.00	1.00
Single infection detected	64	58.2	46	41.8	1.53	1.05 (0.84-1.32)
Both detected	11	55	9	45	1.64	0.85 (0.53-1.38)
Cholesterol						
≤5.5	538	68.2	251	31.8	1.00	1.00
>5.5 (elevated)	119	82.6	25	17.4	0.55 (0.38-0.79)	0.83 (0.58-1.19)
Triglycerides						
≤2	530	68.7	242	31.3	1.00	1.00
>2 (elevated)	126	79.7	32	20.3	0.65 (0.47-0.90)	0.98 (0.71-1.35)
HDL cholesterol						
>1	342	69.1	153	30.9	1.00	1.00
≤1 (low)	274	69.7	119	30.3	0.98 (0.80-1.20)	0.95 (0.79-1.13)
Red cell folate						
≥295	537	74.3	186	25.7	1.00	1.00
<295 (low)	115	56.4	89	43.6	1.7 (1.39-2.07)	1.33 (1.10-1.60)
Fasting glucose						
<4	40	61.5	25	38.5	1.00	1.00
4-4.4	141	62.9	83	37.1	0.96 (0.68-1.40)	0.93 (0.65-1.32)
4.5-4.9	201	64.8	109	35.2	0.91 (0.65-1.29)	0.97 (0.69-1.37)
5-5.5	139	78	39	22	0.56 (0.38-0.86)	0.75 (0.49-1.12)
5.5-6.9 (impaired)	59	83	12	17	0.44 (0.24-0.80)	0.71 (0.40-1.25)
≥7 (diabetic)	74	90.2	8	9.8	0.25 (0.12-0.52)	0.55 (0.27-1.12)
Albumin creatinine ratio						
<3.4	396	69.1	177	30.9	1.00	1.00
3.4-34	113	75.8	36	24.2	0.78 (0.57-1.06)	1.12 (0.84-1.52)
>34	40	88.9	5	11.1	0.36 (0.16-0.83)	0.63 (0.28-1.42)
Gamma-glutamyl transferase						
≤50	538	68.2	251	31.8	1.00	1.00
>50 (elevated)	117	82.4	25	17.6	0.55 (0.38-0.80)	0.93 (0.64-1.35)
Metabolic syndrome ^b						
No	408	66.2	208	33.8	1.00	1.00
Yes	270	78.3	75	21.7	0.64 (0.51-0.81)	0.97 (0.78-1.22)

Notes:

a. Denominators vary because of missing values.

b. Metabolic syndrome defined by International diabetes federation criteria composing of waist circumference ≥80 cm, plus two or more of the following: raised triglycerides (≥1.7 mmol/L), reduced high-density lipoprotein (<1.29 mmol/L), raised blood pressure (systolic ≥130mm Hg or diastolic ≥85 mm Hg) and raised plasma glucose (≥5.6 mmol/L).

Table 2: Predictors of pregnancy loss due to miscarriage.

Characteristic	Birth ^a		Miscarriage ^a		PR (95% CI)	Adjusted for age and ethnicity PR (95% CI)
Indigenous group	n=230	%	n=49	%		
Aboriginal	134	84.8	22	15.2	1.00	
Torres Strait Islander	79	81.4	18	18.6	1.22 (0.70-2.13)	
Aboriginal and Torres Strait Islander	17	70.8	7	29.2	1.92 (0.93-3.96)	
Age						
15-24	133	85.8	22	14.2	1.00	
25-34	89	81.7	20	18.3	1.29 (0.74-2.25)	
35-44	8	53.3	7	46.7	3.29 (1.69-6.40)	
Height						
<157 cm	36	80	9	20	1.00	1.00
157-161 cm	61	83.6	12	16.4	0.82 (0.38-1.79)	0.74 (0.33-1.66)
>161-166 cm	72	80.9	17	19.1	0.96 (0.46-1.97)	0.76 (0.35-1.63)
>166 cm	61	84.7	11	15.3	0.76 (0.34-1.7)	0.64 (0.28-1.48)
Waist circumference						
<80 cm	73	83.9	14	16.1	1.00	1.00
80-89 cm	53	85.5	9	14.5	0.90 (0.42-1.95)	0.84 (0.39-1.83)
90+ cm	103	79.8	26	20.2	1.25 (0.69-2.25)	0.91 (0.47-1.77)
BMI category (kg/m ²)						
<18.5	24	75	8	25	2.04 (0.92-4.55)	2.11 (0.95-4.69)
18.5-25	86	87.8	12	12.2	1.00	1.00
25-30	57	81.4	13	18.6	1.52 (0.74-3.12)	1.30 (0.63-2.69)
30+	63	79.8	16	20.2	1.65 (0.83-3.29)	1.21 (0.57-2.58)
Alcohol intake						
Non-drinker	74	89.2	15	10.8	1.00	1.00
Alcohol drinker (safe)	64	81	9	19	1.75 (0.81-3.77)	1.63 (0.76-3.47)
Alcohol drinker (risky)	84	77.9	25	22.1	2.04 (1.01-4.14)	2.24 (1.11-4.52)
Smoker						
No	68	81	16	19	1.00	1.00
Yes	161	83	33	17	0.89 (0.52-1.53)	0.94 (0.55-1.61)
Fruit and vegetable intake						
<2 and 5 serves	226	82.2	49	17.8		
≥2 and 5 serves	4	-	0	-		
Enough physical activity						
No	187	81.3	43	18.7	1.00	1.00
Yes	43	88	6	12	0.65 (0.30-1.45)	0.63 (0.29-1.39)
Systolic blood pressure						
≤110	92	86.8	14	13.2	1.00	1.00
111-120	65	80.3	16	19.7	1.49 (0.78-2.88)	1.50 (0.78-2.88)
121-130	34	77.3	10	22.7	1.72 (0.83-3.58)	1.79 (0.85-3.77)
131-140	29	85.3	5	14.7	1.11 (0.43-2.87)	1.06 (0.41-2.72)
>140	9	69.2	4	30.8	2.33 (0.90-6.02)	1.94 (0.74-5.06)
Diastolic blood pressure						
≤60	105	85.4	18	14.6	1.00	1.00
61-70	76	79.2	20	20.8	1.42 (0.80-2.54)	1.31 (0.73-2.36)
71-80	37	86.1	6	13.9	0.95 (0.41-2.24)	0.84 (0.35-2.00)
81-90	8	72.7	3	27.3	1.86 (0.65-5.35)	1.45 (0.48-4.42)
>90	3	60	2	40	2.73 (0.86-8.68)	2.36 (0.70-7.94)

Table 2: Predictors of pregnancy loss due to miscarriage (continued).

Characteristic	Birth ^a		Miscarriage ^a		PR (95% CI)	Adjusted for age and ethnicity PR (95% CI)
	n=230	%	n=49	%		
RPR for syphilis						
Non-reactive	192	84.2	36	15.8	1.00	1.00
Reactive	33	76.7	10	23.3	1.47 (0.79-2.74)	1.40 (0.76-2.60)
Chlamydia						
Not detected	193	84.7	35	15.4	1.00	1.00
Detected	33	73.3	12	26.7	1.74 (0.98-3.08)	2.24 (1.26-3.99) ^c
Gonorrhoea						
Not detected	217	84.4	40	15.6	1.00	1.00
Detected	7	50	7	50	3.21 (1.77-5.83)	3.07 (1.80-5.24) ^c
Chlamydia and gonorrhoea						
No infection	187	85.4	32	14.6	1.00	1.00
Single infection detected	34	75.6	11	24.4	1.67 (0.91-3.06)	2.19 (1.18-4.07)
Both detected	3	42.9	4	57.1	3.91 (1.91-8.01)	4.57 (2.21-9.46) ^c
Cholesterol						
≤5.5	206	83.1	42	16.9	1.00	1.00
>5.5 (elevated)	21	84	4	16	0.94 (0.37-2.42)	0.81 (0.31-2.08)
Triglycerides						
≤2	201	84.1	38	15.9	1.00	1.00
>2 (elevated)	24	75	8	25	1.57 (0.81-3.06)	1.40 (0.72-2.73)
HDL cholesterol						
>1	121	80.1	30	19.9	1.00	1.00
≤1 (low)	102	86.4	16	13.6	0.68 (0.39-1.19)	0.63 (0.36-1.09)
Red cell folate						
≥295	150	81.1	35	18.9	1.00	1.00
<295 (low)	76	87.4	11	12.6	0.67 (0.36-1.25)	0.70 (0.37-1.32)
Fasting glucose						
<4.5	95	88.8	12	11.2	1.00	1.00
4.5 – <5	86	80.4	21	19.6	1.75 (0.91-3.37)	1.67 (0.87-4.51)
5 – <5.5	30	76.9	9	23.1	2.06 (0.94-4.5)	1.59 (0.71-3.58)
<5.5	16	80	4	20	1.78 (0.64-4.97)	1.14 (0.38-3.41)
Albumin creatinine ratio						
<34	171	81.4	39	18.6	1.00	1.00
≥34 (elevated)	4	80	1	20	1.08 (0.18-6.36)	1.04 (0.17-6.22)
Gamma-glutamyl transferase						
≤50	212	85.5	36	14.5	1.00	1.00
>50 (elevated)	15	60	10	40	2.76 (1.56-4.86)	2.31 (1.30-4.10)
Metabolic syndrome ^b						
No	174	85.3	30	14.7	1.00	1.00
Yes	56	74.7	19	25.3	1.7 (1.03- 2.86)	1.49 (0.86- 2.59)

Notes:

a. Denominators vary because of missing values.

b. Metabolic syndrome defined by International diabetes federation criteria composing of waist circumference ≥80cm, plus two or more of the following: raised triglycerides (≥1.7 mmol/l), reduced high-density lipoprotein (<1.29 mmol/l), raised blood pressure (systolic ≥130mm Hg or diastolic ≥85mm Hg) and raised plasma glucose (≥5.6 mmol/l).

c. Prevalence ratios and 95% Confidence Intervals for chlamydia, gonorrhoea, and chlamydia and gonorrhoea have been adjusted for age, ethnicity and risky alcohol drinking.

In this study one third of the women who became pregnant had low levels of RCF at their pre-pregnancy health check. RCF is a direct measure of tissue folate stores. These stores fall after about four months of negative folate balance and usually implies significant depletion.²⁷ There is an increased requirement for folate during pregnancy²⁸ and women are dependent on dietary sources or supplementation to ensure adequate supplies.²⁹ Few women in the cohort reported having recommended serves of two fruits and five vegetables in the 24 hours before their health check. Randomised trials show firm evidence of prevention of neural tube defects (NTD) with periconceptional folic acid,³⁰ and folate deficiency during pregnancy has been associated with a range of adverse pregnancy outcomes including pre-term birth, low birth weight, placental abruption, preeclampsia and increased miscarriage.³¹

The 17% of women in this study whose clinically recognised pregnancy ended in miscarriage is slightly higher than reported by other studies among different populations (10-15%), however the women who had low RCF before their pregnancy were not at a higher risk. An association with self-reported risky drinking at baseline was apparent. Other studies have reported similar effects among women using alcohol during the first and second trimesters of pregnancy.^{32,33} The most significant risk factor for miscarriage among the women in this study was a prior diagnosis of chlamydia or gonorrhoea, particularly where diagnosis included the detection of co-infection with both bacteria.

Associations between prior and active chlamydia infection and miscarriage have been documented,³⁴⁻³⁶ however data from a number of studies do not support an association.³⁷⁻⁴¹ A case-control study to analyse risk factors for miscarriage did find a five-fold increase for women who had a history of pelvic inflammatory disease,⁴² a condition common in the sequela of infections with chlamydia and gonorrhoea with well-documented links to primary and secondary infertility. It is also possible that women with an infection before pregnancy are at higher risk of re-infection during pregnancy.

High rates of bacterial STI have persisted in Indigenous communities across Australia.⁴³ Despite the high prevalence of STIs in north Queensland rural and remote communities,¹⁷ young men and women in one study demonstrated extremely low levels of knowledge of personal risk in relation to STI.⁴⁴ Nationally in 2006 the rate of diagnosis of gonorrhoea among Indigenous women of reproductive age (13-39 years) was more than 100 times higher than that among non-Indigenous women and the rate of diagnosis of chlamydia was 9-11 times higher in the 13-19 years age group and 5-6 times higher in 20-29 year olds.⁴³ In north Queensland, initiatives directed at more active detection and management of STIs were implemented after the completion of the WPHC in 2000.

A limitation of this study is the low participation rate of eligible women (<50%) in the baseline survey. However, the associations we found between baseline risk and health outcomes, particularly for STIs and risky alcohol drinking in the study cohort have high internal validity. A larger number of participants may have confirmed an association with obesity, high blood pressure and smoking, and further investigations are warranted.

Conclusion

In addition to high rates of smoking and risky drinking, Indigenous women of childbearing age living in rural and remote north Queensland are confronted with a range of factors that have an adverse effect on health generally, including a high prevalence of sexually transmitted infections, poor nutrition and associated obesity. In this study, miscarriage was associated with pre-pregnancy sexually transmitted infections and risky drinking. Community initiatives aimed at improving reproductive health should have ongoing evaluation using robust and sustainable methods, including the use of linked data.

Acknowledgements

This work was supported by a Postgraduate Scholarship (Award Reference No PP08A 4066) from the National Heart Foundation of Australia, by NHMRC Project Grant 456402, and in part by NHMRC Project Grant 279402. JL is supported by an NHMRC Australia Fellowship. The authors have no conflict of interest. The contributions of each author in this work are: S.C. performed the data analysis and interpretation of data and drafting of the manuscript. R.M. conceived and implemented the baseline study. R.M., J.L. and A.E. contributed to data analysis and critical revision of the manuscript for important intellectual content. The authors would like to thank the health staff in the participating communities, and Apunipima and the Torres Strait Islands and NPA Health Councils for their support for the project. In particular, the authors extend their thanks to all the participants.

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5.2 Paper # 2: Pre-pregnancy predictors of diabetes in pregnancy among Aboriginal and Torres Strait Islander women in North Queensland, Australia

Pre-Pregnancy Predictors of Diabetes in Pregnancy Among Aboriginal and Torres Strait Islander Women in North Queensland, Australia

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Published online: 30 September 2011
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Abstract To identify pre-pregnancy risk factors for diabetes in pregnancy among a cohort of Australian Indigenous women. Data on 1,009 Indigenous women of childbearing age who participated in a 1998–2000 health screening program in far north Queensland were linked to Queensland hospitalisations data. Women who attended hospital after their health check for a pregnancy-related condition were identified. The data on women who were hospitalised for birth were also linked to Queensland perinatal data. Of 220 women who gave birth, 23 had diabetes in the pregnancy following their health check. A strong predictor of having a subsequent pregnancy affected by diabetes was suboptimal glucose control before conception. The presence of the metabolic syndrome predicted over a threefold increase in risk among non-diabetic women after adjustment for age and ethnicity (PR, 3.50; 95% CI, 1.54–8.00). For each 1-cm increase in waist circumference, there was an age-adjusted increase in risk of 4% for diabetes in pregnancy (1.04; 1.01–1.06). For each

1-mmHg increase in blood pressure (systolic and diastolic), there was an age-adjusted increase in risk of 3% (1.03; 1.01–1.05 and 1.03; 1.00–1.07, respectively). Associations between hypercholesterolaemia and dyslipidaemia and diabetes in the subsequent pregnancy were diminished after adjustment for age and ethnicity. The risk for women with “hyper-triglyceridaemic waist” phenotype before pregnancy was diminished by adjustment for age, ethnicity and baseline fasting glucose. Alcohol intake, smoking, level of physical activity and red cell folate showed little effect. Identification of women at particularly high risk for future diabetes in pregnancy, given their pre-pregnancy health, is important so that they can manage their risks and where overweight or obesity is a factor, interventions aimed at weight management should be implemented.

Keywords Indigenous · Pre-pregnancy · Diabetes · Gestational diabetes

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Introduction

Diabetes is highly prevalent among Indigenous peoples in Australian North Queensland communities. A health survey conducted in 1998–2000 with a six year follow-up found 12.6% of all adults and 22.8% of those aged 35 years or more had self-reported previous diagnosis of diabetes [1] at a time when the general Australian prevalence was 7.4%. [2]. In the follow-up study the incidence of diabetes was nearly four times higher than the general Australian population [3]. Importantly, the incidence in women of child bearing age (15–34 years) was 2.89% per year among Aboriginal women, 1.21% among Torres Strait Islander women and 2.44% among women who identified as both Aboriginal and Torres Strait Islander. In the Torres Strait

Islands, situated between the tip of Queensland and Papua and New Guinea, a sixfold increase in type 2 diabetes in pregnancy was documented between 1999 and 2006 [4]. As the numbers of young women who have glucose intolerance increase, more women will begin their pregnancies with diabetes or features of the metabolic syndrome.

This high incidence of diabetes in women of child bearing age has important ramifications on pregnancy outcomes. Maternal hyperglycaemia is associated with increased risks for complications of both mother and infant. Apart from birth injuries and medical interventions for fetal macrosomia, gestational diabetes increases the risk for miscarriage and stillbirth, infant developmental abnormalities, hypoglycaemia and respiratory distress and maternal pre-eclampsia and later development of type 2 diabetes [5, 6]. It is well established that pregnancies complicated by pre-existing maternal type 1 and type 2 diabetes have two to four-fold increased risk for major infant congenital malformations [7].

While the evidence is clear about the need to manage diabetes before and during pregnancy with beneficial effects on the mother, the pregnancy and the fetus [8], there is less evidence addressing the contribution of pre-pregnancy risk factors for development of gestational diabetes (diabetes that is first recognised during pregnancy). This is particularly important for Australian Indigenous women even though their individual risk factors may not vary compared to other groups, because they have a high risk of incident diabetes and often present late for antenatal care [9]. Identifying women at higher risk of diabetes in pregnancy offers the opportunity to implement preventive measures before conception. We examined pre-pregnancy factors that predict diabetes in pregnancy in a cohort of Indigenous women of childbearing age in North Queensland communities.

Methods

Participants

The Aboriginal and Torres Strait Islander women in this study were participants in the 1998–2000 Well Person's Health Check (WPHC) cross-sectional survey [10], which included 26 rural and remote Indigenous communities in the Bowen, Cairns, Cape York, Torres Strait and Mount Isa Health service districts. All adults were invited to participate in the WPHC through printed media, local radio and word of mouth via the local health service, community council and community groups. The survey was attended by 2,862 self-selected Indigenous people aged 15 years and over, giving an overall participation rate of 44.5% [1] (according to local census data); 51.7% were female.

Participants overall, were not different demographically from the age and sex distribution of the Indigenous population who did not attend, based on census data. A subset of women from the original survey data were selected for the current study because the health check occurred when they were aged between 15 and 44 years (a generally accepted range of childbearing age).

Baseline Health Check

Participants were invited to attend in the early morning following at least an 8 h fast. Each person was weighed in light clothing to the nearest 0.1 kg on digital electronic scales (UC300; AND, Tokyo, Japan), and height was measured to the nearest centimetre (Harpender anthropometer; Holtain Ltd, Crymych, United Kingdom). Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Waist measurements were recorded to the nearest centimetre. Anthropometric cut-offs were set according to WHO criteria [11]. Seated blood pressure was recorded three times over approximately 10 min with a Dinamap 800 automated blood pressure monitor (Criticon; Tampa, Florida, USA), and mean systolic and diastolic measurements were calculated.

Fruit and vegetable intake was self-reported by a 24-h recall and a 7-day method was used to assess the duration and intensity of physical activity. If the participant reported a minimum of 30 min of exercise on at least 5 days in the week, they were categorised as having an adequate level of physical activity. Current smoking status was self-reported. Participants who drank alcohol self-reported the types and amounts of alcohol consumed in the week before the health check; they were then categorised as being safe drinkers, non drinkers or harmful ("risky") drinkers according to Australian National Health and Medical Research Council guidelines (2001). Risky drinking for women was defined as more than two standard drinks per day or more than four on any single occasion. The physical activity, smoking and alcohol intake measures have been widely used [1] and the 24-h recall dietary questionnaire and red cell folate measure have been validated against other measures of micronutrient intake and the quality of the diet with respect to fruit and vegetables [12, 13].

Early-morning fasting venous blood samples were collected in ethylenediamine tetra-acetic acid vacuum tubes and clotted serum separator vacuum tubes (centrifuged and separated within 1 h). The biochemical measurements included glucose, triglycerides, total cholesterol, high density lipoprotein cholesterol, γ -Glutamyl transferase and red cell folate. Glucose and lipids were measured using photometric enzyme endpoint assay with Cobas Integra 700/400 (Roche Diagnostic, USA). γ -Glutamyl transferase was measured by a kinetic photometric procedure with

Cobas Integra 800 (Roche Diagnostic). An elevated level was defined as ≥ 50 and < 50 U/l as normal, according to criteria established by Queensland Health Pathology Service (<http://www.health.qld.gov.au/qhcss/qhps/default.asp>). Red cell folate was measured with the Bayer Advia Centaur automated immunoassay system (Bayer, Australia) by the Queensland Health Pathology Service in Brisbane. The reference range for this assay was 295–1,800 nmol/l.

Urine specimens collected in sterile 50-ml containers were either the first morning or at least 2 h after the most recent void. If protein was detected by dipstick urinalysis (Combur-test, Roche) or if the participant was known to have diabetes, hypertension or obesity ($\text{BMI} > 30 \text{ kg/m}^2$), the albumin:creatinine ratio was measured by immunoassay in grams per mole. Microalbuminuria was defined as an albumin:creatinine ratio of 3.4–34 g/mol, and macroalbuminuria as > 34 g/mol [14]. From May 1999 to the end of the project, the albumin:creatinine ratio was measured in all urine specimens.

Metabolic syndrome among women without diabetes is defined according to International Diabetes Federation criteria comprising waist circumference ≥ 80 cm plus two or more of the following: raised triglycerides (≥ 1.7 mmol/l), reduced high-density lipoprotein (< 1.29 mmol/l), raised blood pressure (systolic ≥ 130 mm Hg or diastolic ≥ 85 mm Hg) and raised plasma glucose (≥ 5.6 mmol/l). Family history about diabetes was not collected. “Hypertriglyceridaemic waist” phenotype is defined as triglycerides > 2 mmol/l and waist circumference ≥ 88 cm [15].

Linkage of WPHC data, hospitalisations data and perinatal data: Three datasets were linked to bring together information on pre-pregnancy factors and diabetes in the next pregnancy. First, WPHC records were linked to Queensland hospital Unit Registration numbers by probabilistic matching of name, date of birth and residential address. International Classification of Disease (ICD) 9 and ICD 10 codes and corresponding diagnosis-related groups from hospitalisations data identified women (aged 15–44 years at baseline health check) who were hospitalised for pregnancy-related conditions (censor date: March 2008). The third dataset was provided by Statistical Output, Health Statistics Centre, Queensland Health, and included selected perinatal data specific to those women who were hospitalised for birth; birth of an infant of at least 20 weeks completed gestation or a birthweight > 400 g when gestation was unknown [16]. When a woman was hospitalised for more than one birth during the follow-up period, only perinatal data for the birth nearest to the health check was requested. Women who were likely to have been pregnant at the time of their health check were excluded based on the date of their health check, the date of their subsequent delivery and the estimated gestation of the pregnancy at the time of birth (Fig. 1).

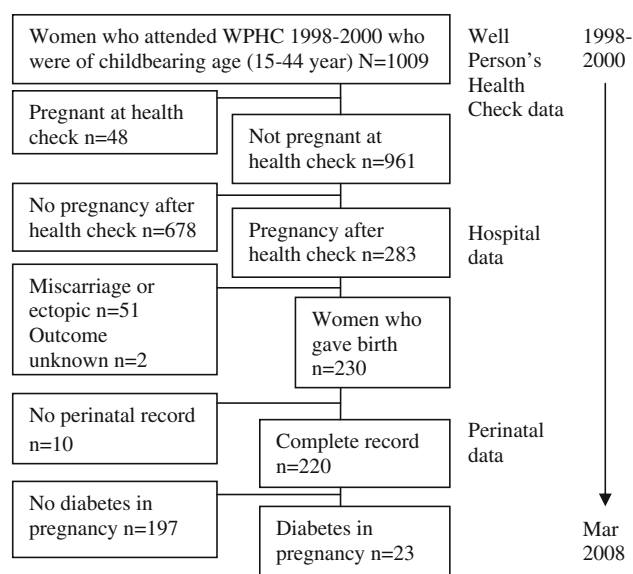


Fig. 1 Flow chart including datasets linked (right) and timeline (far right)

The study was approved by the Cairns Base Hospital and University of South Australia's Human Research Ethics committees with support from the peak health councils representing Indigenous people in the region: Apunipima and the Torres Strait Islands and Northern Peninsula Area Health Councils.

Statistical Analysis

The data were analysed in a generalised linear model (Poisson distribution) with robust variance estimates to calculate prevalence ratios (PRs) and 95% confidence intervals (CIs) with 2 sided P values of 0.05 for baseline characteristics associated with diabetes during the first subsequent pregnancy. The model was adjusted for age and, because it was expected that Aboriginal and Torres Strait Islander women would differ in their anthropometric and metabolic characteristics, ethnicity was included in the adjusted model. The analysis was conducted with STATA 11 (STATAcorp, College Station, Texas, USA).

Results

At baseline (1998–2000), there were 1,009 women of childbearing age (15–44 years) in the study sample. We excluded 48 women because they were likely to have been pregnant at the time of their health check. Table 1 shows most of the remaining 961 women were Aboriginal (61.2%); Torres Strait Islander women made up 30.7% of the cohort, and 8.1% identified as both Aboriginal and

Table 1 Baseline metabolic and behavioural characteristics of all 961 women of childbearing age (15–44 years) who participated in the well person's health check who were not pregnant at the time of their health check

Pre-pregnancy characteristic	No	% of n or mean (SD)
Indigenous group		
Aboriginal	588	61.2
Torres Strait Islander	295	30.7
Aboriginal and Torres Strait Islander	78	8.1
Age group (years)		
15–24	320	33.3
25–34	349	36.3
35–44	292	30.4
Age (mean, SD)	961	29.2 (8.3)
Waist circumference (cm)		
<80	234	24.5
80–87.9	143	15
≥88	579	60.5
Waist circumference (mean, SD)	956	93.8 (17.8)
BMI category (kg/m ²)		
<18.5	101	10.5
18.5–25	271	28.3
25–30	231	24.1
≥30	356	37.1
BMI (mean, SD)	959	28.1 (7.8)
Smoker		
No	375	39.2
Yes	581	60.8
Alcohol use		
Safe drinker	254	27.3
Non drinker	286	30.8
Risky drinker	389	41.9
Fruit and vegetable intake (serves)		
<2–5	945	98.5
≥2–5	14	1.5
Enough physical activity		
No	759	79
Yes	202	21
Systolic blood pressure (mmHg)		
≤120	522	54.6
>120	435	45.4
Systolic blood pressure (mean, SD)	957	120.4 (15.8)
Diastolic blood pressure (mmHg)		
≤80	849	88.7
>80	108	11.3
Diastolic blood pressure (mmHg, SD)	956	66.5 (11.8)
Cholesterol (mmol/l)		
≤5.5	789	84.6
>5.5 (elevated)	144	15.4
Cholesterol (mean, SD)	933	4.6 (1)

Table 1 continued

Pre-pregnancy characteristic	No	% of n or mean (SD)
Triglycerides (mmol/l)		
≤2	772	83
>2 (elevated)	158	17
Triglycerides (mean, SD)	930	1.5 (1.1)
HDL cholesterol (mmol/l)		
>1	495	55.7
≤1 (low)	393	44.3
HDL cholesterol (mean, SD)	888	1.1 (0.3)
Red cell folate (nmol/l)		
≥295	723	78
<295 (low)	204	22
Red cell folate (mean, SD)	927	414.1 (161.7)
Fasting glucose (mmol/l)		
≤5.5	777	83.6
>5.5–6.9	71	7.6
≥7	82	8.8
Fasting glucose (mean, SD)	930	5.3 (2.3)
Albumin:creatinine ratio (mg/mmol)		
≤3.4	573	74.7
>3.4–34	149	19.4
>34	45	5.9
Albumin:creatinine ratio (mean, SD)	767	9.4 (37.3)
γ-Glutamyl transferase (U/l)		
≤50	789	84.8
>50 (elevated)	142	15.2
γ-Glutamyl transferase (mean, SD)	931	33.5 (40.6)
Hyper-triglyceridaemic waist ^a		
No	800	86.4
Yes	126	13.6
Metabolic syndrome ^b		
No	600	71.3
Yes	242	28.7
Diabetes ^c		
No	842	90.5
Yes	88	9.5

Denominators vary because of missing values

^a Defined as raised triglycerides (>2 mmol/l) and waist circumference ≥88 cm)

^b Defined by International Diabetes Federation criteria as comprising waist circumference ≥80 cm plus two or more of the following: raised triglycerides (≥1.7 mmol/l), reduced high-density lipoprotein (<1.29 mmol/l), raised blood pressure (systolic ≥130 mm Hg or diastolic ≥85 mm Hg) and raised plasma glucose (≥5.6 mmol/l). Women with diabetes excluded

^c Defined as confirmed by doctors on a medical chart audit or a fasting glucose level ≥7 mmol/l or 2-h glucose tolerance test result of >11.1 mmol

Table 2 Baseline characteristics of the study cohort, by diabetic status in the subsequent pregnancy

Pre-pregnancy characteristic	No diabetes during pregnancy (n = 197)		Diabetes during pregnancy (n = 23)	
	n	% of n or mean (SD)	n	% of n or mean (SD)
Indigenous group				
Aboriginal	116	58.9	12	52.2
Torres Strait Islander	66	33.5	9	39.1
Aboriginal and Torres Strait Islander	15	7.6	2	8.7
Age years (mean, SD)	197	23.3 (5.2)	23	28.3 (5.7)
Waist circumference (cm)				
<80	66	33.7	4	17.4
80–87.9	40	20.4	2	8.7
≥88	90	45.9	17	73.9
Waist circumference (mean, SD)	196	87.9 (15.2)	23	102.1 (18.3)
BMI category (kg/m ²)				
<18.5	22	11.2	1	4.3
18.5–25	77	39	4	17.4
25–30	48	24.4	6	26.1
≥30+	50	25.4	12	52.2
BMI (mean, SD)	197	25.8 (6.7)	23	31.4 (7.8)
Smoker				
No	59	30.1	6	26.1
Yes	137	69.9	17	73.9
Alcohol use				
Safe drinker	54	28	6	26.1
Non drinker	60	31.1	11	47.8
Risky drinker	79	40.9	6	26.1
Fruit and vegetable intake (serves)				
<2–5	194	98.5	22	95.7
≥2–5	3	1.5	1	4.3
Enough physical activity				
No	158	80.2	19	82.6
Yes	39	19.8	4	17.4
Systolic blood pressure (mmHg)				
≤120	141	71.9	9	39.1
>120	55	28.1	14	60.9
Diastolic blood pressure (mmHg)				
≤80	190	96.9	19	82.6
>80	6	3.1	4	17.4
Cholesterol (mg/dL)				
≤5.5	181	92.8	15	68.2
>5.5 (elevated)	14	7.2	7	31.8
Triglycerides (mmol/l)				
≤2	175	90.7	17	77.3
>2 (elevated)	18	9.3	5	22.7
HDL cholesterol (mmol/l)				
>1	110	57.6	7	31.8
≤1 (low)	81	42.4	15	68.2
Red cell folate (nmol/l)				
≥295	126	65	17	77.3

Table 2 continued

Pre-pregnancy characteristic	No diabetes during pregnancy (n = 197)		Diabetes during pregnancy (n = 23)	
	n	% of n or mean (SD)	n	% of n or mean (SD)
<295 (low)	68	35	5	22.7
Fasting glucose (mmol/l)				
≤5.5	192	98.5	10	45.5
>5.5	3	1.5	12	54.5
Albumin:creatinine ratio (mg/mmol)				
≤3.4	123	83.1	11	61.1
>3.4	24	16.9	7	38.9
γ-Glutamyl transferase (U/l)				
≤50	183	93.8	20	90.9
>50 (elevated)	12	6.2	2	9.1
Hyper-triglyceridaemic waist ^a				
No	184	95.8	17	77.3
Yes	8	4.2	5	22.7
Metabolic syndrome ^b				
No	158	80.2	7	46.7
Yes	39	19.8	8	53.3

Denominators vary because of missing values

^a Defined as raised triglycerides (>2 mmol/l) and waist circumference ≥88 cm)

^b Defined by International Diabetes Federation criteria as comprising waist circumference ≥80 cm plus two or more of the following: raised triglycerides (≥1.7 mmol/l), reduced high-density lipoprotein (<1.29 mmol/l), raised blood pressure (systolic ≥130 mm Hg or diastolic ≥85 mm Hg) and raised plasma glucose (≥5.6 mmol/l). Women with diabetes excluded

Torres Strait Islander. Abdominal obesity (waist circumference ≥88 cm) was found in 60.5% of women, and 37.1% had a BMI > 30. Self-reported rates of tobacco smoking and risky drinking in the week before the health check were high (60.8 and 41.9%, respectively), fruit and vegetable intake and adequate physical activity were low (1.5 and 21% respectively). Impaired glucose tolerance or fasting blood glucose ≥7 was detected in 16.4% of the cohort; 9.5% either self-reported or had a diagnosis of diabetes made at the health check, and 28.7% of non-diabetic women had features of the metabolic syndrome.

Figure 1 shows that 283 women were hospitalised for a pregnancy-related condition between their health check in 1998–2000 and March 2008; 51 pregnancies ended in miscarriage or because of an ectopic pregnancy, and two pregnancy outcomes were unknown. In the time up to the censor date, 230 women were hospitalised for birth and 10 of these women were excluded because perinatal records were not matched. There were no multiple births. Of the remaining 220 women, 23 had diabetes during their next pregnancy. Of these, eight cases had pre-existing glucose intolerance or diagnosed diabetes.

The 23 women who had diabetes in the pregnancy after their health check were on average 5 years older than the 197 women who had no diagnosis of diabetes. Aboriginal women, Torres Strait Islander women and women who

identified as both Aboriginal and Torres Strait Islander were affected similarly. The affected women were also more likely to have a waist circumference ≥88 cm and a mean BMI nearly six unit points above that of the comparison group. The women with diabetes had higher systolic and diastolic baseline blood pressure, and hypercholesterolaemia and dyslipidaemia were more common. Low red cell folate was detected in over 20% of both groups. Elevated pre-pregnancy fasting blood glucose was uncommon among women who did not develop diabetes. Micro- and macroalbuminuria were more prevalent in the women with diabetes, as was pre-pregnancy evidence of “hyper-triglyceridaemic waist” phenotype and the metabolic syndrome (Table 2).

Table 3 includes 8 women who had pre-existing diabetes (who are excluded for analysis of pre-pregnancy metabolic syndrome) that was either self-reported, confirmed by a medical chart audit or diagnosed at the baseline health check with a fasting blood glucose level of ≥7 mmol/l [3]. Two of these cases were detected at the baseline WPHC but were defined in perinatal data as gestational diabetes (first recognised during pregnancy).

A strong predictor of having a subsequent pregnancy affected by diabetes was elevated pre-pregnancy fasting blood glucose level. The presence of the metabolic syndrome

Table 3 Multivariable analysis for effects of pre-pregnancy factors and diabetes during the subsequent pregnancy (n = 220)

Pre-pregnancy characteristic	Unit increase	Crude PR (95% confidence interval)	P value	PR adjusted for age and ethnicity (95% confidence interval)	P value
Indigenous group					
Aboriginal	–	1.00			
Torres Strait Islander	–	1.28 (0.57–2.89)	0.55		
Aboriginal & Torres Strait Islander	–	1.25 (0.31–5.15)	0.75		
Age	1 year	1.15 (1.07–1.23)	<0.001		
Waist circumference	1 cm	1.04 (1.02–1.07)	<0.001	1.04 (1.01–1.06)	0.002
BMI (kg/m ²)	1 unit	1.08 (1.04–1.13)	<0.001	1.06 (1.02–1.11)	0.009
Alcohol intake					
Safe drinker	–	1.00		1.00	
Non drinker	–	1.54 (0.61–3.95)	0.36	1.61 (0.62–4.17)	0.33
Risky drinker	–	2.19 (0.85–5.65)	0.10	1.72 (0.68–4.35)	0.25
Non-smoker	Smoker	1.20 (0.49–2.90)	0.69	1.42 (0.64–3.16)	0.39
Enough physical activity	<30 min/day 5 days per week	1.15 (.41–3.22)	0.78	1.23 (0.44–3.43)	0.69
Systolic blood pressure	1 mmHg	1.04 (1.02–1.06)	<0.001	1.03 (1.01–1.05)	0.002
Diastolic blood pressure	1 mmHg	1.06 (1.02–1.09)	0.001	1.03 (1.00–1.07)	0.037
Cholesterol	1 mmol/l	1.77 (1.07–2.93)	0.026	1.43 (0.88–2.29)	0.14
Triglycerides	1 mmol/l	1.30 (1.06–1.61)	0.014	1.15 (0.90–1.47)	0.26
HDL cholesterol (≤ 1 = low)	1 mmol/l	0.15 (0.03–0.81)	0.028	0.21 (0.04–1.11)	0.066
Red cell folate	1 nmol/l	1.00 (0.99–1.00)	0.11	1.00 (0.99–1.00)	0.23
Fasting glucose	1 mmol/l	1.66 (1.43–1.90)	<0.001	1.55 (1.35–1.76)	< 0.001
Albumin:creatinine ratio	1 mg/mmol	1.01 (1.00–1.02)	0.008	1.01 (1.00–1.01)	0.030
γ -Glutamyl transferase	1 U/l	1.01 (1.00–1.02)	0.029	1.01 (1.00–1.02)	0.074
Hyper-triglyceridaemic waist ^a	No/Yes	4.55 (1.99–10.39)	<0.001	3.23 (1.53–6.84)	0.002
Metabolic syndrome ^b	No/Yes	4.01 (1.53–10.52)	0.005	3.50 (1.54–8.00)	0.003

Denominators vary because of missing values

^a Defined as raised triglycerides (>2 mmol/l) and waist circumference ≥ 88 cm)

^b Defined by International Diabetes Federation criteria as comprising waist circumference ≥ 80 cm plus two or more of the following: raised triglycerides (≥ 1.7 mmol/l), reduced high-density lipoprotein (<1.29 mmol/l), raised blood pressure (systolic ≥ 130 mm Hg or diastolic ≥ 85 mm Hg) and raised plasma glucose (≥ 5.6 mmol/l). Women with diabetes excluded

at baseline predicted over a threefold increase in risk among non-diabetic women (PR, 3.50; 95% CI, 1.54–8.00. For every 1-cm increase in waist circumference, there was an age-adjusted increased risk of 4% for diabetes in pregnancy (1.04; 1.01–1.06). For each 1-mm Hg increase in blood pressure (both systolic and diastolic), there was an age-adjusted increase in risk of 3% (1.03; 1.01–1.05 and 1.03; 1.00–1.07, respectively). Statistically significant associations between hypercholesterolaemia and dyslipidaemia and diabetes were diminished after adjustment for age and ethnicity. The risk for women with “hyper-triglyceridaemic waist” phenotype before pregnancy was diminished by adjustment for age, ethnicity and baseline fasting glucose (1.30; 0.48–3.55). Alcohol intake, smoking, level of physical activity and red cell folate were not statistically significantly associated with diabetes in the subsequent pregnancy.

Discussion

Among the cohort, just over 10% of the 220 women who gave birth in the 8–10 years after their health check had diabetes during that pregnancy, and elevated pre-pregnancy fasting blood glucose was a strong predictor of the condition. Among those free of diabetes at baseline, the presence of features of metabolic syndrome conferred a threefold risk for diabetes in the subsequent pregnancy. The association of body fat with diabetes in the subsequent pregnancy is shown by the statistical significance of age-adjusted increasing BMI and waist circumference. Rising age-adjusted pre-pregnancy blood pressure also increased the risk, but alcohol use, smoking, physical activity and red cell folate showed little effect.

There is convincing evidence for the association between increasing pre-pregnancy BMI and risk for gestational diabetes mellitus. A systematic review and meta-analysis found a linear increase in risk with increasing BMI [17]. The prevalence of overweight and obesity was high among all the women of childbearing age in this study, their nutritional status (demonstrated by fruit and vegetable intake) was poor, and 6 year follow-up of 132 young women from the WPHC (aged 15–34 years at baseline) found a mean annual waist gain of 1.6 cm in Aboriginal women and 1.2 cm in Torres Strait Islander women [3]. The high costs associated with treating obesity and limited success rates suggest that prevention is the best strategy [18]. However, among overweight and obese individuals, even modest weight loss is likely to produce significant health benefits [19].

Recent international recommendations on the diagnosis and classification of hyperglycaemia in pregnancy have recognised the lack of differentiation between gestational diabetes mellitus (defined as diabetes first recognised during pregnancy) and the subset of women who enter pregnancy with undiagnosed diabetes [20]. Ongoing epidemics of obesity and diabetes worldwide have highlighted the increasing importance of identifying and addressing the particular perinatal risks of this group. Their unrecognised pre-existing diabetic condition has often meant a greater degree of untreated hyperglycaemia during pregnancy. The pooled effects of a meta-analysis of pre-pregnancy care for improving outcomes among diabetic women showed impressive results for the reduction of congenital anomalies (RR, 0.25; 95% CI 0.15–0.42), pre-term delivery (0.70; 0.55–0.90) and perinatal mortality (0.35; 0.15–0.82) [8]. Successful pre-pregnancy interventions focussed on glycaemic control, contraception, dietary education, exercise and smoking cessation.

This study shows that rising pre-pregnancy blood pressure increased the risk of women for diabetes in their subsequent pregnancy. Epidemiological and clinical evidence suggests that pre-existing hypertension may predispose to gestational diabetes and conversely, women with pre-existing diabetes are more likely to develop hypertension in pregnancy [21]. The presence of hypertension in pregnancy adds further risk to that posed by diabetes alone [22]. It is clear that all diabetic women contemplating pregnancy need to be counselled regarding the importance of prevention and careful monitoring of complications during pregnancy that include hypertension. Pre-pregnancy health care for Australian Indigenous women will provide the best opportunity for detecting and perhaps reducing adverse consequences of pre-existing hypertension and diabetes during subsequent pregnancies.

This study is limited by its small sample size and the low participation rate of eligible women (<50%) in the

baseline survey. There is possible response bias to self-reported variables including current smoking status, alcohol use, fruit and vegetable intake and levels of physical activity. A limitation of self-reported data generally may be compromised accuracy due to difficulties related to recall or because of sensitivities associated with the health behaviours [23]. Despite the low participation rate at baseline, the cohort was well characterised with standardised body and biochemical measurements and the internal validity of the associations found between baseline risk and diabetes in the subsequent pregnancy among the cohort should be high. The use of measured, rather than self-reported anthropometric variables is an advantage in the study particularly because of the importance of body mass and central adiposity in predicting diabetes in pregnancy.

Prevention of diabetes is an increasingly important aim of primary health care service provision in Indigenous communities. Australia-wide, effective adult health checks in urban, rural and remote health centres provide many opportunities to assess a young woman's pre-pregnancy factors and offer interventions. In the United States, clinical guidelines for pre-pregnancy care have been developed to promote health and prevent disease in women of reproductive age [24], and the American College of Obstetricians and Gynecologists guidelines recommend counselling before pregnancy to encourage lifestyle changes to minimise complications during pregnancy [25]. There has not been the same focus on pre-pregnancy health in Australia, particularly in Indigenous communities. Nevertheless, in all Australian states and territories, health plans aimed at antenatal, pre-pregnancy and teenage sexual and reproductive health in Indigenous communities that include service delivery, data collection and outcome measure components are being implemented by the Commonwealth government (2009–2014) (<http://www.coag.gov.au>). The new services are likely to provide an opportunity to assess the effect of early education for young women and men to enhance preparation for parenthood that includes improving physical health.

This study shows the important effects of high baseline central obesity, hyperglycaemia and the “hyper-triglyceridaemic waist” phenotype in predicting diabetes in pregnancy in this population. Higher prevalence of metabolic risk among Indigenous Australian women of childbearing age confers a higher population attributable risk for a greater burden of diabetes in pregnancy. Identification of women at particularly high risk for future diabetes in pregnancy, given their pre-pregnancy health, is important so that they can manage their risks and where overweight or obesity is a factor, interventions aimed at weight management should be implemented.

Acknowledgments This work was supported by a Postgraduate Scholarship (Award Reference No PP08A 4066) from the National Heart Foundation of Australia, by NHMRC Project Grant 456402 and in part by NHMRC Project Grant 279402. JL is supported by an NHMRC Australia Fellowship. RM is supported by a NHMRC Practitioner Fellowship. The authors have no conflict of interest to declare. The contributions of each author in this work are: SC performed the data analysis, interpreted the data and drafted the manuscript. RM conceived and implemented the baseline study and linked hospitalisation data. RM, JL and AE contributed to data analysis and critical revision of the manuscript. The authors would like to thank Dr Katina D'Onise and Dr India Bohanna for their comments on the final draft. The authors would like to thank the health staff in the participating communities, and Apunipima and the Torres Strait Islands and NPA Health Councils for their support for the project and the Brisbane Statistics Centre for matching and providing perinatal data. In particular, the authors extend their thanks to all the participants.

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5.3 Paper # 3: Pre-pregnancy predictors of hypertension in pregnancy among Aboriginal and Torres Strait Islander women in North Queensland, Australia

Paper # 3:

Pre-pregnancy predictors of hypertension in pregnancy among Aboriginal and Torres Strait Islander women in North Queensland, Australia

Background

Compared to other Australian women, Indigenous women are frequently at greater risk for all hypertensive disorders of pregnancy.

Aims

To identify pre-pregnancy risk factors for hypertension in pregnancy in a cohort of Australian Indigenous women.

Methods

Data on 1009 Indigenous women of childbearing age who participated in a 1998-2000 health screening program in north Queensland were linked to Queensland hospitalisations data. The data on women who were hospitalised for birth were also linked to Queensland perinatal data.

Results

Of 220 women who gave birth, 22 had hypertension in the pregnancy after their health check. The mean age of women with and without hypertension was similar (23.7 years and 23.9 years respectively) however, Aboriginal women were more affected compared to Torres Strait Islanders. Pre-pregnancy adiposity and elevated blood pressure were predictors of a subsequent pregnancy affected by hypertension. After adjusting for age and ethnicity, each 1 cm increase in waist circumference showed a 4% increased risk for hypertension in pregnancy (PR 1.04; 95% CI; 1.02-1.06); each 1 point increase in BMI showed a 9% adjusted increase in risk (1.09; 1.04-1.14). For each 1mmHg increase in baseline systolic blood pressure there was an age and ethnicity adjusted 6% increase in risk and each 1mmHg increase in diastolic blood pressure showed a 7% increase in risk (1.06; 1.03-1.09 and 1.07; 1.03-1.11 respectively). Among those free of diabetes at baseline, the

presence of the metabolic syndrome predicted over a three-fold increase in age-ethnicity-adjusted risk (3.5; 1.50-8.17).

Conclusions

Adiposity and features of the metabolic syndrome among these young Aboriginal and Torres Strait Islander women track strongly to increased risk of hypertension in subsequent pregnancies with associated risks to the health of babies.

Keywords

Indigenous, pre-pregnancy, hypertension, preeclampsia

Introduction

Hypertensive disorders of pregnancy complicate 5-10% of pregnancies and contribute greatly to maternal and fetal morbidity and mortality throughout the world.¹⁻³ Population-based Australian studies undertaken in Victoria⁴ and South Australia⁵ have shown a prevalence of 9.8% and 9.2% respectively. The South Australian study found that Aboriginal and Caucasian women were at higher risk compared with Asian women. Other Australian studies describe a higher risk among Aboriginal and Torres Strait Islander women for both pre-existing hypertension^{6,7} and hypertension during pregnancy.⁸

Hypertension during pregnancy can be classified into two major groups: women who are hypertensive when they become pregnant and those who develop hypertension for the first time during pregnancy.⁹ Chronic hypertension pre-dates and continues throughout pregnancy whereas gestational hypertension is defined as new onset hypertension after mid-pregnancy in the absence of proteinuria.¹⁰ Preeclampsia, a disorder of unknown cause that involves many organs systems, characterised by new-onset hypertension and proteinuria in the second half of pregnancy, is a major cause of pre-term birth¹¹ because delivery is often the only option to protect the mother and infant from life-threatening deterioration.¹ The disorder is an early marker not only for future maternal cardiovascular and metabolic diseases,^{1,11,12} but may also confer a long-term risk for cardio-vascular disease among infants, particularly when they are affected by intrauterine growth restriction which occurs more often in pregnancies where preeclampsia is a factor.² Preeclampsia occurs in about 3-5% of pregnancies¹² and is the hypertensive condition (whether it occurs alone or superimposed on chronic hypertension) most often associated with maternal and fetal complications including fatalities.¹

Australian Aboriginal and Torres Strait Islander women are at comparatively greater risk of developing cardiovascular disease and metabolic disorders at a younger age than other Australian women.^{6,7} Cardiovascular and metabolic health prior to pregnancy modulates maternal preeclamptic syndrome so that frequency and severity of hypertensive disease in pregnancy are substantially higher among women with chronic hypertension and pre-pregnancy diabetes mellitus.¹¹ Most studies,^{5,13-16} but not all^{17,18} have shown an association between the incidence of hypertension in pregnancy and the presence of diabetes in pregnancy (both pre-existing and gestational diabetes). While women with chronic (pre-existing) hypertension are at greater risk of preeclampsia ($\geq 20\%$),¹⁹ they may have

uneventful pregnancies when their blood pressure is controlled, though overall outcomes are poorer than for normotensive women and can be complicated by increased maternal and fetal mortality, and major maternal morbidity including stroke, renal failure, pulmonary oedema, severe preeclampsia and placental abruption.¹ Morbidity among infants of mothers with chronic hypertension includes intrauterine growth retardation, prematurity, low birthweight and respiratory distress syndrome.¹⁹

Hypertension during pregnancy has been identified as a predictor of poor birth outcomes among Aboriginal and Torres Strait Islander women in north Queensland.²⁰ Despite wide availability of antenatal care, national prevalences of preterm birth, low birthweight and perinatal mortality remain up to twice that of the non-Indigenous population.^{21,22} All cause maternal mortality rate among is reported as five times greater among Aboriginal and Torres Strait Islander women.²³ We examined pre-pregnancy factors that predict any hypertension in pregnancy (pre-existing or new onset during pregnancy) in a cohort of Aboriginal and Torres Strait Islander women in north Queensland.

Methods

Study design and data sources

Three datasets were linked to bring together information on pre-pregnancy factors and hypertension in the next pregnancy. First, records of Aboriginal and Torres Strait Islander women of childbearing age who attended the Well Person' Health Check (WHPC) cross-sectional survey were linked to Queensland hospital Unit Registration numbers by probabilistic matching of name, date of birth and residential address. Hospitalisations data (containing International Classification of Disease (ICD) 9 and ICD 10 codes and adjacent diagnosis-related groups and descriptions) identified women who were hospitalised for pregnancy-related conditions between the date of their health check and the study censor date on 30 March 2008.

The third dataset was provided by Statistical Output, Health Statistics Centre, Queensland Health, and included selected perinatal data specific to those women who had been hospitalised for birth of an infant of at least 20 weeks completed gestation or a birthweight > 400 g when gestation was unknown.²⁴ When a woman was hospitalised for more than one birth during the follow-up period, only perinatal data for the birth nearest the health

check was requested. Women who were likely to have been pregnant at the time of their health check were excluded based on the date of their health check, the date of their subsequent delivery and the estimated gestation of the pregnancy at the time of birth.

ICD codes within the perinatal data identified women who had hypertensive conditions (ICD O10-O16) during their pregnancy (Figure 1). The outcome measure "hypertension in pregnancy" in this study applies to women who were recorded in the perinatal dataset as receiving a diagnosis of one of the forms of the disorder; pre-existing hypertension (ICD O10), pre-existing hypertension with superimposed preeclampsia-eclampsia (ICD O11), gestational hypertension without proteinuria (ICD O13) and preeclampsia-eclampsia (ICD O14 and O15).

Study population

The Aboriginal and Torres Strait Islander women in this study were participants in the March 1998-December 2000 WPHC cross-sectional health survey,²⁵ which included 26 rural and remote Indigenous communities in the Bowen, Cairns, Cape York, Torres Strait and Mount Isa Health service districts. All adults were invited to participate through printed media, local radio and word of mouth via the local health service, community council and community groups. The survey was attended by 2862 Indigenous people aged 15 years and over, giving an overall participation rate of 44.5%²⁶ (according to local census data); 51.7% were female. Participants overall, were not different demographically from the age and sex distribution of the Indigenous population who did not attend, based on census data. A subset of women from the original survey data were selected because the health check occurred when they were aged between 15-44 years (a generally accepted range of childbearing age).

Data collection

A standardised proforma was used for data collection in the baseline WPHC survey. Body measurements and specimen collection were performed by a multidisciplinary team of trained staff from the Cairns Tropical Public Health Unit (Queensland Health) and local health staff in each community. Face-to-face interviews followed a structured questionnaire. Fasting venous blood samples were collected by a medical officer, registered nurse or trained phlebotomist.²⁵

Anthropometric measures

Participants were invited to attend in the early morning following at least an 8 h fast. They were weighed in light clothing to the nearest 0.1 kg on digital electronic scales (UC300; AND, Tokyo, Japan), and height was measured to the nearest centimetre (Harpenden anthropometer; Holtain Ltd, Crymych, United Kingdom). Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Waist circumference was measured to the nearest centimetre. Anthropometric cut-offs were set according to World Health Organisation criteria.²⁷

Blood pressure and self-reported behavioural factors

Seated blood pressure was recorded three times over approximately 10 min with a Dinamap 800 automated blood pressure monitor (Criticon; Tampa, Florida, USA), and mean systolic and diastolic measurements were calculated. Fruit and vegetable intake was self-reported by 24-h recall and 7-day recall was used to assess the duration and intensity of physical activity. If the participant reported a minimum of 30 min of exercise on at least 5 days in the week, they were categorised as having an adequate level of physical activity. Current smoking status was self-reported. Participants who drank alcohol self-reported the types and amounts of alcohol consumed in the week before the health check; they were then categorised as being safe drinkers, non-drinkers or harmful ("risky") drinkers according to Australian National Health and Medical Research Council guidelines (2001). Risky drinking for women was defined as more than two standard drinks per day or more than four on any single occasion. The physical activity, smoking and alcohol intake measures have been widely used²⁶ and the 24-h recall dietary questionnaire and red cell folate measure have been validated against other measures of micronutrient intake and the quality of the diet with respect to fruit and vegetables.^{28,29}

Biochemical measures

Early-morning fasting venous blood samples were collected in ethylenediamine tetra-acetic acid vacuum tubes and clotted serum separator vacuum tubes (spun for 10 min at 1000 RCF in a swinging bucket centrifuge and separated within 1 h). Samples were stored in 4–8°C and transported for analysis within 24 hours. The biochemical measurements included glucose, triglycerides, total cholesterol, high density lipoprotein cholesterol, gamma-

glutamyl transferase and red cell folate. Glucose and lipids were measured using photometric enzyme endpoint assay with Cobas Integra 700/400 (Roche Diagnostic, Rotkreutz, Switzerland). Gamma-glutamyl transferase was measured by a kinetic photometric procedure with Cobas Integra 800 (Roche Diagnostic, Rotkreutz, Switzerland). An elevated level was defined as ≥ 50 U/L and < 50 U/L as normal, according to criteria established by Queensland Health Pathology Service (<http://www.health.qld.gov.au/qhcss/qhps/default.asp>). Red cell folate was measured with the Bayer Advia Centaur automated immunoassay system (Bayer, Australia) by the Queensland Health Pathology Service in Brisbane. The reference range for this assay was 295-1800 nmol/L.

Urine specimens collected in sterile 50-ml containers were either the first morning or at least 2 h after the most recent void. If protein was detected by dipstick urinalysis (Combur-test, Roche) or if the participant was known to have diabetes, hypertension or obesity (BMI > 30 kg/m²), the albumin: creatinine ratio was measured by immunoassay in grams per mole. Microalbuminuria was defined as an albumin: creatinine ratio of 3.4-34 g/mol, and macroalbuminuria as > 34 g/mol.³⁰ From May 1999 to the end of the project, the albumin: creatinine ratio was measured in all urine specimens.

Ethics

Ethics approval for the WPHC was provided by the Cairns Base Hospital Ethics Committee in March 1998. The current data linkage study was approved by the University of South Australia and Cairns Base Hospital Human Research Ethics Committees (June 2009 and September 2009) with support from the peak health councils representing Indigenous people in the region: Apunipima and the Torres Strait Islands and Northern Peninsula area Health Councils.

Statistical analysis

The data were analysed in a generalised linear model (Poisson distribution) with robust variance estimates to calculate prevalence ratios (PRs) and 95% confidence intervals (CIs) with 2 sided p-values of 0.05 for baseline characteristics associated with hypertension during the first subsequent pregnancy. An *a priori* decision was taken to adjust the model for age because hypertension is commonly associated with increasing age and, because it

was expected that Aboriginal and Torres Strait Islander women would differ in their anthropometric and metabolic characteristics, ethnicity was included in the adjusted model. Further adjustment for months from participation in the baseline survey to time of admission for birth was not associated with the outcome and was not retained. The analysis was conducted with STATA 11 (STATAcorp, College Station, Texas, USA).

Results

Figure 1 shows that 283 women were hospitalised for a pregnancy-related condition between their health check in 1998-2000 and March 2008; 51 pregnancies ended in miscarriage or because of an ectopic pregnancy, and two pregnancy outcomes were unknown. In the time up to the censor date, 230 women were hospitalised for birth. Ten of these women were excluded because perinatal records were not matched. Of the remaining 220 women, 22 had hypertension in their next pregnancy. Nine of the women had pre-existing hypertension at the time of their health check. Seven women (3.2%) developed preeclampsia; six cases were described as moderate and one severe case was superimposed on chronic hypertension. Seven women free of hypertension at baseline developed gestational hypertension (new-onset hypertension after mid-pregnancy, in the absence of proteinuria)⁴.

At baseline, there were 1009 women of childbearing age (15-44 years) in the study sample. We excluded 48 women because they were pregnant at the time of their health check. Characteristics of women who were hospitalised for a pregnancy related condition (n=283) in the 8-10 years following their 1998-2000 health check compared with those who were not (n=678) are reported elsewhere.³¹ The likelihood of pregnancy decreased with age and adjustment for ethnicity and age greatly diminished many protective associations of pre-pregnancy characteristics for risk of a subsequent pregnancy (waist circumference ≥ 90 cm, BMI 30+, elevated blood pressure, elevated total cholesterol or triglycerides, fasting blood glucose > 5 , elevated GGT).

Unadjusted analysis in Table 1 shows the 22 women who had hypertension in the pregnancy after their health check 72.7% were Aboriginal; the remaining 27.3% of the women identified as Torres Strait Islander or Torres Strait Islander and Aboriginal (p =0.157). There was no difference in mean age between the women who did and did not have hypertension in pregnancy (p =0.914). The affected women were more likely to have

a higher mean waist circumference ($p=0.054$) and a mean BMI three points above the women with no hypertension ($p=0.033$). Elevated pre-pregnancy systolic and diastolic blood pressure predicted more than a three-fold risk for hypertension in the subsequent pregnancy ($p=0.001$ and 0.025 respectively). More women who had hypertension reported risky drinking (50% versus 38%; $p=0.236$). Elevated albumin:creatinine ratio and low levels of high density lipoprotein cholesterol were more common (31.6% versus 17.7% and 59.1% versus 43.5% respectively) though not statistically significant ($p=0.366$ and 0.170 respectively). Non-diabetic women who were diagnosed with hypertension in their subsequent pregnancy had more than twice the prevalence of features of the metabolic syndrome at the baseline health check (42.9% versus 19.9%; $p=0.018$). Baseline self-reported smoking rates among all the women were high (70%) and adequate physical activity levels and fruit and vegetable intake were low (19.5% and 1.8% respectively).

In a multivariable analysis adjusted for age and ethnicity (Table 2), pre-pregnancy central adiposity was a predictor of hypertension in the subsequent pregnancy. For each 1 cm increase in waist circumference there was a 4% increase in risk (PR 1.04; 95% CI 1.02-1.06). For each 1 point increase in BMI, there was a 9% age and ethnicity adjusted increase in risk (1.09; 1.04-1.14). A strong predictor for having hypertension in pregnancy was elevated baseline blood pressure. For each 1 mmHg increase in pre-pregnancy systolic blood pressure there was an age and ethnicity adjusted 6% increase in risk of hypertension in pregnancy (1.06; 1.03-1.09) and for each 1 mmHg increase in diastolic blood pressure there was a 7% increase in risk (1.07; 1.03-1.11). For each 1 mg/mmol increase in pre-pregnancy albumin:creatinine ratio or 1 U/L increase in gamma-glutamyl transferase there was an age and ethnicity adjusted 1% increase in risk of hypertension in the subsequent pregnancy (1.01; 1.00-1.02 and 1.01; 1.00-1.02 respectively). The presence of metabolic syndrome at baseline predicted over a three-fold increase in adjusted risk among women free of diabetes at baseline (3.5; 1.50-8.17). Pre-pregnancy alcohol use, smoking, physical activity, fasting glucose, red cell folate and blood fats were not statistically significantly associated with hypertension in pregnancy in this study.

Discussion

Twenty-two of the 220 women who gave birth in the 8-10 years after their health check had hypertension during that pregnancy. Seven of these women (3.2%) were diagnosed with moderate (n=6) or severe (n=1) preeclampsia, a rate equivalent to that found among other population groups.¹² The strongest pre-pregnancy predictors of hypertension in the subsequent pregnancy were increasing central adiposity (assessed by waist circumference and BMI) and elevated blood pressure. Age and ethnicity adjusted increasing pre-pregnancy albumin:creatinine ratio and gamma-glutamyl transferase also increased the risk. The presence of the metabolic syndrome among women free of diabetes at baseline conferred greater than three-fold adjusted risk of hypertension in the next pregnancy.

The study results add to previous Australian research that has identified elevated pre-pregnancy BMI as an important factor in the development of serious hypertensive disorders of pregnancy.³² A systematic review of controlled studies of risk factors for preeclampsia at antenatal booking showed that raised BMI before pregnancy (relative risk 2.47, 1.66-3.67) is one of the few amenable to intervention.¹³ Other factors include previous history or family history of preeclampsia, multiple pregnancy, nulliparity, raised blood pressure and maternal age among multiparous women. A systematic overview of maternal BMI and the risk of preeclampsia (13 studies comprising 1.4 million women) found the risk doubled with each 5-7 kg/m² increase in pre-pregnancy BMI.³³ In studies where women with chronic hypertension or diabetes mellitus were excluded, the relationship persisted and the authors concluded that pre-pregnancy weight reduction programs should be considered.

It has been shown that the risk of preeclampsia is reduced when women exercise between 3 months and 1 year before or during pregnancy.³⁴ In a case-control study, increased self-perceived exertion from physical activity in the year before pregnancy was strongly and inversely related to subsequent preeclampsia, independent of pre-pregnancy BMI.³⁵ The benefits of exercise prior to pregnancy for reducing the risk of preeclampsia, suggest that weight reduction interventions should feature well-designed physical activity components that focus on fitness, nutrition and weight loss in preference to weight loss alone.

This study is limited by its small sample size and low participation rate of eligible women (< 50%) in the baseline survey and there is a possible downward and upward response bias

to self-reported variables including current smoking status, alcohol use, fruit and vegetable intake and levels of physical activity. Despite the low participation rate, the cohort was well characterised at baseline with standardised body and biochemical measurements and the internal validity of the associations found between baseline risk and hypertension in the subsequent pregnancy should be high. The study is further limited by the inability to adjust for socio-economic position among the participants, however, the study regions are categorised as being among the most economically disadvantaged in Australia and it is likely that there is considerable homogeneity regarding socio-economic position among Indigenous residents. A potential limitation of the study is the ability of perinatal data collections to report maternal health indicators accurately. A Canadian validation study found that gestational hypertensive disorders were more accurately coded (sensitivity 88%) than other variables, for example fetal/birth asphyxia (sensitivity 14.3%).³⁶ The study is further limited by lack of data regarding whether or not women had a hypertensive disorder during a previous pregnancy as risk factors for recurrence are likely to be different for those women whose pregnancy is affected for the first time. The use of measured, rather than self-reported, anthropometric variables is an advantage in the study particularly because of the importance of body mass and central adiposity in predicting hypertension in pregnancy.

These data demonstrate low levels of physical activity among Aboriginal and Torres Strait Islander women of child-bearing age in north Queensland. The study was undertaken in remote communities situated in isolated areas of Cape York and on Torres Strait Islands that frequently have limited resources for safe exercise environments. Consideration should be given to improving community infrastructures to include identified facilities (gymnasiums, walking paths and improved night lighting) which provide physical activity programs aimed at improving the health of young women prior to their first pregnancy and between subsequent pregnancies. Beneficial effects of better metabolic health of a woman of childbearing age may also have a strong positive effect on the health of her children across their lifespan.

Figure: Flow chart including datasets linked (right) and timeline (far right)

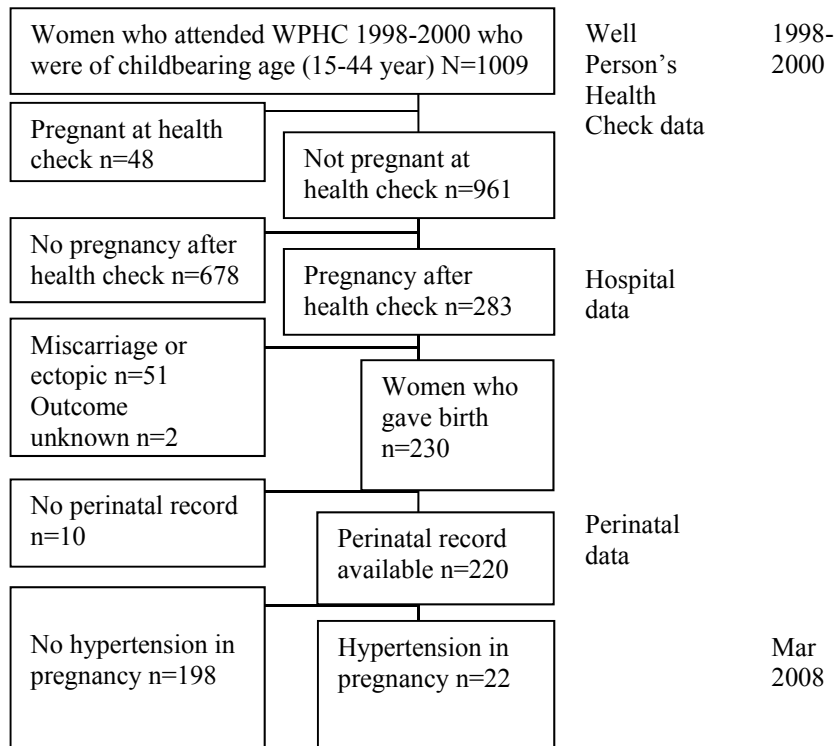


Table 1: Baseline characteristics of the cohort, by hypertension in pregnancy (n=220)

Pre-pregnancy characteristic	No hypertension during pregnancy (n=198)		Hypertension during pregnancy (n=22)		Unadjusted PR (95% CI)	p value
	n	% of n or mean (sd)	n	% of n or mean (sd)		
Indigenous group						
Aboriginal	112	56.6	16	72.7	1.00	
Torres Strait Islander and Torres Strait Islander & Aboriginal	86	43.4	6	27.3	0.52 (0.21-1.28)	0.157
Age years (mean, sd)	198	23.9 (5.4)	22	23.7 (6)	0.99 (0.92-1.07)	0.914
Waist circumference (cm)						
< 80	65	33	5	22.7	1.00	
80-87.9	40	20.3	2	9.1	0.67 (0.13-3.30)	0.619
≥ 88	92	46.7	15	68.2	1.96 (0.74-5.17)	0.372
Missing	1					
Waist circumference (mean, sd)	197	88.7 (15.8)	22	95.4 (17.6)	1.02 (1.00-1.04)	0.054
Missing	1					
BMI category (kg/m ²)						
< 18.5	23	11.6	0	0		
18.5-25	74	37.4	7	31.8	1.00	
25-30	48	24.2	6	27.3	1.29 (0.46-3.63)	0.635
≥ 30+	53	26.7	9	40.9	1.68 (0.66-4.26)	0.276
BMI (mean, sd)	198	26.1 (7)	22	29 (6.5)	1.05 (1.00-1.09)	0.033
Smoker						
No	57	28.9	8	36.4	1.00	
Yes	140	71.1	14	63.6	0.74 (0.33-3.68)	0.469
Missing	1					
Alcohol use						
Safe drinker	56	28.9	4	18.2	1.00	
Non drinker	64	33	7	31.8	1.48 (0.45-4.82)	0.517
Risky drinker	74	38.1	11	50	1.94 (0.65-5.82)	0.236
Missing	4					

5. Presentation of the studies

Fruit and vegetable intake(serves)						
< 2–5	197	99.5	19	86.4	Undetermined	
≥ 2–5	1	0.5	3	13.6		
Enough physical activity						
No	160	80.8	17	77.3	1.00	
Yes	38	19.2	5	22.7	1.23 (0.47-3.11)	0.691
Systolic blood pressure (mmHg)						
≤ 120	142	72.1	8	36.4	1.00	
> 120	55	27.9	14	63.6	3.80 (1.67-8.67)	0.001
Missing	1					
Diastolic blood pressure (mmHg)						
≤ 80	190	96.5	19	86.4	1.00	
> 80	7	3.5	3	13.6	3.30 (1.16-9.35)	0.025
Missing	1					
Cholesterol (mg/dL)						
≤ 5.5	176	90.3	20	90.9	1.00	
> 5.5 (elevated)	19	9.7	2	9.1	0.93 (0.23-3.73)	0.922
Missing	3					
Triglycerides (mmol/L)						
≤ 2	173	89.6	19	86.4	1.00	
> 2 (elevated)	20	10.4	3	13.6	1.31 (0.42-4.12)	0.635
Missing	5					
HDL cholesterol (mmol/L)						
> 1	108	56.5	9	40.9	1.00	
≤ 1 (low)	83	43.5	13	59.1	1.76 (0.78-3.95)	0.170
Missing	7					
Red cell folate (nmol/L)						
≥ 295	126	65	17	77.3	1.00	
< 295 (low)	68	35	5	22.7	0.58 (0.22-1.50)	0.260
Missing	4					

5. Presentation of the studies

Fasting glucose (mmol/L)						
≤ 5.5	182	93.3	20	90.9	1.00	
> 5.5	13	6.7	2	9.1	1.35 (0.35-5.24)	0.668
Missing	3					
Albumin:creatinine ratio (mg/mmol)						
≤ 3.4	121	82.3	13	68.4	1.00	
>3.4	26	17.7	6	31.6	2.25 (0.39-13.05)	0.366
Missing	51		2			
Gamma-glutamyl transferase (U/L)						
≤ 50	183	93.9	20	90.9	1.00	
> 50 (elevated)	12	6.1	2	9.1	1.45 (0.37-5.60)	0.590
Missing	3					
Metabolic syndrome ^a						
No	153	80.1	12	57.1	1.00	
Yes	38	19.9	9	42.9	2.63 (1.18-5.88)	0.018
Missing	7		1			

Denominators vary because of missing values

^aDefined by International Diabetes Federation criteria as comprising waist circumference ≥ 80 cm plus two or more of the following: raised triglycerides (≥ 1.7 mmol/L), reduced high-density lipoprotein (< 1.29 mmol/L), raised blood pressure (systolic ≥ 130 mm Hg or diastolic ≥ 85 mm Hg) and raised plasma glucose (≥ 5.6 mmol/L). Women with diabetes excluded.

Table 2. Multivariable analysis for effects of pre-pregnancy factors and hypertension during the subsequent pregnancy (n=220)

Pre-pregnancy characteristic	Unit increase	Crude PR (95% confidence interval)	p value	PR adjusted for age and ethnicity (95% confidence interval)	p value
Indigenous group					
Aboriginal	-	1.00			
Torres Strait Islander and Aboriginal & Torres Strait Islander	-	0.52 (0.21-1.28)	0.16		
Age	"1 year"	1.00 (0.92-1.07)	0.91		
Waist circumference	"1 cm"	1.02 (1.00-1.04)	0.05	1.04 (1.02-1.06)	0.001
BMI (kg/m ²)	"1 unit"	1.05 (1.00-1.09)	0.03	1.09 (1.04-1.14)	<0.001
Alcohol intake					
Safe drinker	-	1.00		1.00	
Non drinker	-	1.47 (0.45-4.82)	0.52	1.38 (0.43-4.47)	0.59
Risky drinker	-	1.94 (0.64-5.91)	0.24	1.79 (0.58-5.49)	0.31
Non-smoker	Smoker	0.74 (0.33-1.68)	0.47	0.68 (0.30-1.55)	0.36
Enough physical activity	< 30 min/day 5 days per week	0.83 (0.32-2.12)	0.69	0.78 (0.31-1.55)	0.60
Systolic blood pressure	"1 mmHg"	1.05 (1.02-1.07)	<0.001	1.06 (1.03-1.09)	<0.001
Diastolic blood pressure	"1 mmHg"	1.06 (1.03-1.10)	<0.001	1.07 (1.03-1.11)	<0.001
Cholesterol	"1 mmol/L"	1.27 (0.88-1.83)	0.21	1.38 (0.93-2.06)	0.10
Triglycerides	"1 mmol/L"	1.18 (0.96-1.46)	0.12	1.17 (0.92-1.49)	0.20
HDL cholesterol (≤ 1 = low)	"1 mmol/L"	0.74 (0.13-4.22)	0.73	0.61 (0.09-3.82)	0.60

5. Presentation of the studies

Red cell folate	"1 nmol/L"	1.00 (1.00-1.01)	0.006	1.00 (1.00-1.01)	0.009
Fasting glucose	"1 mmol/L"	1.06 (0.82-1.37)	0.67	1.14 (0.87-1.50)	0.33
Albumin:creatinine ratio	"1 mg/mmol"	1.01 (1.00-1.02)	0.02	1.01 (1.00-1.02)	0.003
Gamma-glutamyl transferase	"1 U/L"	1.01 (1.00-1.02)	0.02	1.01 (1.00-1.02)	0.003
Hyper-triglyceridemic waist ^a - No	Yes	1.55 (0.40-5.93)	0.53	1.53 (0.39-6.01)	0.54
Metabolic syndrome ^b - No	Yes	2.63 (1.18-5.88)	0.02	3.50 (1.50-8.17)	0.004
Denominators vary because of missing values					
^a Defined as raised triglycerides (> 2 mmol/l and waist circumference ≥ 88cm)					
^b Defined by International Diabetes Federation criteria as comprising waist circumference ≥ 80cm plus two or more of the following: raised triglycerides (≥ 1.17 mmol/l), reduced high-density lipoprotein (< 1.29 mmol/L), raised blood pressure (systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg) and raised plasma glucose (≥ 5.6 mmol/L). Women with diabetes excluded.					

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5.4 Paper # 4: Pre-pregnancy predictors of infant birth outcomes among Aboriginal and Torres Strait Islander women in North Queensland, Australia: Could increasing birthweights be misleading?

Paper # 4:

Pre-pregnancy predictors of infant birth outcomes among Aboriginal and Torres Strait Islander women in North Queensland, Australia: Could increasing birthweights be misleading?

Background

The incidence of low birthweight (LBW, < 2500g) among Indigenous Australians remains double that for the general population. Reduced LBW has been adopted as a key measure of improved health outcomes for Aboriginal and Torres Strait Islander health services. However, the pre-pregnancy health, especially rising rates of obesity and diabetes, of Australian Indigenous women may be impacting on the incidence of low birthweight in a way that is counterintuitive if infants achieve a birthweight $\geq 2500\text{g}$ due to maternal hyperglycaemia during pregnancy rather than improved maternal and infant health. We investigate associations between maternal pre-pregnancy characteristics and infant birth outcomes with a focus on maternal hyperglycaemia and infant birthweight.

Methods

Cohort study of 1009 Indigenous women of childbearing age who participated in a 1998-2000 health screening program in north Queensland, using linked records for hospitalisations and birth outcomes. Of these women, 220 attended hospital for birth during the follow-up period to March 2008.

Results

Of 220 women who gave birth, 36 (16.4%) had a baby that was LBW and/or pre-term. Thirteen babies were both pre-term and small (<2500g), 13 were born at term and small suggesting intrauterine growth restriction (IUGR) and 10 were pre-term and $\geq 2500\text{g}$. There were no apparent pre-pregnancy predictors for having a pre-term small baby. Women who had a baby that was IUGR were more likely to be small themselves and all reported tobacco smoking pre-pregnancy. The babies born pre-term and $\geq 2500\text{g}$ had larger mothers who were more likely to have elevated blood pressure, features of the metabolic syndrome or hyper-triglyceridaemic waist prior to their pregnancy, and they were more likely to have a diagnosis of diabetes or hypertension during pregnancy. There were no

associations found between pre-pregnancy blood fats, red cell folate or the presence of pre-pregnancy chlamydia and gonorrhoea and the categories of adverse birth outcomes.

Conclusions

Population decreases in the incidence of LBW should be confirmed as a result of better, not poorer health. Birthweight should be supplemented by more sensitive measures of infant health.

Keywords

Indigenous – Pre-pregnancy – Infant outcomes

Introduction

Despite extreme levels of social disadvantage,¹ many Indigenous women in Australia have pregnancies that are medically uncomplicated, with favourable outcomes for both mother and infant.² However, Australian perinatal data provide accounts of persisting disparities in birth outcomes among Indigenous women compared with other Australian women.^{3,4} The most serious adverse outcomes of pregnancy are maternal or infant mortality. These severe events are rare in Australia at a population level, nevertheless the maternal mortality rate for Aboriginal and Torres Strait Islander women is reported as 5.3 times greater (45.9 vs 8.7 per 100 000)⁵ and perinatal mortality as almost double that of other Australian infants (17.3 vs 9.7 per 1000).⁴

Most research that assesses or monitors birth outcomes uses measures that are more prevalent than the outcomes of mortality and severe morbidity. Low birthweight (defined by the World Health Organisation (WHO) as < 2500g and pre-term birth (defined by the WHO as birth at < 37 weeks completed gestation) are commonly adopted as alternate outcome measures in studies around the world.⁶ The proportion of low birthweight and pre-term birth (12.3% and 13.3% respectively) among Australian Indigenous infants remains approximately twice that of non-Indigenous infants (5.9% and 8% respectively).⁴ Similar disparities in birthweight and gestational age at birth between Indigenous and non-Indigenous infants are documented in Queensland.⁷ Low birthweight and prematurity increase the risk of infant mortality and childhood morbidity⁸ and there is evidence of associations of low birthweight with increased risks for adult morbidities including type 2 diabetes, hypertension and coronary heart disease.⁹

In 2005 the Australian Medical Association released a 'report card', "Lifting the Weight – Low Birth Weight Babies: An Indigenous health burden that must be lifted" and outlined a range of Indigenous health programs that have demonstrated a clear reduction in the prevalence of low birthweight among their clientele. It was reported that failure to achieve a reduction in low birthweight was an indication that the program was simply not working and that funding should be discontinued.¹⁰ However, it is important to additionally consider the potential effect of maternal metabolic syndrome and diabetes before and during pregnancy on birthweights across this population. A high incidence of type 2 diabetes and increasing central obesity associated with poor nutrition are affecting the health of young Indigenous women of childbearing age¹¹⁻¹³ and may be impacting on the

prevalence of low birthweight in a way that is counterintuitive to the headline result. Affected infants may achieve a birthweight $\geq 2500\text{g}$ due to a macrosomic phenotype rather than improved maternal and infant health. Classification of newborns in extremely poor health due to maternal diabetes to the normal and therefore ‘healthy’ birthweight category may become increasingly misleading at a population health level as the number of young women who have glucose intolerance increases.

Antenatal care services are widely available across Australia, and this is generally also true of many rural and remote communities with largely Indigenous populations situated in far north Queensland. By the time a pregnant woman attends her first antenatal appointment, even if the visit occurs in the first trimester, most fetal organs are formed¹⁴ and opportunities to prevent birth defects are missed (e.g. immunisation against rubella, hepatitis B) or less effective (e.g. folic acid supplementation). If a woman presents for care later in her pregnancy, opportunities to effectively manage pre-existing complications such as detection and control of maternal diabetes, hypertension and sexually transmitted infections also decline.¹⁵ Furthermore, a 2003 review in the United States found that in its current form antenatal care was not effective in preventing either of the two constituents of low birthweight, pre-term birth and intrauterine growth restriction (IUGR).¹⁶ On the other hand, some of the greatest influences on pregnancy outcome, for example nutritional status or the presence of infection, can be related to maternal health status long before conception.¹⁷

In this study we examine maternal pre-pregnancy characteristics and their association with infant birth outcomes in a cohort of Aboriginal and Torres Strait Islander women of child-bearing age from rural and remote communities in North Queensland. The adverse birth outcomes of interest include infants who are pre-term and therefore low birthweight, infants who are born at term with low birthweight (IUGR) and particularly infants who are born pre-term with a birthweight $\geq 2500\text{g}$. We aim to identify pre-pregnancy factors associated with adverse birth outcomes amenable to intervention prior to pregnancy.

Methods

Datasets and Linkage

Three datasets were linked to bring together information on: 1. characteristics of a cohort of Aboriginal and Torres Strait Islander women of childbearing age from North Queensland; 2. their subsequent pregnancy related hospital admissions for birth; and 3. associated infant birth outcomes.

First, data from women of child-bearing age (15-44 yrs) who participated in the 1998-2000 Well Person's Health Check (WPHC) cross-sectional survey¹⁸ were selected and are used as a proxy for maternal pre-pregnancy health status. The survey included 26 rural and remote Indigenous communities in the Bowen, Cairns, Cape York, Torres Strait and Mount Isa Health service districts. All adults were invited to participate in the WPHC through printed media, local radio and word of mouth via the local health service, community council and community groups. The survey was attended by 2,862 self-selected Indigenous people aged 15 years and over, giving an overall participation rate of 44.5%¹⁹ (according to local census data); 51.7% were female. Participants overall, were not different demographically from the age and sex distribution of the Indigenous population who did not attend, based on census data.

Second, WPHC records were linked to Queensland hospital Unit Registration numbers by probabilistic matching of name, date of birth and residential address. International Classification of Disease (ICD) 9 and ICD 10 codes (Text Box) and corresponding diagnosis-related groups from hospitalisations data identified women aged 15-44 years at the baseline health check who were hospitalised for subsequent pregnancy-related conditions (censor date: March 2008).

The third dataset (Queensland perinatal data) focuses on infant birth outcomes and was provided by Statistical Output, Health Statistics Centre, Queensland Health. Included are selected perinatal data specific to those women who were hospitalised for birth defined as birth of an infant of at least 20 weeks gestation or a birthweight > 400g when gestation was unknown.²⁰ When a woman was hospitalised for more than one birth during the follow-up period, only perinatal data for the birth nearest to the WPHC were requested. Women who were likely to have been pregnant at the time of their health check were excluded based on

the date of their health check, the date of their subsequent delivery and the estimated gestation of the pregnancy at the time of birth (Figure).

Pre-pregnancy health assessment derived from the WPHC cross sectional survey

Participants in the WPHC had anthropometric measures taken, a face to face interview to assess lifestyle factors and provided early morning fasting venous blood samples and urine specimens. The methods for the health check and biochemical assays have been reported in detail previously.²¹ Briefly each person was weighed to the nearest 0.1 kilogram and height and waist were measured to the nearest centimetre. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m²). Seated blood pressure was recorded three times over approximately 10 min and mean systolic and diastolic measurements were recorded. Current smoking status, 24-hr recall for fruit and vegetable intake and 7-day recall for alcohol use and levels of physical activity were self-reported. Biochemical measurements included glucose, triglycerides, total cholesterol, high density lipoprotein cholesterol, gamma-glutamyl transferase and red cell folate. Analysis of urine specimens included albumin:creatinine ratio and polymerase chain reaction testing for chlamydia and gonorrhoea.

Metabolic syndrome among women free of diabetes at the WPHC baseline is defined according to International diabetes Federation criteria comprising waist circumference ≥ 80 cm plus two or more of the following: raised triglycerides (≥ 1.7 mmol/l), reduced high-density lipoprotein (< 1.29 mmol/l), raised blood pressure (systolic ≥ 130 mm Hg or diastolic ≥ 85 mm Hg) and raised plasma glucose (≥ 5.6 mmol/l). “Hypertriglyceridaemic waist” phenotype is defined as triglycerides > 2 mmol/l and waist circumference ≥ 88 cm.²²

Primary and secondary outcome measures

Primary outcome measures were developed from infant birthweights and pregnancy gestation recorded in Queensland perinatal data. Birthweights were categorised as low birthweight (< 2500 g) or not low birthweight (≥ 2500 g) and length of gestation as pre-term (< 37 completed weeks) or term (≥ 37 weeks). These variables were cross tabulated to classify the infants as: 1. Term and > 2500 g (normal birth outcome); 2. Pre-term and < 2500 g (pre-term and small); 3. Term and < 2500 g (IUGR); and 4. Pre-term and ≥ 2500 g. Secondary outcome measures included method of birth, Apgar scores at 1 and 5 minutes,

whether the infant was admitted to special care or intensive care nursery and mean birthweights of term infants.

Statistical analysis

Log binomial generalised linear modelling (GLM) was used to calculate prevalence ratios and 95% confidence intervals (CIs) with 2 sided *P* values of 0.05 for baseline characteristics associated with becoming pregnant (Table 1). The model was adjusted for age and ethnicity. In Table 2 the effect of each explanatory variable on birth outcome categories was investigated with bivariate analysis in GLMs (Poisson distribution) with robust variance estimates to calculate unadjusted prevalence ratios (PRs) and 95% CIs for baseline and pregnancy characteristics associated with infant birth outcomes. Mothers with infants born at term and > 2500g (normal birth outcome; n=184) are compared with mothers who had infants in aggregated adverse birth outcome categories (n=36). Each of the separate adverse birth outcome categories are compared with the group of mothers who had infants in the normal birth outcome category. Adjustment for potential confounders was not undertaken in this analysis because the aim was to understand pre-pregnancy predictors for each of the birth outcome categories. Fisher's exact p-values were calculated for statistically significant categorical variables. Differences between secondary outcome continuous measures including mean birthweights or Apgar scores associated with maternal characteristics were tested with independent samples Student t tests. All analyses were conducted using STATA 11 (STATAcorp, College Station, Texas, USA).

Ethics

Ethics approval for the WPHC was provided by the Cairns Base Hospital Ethics Committee in March 1998. The current data linkage study was approved by the University of South Australia and Cairns Base Hospital Human Research Ethics Committees (June 2009 and September 2009 respectively) with support from the peak health councils representing Indigenous people in the region: Apunipima and the Torres Strait Islands and Northern Peninsula Area Health Councils.

Results

The figure shows of 1009 women of childbearing age at the baseline WPHC, 48 were excluded because they were likely to have been pregnant at their health check. Of the remaining 961 women, 283 were recorded in hospitalisations data as having a pregnancy related admission. Table 1 describes the pre-pregnancy characteristics of the 283 women who had a subsequent pregnancy-related hospital admission compared with 678 women who did not. The likelihood of pregnancy decreased with age. Women aged 35 to 44 were much less likely to become pregnant (PR 0.10 [0.06-0.17]). Adjustment for ethnicity and age greatly diminished many associations with the likelihood of pregnancy (waist circumference ≥ 90 cm, BMI 30+, elevated blood pressure, presence of gonorrhoea or chlamydia, elevated total cholesterol or triglycerides, fasting blood glucose > 5 , elevated GGT). Of the 1009 women in the cohort, only 14 reported having the recommended two serves of fruit and five serves of vegetables in the 24 hours before their health check. Approximately 20% of the cohort had low serum RCF. It was this group of women that were more likely to become pregnant (PR 1.33 [1.10-1.60]) and pre-pregnancy low RCF was a factor among nearly 30% of pregnancies. Women who experienced a subsequent pregnancy were also more likely to report current smoking at their health check (PR 1.38 [1.13-1.69]). Of these 283 admissions, 49 were because of miscarriage (17.3%)²³ or ectopic pregnancy ($n < 5$) and the outcome of 2 pregnancies is not known (Figure). In the time up to the censor date, 230 women were hospitalised for birth and 10 of these women were excluded because perinatal records were not matched. There were no multiple births. Of the remaining 220 women, 184 women had a baby that was both normal gestation (≥ 37 completed weeks) and birthweight (≥ 2500 g), and 36 women (16.4%) had a baby that was low birthweight and/or pre-term.

Among the group of 36 low birthweight and/or pre-term infants there were 13 babies who were both pre-term and small (< 2500 g), 13 who were born at term and small (IUGR) and 10 who were pre-term with a birthweight ≥ 2500 g. Table 2 presents a bivariate analysis of maternal pre-pregnancy and pregnancy characteristics linked to each of the birth outcome categories compared with 184 women who had infants with normal birth outcomes (< 37 weeks gestation with birthweight ≥ 2500 g). Aboriginal women were more likely than Torres Strait Islander women to have a baby with an adverse birth outcome across each category.

Table 2 shows there were no apparent predictors for having a pre-term and small baby except perhaps having a diagnosis of hypertension during pregnancy documented in perinatal records (pre-existing or gestational hypertension). Women who had an IUGR baby were more likely to be small themselves. With each 1 unit increase in waist circumference there was a 5% decrease in risk (PR 0.95 [95%CI 0.91-0.99]) and with each 1 unit increase in BMI, risk decreased by 15% (PR 0.85 [0.77-0.94]). The impact of smoking on this outcome was statistically undetermined because all of the mothers who had an IUGR baby reported current smoking at their pre-pregnancy health check. This group of mothers were less likely to have elevated blood pressure and more likely to have elevated gamma-glutamyl transferase. Given the smaller size of these mothers, elevation of this liver function test was unlikely to be related to fatty liver disease and so is possibly more likely linked with risky pre-pregnancy alcohol use. The babies born pre-term and $\geq 2500\text{g}$ had larger mothers who were more likely to have elevated blood pressure. This group of mothers was more likely to have features of the metabolic syndrome (PR 4.44 [1.30-15.13]) or hyper-triglyceridaemic waist (PR 6.32 [1.86-21.50]) prior to their pregnancy and they were also more likely to have a diagnosis of diabetes (PR 7.81 [2.45-24.95]) or hypertension in pregnancy (PR 6.51 [2.02-21.03]) documented in their perinatal records. There were no associations found between pre-pregnancy blood fats, red cell folate or the presence of pre-pregnancy chlamydia and gonorrhoea and any of the categories of adverse birth outcomes (results not shown).

Table 3 demonstrates the effect of the 3 categories of adverse birth outcomes on method of birth, mean Apgar scores and whether or not the infant was admitted to special care or intensive care nursery in the post-natal period. Compared with infants classified as having a normal birth outcome, infants with adverse outcomes were more likely to be born by caesarean section, forceps delivery or vacuum extraction and their mean Apgar scores after birth were lower. The babies with adverse outcomes were much more likely to require admission for specialist post-natal care.

Table 4 presents mean birthweights of term infants born to mothers who had features of the metabolic syndrome prior to pregnancy, diabetes during pregnancy or who self-reported pre-pregnancy cigarette smoking compared to infants of mothers who did not. Smoking and diabetes in pregnancy appear to have a significant though opposing effects on infant

birthweights. Smoking decreased birthweight by an average of 234g ($p=0.003$) and diabetes increased birthweight by 304g ($p=0.011$).

Discussion

In this study we defined maternal pre-pregnancy characteristics and selected pregnancy characteristics (diabetes and hypertension during pregnancy) and used infant birthweight categories and length of pregnancy gestation to determine specific associations with adverse birth outcome categories. Among the factors associated with infant birthweight were gestational age, maternal size, smoking and maternal disease such as diabetes. Women with IUGR babies were small themselves with lower blood pressure and increased levels of gamma-glutamyl transferase possibly associated with risky alcohol intake. All of these mothers self-reported current smoking at their pre-pregnancy health check. The mothers of babies that were pre-term and ≥ 2500 g were quite different. This group of women had larger waist circumferences, higher BMIs and higher blood pressures. They were also much more likely to have features of the metabolic syndrome or hypertriglyceridaemic waists prior to the pregnancy, or to have a diagnosis of diabetes or hypertension during their pregnancy.

The findings suggest that mothers of IUGR babies may themselves be affected by under-nutrition and that their infants are exposed to high rates of risky maternal behaviours prior to and during pregnancy. Importantly, nearly one third of the infants with an adverse birth outcome were pre-term and ≥ 2500 g possibly due to a macrosomic phenotype related to maternal glucose intolerance during pregnancy. These infants may be a significant group regardless of pregnancy gestation at birth because despite their poor health they will be categorised in the 'healthy' range due to the common though problematic research practice of dichotomisation of birthweight to < 2500 g and ≥ 2500 g. It follows that a proportion of 184 infants in this study born with a normal birth outcome (term and ≤ 2500 g) may also be affected by hyperglycaemic pregnancies, the result of which masks what may otherwise have been low birthweight status.

Birthweight is a commonly used epidemiological tool in perinatal studies because it can be measured with very high validity and precision.⁶ There are however limitations in using birthweight as a singular outcome measure because it is determined by both rate of fetal growth and length of gestation. To assess the two major adverse pregnancy outcomes

closely associated with low birthweight, which are pre-term birth and intra-uterine growth restriction (IUGR), a valid estimate of gestation is necessary. However, not all small babies are pre-term and not all pre-term babies are small. Accuracy in determining gestation at birth is largely dependent on early and regular access to antenatal services. Categories such as small for gestational age and large for gestational age are useful, however they are also dependent on the validity of gestational age. Although low birthweight due to pre-term birth or IUGR are more difficult to classify, the distinction between them is important because their etiologic pathways differ²⁴ and this has implications for the design and implementation of public health interventions aimed at closing the gap between Indigenous and non-Indigenous birth outcomes in Australia. It is equally important to distinguish infants who are of normal birthweight due primarily to maternal obesity and hyperglycaemia during pregnancy rather than improved health.

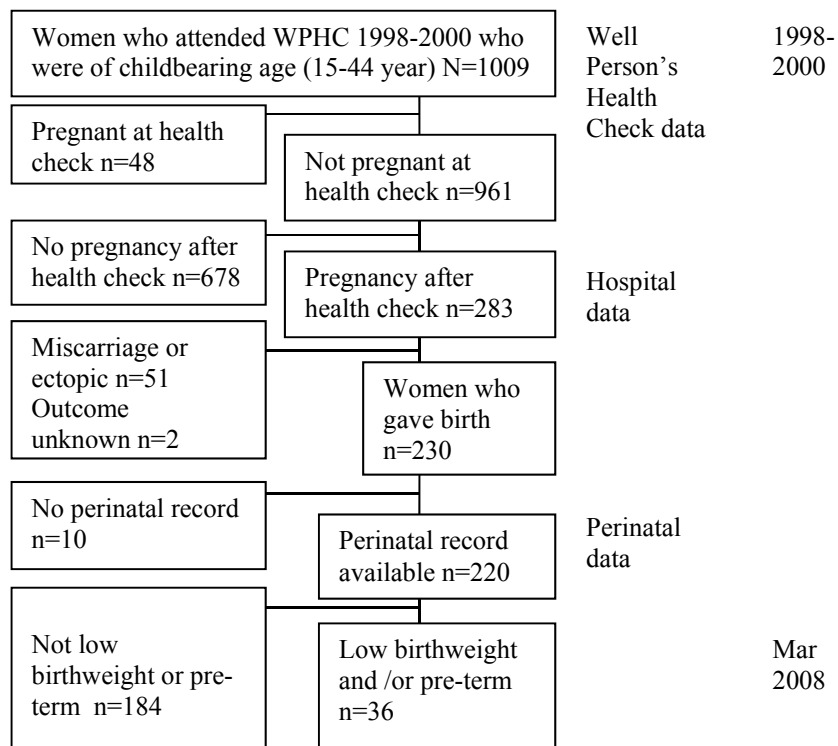
Increasing trends in large for gestational age births have been documented in Europe, North America and Canada over time despite rises in pre-term birth, and the paradox is explained by increases in maternal body mass index and decreases in smoking.^{25,26} In the current study, the prevalence of smoking remains extremely high (70% of the women who had a term birth reported current smoking at their pre-pregnancy health check) suggesting that birthweight increases due to increased maternal anthropometry and hyperglycaemia may be somewhat tempered. When decreases in low birthweight can robustly be attributed to maternal smoking cessation in the absence of maternal pre-pregnancy obesity, excessive pregnancy weight gain or hyperglycaemia in pregnancy, there would be little doubt that Indigenous birth outcomes in Australia are improving. Decreases in low birthweight where high rates of smoking continue may require more caution in interpretation.

This study is limited by its small sample size and the low participation rate of eligible women (< 50%) in the baseline survey. There is possible response bias to self-reported variables including current smoking status, alcohol use and levels of physical activity. A limitation of self-reported data generally will be compromised accuracy due to difficulties related to recall or because of sensitivities associated with the health behaviours.²⁷ Despite the low participation rate at baseline, the cohort was well characterised with standardised body and biochemical measurements and the internal validity of the associations found between baseline risk and birth outcomes (birthweight and gestation) of the subsequent

pregnancies among the cohort should be high. The use of measured, rather than self-reported anthropometric variables is an advantage in the study because of the importance of body mass and central adiposity in predicting adverse birth outcomes.

In summary, despite the small sample sizes, particularly in the primary outcome categories, this study suggests that glycaemic disorders among young Indigenous women of childbearing age are impacting to an unknown degree on infant birthweights. Further it is known that the incidence of hyperglycaemia is high among Indigenous Australians,²⁸ including the young women who participated in the WPHC and are therefore the subjects of this study.²⁹ Taken together and adding high rates of risky health behaviours prior to pregnancy, it may be important to support well designed interventions aimed at young men and women before they begin their childbearing years. It may also be important to monitor the impact of maternal obesity and hyperglycaemic pregnancies on infant birthweights nationally so that health gains and therefore successful interventions can be clearly identified.

Figure: Flow chart including datasets linked (right) and timeline (far right)



Text Box: International Classification of Disease (ICD) 9 and ICD 10 codes which identified women who were admitted to hospital for a pregnancy related condition after the Well Person's Health Check

ICD 9 codes	ICD 10 codes	Description
630-639	O00-O08	Pregnancy with abortive outcome
640-649	O10-O16	Oedema, proteinuria and hypertensive disorders in pregnancy, childbirth and the puerperium
	O20-O29	Other maternal disorder predominately related to pregnancy
	O30-O48	Maternal care related to the foetus and amniotic cavity and possible delivery problems
660-669	O60-O75	Complications of labour and delivery
650-659	O80-O84	Delivery
670-679	O85-O92	Complications predominately related to the puerperium
678-679	O94-O99	Other obstetric conditions, not elsewhere classified

Table 1. Characteristics of women who became pregnant in the 8-10 years following their 1998-2000 health check and those that did not become pregnant (n = 961)

Characteristic	No pregnancy subsequent to health check		Became pregnant subsequent to health check		PR (95%CI)	Adjusted for Age and ethnicity PR (95%CI)
	n = 678	%	n = 283	%		
Indigenous group						
Aboriginal	426	72.4	162	27.6	1.00	
Torres Strait Islander	198	67.1	97	32.9	1.19 (0.97- 1.47)	
Aboriginal & Torres Strait Islander	54	69.2	24	30.7	1.12 (0.78- 1.60)	
Age						
15-24	162	50.6	158	49.4	1.00	
25-34	239	68.5	110	31.5	0.64 (0.53 - 0.77)	
35-44	277	94.9	15	5.1	0.10 (0.06 -0.17)	
Waist circumference						
< 80cm	145	62	89	38	1.00	1.00
80-89cm	109	63	64	37	0.97 (0.75-1.25)	1.23 (0.99 – 1.54)
≥ 90cm	420	76.5	129	23.5	0.62 (0.49 - 0.77)	1.00 (0.80 – 1.26)
Missing	4		1			
BMI category (kg/m ²)						
< 18.5	68	67.3	33	32.7	0.87 (0.64 - 1.21)	1.00
18.5-25	170	62.7	101	37.3	1.00	1.00 (0.80 -1.25)
25-30	161	69.7	70	30.3	0.81 (0.63 -1.04)	0.85 (0 .67 – 1.09)
30+	277	77.8	79	22.2	0.60 (0 .46 - 0.76)	0.84 (0.62 - 1.13)
Missing	2					

Alcohol intake						
Non-drinker	203	71	83	29	0.92 (0.71 – 1.19)	1.03 (0.88 – 1.34)
Alcohol drinker (safe)	174	68.5	80	31.5	1.00	1.00
Alcohol drinker (risky)	274	70.4	115	29.6	0.93 (.74 – 1.19)	1.08 (.87 – 1.34)
Missing	27		5			
Smoker						
No	290	77.3	85	22.7	1.00	1.00
Yes	384	66.6	192	33.3	1.50 (1.20 - 1.86)	1.38 (1.13 - 1.69)
Missing	4		6			
Fruit & vegetable intake						
< 2 & 5 serves	668	70.5	279	29.5	1.00	1.00
≥ 2 & 5 serves	10	71.4	4	28.6	0.97 (0.42 - 2.23)	0.77 (0.37 – 1.62)
Enough physical activity						
No	525	69.2	234	30.8	1.00	1.00
Yes	153	75.7	49	24.3	0.79 (0.60 - 1.03)	0.80 (0.63 - 1.02)
Systolic blood pressure						
≤ 110	162	63.5	108	36.5	1.00	1.00
111-120	171	67.9	81	32.1	0.80 (0.64 -1.01)	0.85 (0.69 – 1.05)
121-130	173	79.4	45	20.6	0.52 (0.38 – 0.70)	0.65 (0.49 – 0.87)
131-140	101	74.3	35	25.7	0.64 (0.47 – 0.89)	0.91 (0.67 – 1.24)
> 140	68	84	13	16	0.40 (0.24 – 0.67)	0.85 (0.51 – 1.43)
Missing	3		1			

Diastolic blood pressure						
≤ 60	189	60.2	125	39.8	1.00	1.00
61-70	229	70.3	97	29.7	0.75 (0.60 – 0.93)	0.97 (0.78 – 1.19)
71-80	165	79	44	21	0.53 (0.39 – 0.71)	0.88 (0.65 – 1.18)
81-90	62	84.9	11	15.1	0.38 (0.22 – 0.66)	0.82 (0.47 – 1.41)
> 90	30	85.7	5	14.3	0.36 (0.16 – 0.82)	0.90 (0.41 – 2.01)
Missing	3		1			
Chlamydia & gonorrhoea						
No infection	584	72.6	220	27.4	1.00	1.00
Single infection detected	64	58.2	46	41.8	1.53	1.05 (0.84- 1.32)
Both detected	11	55	9	45	1.64	0.85 (0.53 – 1.38)
Missing	19		8			
Cholesterol						
≤ 5.5	538	68.2	251	31.8	1.00	1.00
> 5.5 (elevated)	119	82.6	25	17.4	0.55 (0.38 – 0.79)	0.83 (0.58 – 1.19)
Missing	21		7			
Triglycerides						
≤ 2	530	68.7	242	31.3	1.00	1.00
> 2 (elevated)	126	79.7	32	20.3	0.65 (0.47 – 0.90)	0.98 (0.71 – 1.35)
Missing	22		9			
HDL cholesterol						
> 1	342	69.1	153	30.9	1.00	1.00
≤ 1 (low)	274	69.7	119	30.3	0.98 (0.80 - 1.20)	0.95 (0.79 - 1.13)
	62		11			

Red cell folate						
≥ 295	537	74.3	186	25.7	1.00	1.00
< 295 (low)	115	56.4	89	43.6	1.7 (1.39 - 2.07)	1.33 (1.10 – 1.6)
Missing	26		8			
Fasting glucose						
< 4	40	61.5	25	38.5	1.00	1.00
4 -4.4	141	62.9	83	37.1	0.96 (0.68 – 1.40)	0.93 (0.65 – 1.32)
4.5 – 4.9	201	64.8	109	35.2	0.91 (0.65 – 1.29)	0.97 (0.69 – 1.37)
5 – 5.5	139	78	39	22	0.56 (0.38 – 0.86)	0.75 (0.49 - 1.12)
5.5 – 6.9 (impaired)	59	83	12	17	0.44 (0.24 – 0.80)	0.71 (0.40 – 1.25)
≥ 7 (diabetic)	74	90.2	8	9.8	0.25 (0.12 – 0.52)	0.55 (0.27 – 1.12)
Missing	24		7			
Albumin:creatinine ratio						
< 3.4	396	69.1	177	30.9	1.00	1.00
3.4 – 34	113	75.8	36	24.2	0.78 (0.57 – 1.06)	1.12 (0.84 – 1.52)
> 34	40	88.9	5	11.1	0.36 (0.16 – 0.83)	0.63 (0.28 – 1.42)
Missing	129		65			
Gamma-glutamyl transferase						
≤ 50	538	68.2	251	31.8	1.00	1.00
> 50 (elevated)	117	82.4	25	17.6	0.55 (0.38 - 080)	0.93 (0.64 – 1.35)
Missing	23		7			

Denominators vary because of missing values

Table 2. Bivariate analysis of maternal pre-pregnancy and pregnancy characteristics linked to birth outcome categories

Maternal characteristic	Unit increase	Normal birth outcome n=184 Crude PR (95% confidence interval)	p-value	Pre-term and small n=13 Crude PR (95% confidence interval)	p-value	IUGR n=13 Crude PR (95% confidence interval)	p-value	Pre-term and ≥ 2500g n=10 Crude PR (95% confidence interval)	p-value
Indigenous group									
Aboriginal	-	1.00		1.00		1.00		1.00	
Torres Strait Islander	-	1.18 (1.06-1.32)	0.009 ^a	0.15 (0.20-1.20)	0.052	0.50 (0.14-1.80)	0.290	0.19 (0.02-1.51)	0.117
Aboriginal and Torres Strait Islander	-	0.97 (0.73-1.28)	0.761	1.48 (0.36-6.14)	0.589	0.87 (0.12-6.42)	0.894	0.97 (0.13-7.25)	0.979
Maternal age at infant's birth (years)									
< 20	-	1.00		1.00		1.00		1.00	
≥ 20	-	1.09 (0.83-1.38)	0.470	0.37 (0.11-1.26)	0.113	1.21 (0.17-8.80)	0.853	0.92 (0.12-6.89)	0.936
Waist circumference	1 cm	1.00 (0.99-1.02)	0.293	0.98 (0.94-1.03)	0.421	0.95 (0.91-0.99)	0.025	1.02 (0.99-1.05)	0.081
BMI (kg/m ²)	1 unit	1.01 (1.00-1.02)	0.061	0.93 (0.83-1.04)	0.205	0.85 (0.77-0.94)	0.002	1.05 (0.99-1.12)	0.130
Non-smoker	Smoker	0.91 (0.82-1.02)	0.103	1.50 (0.43-5.29)	0.523	Undetermined		0.71 (0.21-2.43)	0.586
Alcohol use									
Non drinker or safe drinker	-	1.00		1.00		1.00		1.00	
Risky drinker	-	0.89 (0.78-1.01)	0.091	1.92 (0.66-5.5)	0.226	1.92 (0.66-5.5)	0.226	1.67 (0.50-5.61)	0.402
Systolic blood pressure	1 mm/Hg	1.00 (0.99-1.00)	0.961	1.01 (0.98-1.05)	0.439	0.95 (0.90-0.99)	0.029	1.03 (0.99-1.07)	0.098

Diastolic blood pressure	1 mm/Hg	1.00 (0.99-1.00)	0.453	1.02 (0.98-1.06)	0.390	0.96 (0.90-1.02)	0.149	1.06 (1.01-1.11)	0.017
Fasting glucose	1 mmol/L	0.98 (0.92-1.05)	0.652	0.83 (0.57-1.22)	0.346	0.86 (0.59-1.25)	0.448	1.34 (0.97-1.83)	0.069
Albumin:creatinine ratio	1 mg/mmol	1.00 (0.99-1.00)	0.751	0.96 (0.81-1.14)	0.640	1.01 (1.00-1.02)	0.167	0.77 (0.63-0.95)	0.003
Gamma-glutamyl transferase	1 U/L	1.00 (0.99-1.00)	0.273	0.99 (0.96-1.02)	0.436	1.02 (1.00-1.03)	0.010	1.01 (0.99-1.02)	0.387
Hyper-triglyceridaemic waist ^b	No/Yes	0.82 (0.57-1.18)	0.286	1.65 (0.23-11.57)	0.617	Undetermined	-	6.32 (1.86-21.50)	0.020 ^a
Metabolic syndrome ^c	No/Yes	0.95 (0.81-1.10)	0.478	1.21 (0.34-4.31)	0.758	0.69 (0.16-3.00)	0.622	4.44 (1.30-15.13)	0.020 ^a
Diabetes in pregnancy	No/Yes	0.87 (0.68-1.12)	0.283	0.82 (0.11-6.04)	0.853	Undetermined	-	7.81 (2.45-24.95)	0.020 ^a
Hypertension in pregnancy	No/yes	0.74 (0.54-1.02)	0.014 ^a	3.18 (0.96-10.47)	0.089	1.01 (0.14-7.29)	0.991	6.51 (2.02-21.03)	0.012 ^a

Denominators vary because of missing values.

Mothers with normal birth outcomes are compared with mothers who had infants in aggregated adverse outcomes (n=36). Each adverse outcome category is compared with the normal category.

^a Fisher's exact p-value

^b Defined as raised triglycerides (> 2 mmol/l) and waist circumference ≥ 88 cm) to identify women with abdominal adiposity and associated metabolic abnormalities.

^c Defined by International Diabetes Federation criteria as comprising waist circumference ≥ 80 cm plus two or more of the following: raised triglycerides (≥ 1.7 mmol/L), reduced high-density lipoprotein (< 1.29 mmol/L), raised blood pressure (systolic ≥ 130 mm Hg or diastolic ≥ 85 mm Hg) and raised plasma glucose (≥ 5.6 mmol/L). Women with diabetes excluded

Table 3. Associations between adverse birth outcomes on method of birth, Apgar scores and admission to special or intensive care nursery.

Infant outcomes	Normal birth outcome		Pre-term and small		IUGR		Pre-term and ≥ 2500 g	
	PR and 95%CI or mean (SD) n= 184	Fisher's exact p. value	PR and 95%CI or mean (SD) n=13	Fisher's exact p. value	PR and 95%CI or mean (SD) n=13	Fisher's exact p. value	PR and 95%CI or mean (SD) n=10	Fisher's exact p. value
Method of birth								
Normal	1.00		1.00		1.00		1.00	
Intervention ^a	0.41 (0.28-0.61)	< 0.001	1.37 (0.57-3.18)	0.506	3.03 (1.93-4.75)	<0.001	2.67 (1.68-4.26)	0.006
Apgar Score								
1minute	8.15 (1.57) Ref.		6.00 (3.19)	< 0.001	7.69 (2.06)	0.326	6.6 (1.84)	0.003
5minutes	9.29 (1) Ref.		8.10 (2.81)	< 0.001	9.15 (0.99)	0.619	8.5 (1.43)	0.018
Admission to Special Care Nursery								
No	1.00		1.00		1.00		1.00	
Yes	0.13 (0.8-0.21)	< 0.001	8.51 (5.18-13.99)	< 0.001	7.74 (4.55- 13.16)	< 0.001	3.17 (2.26-6.10)	< 0.001

^aIncludes caesarean section, forceps delivery, vacuum extraction and breech delivery

Table 4. Comparison of mean birth weights of term babies (n = 197) born to mothers with or without risk factors and conditions

	n (%)	Mean birthweight (g)	SD	Birthweight range (g)	2-tailed p-value t-test
Metabolic syndrome ^a					
No	152	3229	497.5	1280-4170	
Yes	40	3314	508.7	1870-4340	0.339
Diabetes in pregnancy					
No	180	3226	496.3	1280-4340	
Yes	17	3549	501.1	2760-4460	0.011
Pre-pregnancy smoking					
No					
Yes	58	3420	441.5	1280-4460	
	138	3187	514.2	2600-4340	0.003

^aAmong women free of diabetes at baseline

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6. Discussion and conclusions

The central aim of this thesis was to assess pre-pregnancy health in a cohort of north Queensland Aboriginal and Torres Strait Islander women and to examine associations between that health status and events during future pregnancies and birth outcomes. The included papers provide evidence of modifiable pre-pregnancy risk factors associated with pregnancy and birth outcomes known to potentially impact negatively on the immediate and long term health of mothers and babies. The results suggest that interventions to address maternal adiposity, sub-optimal glucose control, hypertension, high rates of risky drinking and smoking, and the presence of sexually transmitted infections before pregnancy provide a plausible pathway to improving maternal and infant health. Importantly, risk factors including poor nutrition and low levels of physical activity are highly prevalent among women during their childbearing years.

There is a substantial and growing body of national and international literature from observational studies on maternal pre-pregnancy risk factors and associations with events during the course of pregnancy and birth outcomes. The pre-pregnancy health of Indigenous women however, has not received a great deal of attention in the field. A literature review limited to a title search strategy, has uncovered a single study undertaken among First Nations women in Canada on associations between pre-pregnancy weight, gestational weight gain and adverse birth outcomes.¹ The Cree women included in the study live in settings that have similarities to those of many Aboriginal and Torres Strait Islander women in north Queensland. Cree women reside in rural and remote areas of northern Quebec, receive antenatal care at local community clinics and usually have their babies at hospitals outside their homelands and therefore, like many north Queensland Aboriginal and Torres Strait Islander women, relocate from their home up to a month before giving birth. This thesis extends the pre-pregnancy literature on Indigenous women who have the common experience of being minority populations, often living in remote areas, with socioeconomic and health disadvantage that does not reflect the wealth of their respective countries.

This is the first study to bring together self-reported health behaviours and clinical measures of pre-pregnancy health (smoking, alcohol use, nutrition, obesity, metabolic health and sexually transmitted infections) in a cohort of Aboriginal and Torres Strait

Islander women. The study evaluates how these factors contribute to the experience of pregnancy and short-term outcomes for the offspring in this high risk population.

Among the 1009 Aboriginal and Torres Strait Islander women of childbearing age in the WPHC survey, only 14 women self-reported an intake of fruit and vegetables equal to that recommended for good health. Overweight, obesity and low levels of serum red folate were common. One third of the women who became pregnant in the study period had low pre-pregnancy red cell folate (paper 1). A major challenge to living in or even visiting remote communities in north Queensland is accessing an affordable supply of nutritious food that includes fresh fruit and vegetables. There is less variety of fruit and vegetables available and other basic healthy food items are often missing from grocery store shelves (e.g. bananas, wholemeal flour, powered skim milk).² The extra expenditure needed to purchase basic healthy food over cheaper, energy dense options is an additional barrier to the health benefits of a diet low in fat and rich in nutrients. High costs associated with purchasing and transporting resources such as refrigerators, freezers and kitchen items essential for food storage and preparation put further constraints on nutritional choices available in rural and remote communities.

Poor nutrition, combined with low levels of physical activity contributes to maternal pre-pregnancy adiposity associated with adverse pregnancy events (diabetes in pregnancy (paper 2) and hypertensive disorders of pregnancy - paper 3) and birth outcomes. Finding ways of encouraging appropriate body weight and activity levels remains a challenge in communities experiencing disparities in rates of sedentariness, related chronic diseases and poor infrastructure in terms of identified facilities for physical activity.^{3,4} Other contextual factors include competing health needs and priorities. However, similarities among intervention approaches that have reported success in achieving weight loss among participants have been identified. Common characteristics of successful programmes include an emphasis on physical activity and diet, rather than diet alone, presentation of the programme in group settings while accommodating preferences of individual participants, and the inclusion of varied and progressive levels and types of exercise activities.⁵ In addition, physical activity programmes should be built into the daily cultural practices of targeted communities with adequate infrastructure investment.⁴

High prevalence of smoking and risky drinking among young women are further examples of proximal factors that must be overcome to improve infant and child outcomes. A

Western Australian study on poor outcomes in a cohort of Indigenous infants is notable for the extreme level of social disadvantage experienced by participating mothers.⁶ Maternal smoking was extremely high (64.3%), however, even more women (83.3%) reported living in a house where others smoked. Mothers who reported that alcohol use among family members caused hardship (22.1%) were twice as likely to have a poor birth outcome defined as birthweight < 2500 g and/or preterm birth (OR 2.1, 95% CI 0.9-4.6). Alcohol Management Plans were introduced in Aboriginal and Torres Strait Islander communities in Cape York from 2002 (after the WPHC survey) however, smuggling of alcohol and unlicensed liquor sales remain as well recognised problems. Penalties including removal of driver's licenses, fines and periods of incarceration metered to community members who cannot or don't want to abstain from alcohol add extra dimensions of personal, family and financial hardship. An impact evaluation has shown evidence that legislated reduction of alcohol supply associated with the plans is effective in reducing serious injury,⁷ however, they remain controversial. A human rights perspective questions the legitimacy of legally enforceable policies distinctly for Aboriginal and Torres Strait Islander peoples compared to the rest of the Australian population.⁸

Smoking remains a serious risk factor for poor health among Indigenous populations across Australia. Self-reported pre-pregnancy maternal smoking was a risk factor common to all babies categorised as IUGR in this study (paper 4). Over the last three to four decades, smokers in Australian cities and towns have been exposed to news, information and policies to turn them off smoking.⁹ Advertising bans, price increases, strong health warnings and clean air policies meant that "mainstream" Australians were confronted with subtle and overt tobacco control messages every day. Dramatic reductions in demand for tobacco have also been apparent in countries such as Canada and New Zealand, however, rates of smoking also remain high among the Indigenous populations of those countries.¹⁰ Interventions to reduce the harmful impact of tobacco smoking on Indigenous infants and children must continue.

Pre-pregnancy sexually transmitted infections were associated with a higher risk of miscarriage in this study, possibly due to recurrent infection during pregnancy (paper 1). The sexual health of Aboriginal and Torres Strait Islander Australians measured by the prevalence of sexually transmitted infections, is another important marker of overall health that is likely improve as other health and social indicators (education level, employment

prospects and financial status) improve.¹¹ In contrast to other factors associated with poor birth outcomes (e.g. food insecurity and smoking), bacterial sexually transmitted infections are an easily modifiable risk factor due to simple screening techniques (polymerase chain reaction) and single-dose antimicrobial therapy.¹²

The health challenges faced by this cohort of young Aboriginal and Torres women are multi-faceted. However, the situation can be viewed as one where potential for health gains is enormous. It is important that policy makers give priority to improving Aboriginal and Torres Strait Islander health. Prevention of disease has clear benefits for individuals, communities and the health care system. Apart from approaches that require commitment from governments; and high levels of training and awareness among clinical carers and teachers, it is also important to enable local Indigenous people to have primary responsibility for programmes and services that affect their health.

6.1 Study strengths and limitations

By utilising existing data, the study design aimed to fulfill aspects of the framework set out in the 2003 National Health and Medical Research Council Road Map: A strategic framework for improving Aboriginal and Torres Strait Islander health through research.¹³ The Aboriginal and Torres Strait Islander Research Agenda Working Group identified "a research focus on the factors and process that promote resilience and wellbeing; in particular but not exclusively, during the periods of pregnancy, infancy, childhood and adolescence and form the basis for good health throughout the lifespan" as one of the six research themes critical to achieving substantial health gain for Aboriginal and Torres Strait Islander people. A key strategy identified for harnessing knowledge to improve health included "developing data linkages able to monitor social and health inequalities in non-invasive ways, while addressing privacy and ownership issues". This study makes extensive use of existing data, information and research and it was carried out with the support of peak agencies representing the health needs of Aboriginal and Torres Strait Islander people in the region; Apunipima Cape York Health Council and the Torres Strait and Northern Peninsula Area Health Council.

The study is limited by the low participation rate of eligible women (< 50%) at the baseline WPHC survey which may have introduced selection bias. However, the associations we found between baseline risk and health outcomes should have high internal validity

because the cohort was well characterised with standardised anthropometric and biochemical measurements. A larger baseline sample size would have resulted in corresponding increase in the sample size of women who experienced pregnancy in the study follow-up period. A prospective design is able to demonstrate the temporal sequence between pre-pregnancy exposures and pregnancy events and outcomes.

Data linkage designs are ideal for examining some research questions efficiently, however, study validity is dependent on the ability (in this case hospitalisations and perinatal data) of surveillance systems to accurately identify and report on each variable. It is well-documented that identification of Indigenous status in datasets on health is problematic Australia wide, and greater attention needs to be given to better recording of Indigenous identifiers.¹⁴ An assessment of the accuracy and reliability of perinatal morbidity in the New South Wales Inpatient Statistics collection found a wide range of sensitivities among selected medical conditions which indicated a variable level of under-enumeration, however, perinatal data remains a useful source for monitoring the health of mothers and babies.¹⁵

The study is strengthened by the use of measured anthropometric measures and is one of the few studies internationally that has not relied on maternal self-report of pre-pregnancy height and weight. This is an advantage because of the particular importance of body mass and central adiposity in predicting conditions such as diabetes and hypertension during pregnancy. Lifestyle risk factors (smoking, nutrition, alcohol use and levels of physical activity) were self-reported. There is a possible response bias among these variables related to recall or because of sensitivities associated with the health behaviours.¹⁶

6.2 Practice and further research

The model of primary health care in place in many rural and remote communities in north Queensland provides existing opportunities for offering screening and advice for all women who may become pregnant in the future. Attention to the sexual health needs of young people could include safe sex education, contraceptive advice and screening for sexually transmitted infections.

Future intervention studies that integrate community-driven prevention strategies could, for example, be aimed at improved nutrition, physical activity and tobacco control. The higher

prevalence of metabolic risk among Indigenous Australian women of childbearing age in turn, confers a higher risk for a greater burden of diabetes in pregnancy. Identification and monitoring of women at particularly high risk for diabetes in pregnancy will be an important strategy for improving health outcomes among offspring. In the future, it may be equally important to track the health of affected infants as they move into their own childbearing years. Such surveillance initiatives would benefit from appropriate linkages between data collected during epidemiological studies and routinely collected data. An additional area for future research and intervention will be on the impact of alcohol use during pregnancy on the developing foetus. Enormous health gains for future generations will be realised if the entirely preventable foetal alcohol disorder spectrum can be removed from Australian communities. Importantly, community initiatives aimed at improving reproductive health outcomes should have ongoing evaluation using robust and sustainable methods.

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7. Appendices

Appendix A: Ethics Approvals

Appendix B: Permissions to reprint published papers

Appendix C: Authorship declaration forms

Appendix A: Ethics approvals

Campbell, Sandra Kaye - camsk003

From: Melissa Alagich on behalf of Alice Granger
Sent: Friday, 12 June 2009 3:37 PM
To: Campbell, Sandra Kaye - camsk003
Cc: Robyn McDermott
Subject: Ethics protocol P023/09 "Pre-pregnancy health and reproduction among Indigenous women in North Queensland"
Attachments: Conditions September 2008 (2).doc
Importance: High

Dear Sandra

Re: Ethics protocol P023/09 "Pre-pregnancy health and reproduction among Indigenous women in North Queensland"

Thank you for providing the amendments and/or additional information requested by the Deputy Chairperson of the University's Human Research Ethics Committee (email dated 6 March 2009) and for submitting variations to your original protocol for approval (as detailed in your email and attached letter dated 1 June 2009).

I am pleased to advise that your protocol has been granted ethics approval and meets the requirements of the *National Statement on Ethical Conduct in Human Research*.

Please regard this email as formal notification of approval.

Ethics approval is always made on the basis of a number of conditions detailed in the attachment; it is important that you are familiar with, and abide by, these conditions. It is also essential that you conduct all research according to UniSA guidelines, which can be found at <http://www.unisa.edu.au/res/ethics/default.asp>

Please note, if your project is a clinical trial you are required to register it in a publicly accessible trials registry prior to enrolment of the first participant (eg Australian New Zealand Clinical Trials Registry <http://www.anzctr.org.au/Survey/UserQuestion.aspx>) as a condition of ethics approval.

Best wishes for your research.

Regards, Vicki

Alice Granger
Compliance Officer
Research and Innovation Services
University of South Australia
Mawson Lakes Campus
Tel: 08 8302 3523
email: alice.granger@unisa.edu.au



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Office of the Human Research Ethics Committee
P O Box 902 Cairns Q 4870
01 April 2009

Enquiries to: Margaret Grasso
Phone: 07 40 50 8012
Fax: 07 40 50 6331
Our Ref: HREC/09/QCH/18- 564
E-mail: Margaret_Grasso@health.qld.
gov.au

Ms Sandra K. Campbell
University of South Australia
Division of Health Sciences C/-PVC Office
GPO Box 2471
Adelaide SA 5001

Dear Ms Campbell

HREC Reference number: HREC/09/QCH/18- 564

Project title: Pre-pregnancy health status and birth outcomes among a cohort of Indigenous mothers in rural and remote north Queensland communities.

Protocol number: Protocol Ref N/A

Thank you for submitting the above project for ethical and scientific review. This project was first considered by the Cairns & Hinterland Health Service District Human Research Ethics Committee (HREC) held on 12 March 2009.

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007)*, *NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007)* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*. Attached is the HREC Composition with specialty and affiliation with the Hospital (Attachment I).

I am pleased to advise that the Human Research Ethics Committee has granted approval of this research project. The documents reviewed and approved include:

Document	Version	Date
Application: NEAF	2.0	19 February 2009
Covering Letter		18 February 2009
Investigator CV		30 January 2009
Other (No Description Entered)		18 February 2009
Other (No Description Entered)		06 August 2008
Other (No Description Entered)		22 December 2008
Other (No Description Entered)		18 February 2009
Other (No Description Entered)		18 February 2009
Peer Review		05 December 2008
Response to Request for Further Information: Address queries raised		26 March 2009

Please note the following conditions of approval:

1. If relevant to your project, your attention is drawn to standards for clinical trials reporting as enunciated in the CONSORT statement (<http://www.consort-statement.org/?o=1001>) and a requirement by many journals for certain categories of clinical trials to be registered (see: <http://www.actr.org.au>)
2. The Principal Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including:
 - a. Unforeseen events that might affect continued ethical acceptability of the project. Serious Adverse Events must be notified to the Committee as soon as possible. In addition the Investigator must provide a summary of the adverse events, in the specified format, including a comment as to suspected causality and whether changes are required to the Patient Information and Consent Form. In the case of Serious Adverse Events occurring at the local site, a full report is required from the Principal Investigator, including duration of treatment and outcome of event.
3. Amendments to the research project which may affect the ongoing ethical acceptability of a project must be submitted to the HREC for review. Major amendments should be reflected in a revised online NEAF (accompanied by all relevant updated documentation and a cover letter from the principal investigator, providing a brief description of the changes, the rationale for the changes, and their implications for the ongoing conduct of the study). Hard copies of the revised NEAF, the cover letter and all relevant updated documents with tracked changes must also be submitted to the HREC coordinator as per standard HREC SOP. Further advice on submitting amendments is available from http://www.health.qld.gov.au/cpic/documents/ethics/researcher_userguide.pdf
4. Amendments to the research project which only affect the ongoing site acceptability of the project are not required to be submitted to the HREC for review. These amendment requests should be submitted directly to the Research Governance Office/r (by-passing the HREC).
5. Proposed amendments to the research project which may affect both the ethical acceptability and site suitability of the project must be submitted firstly to the HREC for review and, once HREC approval has been granted, then submitted to the RGO.
6. Amendments which do not affect either the ethical acceptability or site acceptability of the project (e.g. typographical errors) should be submitted in hard copy to the HREC coordinator. These should include a cover letter from the principal investigator providing a brief description of the changes and the rationale for the changes, and accompanied by all relevant updated documents with tracked changes.
7. The HREC will be notified, giving reasons, if the project is discontinued at a site before the expected date of completion.
8. The Principal Investigator will provide an annual report to the HREC and at completion of the study in the specified format.

Queensland Health

Enquiries to: Sue Jenkins-Manning, A/Director
Research Ethics & Governance Unit
Telephone: (07) 3234 0628
Facsimile: (07) 3405 6131
File Ref: RD001787

Ms Sandra K Campbell
University of South Australia
Div of Health Sciences C/PVC Office
GPO Box 2471
ADELAIDE SA 5001

Dear Ms Campbell

It is with pleasure that I am writing to inform you that your request for access to confidential health information for the project **"Pre-pregnancy health status and birth outcomes among a cohort of Indigenous mothers in rural and remote north Queensland communities"** has received approval from the Chief Executive Officer – Centre for Healthcare Improvement, (CHI), under delegation by the Director-General, Queensland Health. In accordance with section 281, of the Public Health Act 2005 the applicants listed in your application can access and use the specified confidential information, providing they act within the limits detailed in your application.

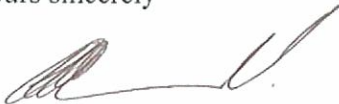
Please display this letter, a signed copy of the Undertaking of Confidentiality and a copy of your application when requesting the confidential information from the relevant information gatekeepers and provide a copy of this approval to the HREC that reviewed your protocol

- **This approval is valid till 31 December 2010**

You are required to provide an *annual or final progress report as is required* to the Research Ethics & Governance Unit. The templates can be found on the web page
http://www.health.qld.gov.au/ohmr/html/regu/aces_conf_hth_info.asp

Should you wish to extend your research project beyond this time, you will need to re-apply for further approval for the release of confidential data by the same process. This includes disclosing this information to and recruiting additional people to this project.

Yours sincerely



Dr Tony O'Connell
Chief Executive Officer
Centre for Healthcare Improvement
1/19/2009

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21 May 2009

To Whom It May Concern:

Re: Letter of support for "Indigenous mothers and babies" study

This letter indicates support for the abovementioned study by Sandy Campbell at the University of South Australia.

The study will investigate the impact of maternal pre-pregnancy health status on subsequent pregnancies and birth outcomes, among a group of Indigenous women from far north Queensland communities.

The Torres Strait and Northern Peninsula District Health Service regards the health of young women and their children as an important issue and is willing to actively support this initiative which has the aim of providing evidence to inform interventions for improving the birth outcomes of Indigenous babies in North Queensland.

Yours sincerely,



Peter Sladden
A/District Chief Executive Officer
Torres and Northern Peninsula Health Service District



APUNIPIMA CAPE YORK HEALTH COUNCIL

To whom it may concern:

Re: Letter of support for "Indigenous mother's and babies" study.

On behalf of Apunipima Cape York Health Council, I wish to formalise this organisation's support for the above mentioned study by Sandy Campbell at the University of South Australia. The study will investigate the impact of maternal pre-pregnancy health status on subsequent pregnancies and birth outcomes, among a group of Indigenous women from far north Queensland communities.

Apunipima Cape York Health Council regards the health of young women and their children as an important issue and is willing to actively support this initiative which has the aim of providing evidence to inform interventions for improving the birth outcomes of Indigenous babies in north Queensland.

Cleveland Fagan
Chief Executive Officer

03 / 10 / 2008

*"Cape York communities own solutions to live long healthy lives,
strengthen our culture and regain our spirit"*

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Appendix C: Authorship Declaration Forms

Appendix C – Paper #1

**Pre-pregnancy predictors linked to miscarriage among Aboriginal and Torres Strait Islander
women in North Queensland.**

Campbell S, Lynch J, Esterman A, McDermott R.

University of South Australia
GPO Box 2471 Adelaide South Australia 5001

***Australian and New Zealand Journal of Public Health; 2012, Volume 35, Issue 4 (2011),
Pages 343-351***

STATEMENT OF AUTHORSHIP

***Pre-pregnancy predictors linked to miscarriage among Aboriginal and Torres Strait Islander women in North Queensland.
Australian and New Zealand Journal of Public Health; 2012, Volume 35, Issue 4 (2011),
Pages 343-351***

Name of candidate: Sandra Campbell

SC contributed to the concept and design of the study, managed and analysed the data, interpreted the findings and drafted the manuscript, all under the supervision of RM, JL and AE.

I hereby certify that this statement of contribution to the above-named paper is correct.

Signed:



Date: 15th July, 2012

Author 2:

Professor John Lynch

JL contributed to the concept of the study, supervised SC's work and critically reviewed the manuscript.

I hereby certify that this statement of contribution to the above-named paper is correct, and I give permission for the inclusion of the paper in the thesis.



Signed:

Date: 16th July 2012

Author 3:

Professor Adrian Esterman

AE contributed to the concept of the study, supervised SC's work and critically reviewed the manuscript.

I hereby certify that this statement of contribution to the above-named paper is correct, and I give permission for the inclusion of the paper in the thesis.



Signed:

Date: 16th July 2012

Author 4:

Professor Robyn McDermott

RM conceived and implemented the baseline study and linked hospitalisation data. RM contributed to the concept of the study, supervised SC's work and critically reviewed the manuscript.

I hereby certify that this statement of contribution to the above-named paper is correct, and I give permission for the inclusion of the paper in the thesis.



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Date: 16th July 2012

Appendix C – Paper #2

**Pre-pregnancy predictors of diabetes in pregnancy among Aboriginal and Torres Strait
Islander women in North Queensland, Australia**

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Maternal and Child Health Journal; 2012, Volume 16, Issue 6 (2012), Pages 1284-1292

STATEMENT OF AUTHORSHIP

***Pre-pregnancy predictors of diabetes in pregnancy among Aboriginal and Torres Strait
Islander women in North Queensland, Australia
Maternal and Child Health Journal; 2012, Volume 16, Issue 6 (2012), Pages 1284-1292***

Name of candidate: Sandra Campbell

*SC contributed to the concept and design of the study, managed and analysed the data,
interpreted the findings and drafted the manuscript, all under the supervision of RM, JL and AE.*

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Date: 16th July 2012

Appendix C – Paper #3

**Pre-pregnancy predictors of hypertension in pregnancy among Aboriginal and Torres Strait
Islander women in North Queensland, Australia**

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Text in manuscript

STATEMENT OF AUTHORSHIP

Pre-pregnancy predictors of diabetes in pregnancy among Aboriginal and Torres Strait Islander women in North Queensland, Australia

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Author 2:

Professor John Lynch

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Date: 16th July 2012



Signed:

Appendix C – Paper #4

**Pre-pregnancy predictors of infant birth outcomes among Aboriginal and Torres Strait
Islander women in North Queensland, Australia: Could increasing birthweights be
misleading?**

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Australian and New Zealand Journal of Public Health; 2012: submitted paper

STATEMENT OF AUTHORSHIP

***Pre-pregnancy predictors of infant birth outcomes among Aboriginal and Torres Strait
Islander women in North Queensland, Australia: Could increasing birthweights be
misleading?
Australian and New Zealand Journal of Public Health; 2012: submitted paper***

Name of candidate: Sandra Campbell

*SC contributed to the concept and design of the study, managed and analysed the data,
interpreted the findings and drafted the manuscript, all under the supervision of RM, JL and AE.*

I hereby certify that this statement of contribution to the above-named paper is correct.



Signed:

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Professor John Lynch

*JL contributed to the concept of the study, supervised SC's work and critically reviewed the
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permission for the inclusion of the paper in the thesis.



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Professor Adrian Esterman

AE contributed to the concept of the study, supervised SC's work and critically reviewed the manuscript.

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Date: 16th July 2012

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Professor Robyn McDermott

RM conceived and implemented the baseline study and linked hospitalisation data. RM contributed to the concept of the study, supervised SC's work and critically reviewed the manuscript.

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Date: 16th July 2012